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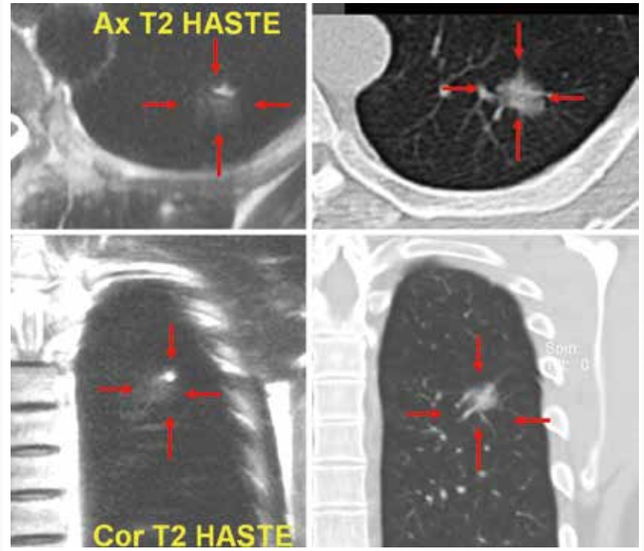

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Cover image:

A 42-year-old male. T2 weighted HASTE MR axial (top left) and coronal (lower left) imaging of the chest shows a nodule (arrows). It was also shown by CT (top right: axial; lower right: coronal) and confirmed to be a bronchioalveolar carcinoma by surgery. (See P1342 in this issue).

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Editorial

Thoracoscopic sleeve resection—the better approach?

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In the past, thoracoscopic sleeve resection has been reserved for the most adventurous and capable minimal invasive thoracic surgeons. However, with improvements in thoracoscopic competency, greater exchange of knowledge and technical know-how, and advances in equipment, increasing number of centers are able to perform sleeve resections thoracoscopically. Jianxing He's team from China, a group known for their innovation and thoracoscopic excellence, has recently published their experience of bronchial sleeve resections (1). Among the 49 patients, 20 (41%) received the bronchial sleeve lobectomy thoracoscopically, with one patient requiring half-carinal reconstruction in combination with right upper sleeve lobectomy. A 3-port VATS technique was used, with the utility thoracotomy placed anteriorly, and the camera port inferiorly. In just under half of their initial cases, a modified interrupted suture anastomosis technique of closing the membranous posterior wall of the bronchus with continuous 4-O polypropylene followed by alternating figure-of-eight and mattress with 4-O single-strand absorbable suture for the cartilaginous anterior wall was used. For the subsequent remaining cases, a continuous suture technique was used for both the posterior and anterior bronchial walls. Neither covering nor buttressing techniques were needed for the anastomoses, and no postoperative anastomotic leakage was detected. With no perioperative mortality and excellent immediate results, this study seem to further support the relative safety and efficacy of thoracoscopic sleeve resection in experienced thoracoscopic surgery centers. In addition, the study has highlighted the evolution in thoracoscopic bronchial anastomotic technique from the traditional emphasis on the security of interrupted suturing (2), to the increasing use of the more convenient continuous suturing techniques over recent years (1,3,4). Evidently, continuous suturing techniques will result in less suture tangling and may be quicker, while proponents of interrupted suturing have emphasized the potential advantages of less anastomotic site ischemia and security of their technique. It seems impossible to have a meaningful comparison of clinical outcomes between the different anastomotic approaches for thoracoscopic sleeve lobectomy because of the relatively low case numbers, patient heterogeneity and the wide variations in technique within each anastomotic approach, for example, suture size and type used, or stitch spacing, just to mention a few. In thoracic surgery, perhaps more so in thoracoscopic surgery, it is often the technique which the surgeon has been trained and is most comfortable with which produces the best results. The bronchial anastomotic technique chosen should be the one most familiar to the surgeon.

Doing less for more

Although there are no randomized trials comparing outcomes following thoracoscopic sleeve resection lobectomy with thoracoscopic pneumonectomy in patients suitable for both procedures, it is well known that the latter is associated with a higher perioperative mortality rate and complications, including pleural space infection, bronchopleural fistula, atrial fibrillation and respiratory failure (5). Furthermore, less clinically apparent parameters such as right ventricular strain and pressure are likely to be higher following thoracoscopic pneumonectomy compared with thoracoscopic sleeve resection lobectomy. Therefore, despite the improving outcomes following thoracoscopic pneumonectomy over the years (6,7), few would argue

against sleeve resection lobectomy being the procedure of choice for those patients with suitable anatomy, to achieve better lung preservation, and lower morbidity and mortality.

There is currently no prospective study comparing outcomes between thoracoscopic and open sleeve lobectomy. However, we know that the thoracoscopic approach to major lung resection has been associated with attenuated inflammatory cytokine response (8), better preserved postoperative immune function (9,10), attenuated postoperative angiogenic environment (11), less impairment of lung function (12), reduced postoperative pain and less disturbed shoulder dysfunction (13) amongst other advantages, when compared with their open counterparts. Of greater importance is the positive effect of minimizing surgical access trauma through thoracoscopic lung cancer resection on patient survival. Several studies have shown a small 5-year survival advantage in those who underwent thoracoscopic lobectomy for early stage lung cancer when compared with open approach (14,15). Interestingly, a similar survival advantage can be detected in other cancers, such as colon cancer, when resections were performed laparoscopically rather than by open laparotomy (15). Another often forgotten advantage of a quicker postoperative recovery from the thoracoscopic approach is earlier commencement and higher tolerance to adjuvant therapy for advance lung cancer patients (16). Future studies may be needed to determine if similar advantages can be found following minimally invasive thoracoscopic sleeve lobectomy when compared with open approach.

The new horizon

Thoracoscopic sleeve lobectomy, and indeed the whole of minimal invasive thoracic surgery, is undergoing a major evolution (17), from hybrid mini thoracotomy procedures with video-assistance (18), to the 2-port thoracoscopic technique (19), and more recently the single port approach (20). The challenges of thoracoscopic sleeve lobectomy, particularly when the surgery is increasingly being performed through smaller and fewer incisions, are achieving good visualization, utilizing endoscopic instruments for tissue dissection and manipulation, and reducing the difficulty associated with thoracoscopic bronchial anastomosis. Specialized thoracoscopic instruments continue to undergo refinement by producing angulated double hinged and narrower shafted instruments which significantly improves ergonomics and minimize fencing when placed through small surgical incision(s) (21). Another recent advancement is the development of variable wide angled thoracoscopes that allow up to 120 degrees of vision by either flexible scope tip or rotating prism mechanism. These thoracoscopes improve the surgeon's visual field and flexibility, even when the scope movement and position is limited within the confines of a small single incision (22). The laborious task of intracorporeal knot tying for bronchial anastomosis can now be significantly simplified by using an endoscopic "knot tying" device, such as TK Ti-KNOT® (LSI Solutions, Rochester, USA), that conveniently tightens and then secures the suture using a titanium crimp (23). Also, rapid development in barbed suture technology may soon obviate the need for intracorporeal knot tying. On the horizon will be endoscopic robotic arm devices that open inside the thoracic cavity capable of tissue recognition and precision automated micro-suturing (24). Until that day, many of us flesh and bone mortals will need to continue to strive for technical excellence, and be acquainted with the latest and best equipment for our endeavours.

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Editorial

Breast cancer control in China: challenges and opportunities of the use of population-based routine data studies

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Breast cancer is a major global public health problem, representing the first or second most common malignancy in the female population all over the world (1), accounting for about 1.4 million new cases annually (2). The worldwide trends are for an increase in breast cancer incidence and a decrease in mortality rates, although the latter is mostly seen only in the wealthier countries (3). Numerous efforts have been made to periodically assess cancer incidence and mortality rates for several cancers throughout the world, namely by the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) (4). Nevertheless, 5-year survival data of good quality with proper long-term follow-up are not widely available (4). One of the main reasons pertains to varying methods of estimating incidence and mortality across different countries, on one hand, and to shortcomings observed in national population-based cancer registries of some countries, on the other (4). Breast cancer 5-year survival rates vary geographically with lower rates noted in the most deprived areas, as shown in a worldwide population-based study using cancer registries' data (5). Moreover, disparities in mortality and survival seen worldwide highlight not only the inequities in accessing healthcare but also the existent gap in developing countries between cancer burden and ability to put in place effective cancer control measures (6).

China is the third largest country in the world, with an emerging economy (7). The reporting of breast cancer epidemiology in the Chinese female population is of utmost importance, since it relates to the highest number of new malignant cases per year in the female population (highest incidence) of the most populous country in the world (8). However, the exact incidence and mortality rates are unknown due to the inexistence or poor quality of cancer registries before 2002. Acknowledging this, the Chinese National Central Cancer Registry (NCCR) was established in 2002 and has published annual reports since 2008 (7). Zeng *et al.* (9) reported estimates of incidence and mortality in 2010 in China based on population-level data extracted from 145 regional cancer registries. The number of registered new cases was 30,819 and the one of new deaths 7,615, accounting for a mortality to incidence ratio (M/I) of 0.25. The M/I ratio was highest in the Western area of China (0.35) and lowest in the Eastern area of the country (0.23). The proportion of morphological verification was 89.88% overall, being higher in urban than rural areas and in Eastern compared to Western China. Death certificate verification was very low in the whole country, with percentages varying between 0.49 (Eastern area) and 1.81 (Western area). The authors estimated that the number of female breast cancer cases in China in 2010 was roughly 208,192, with a crude incidence of 32.43 per 100,000 inhabitants. Both the crude and age-standardised rate were higher in urban than rural areas. The Eastern and Middle area's incidence rates were quite similar (35.57 and 35.58 per 100,000, respectively) but much higher than in the Western region (23.47). Regarding mortality, a total of 55,500 deaths due to breast cancer were reported in Chinese females in 2010. Breast cancer accounted for 7.90% of all cancer deaths, ranking fifth among them. Concerning geographical distribution, the same trends observed for incidence apply.

The geographical differences illustrated by Zeng *et al.* in breast cancer incidence between urban and rural areas need to be understood taking into account the socio-demographic

trends in China and the recent westernised urban life style. Although the Chinese population is increasingly older, there was no pairwise development of the social security system (7). Moreover, healthcare is not equally accessible throughout the country with the population living in rural areas and with lower socio-economic status often receiving suboptimal care (7). The economic growth and urbanisation, on the other side, account for new modifiable risk factors for breast cancer such as obesity and sedentariness. As result of the established one-child-per-family policy, pregnancy and childbearing patterns have changed concomitantly with an increasing rate of abortion and oral contraception intake. Although this was not the scope of the work of Zeng *et al.*, combining cancer registries' information with other sources of data (e.g., hormonal intake, induced abortions rate, obesity) could yield important findings regarding priority areas for prevention and screening of breast cancer.

When comparing age-standardised incidence (ASI) and age-standardised mortality (ASM) to those estimated for European countries (10), both ASI and ASM are inferior in China (ASI of 94 per 100,000 in Europe versus 25.89 per 100,000; ASM of 23 per 100,000 in Europe versus 6.56 per 100,000). Chinese estimates were lower than the lowest ones in Europe (Bosnia-Herzegovina). Zeng *et al.* estimates were based on data from 145 cancer registries that fulfilled quality criteria defined by the Chinese Ministry of Health and international guidance from IARC, out of a total of 219. The authors of this work have also published global estimates of cancer burden for the same time-period using the same method (11). The female population covered by eligible cancer registration areas in 2010 was 12.96% of the target population, which is very low when compared with cancer registries with nearly full coverage, like those of the United Kingdom (7). The authors of the present paper state the incompleteness of cancer registration on their country and present extremely low numbers of death certification records, reflecting the sparse availability of vital registration records in China, which are an important source for epidemiological studies of the kind (4). Nevertheless, coverage is only one item that needs to be taken into account when extrapolating data from cancer registries for the general population. The quality of cancer registry data must be assessed for its completeness, validity and timeliness (12) and, therefore, constitute a representative capture of the whole country ethnic, socio-economic and demographic heterogeneity while adequately respecting the report of cancer cases. In China, the piecemeal development of cancer registries throughout the country resulted in a higher number being created in rural areas with increased risk for specific kinds of cancer, such as gastric tumours (13), which might contribute to underestimation of the real burden of breast cancer. Moreover, the definition of cancer case and its coding also often poses problems (12), which apply to breast cancer (e.g., non-invasive or multifocal tumours).

Having access to accurate and reliable epidemiological data is crucial for adequate healthcare needs' assessment and, subsequently, for healthcare planning. Epidemiologic surveillance systems and other sources of data routinely collected, such as census data, offer a time and cost-saving alternative for primary data collection that can be used to improve healthcare worldwide. Systems to collect data routinely may be found worldwide but their degree of development is widely variable. Systems to obtain data on demographic characteristics are almost ubiquitous, e.g., census data. Mortality data might not be available and when it is, the accuracy diverges according to the death certification process and its coding systems, especially in developing countries (14). Important reasons for the low death certification pertain to the fact that this is voluntary in China (13). When comparing breast cancer mortality data from the Chinese Cancer Registries (2008 Report) with those from the National Death Survey conducted in 2006 in China at 160 surveillance points, there were differences in the estimated mortality, with a statistically significant underestimation from cancer registries (13). However, this difference lost significance when taking into account the registry area (urban versus rural).

Breast cancer burden in China seems to follow global trends, despite the limitations inherent to the low coverage of the cancer registry network and the statistical model used for rates' estimation. However, reported estimates are lower than those known for Europe which might reflect some degree of underestimation. Disparities seen among the different regions in what concerns modifiable risk factors and differential access to health care, as well as inherent limitations of the cancer registry coverage and death certification, might account for these results. National emphasis must be placed on improving epidemiological surveillance systems such as cancer registries, to be used alone or in combination with other sources of routine data collection, in order to enhance the country's capacity to monitor the disease impact. Major limitations concerning the type and quality of data gathered might be overcome by improving staff training, motivation levels and establishing mandatory registry and standardisation of

death certification. Improving epidemiologic surveillance with robust, reliable and continuous population data is paramount to develop and evaluate effectiveness and cost-effectiveness of health care services and interventions to control breast cancer in China.

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Editorial

Moving beyond the boundary: the emerging role of video-assisted thoracic surgery for bronchoplastic resections

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Abstract: Sleeve resections with parenchymal sparing should be attempted whenever possible when operating a central lung cancer rather than performing a pneumonectomy. Long-term results conclusively favored sleeve procedures in improved survival, quality of life, reduced loss in lung function, and improved operative mortality. Therefore, all surgeons should own this technique in their surgical *armamentarium*. In the last two decades, the minimally invasive surgical approach has slowly gained positions in Thoracic Surgery and now more and more patients ask for a minimally invasive procedure when surgery is required. This technical revolution in thoracic surgery advocates that almost every open procedure could be done in video-assisted thoracic surgery (VATS). Nevertheless, like all other minimally invasive procedures, VATS sleeve lobectomy has a long learning curve. With the skills and the experience derived from major VATS procedures, these demanding surgical operations may also be performed with a minimally invasive approach.

Keywords: Sleeve lobectomy; carinal resection; video-assisted thoracic surgery (VATS)

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In oncological lung surgery, the sleeve resection is indicated when the tumor arises or involves the origin of a lobar bronchus, precluding the possibility of a standard lobectomy, but is not infiltrating the main stem bronchus so far as to require pneumonectomy (1). In 1947, Thomas Price completed the first documented bronchial sleeve resection in a patient with a pulmonary carcinoid of the right main stem bronchus; subsequently, the patient could return to active flying in the Royal Air Force (2). Five years later, in 1952, Allison performed the first successful right upper lobe sleeve lobectomy for a high-grade thoracic malignancy (3). Although at the beginning indications for sleeve resections were for patients who could not tolerate a pneumonectomy and intended as a parenchyma-sparing procedure, sleeve lobectomy is nowadays the standard for all anatomically suitable tumors, regardless of pulmonary function (4). Abbott, in 1950, reported the case of a right pneumonectomy with en-bloc excision of the carina, lateral wall of the trachea, and part of the left main bronchus (5). Nine years later, Gibbon reported the first case of sleeve pneumonectomy (6). In 1982, the era of carinal resection started with Grillo (7).

In a Best Evidence Topic evaluating whether a sleeve lobectomy results in a better survival rate than pneumonectomy, the results conclusively favored sleeve procedures in terms of an improved survival, quality of life, a reduced loss in lung function, and an improved operative mortality without, in most cases, difference in the loco-regional recurrence (8). The authors conclude that no more cohort studies should be performed, no more research should be done on this topic, and all surgeons should own this technique in their surgical *armamentarium*. Until recently, the sleeve lobectomy techniques were performed through a thoracotomy. Even in centers with wide experience in video-assisted thoracic surgery (VATS), the surgical indication to a sleeve resection usually precluded a minimally invasive approach (9). Only a few papers report about VATS sleeve resection; usually in the right upper sleeve lobectomy bronchial anastomosis is easier to complete compared with left lower sleeve lobectomy due to

the need of retraction of pulmonary artery, the presence of the left atrium and the left upper lobe vein (10).

Recently, Dr. He *et al.* from the Guangzhou Medical University published a paper about the surgical techniques and clinical outcome of thoracoscopic half carina resection and thoracoscopic bronchial sleeve resection for central lung cancer (11). In this remarkable paper, Authors describe a series of 20 entirely VATS bronchial sleeve lobectomy; none of the patients developed anastomotic leak and perioperative mortality was absent. The bronchial suture was initially performed with a modified interrupted suture and subsequently with a continuous suture during which the membranous posterior and the cartilage wall were anastomosed with single 3-0 or 4-0 Polypropylene suture.

The minimally invasive steps for sleeve lobectomy are similar to the open techniques. Once the camera was inserted, the pre-operative assessment should be confirmed intraoperatively by evaluation of hilum, lung parenchyma, pleural surfaces, lymph nodes, and other surrounding structures. If no major contraindications are encountered, mobilization of the lobe should follow, with a careful dissection of the pulmonary lobar branches at the hilum. The dissection should be carried out with respect for bronchial vessels for the remaining lung parenchyma. Airway dissection should be completed only after other hilar structures have been divided. Most anastomotic complications result from disruption of mucosal blood flow due to excessive skeletonization of the bronchial tissue. Frozen section histological examination of bronchial margins is recommended: the minimal requirements are 5 mm tumor-free margins in high-grade carcinomas and 3 mm margins in low-grade neoplasms (12).

The divided airways should be anastomosed in a tension free way. Most surgeons perform the anastomosis in an interrupted fashion; however also running suture is acceptable. Short and long-term results are comparable in both human series (13) and canine models (14). At the end of the procedure, a flexible bronchoscopy should be performed to evaluate anastomotic patency, orientation and to remove secretions and blood from the airway. The placement of the sutures is more important in VATS than in open thoracotomy as it is very important to keep tension and tie sutures once they are in place. From a technical point of view, the left lower sleeve anastomosis is the most difficult to perform as the posterior bronchial wall is deep and difficult to access (10).

In their paper, He *et al.* report the technique of thoracoscopic half carina resection for central lung cancer (11). They stated that the side of the lower segment of trachea was sutured first to narrow the rim of proximal trachea to better match the caliber of the distal right intermediate bronchus; the entire operation was completed only by VATS.

The usual approach for carinal resection is the right thoracotomy. Several techniques for reconstruction the continuity of airways following a carinal resection have been proposed. For limited resections of the carina, the left, and the right main bronchus can be re-approached to form a new carina and then reanastomized to distal trachea. In carinal resection with extensive airway resection, the trachea can be anastomosed end to end with either right or left main bronchus (15).

In the last two decades, the minimally invasive surgical approach has slowly gained positions in thoracic surgery and now more and more patients ask for a minimally invasive procedure when surgery is required. This technical revolution in thoracic surgery advocates that almost every open procedure could be done in VATS. Nevertheless, when compared to thoracotomy, the VATS procedures result more technically challenging because of the transmission of a multi-angle operation field in direct-view to a two dimensional flat screen. Like all other minimally invasive procedures, VATS sleeve lobectomy has a long learning curve. The geometrical approach of VATS displays some potential advantages over conventional approaches. In particular, it could obtain an angle of view similar to that obtained in thoracotomy and a more natural direction of the instruments. As a result, the anastomosis can be accomplished from a straight perspective (16).

In conclusion, the sleeve resections with parenchymal sparing should be attempted whenever possible when operating a central lung cancer rather than performing a pneumonectomy. With the skills and the experience derived from major VATS procedures, these demanding surgical operations may also be performed with a minimally invasive approach. Follow-up of patients who underwent a bronchoplastic procedure through a minimally invasive way will tell us whether we are or not on the right way.

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Original Article

Wedge resection for localized infectious lesions: high margin/lesion ratio guaranteed operational safety

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Objective: This study aims to elucidate the risk factors of pulmonary complications for localized infectious lesions with limited resection.

Methods: We retrospectively investigated 139 cases for which wedge resection had been performed for localized pulmonary infectious lesions. Patients included 85 males and 54 females with a median age of 53 years (range: 21-74 years old). Forty-six patients had focal organizing pneumonia (OP), sixty patients had lung abscess, twenty-three patients had aspergilloma, five patients had lung abscess combining aspergillus fumigatus, and five patients had lung abscess combined with tuberculosis granuloma. Information regarding perioperative manipulations, surgical complications, and follow-ups were collected for further analysis.

Results: Prominent pneumonia developed in eight cases post-operation. In follow-up, one patient had a recurrence of lung abscess five months post-operation and underwent a left upper lobectomy and one patient died two months after discharge because of respiratory failure that resulted from pneumonia. Univariate and multivariate analysis showed a significant difference in the margin/lesion ratio (distance between staple margins to lesion/the maximum tumor diameter) between patients with pulmonary complications and those without complications (P=0.01). The best cut-off value of margin/lesion ratio to complication was 0.985, and a margin/lesion ratio less than 0.985 was associated with high post-operative complications.

Conclusions: The present case series shows that partial resection for localized pulmonary infection is an acceptable surgical manipulation. A high margin/lesion ratio achievement may guarantee operational safety.

Keywords: Wedge resection; infectious lesions; complication; operation; lung

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Introduction

Localized infectious pulmonary lesions may form from abscess, aspergilloma and other granulomatous infections such as tuberculosis and coccidioidomycosis (1). Surgical management for these infectious lesions is commonly comprised of partial resection, lobectomy or pneumonectomy. The most difficult aspect of intraoperative planning for these focal diseases lies in determining whether the majority of the infiltrate could be anatomically excised (2).

Some surgeons chose partial resection for some small peripheral infectious lesion formations, would such non-anatomic resection increase the risk for post-operative complication?

In the present study, the authors retrospectively investigated clinical and pathological features for patients that received partial resection for infectious pulmonary lesions and also analyzed the risk factors for pulmonary complications of localized infectious lesions with limited resection.

Materials and methods

Patients

Wedge resection was in 1,325 cases of peripheral benign

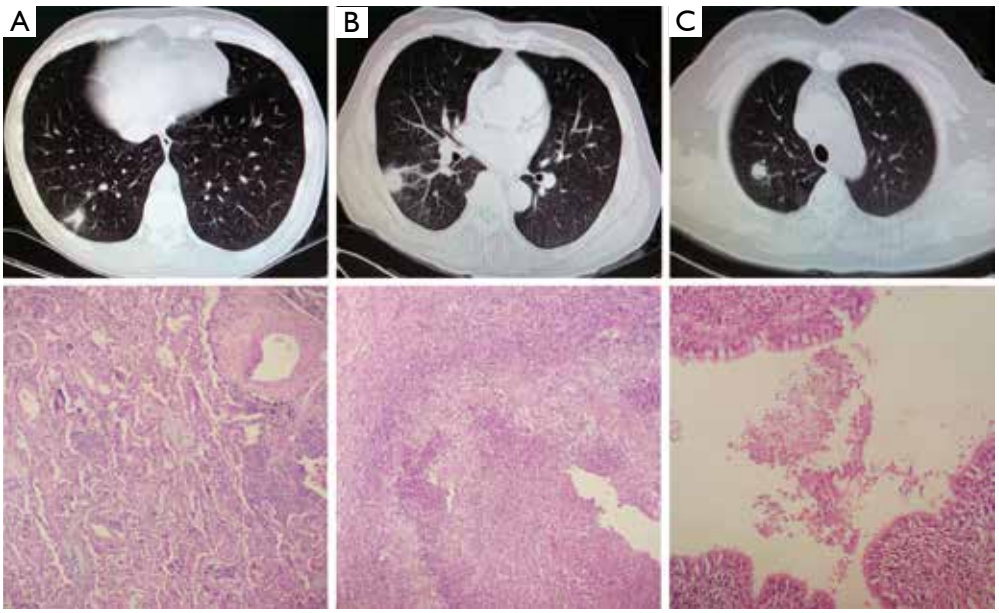

Figure 1 CT scanning and HE staining of focal organization pneumonia, aspergilloma and lung abscess. (A) Focal organization pneumonia. Upper: CT images of focal organization pneumonia. Low: alveolar spaces are filled with fibromyxoid plugs. Interstitial thickening with chronic inflammatory cells infiltrating are also evident (HE staining, 100×); (B) lung abscess. Upper: CT images of lung abscess. Low: suppuative necrosis with surrounding fibrosis was present in HE staining slides (100×); (C) aspergilloma. Upper: CT images of aspergilloma. Low: aspergillus within bronchiole was visible (100×).

lung nodules in our centre between January 2008 and December 2012, included granuloma diseases 576 cases (tuberculosis granuloma in 534 cases, cryptococcal granuloma in 42 cases); infectious disease 171 cases [focal organizing pneumonia (OP) in 78 cases, lung abscess in 60 cases, aspergilloma in 23 cases, lung abscess combining aspergillus fumigates in 5 cases, and lung abscess combined with tuberculosis granuloma in 5 cases]; and other lung tumor 578 cases (hamartoma or fibroma in 310 cases, sclerosing hemangioma in 120 cases, pulmonary lymph node in 36 cases, pleuropulmonary sarcoidosis in 78 cases, bronchogenic cyst in 34 cases).

All of 171 cases of infectious disease were retrieved and corresponding H&E slides were reviewed by two pathologists (LK Hou and HK Xie), respectively. Focal OP was diagnosed by using criteria outlined in the American-European consensus statement on idiopathic interstitial pneumonias (3), cases with infiltrating inflammatory cells were included in our study. Neutrophils were present in the necrosis tissue of lung abscess which were characterized by suppurative inflammation with fibrosis in microscope. Final diagnosis of aspergilloma was achieved based on aspergillus founding in HE staining (*Figure 1*).

Finally, total 139 cases of localized infectious lesions were enrolled in our study, including focal OP in 46 cases, lung abscess in 60 cases, aspergilloma in 23 cases, lung abscess combining aspergillus fumigates in 5 cases, and lung abscess combined with tuberculosis granuloma in 5 cases. The group was 85 males and 54 females with a median age of 53 years (range: 21-74 years old). All patients underwent partial pulmonary resection (wedge resection) due to lesions in an HRCT slice that were highly suspect for lung cancer. Preliminary fibrobronchoscopy was routinely performed to preclude lesion involvement of the lobar and segment bronchus. Mediastinoscopy or endobronchial ultrasound-guided trans-bronchial needle aspiration (EBUS-TBNA) was performed for patients with mediastinal lymph node enlargement.

Preoperative evaluations and operations

A thoracotomy or video-assisted thoracoscopic surgery (VATS) procedure was applied to all patients; partial resection was carried out with a linear stapler or endoGIA. Stitches were routinely placed in the junction of staplers when more than two staplers using. The whole lesion

was contained in resected specimens ensuring at least one centimeter of visibly lesion-free surrounding margins of the deflated lung. Frozen-section analysis was mandatory to determine the pathological nature of the lesion. Two chest tubes were positioned to the anterior and posterior for air leakage, blood, and plural effusion drainage. Chest tubes were removed when there was no air leakage and drainage was less than 100 mL over 24 h. Hospital mortality was defined as death that occurred within 30 days of the operation.

Post-operative management and pathological evaluation

The diameters, location, lesion-free stapled margins of all lesions were measured from the resected specimens.

Postoperative treatment

Patients with detection of tuberculosis received regular therapy with anti-tuberculosis drugs and follow-up from the outpatient service of the Tuberculosis Department. Patients with aspergillosis were given itraconazole orally for two weeks. Patients with lung abscesses were given intravenous antibiotics for three days.

Data collection

Information regarding underlying disease, clinical presentation, radiologic findings, diagnosis, operative procedure, complications, and follow-up was collected for further statistical analysis.

Radiological re-measurement

Preoperative high-resolution chest CT (HRCT) scan was available for all patients to assess the size, location, and characteristic of the lesion image. The data from HRCT included the diameter of the lesion and the distance (D) from the centre of the lesion to the lobe bronchus orifice (lobe where the lesion was located). We positioned the center of the lesion as one point at the lobe-orifice level with the help of an axis of coordinate using the CT scanning computer and measured the distance point to the lobe-orifice (lobe where the lesion was located) as D1. The distance between the cross section of the center of the lesion to the cross section of the lobe orifice was considered as D2, and we then deduced the following $D=\sqrt{D_1^2+D_2^2}$ (*Figure 2*).

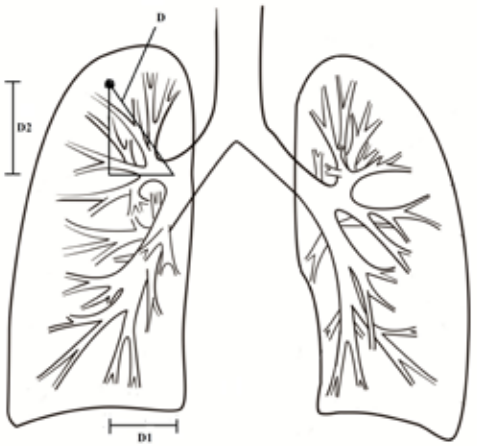

Figure 2 The way to calculate the distance of lesion centre to the lobe-orifice. The center of the lesion as one point at the lobe-orifice level with the help of an axis of coordinate using the CT scanning computer and measured the distance point to the lobe-orifice (lobe where the lesion was located) as D1; the distance between the cross section of the center of the lesion to the cross section of the lobe orifice was considered as D2; the formula $D=\sqrt{D_1^2+D_2^2}$ was used to deduce the distance of lesion centre to the lobe-orifice.

Statistical analysis

Data were expressed as median and interquartile range (IQR). Variables were compared between the two groups using a Mann Whitney U test. Categorical variables were compared using Fisher's exact test. Multivariate analysis association with pulmonary complication was done using logistic regression analysis to identify potential independent risk factors. Statistical analysis was performed with SPSS 17.0 software (SPSS Inc.). A significant difference was defined as a P value less than 0.05. The best cutoff value of the margin/lesion ratio to complication was determined by the receiver operating characteristic curve (ROC).

Results

General information

On initial presentation, 32 patients (23.0%) complained of hemoptysis, 30 patients (21.5%) had cough only, 18 patients (12.9%) had cough with bloody sputum, 18 patients (12.9%) had chest pain, 23 (16.5%) patients had high fever, one (0.7%) patient experienced shortness of breath, and 17 patients (12.2%) had a slight fever. According to

medical histories, hypertension and type II diabetes were observed in four patients (2.8%), gastric ulcer was observed in two patients (1.4%), and emphysema in two patients (1.4%). Additionally, 36 patients (25.8%) had a history of smoking and 103 patients (74.2%) had never smoked. The distribution of infected lesion localization is presented in *Table 1*. All patients received fibrobronchoscopy. Four patients and 12 patients received mediastinoscopy and EBUS-TBNA examination respectively, and malignant cells were not obtained. Negative results were found in 22 cases receiving CT guided transthoracic needle biopsy.

There were 55 thoracotomies and 84 VATS procedures. Partial resection (wedge resection) in one lobar was completed in 137 patients and wedge excision in bilobar was performed in two patients. Median operative time and intraoperative bleeding were 97.5 min (IQR, 75-120 min) and 50 mL (IQR, 50-100 mL), respectively. The median chest tube drainage duration and intensive care unit (ICU) stay was 3 days (IQR, 2-4 days) and 2 days (IQR, 1-3 days), respectively. The median hospital stay was eight days (IQR, 5.25-12 days). In pathologic review, the median diameter of the lesions was 2 cm (1.2-3 cm) in a pathologic specimen, the median lesion-free stapled margin was 2.07 cm (IQR, 1.48-2.71 cm), and median rate of margin/tumor was 1.08 cm (IQR, 0.70-1.70 cm).

Table 1 Distribution of infected lesion localization

Localization	Number of patients
Right lung	
Superior lobe	27 (19.4%)
Apical segment	12
Anterior segment	2
Posterior segment	13
Middle lobe	5 (3.3%)
Lateral segment	5
Inferior lobe	45 (32.2%)
Dorsal segment	26
Basalsegment anterior	7
Basalsegment laterale	7
Basalsegment posterior	5
Left lung	
Superior lobe	31 (22.6%)
Apicoposterior segment	9
Anterior segment	3
Posterior segment	2
Lingular segment	17
Inferior lobe	31 (22.6%)
Dorsal segment	18
Basalsegment anterior	7
Basalsegment laterale	6

Radiographic finding

Lesions had the appearance of a nodule, mass, or cavity in 81, 35, and 23 cases, respectively. Lesions located at the peripheral lung tissue and the localization of lesions is detailed in *Table 1*. Eight cases had a thin wall cavity and 15 cases had a thick wall cavity; in the group of the nodules or mass (nodule: smaller than 3 cm in diameter) (4), well defined, irregular, and a linear outer margin was found in 18, 78, and 20 cases, respectively. Other simultaneous computed tomography findings included a satellite nodule in 10 cases, bronchiectasis in 16 cases, an air crescent sign in 14 cases, a gas fluid level in 10 cases, calcification in six cases, a vacuole sign in eight cases, and pleural indentation in five cases. The median distance from the centre of lesion to lobe bronchus opening was 6.78 cm (IQR, 5.82-7.92 cm), while the diameter of lesions was 1.89 cm (IQR, 1.29-2.63 cm). There was no significant difference in the diameter of lesions between CT scans and pathologic measurements.

Complications

A total of 12 cases (8.6%) developed post-operative complications in the present study. Post-operative pneumonia was confirmed in eight patients in this group, including three patients of lung abscess, three patients of lung abscess combining aspergillus fumigates infection and two patients of focal organization pneumonia excision. All patients had high fever 2-3 days post-operation, accompanying with elevating WBC count and mainly neutrophils; radiographic imagination showed a large patching dense shadow in the surgical lobe. Pseudomonas aeruginosa, Klebsiella Pneumoniae and Candida were found by sputum culture respectively in three patients of lung abscess, these three patients were cured with sensitive intravenous antibiotics according to antimicrobial susceptibility testing. Three patients of lung abscess combining aspergillus fumigates infection were cured with empirical intravenous antibiotics and simultaneous oral itraconazole capsules. Two patients of focal organization pneumonia excision were cured with empirical intravenous antibiotics. Postoperative prolonged air leak (>7 days), which required no surgical intervention,

Table 2 Univariate analysis of patients with pulmonary complication and without pulmonary complication

Characteristic	All groups	No complication (n=129)	Complication (n=10)	P value
Gender				0.79[1]
Male	85	78	7	
Female	54	51	3	
Age	53 [46-59]	53.5 [46-59]	50 [35-62]	0.76
Smoking history				0.58[1]
Yes	36	33	3	
No	103	96	7	
Diabetes mellitus	4	3	1	0.16[1]
Operation type				0.76[1]
Thoracotomy	55	51	4	
VATS	84	78	6	
Anatomic side (right/left)	77/62	71/58	6/4	0.61[1]
FEV1 (L)	2.48 (1.87-3.17)	2.51 (1.84-3.25)	2.82 (2.24-3.28)	0.92
Operative time (min)	97.5 [63.75-120]	95 [67.5-120]	90 [90-120]	0.90
Blood losing (mL)	50 [50-100]	50 [47.5-150]	50 [50-100]	0.93
D	6.78 (5.82-7.92)	6.79 (5.81-8.42)	7.53 (6.63-8.60)	0.87
Lesion diameter* (cm)	2 (1.2-3)	1.7 (1.2-3.0)	2.5 (2-3.5)	0.059
Lesions-free margins (cm)	2.07 (1.48-2.71)	2.07 (1.49-2.63)	2.43 (1.09-3.20)	0.87
Margin/lesion ratio	1.08 (0.70-1.70)	1.23 (0.77-1.79)	0.74 (0.57-1.15)	0.013

FEV1, forced expiratory volume in 1 second; RSL, right superior lobe; RML, right middle lobe; RIL, right inferior lobe; LSL, left superior lobe; LIL, left inferior lobe; VATS, video-assisted thoracoscopic surgery; D, distance from the centre of lesion to lobe bronchus opening (lobe which the lesion located); *, lesion diameter, the data from pathologic specimens; [1], Fisher's exact test.

occurred in two patients and was cured on the 11th and 12th postoperative days, respectively, by continuous negative pressure suction in a drainage bottle system and chest physiotherapy. Atrial fibrillation occurred in two patients on the 2nd and 3rd postoperative day and recovered with medical intervention. There was no perioperative or postoperative mortality in this group. Recurrences of infections were not found within 30 days of the operation.

Follow-up

Five (3.6%) patients were lost to follow-up, and 134 (96.4%) patients had regular follow-up. The end-point of follow-up was December 2012. The median period of follow-up was 21.5 months (range, 1-61 months; IQR, 6.75-35.25 months). One patient underwent wedge resection for lung abscess, and recurrence of high fever and purulent sputum five months postoperation and a lung abscess was confirmed by CT-guided percutaneous transthoracic needle biopsy, and he underwent a left superior lobectomy after the diagnosis was confirmed; this patient fully recovered and was discharged one week after operation. One patient died two months after discharge because of pneumonia resulting in respiratory failure. One patient had accompanying intermittent incision pain and relied on painkillers. The remaining 131 patients were asymptomatic after surgery and had no evidence of disease elsewhere in the lung in the follow-up.

Univariate and multivariate analysis for pulmonary complications

The univariate analysis considered 13 variables between groups with no complications and complications with definite pneumonia (including two patients during follow-up within six months). *Table 2* reports the results of the analysis. A risk factor associated with pulmonary complication was the margin/lesion ratio. All clinical variables were included in the multivariate analysis. The results are summarized in *Table 3*.

Only one factor was independently associated with pulmonary complication: margin/lesion ratio (P=0.01). The relationship of the margin/lesion ratio to complication was analyzed by the receiver ROC, and the results showed that the best cut-off value for the margin/lesion ratio was 0.985 (*Figure 3*).

Discussion

Some localized lesions underwent surgical resection because the lesions mimicked lung cancer. Localized infectious lesions appearing in pulmonary parenchyma may be nodules, masses, or cavities, and some cases were accompanied by a vacuole sign or pleural indentation sign, thus, it was difficult in most cases to distinguish in the CT reading between benign or malignant. Even in PET-CT examination, abscess or fungal infection were common causes of increased 18F-FDG uptake, which mimicked lung cancer (5). In the present study, 83.5% (116/139) of lesions were nodule or mass, and 67.2% (78/116) of the nodules or masses had irregular margins. The lesions were highly suggestive of lung cancer through radiographic imaging, and surgical resection for those cases allowed for both diagnosis and cure.

Several studies have referred complications of limited resection for localized infection lesion exclusively. The most common complications for patients who underwent wedge resections were pulmonary related, regardless of open thoracotomy or VATS (6). In the reports by Mitchel *et al.* (7), 171 patients underwent 212 consecutive thoracoscopic lobectomies or sub-lobar for infectious lung disease and postoperative complications occurred in 19 cases (8.9%). In the study by Maldonado *et al.* (8), 24 patients had focal OP lesions and received sub-lobar resection by thoracotomy or VATS procedures, with postoperative pulmonary complications noted in two patients (8.3%). According to series reports for patients with infectious lesions, such as bronchiectasis, undergoing resection, the morbidity rates varied from 9% to 23% (9,10). Our findings in the present study were comparable with these results; the in-hospital complication rate was 8.6% (12/139) and pulmonary complications 5.7% (8/139). It was suggested that the approach of partial resection was feasible in patients with focal infectious.

The goal of surgery for treatment of localized infectious disease is to remove damaged lung parenchyma that can serve as a reservoir or nidus for recurrent infection (11). All reports emphasize the need for complete resection of focal infectious lung tissue associated with recurrent lung infection. Non-anatomic (wedge) resection for this kind of disease may result in insufficient resection range, and residual infectious tissue may contribute to pulmonary complications. In our study,

Table 3 Multivariate analysis of risk factors of pulmonary complication

Variables	P value	HR	95% CI	
			Lower	Upper
Margin/lesion ratio	0.01	36.53	2.01	663.74
FEV1	0.18	4.55	0.49	42.05
lesions-free margins	0.20	4.76	0.43	52.68
Smoking	0.23	3.18	0.44	22.92
Age	0.24	0.29	0.04	2.26
Comorbidity	0.30	0.29	0.08	4.63
Diameter	0.38	0.32	0.02	4.20
Operation time	0.61	0.59	0.08	4.36
Anatomy location	0.62	0.58	0.07	4.83
Operation type	0.68	0.55	0.33	9.03
D	0.73	0.71	0.10	5.03
Blood losing	0.87	1.21	0.12	12.12
Gender	0.93	0.90	0.11	7.42

HR, hazard ratio; CI, confidence interval; FEV1, forced expiratory volume in 1 second; D, distance from the centre of lesion to lobe bronchus opening (lobe which the lesion located).

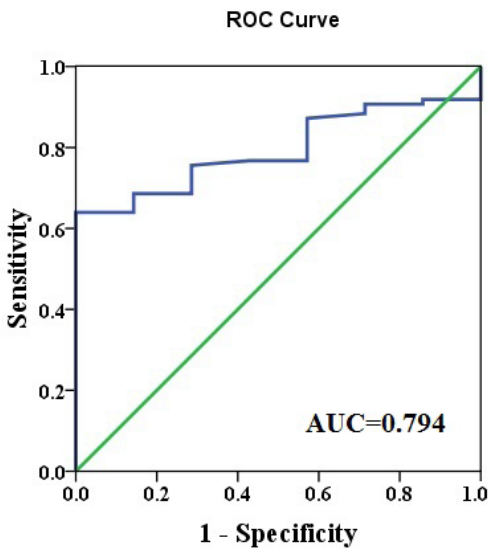

Figure 3 ROC Curve of margin/lesion ratio. The best cut-off to margin/lesion ratio that maximizes (sensitivity + specificity) is 0.985. At this point, the sensitivity is 0.64 and specificity is 1 (1-specificity =0). AUC, area under roc curve.

univariate and multivariate analysis showed that the group with pulmonary complications yielded a significant difference in the margin/lesion ratio compared to the no complications group. Patients without complications had higher margin/lesion ratios (see *Tables 2*,*3*), and thus, it is implied that larger lesions should obtain longer lesion-free stapled margins to ensure sufficient excision.

It's also reported that a margin/tumor ratio of less than one is associated with a higher rate of recurrence in patients of early-stage NSCLC that had undergone partial excision (12,13). The results of our research also demonstrated that the best cut-off value of the margin/lesion ratio for complications was 0.985; and a ratio of less than 0.985 had high pulmonary complications. The best cut-off value was approximately equal to one in our finding. We can draw a conclusion that relatively larger lesions should have a longer free margin, and that maintaining a margin/lesion ratio of more than one ensure better safely for limited resection of focal infectious lung disease.

Our study has several limitations. This was a retrospective study and only partial resection cases were included. The participants included in this study consisted of only 139 cases. Therefore, the small population may potentially influence the results.

Conclusions

For small peripheral pulmonary local infectious lesions, partial resection is an acceptable surgical manipulation choice, and maintaining a high margin/lesion ratio may better guarantee operational safety.

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Original Article

Effectiveness and safety of a protocolized mechanical ventilation and weaning strategy of COPD patients by respiratory therapists

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Introduction: Prior researches have showed that weaning protocols may decrease the duration of mechanical ventilation. The effect of these protocols on chronic obstructive pulmonary disease (COPD) patients is unknown. The purpose of this study was to evaluate the impact of an extensive mechanical ventilation protocol including weaning applied by a respiratory therapist (RT) on the duration of mechanical ventilation and intensive care unit (ICU) stay in COPD patients.

Materials and methods: A novel mechanical ventilation protocol including weaning was developed and initiated for all intubated COPD patients by a respiratory therapist. Outcomes of patients treated using this protocol during a 6-month period were compared to those of patients treated by physicians without a protocol during the preceding 6 months.

Results: A total of 170 patients were enrolled. Extubation success was significantly higher (98% *vs.* 78%, P=0.014) and median durations of weaning, mechanical ventilation and ICU stay compared with time to event analysis were significantly shorter in the protocol based group (2 *vs.* 26 hours, log rank P<0.001, 3.1 *vs.* 5 days, log rank P<0.001 and 6 *vs.* 12 days, log rank P<0.001, respectively). Patients who were successfully extubated and patients in the protocol based group were more likely to have shorter ventilation duration [HR: 1.87, 95% confidence intervals (CI): 1.13-3.08, P=0.015 and HR: 2.08, 95% CI: 1.40-3.10, P<0.001 respectively].

Conclusions: In our center, a protocolized mechanical ventilation and weaning strategy improved weaning success and shortened the total duration of mechanical ventilation and ICU stay in COPD patients requiring mechanical ventilation.

Keywords: Mechanical ventilation; weaning; chronic obstructive pulmonary disease (COPD)

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Introduction

Mechanical ventilation is a common procedure used to treat patients with respiratory failure due to chronic obstructive pulmonary disease (COPD). Although it is life saving, it is invasive, expensive and associated with some serious potential risks such as ventilator associated pneumonia, ventilator induced lung injury, hemodynamic problems and prolonged intensive care unit (ICU) stay. Therefore, reducing the time patients spend on mechanical ventilation will lead to improvements in patient care, decrease in related complications and reduced costs.

Prior research has demonstrated that the use of standardized weaning protocols can shorten the duration of mechanical ventilation (1-4). Assessing readiness to wean and the choice of ventilator strategies and modes vary among physicians, and protocols performed by non-physician medical staff such as nurses and respiratory therapists (RTs) may reduce the total duration of mechanical ventilation and ICU length of stay (5,6). However, these previous studies were performed in mixed medical and surgical patient populations and only evaluated the role of these protocols during the weaning period. Furthermore, there is little data evaluating the effect of implementing these protocols in

difficult to wean patients such as COPD (7-9).

In 2011 January, our ICU recruited a RT and implemented a mechanical ventilation and weaning protocol. Prior to this date, the choice of ventilator mode and approach to weaning was left to the discretion of individual respiratory physicians. The aim of this study was to evaluate the impact of this protocol on total duration of mechanical ventilation and weaning, ICU stay, weaning success rates and mortality in COPD patients.

Materials and methods

This cohort study was conducted in the 29-bed ICU of a 450-bed teaching hospital specializing in pulmonary diseases and thoracic surgery. The data of patients who were managed before the implementation of the protocol was collected retrospectively and compared with the prospectively collected data of patients managed with a protocol. We included all COPD patients who required mechanical ventilation due to an exacerbation more than 48 hours. There was no change in the physicians, treatment modalities and other medical staff working in the ICU between the study periods. COPD diagnosis was made according to the Global Initiative for Chronic Obstructive Lung Disease criteria and confirmed by the medical records of our hospital (10). Patients who needed advanced ventilatory techniques (PEEP level greater than 10 cmH_2O, inverse ratio ventilation, airway pressure release ventilation, prone positioning) at the beginning or during the follow up period due to acute respiratory distress syndrome were excluded in both intervention and control groups due to the incompatibility with the protocol and the exceptional nature of the disease. Patients with a tracheostomy, who were ventilated shorter than 48 hours, patients with a cause of ICU admission different from COPD exacerbation and patients who were under home mechanical ventilation support were also excluded. The study was approved by the institutional review board (number: 298) and written informed consent was obtained from the patients and/or next of kin.

Protocol-based group

A full time RT was assigned to work in the ICU in January 2011. From that time, a novel protocol-based mechanical ventilation and weaning protocol for our center was developed and pilot tested. After some adjustments, the protocol was initiated for all intubated COPD patients. When an intubated patient was admitted to the ICU or a patient was intubated during ICU stay, the RT set the following parameters and settings: Assisted pressure controlled mode, inspiratory pressure titration to achieve a tidal volume (Vt) of 6-8 mL/kg, minimum respiratory frequency (f) of 15 breaths/min, 3-5 cmH_2O of positive end expiratory pressure (PEEP), flow triggering at minimum level but avoiding auto-triggering, inspiratory time (Tinsp) set to maximum 1.5 seconds and fractional inspired oxygen concentration (FiO_2) titrated to achieve an arterial oxygen saturation (SaO_2) greater than 90% (11). The patients were evaluated at least two times a day and manipulations in Tinsp, f or both were done to achieve a partial arterial carbon dioxide pressure ($PaCO_2$) lower than 50 mmHg and a pH value greater than 7.25. FiO_2 levels were decreased gradually until 50%. Patients were assigned for a spontaneous breathing trial (SBT) with a t-piece for 2 hours when they met the following criteria: PaO_2/FiO_2 >150, PEEP ≤8 mmHg, Glasgow coma score (GKS) >8, number of controlled breaths=0, number of patient triggered breaths ≤35, pH >7.25 or $PaCO_2$ <50 mmHg, mean arterial pressure ≥60 mmHg with no or low doses of vasopressors (≤5 μg/kg/min), adequate cough for airway protection (10). If the patients showed good tolerance with an acceptable arterial blood gas analysis (pH ≥7.35, PaO_2/FiO_2 >150 with a FiO_2 ≤50%, f ≤35 breaths/min), they were extubated. If signs of intolerance occurred (change in neurologic status, f >35 breaths/min, pH <7.32, increase in $PaCO_2$ >10 mmHg, heart rate >140 beats/min, systolic blood pressure >180 or <90 mmHg), patients were re-connected to the ventilator and SBT was repeated the following day (11). If the patients failed the SBT for three consecutive days, then they were switched to pressure support ventilation and weaning was continued by gradual reductions in pressure support level until 7 cmH_2O is tolerated as described elsewhere (12,13). If the patients tolerated the SBT with 7 cmH_2O of pressure support for 2 hours (with the same tolerability criteria for SBT with a t-piece as above) they were extubated.

Physician-directed group

Before January 2011, the choice of mechanical ventilation mode was made by the physician's individual preferences. The most common preferred modes were assisted volume controlled ventilation, synchronized intermittent mandatory ventilation, pressure controlled ventilation and pressure support ventilation. Weaning procedures were also determined by the physician in charge of the patient.

Table 1 Baseline characteristics of patients

Patient characteristics	Protocol based (n: 73)	Physician directed (n: 97)	P
Age, years	71 [62-77]	65 [54-70]	<0.001
Gender, M/F	56/17	74/23	1
APACHE II	19 [16-21]	16 [14-19]	0.001
pH*	7.22 [7.16-7.26]	7.23 [7.17-7.26]	0.92
$PaCO_2$, mmHg*	88 [68-109]	90 [74-106]	0.77
Baseline PEEP, cmH_2O	5 [5-6]	5 [5-6]	0.60

Data are expressed as median (IQR) or n [%]. APACHE, acute physiologic and chronic health evaluation; $PaCO_2$, partial arterial carbon dioxide pressure; PEEP, positive end expiratory pressure; *, the last arterial blood gas results before intubation.

Weaning criteria were not monitored daily and the assessing readiness to wean and decisions for extubation were also physician directed and performed according to subjective criteria differing among physicians. Specific mechanical ventilation and weaning protocols did not exist, but in general physicians employed commonly recommended procedures such as 2 hours of SBTs with t-piece or 7 cmH_2O pressure support.

Definitions

Extubation success was defined as 48 hours independence from mechanical ventilation (invasive or noninvasive). If the patients could never reach the weaning period during hospitalization (deterioration in the clinical status, death etc.) they were classified as non-weaned for the primary analysis. Duration of mechanical ventilation (MV) was defined as the time from intubation until successful extubation. Length of stay (LOS) in ICU was defined as the time from intubation until ICU discharge. Weaning duration was defined as the time from the beginning of the first SBT (either with t-piece or pressure support) until successful extubation.

Statistical analysis

Statistica 8.0 software (StatSoft Inc. Tulsa, USA) was used for the analysis. Continuous variables were expressed as medians with interquartile range (IQR) and categorical variables were expressed as numbers with percentages. Medians were compared by Mann Whitney U test and frequencies were compared by Fisher's exact test. Kaplan-Meier curves with log rank test were used to compare the time to successful extubation and liberation from mechanical ventilation and time to ICU discharge. Patients who died during ICU follow-up were censored in the primary analysis; rates of deaths in both study periods were compared as a secondary outcome. Cox proportional hazards regression was used to adjust for other factors that can affect MV duration and ICU length of stay. Results were expressed as hazard ratio (HR) with 95 % confidence intervals (CIs). A two sided P value of <0.05 was considered as significant.

Results

Seventy three patients were enrolled in the protocol based RT directed group and compared with 97 patients in the physician directed group (*Table 1*). Patients in the protocol based RT directed group were significantly older with a significantly higher median APACHE II score. Weaning success rates were comparable between the two groups (72% *vs.* 68%, P=0.52). When the non-weaned patients were excluded from the analysis, extubation success rate was significantly higher (94% *vs.* 78%, P=0.014) in the protocol based RT directed group. Mortality rates were comparable between the two groups (*Table 2*). Time to successful liberation from mechanical ventilation was significantly shorter in the protocol based RT directed group (*Figure 1*). MV duration until the first SBT (2.8 *vs.* 3 days, P=0.018), weaning duration (2 *vs.* 26 hours, P<0.001), total MV duration (3.1 *vs.* 5 days, P<0.001) and LOS in the ICU (6 *vs.* 12 days, P<0.001) were also significantly shorter in the protocol based RT directed group (*Table 2*, *Figure 2*). Overall, patients in the protocol based group were more likely to become liberated from mechanical ventilation when compared with the physician directed group (unadjusted HR: 2.06 with 95% CI: 1.44-

Table 2 Processes and outcomes during ICU stay

Patient characteristics	Protocol based (n: 73)	Physician directed (n: 97)	P
Weaning outcome			
Extubation success	53 [94]	66 [78]	0.014
Extubation failure	3 [6]	18 [22]	
Non-weaned	17 [23]	13 [13]	0.07
MV duration until the first SBT, days	2.8 [1.1-3.3]	3 [2-4]	0.018
Patients needed sedation	22 [30]	31 [32]	0.86
Weaning duration, hours	2 [2-24]	26 [20-72]	<0.001
Total MV duration, days	3.1 [1.7-4.2]	5 [3-12]	<0.001
LOS in ICU, days	6 [4-8]	12 [6-15]	<0.001
ICU mortality	18 [25]	18 [19]	0.35

Data are expressed as median (IQR) or n [%]. APACHE, acute physiologic and chronic health evaluation; MV, mechanical ventilation; SBT, spontaneous breathing trial; LOS, length of stay; ICU, intensive care unit; non-weaned, unable to be eligible for weaning period; *, the last arterial blood gas results before intubation.

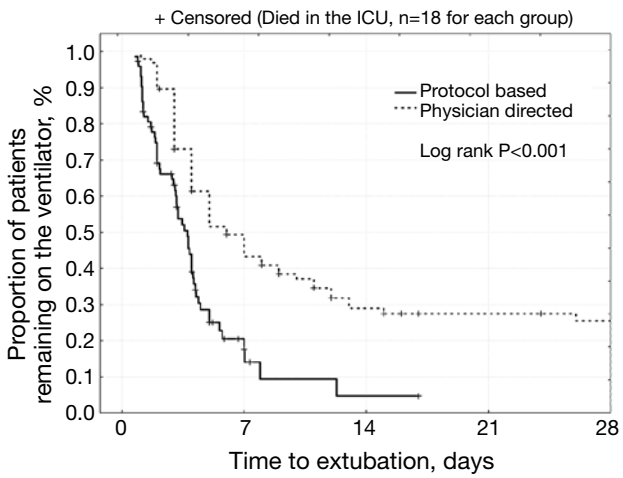

Figure 1 Comparison of time to becoming successfully liberated from mechanical ventilation between the protocol based RT directed group and physician directed group by the Kaplan-Meier method. Follow up was terminated at day 28. RT, respiratory therapist; ICU, intensive care unit; MV, mechanical ventilation.

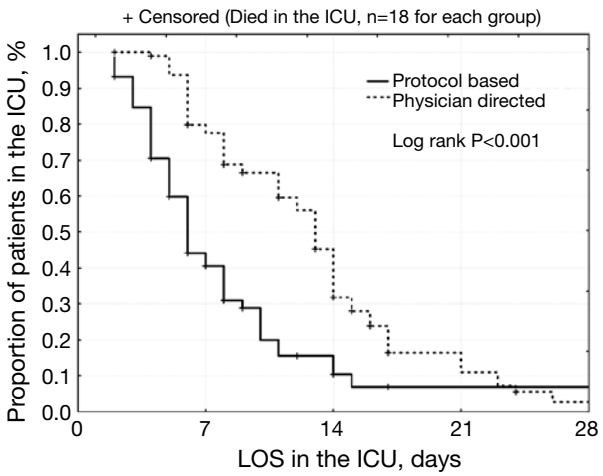

Figure 2 Comparison of length of ICU stay between the protocol based RT directed group and physician directed group by the Kaplan-Meier method. Follow up was terminated at day 28. RT, respiratory therapist; ICU, intensive care unit; LOS, length of stay.

2.95, P<0.001) We included the a-priori specified variables in a multivariable Cox-proportional hazard model to evaluate the adjusted likelihood of becoming liberated from mechanical ventilation. Age, APACHE II, $PaCO_2$ and weaning outcome were selected as covariates for the main effect model (purposeful selection). MV duration until the first SBT, weaning duration and LOS in ICU were significantly correlated with total MV duration so they were not included in the model. Model check using Kolmogorov-Smirnov test was performed and all the variables included in the model were normally distributed. There were no colinearities between covariates. The only factors shortening total MV duration was found as being in the protocol based group (HR: 2.08, 95% CI: 1.40-3.10, P<0.001) and extubation success (HR: 1.87, 95% CI: 1.13-3.08, P=0.015) after adjusting for age, APACHE II and $PaCO_2$

levels just before intubation.

Discussion

This study suggests that the implementation of mechanical ventilation and weaning protocol directed by a respiratory therapist can reduce both weaning and total MV duration and LOS in the ICU in COPD patients. The impact of the RT directed protocol remained the same after adjusting for some probable confounding factors such as age, APACHE II and $PaCO_2$. Moreover, this kind of practice may improve the weaning success rates in this patient group for whom weaning can often be difficult and prolonged.

It is a well-known fact that intubation and mechanical ventilation have some very important potential risks in addition to obvious benefits. Ventilator associated pneumonia, probably the most common complication of intubation occurs at a rate of 1% to 3% per day of mechanical ventilation (14). These complications lead to increased costs and mortality in ICU patients. For this reason, reducing the duration of MV and ICU stay has always been an important aim for critical care physicians.

Selection of mechanical ventilation mode is often based on clinician familiarity and institutional preferences since there is a paucity of evidence indicating that choice of mode affects clinical outcome. In an observational study enrolling 412 ICUs in eight countries, the most commonly used ventilator modes were assisted controlled ventilation, synchronized intermittent mandatory ventilation, pressure support ventilation and pressure controlled ventilation. Tidal volumes were set around 8-9 mL/kg, respiratory rate around 12-15 breaths/min and PEEP around 5 cmH_2O (15). There are studies reporting that this variety of decisions made by physicians during follow up and weaning period may lead to prolonged MV duration and ICU stay (16). Therefore, we decided to use a standard ventilation mode and weaning protocol for all patients.

Our findings are consistent with other studies that have implemented weaning protocols. Tonnelier *et al.* reported that a weaning protocol directed by nurses instead of physicians resulted in a 6 days of shortening in MV duration and ICU stay in a combined group of ICU patients which included COPD patients. However, the improvements in COPD patients did not reach statistical significance (5). In another study performed by Wood and colleagues on cardiac surgery patients, a progressive increase in the proportion of patients weaned by the RTs and a slight decrease in total ventilation time and weaning duration was observed (3). Marelich *et al.* reported a decrease in MV duration from median 124 hours to 68 hours for a mixed group of ICU patients of which 16 were COPD in their randomized controlled study (6). Ely *et al.* also reported a significant decrease in weaning and total MV duration with a weaning protocol including daily screening of patients' respiratory functions (17). In a recently published meta-analysis, Blackwood *et al.* reported that weaning protocols decreased the mean duration of mechanical ventilation by 25%, duration of weaning by 78% and ICU stay by 10% (16). These findings were consistent with our results. Moreover, we detected a significant decrease also in the duration of MV until first SBT. This finding also supports the importance of a mechanical ventilation protocol including daily screening and assessing readiness to wean according to some objective criteria.

Weaning outcomes vary among studies. Esteban *et al.* reported 82% of extubation success with SBT with t-piece in a combined group of patients of which 21% were COPD (13). Lower success rates around 65% are also reported in some other studies (18). These alterations might be due to the experience of the ICU staff, severity or the patients and differences in the ventilation and weaning modes used in different centers. Our extubation success rate was consistent with the literature in the physician directed group whereas it was significantly higher in the Protocol based RT directed group. There is also some evidence that weaning protocols may increase the extubation success rates. Teixeira *et al.* reported an increase in extubation success around 17% with a weaning protocol (19). This is probably due to the strict protocol used for assessing readiness to wean patients in protocol group. This finding also suggests that the alterations in the physicians' individual decisions to extubate the patients might worsen the success rates as reported in some other studies (2).

To our knowledge, this is the first study that evaluates the impact of non-physician directed mechanical ventilation "plus" weaning protocol beginning from the intubation until extubation in adults in a developing country. Hermeto *et al.* performed a similar study in premature infants and reported outcomes consistent with our study (20). Nevertheless, our study has several limitations. First, because of the non-randomized design, the two groups compared may not be comparable although we have performed a regression analysis. We only could compare the APACHE II score for the severity of the disease because other indices like pulmonary function tests were not available for all patients. Second, the idea that things get better over time regardless

of what we do might have an impact on the positive results in the intervention group. Even though the unit staff remained the same throughout the study period, their skills could have improved with experience. Although protocols are helpful in improving outcomes in the ICU, we must take into account that every patient is unique and sometimes it may not be possible to follow protocols for each patient. An experienced physician and a vigilant nurse who perform a once daily SBT may have a big role to play in the successful weaning of mechanically ventilated patients. It may not be cost effective to recruit a respiratory therapist if ICU physicians perform the mechanical ventilation and weaning protocols but because of the lack of intensivists in most of the centers throughout the world, non-physician medical staff such as nurses or respiratory therapists able to perform these protocols may decrease the workload of intensivists. Last but not least, this study enrolled a homogenous patient group in a single center so the results are not generalizable to other patient groups and centers.

Conclusions

This study demonstrated that, a simple mechanical ventilation and weaning protocol applied by non-physician ICU staffs like respiratory therapists might improve weaning success and shorten the total duration of mechanical ventilation and ICU stay in COPD patients requiring mechanical ventilation over a 48-hour period. These improvements may also be achieved without a change in mortality rates. Further multi-centric studies are needed to evaluate the impact of these protocols on heterogeneous patient groups in different centers.

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Original Article

An analysis of and new risk factors for reexpansion pulmonary edema following spontaneous pneumothorax

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Background: The major risk factor for reexpansion pulmonary edema (RPE) following the treatment of spontaneous pneumothorax is thought to be chronic lung collapse. However, a long-term collapsed lung does not always cause RPE. The purpose of this study was to define other risk factors for RPE among patients undergoing drainage for the treatment of spontaneous pneumothorax.

Methods: We retrospectively reviewed all the patients with spontaneous pneumothorax who had been treated at our hospital during a 5-year period. The duration of symptoms, location and size of the pneumothorax, size of the chest tube, and pleural effusion, which can occur coincidentally with pneumothorax, were compared in patients who did and did not experience RPE.

Results: Forty patients were underwent drainage for the treatment of a spontaneous pneumothorax between January 2007 and December 2012. RPE developed in 13 of the 40 (32.5%) patients. In the multivariate analysis, the presence of pleural effusion coincident with pneumothorax contributed to the risk for RPE [odds ratios (OR), 1.557; 95% confidence intervals (CI), 1.290-1.880]. The duration of symptoms, location and size of the pneumothorax and size of the chest tube were similar between the groups. Symptomatic RPE was associated with a larger pneumothorax size.

Conclusions: The rate of RPE following spontaneous pneumothorax is higher than was previously reported. Our findings suggest the presence of pleural effusion coincidentally with pneumothorax may therefore be a new risk factor for RPE.

Keywords: Lung; pneumothorax

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Introduction

Reexpansion pulmonary edema (RPE) is a potentially life-threatening complication that can occur after rapid lung reexpansion following the treatment of pneumothorax or pleural effusion. RPE was first described by Pinault in 1853 as a complication of thoracentesis (1) and in 1959, Carlson *et al.* reported that RPE occurred after treatment of a pneumothorax (2). Since then, there have been many reports regarding RPE. Although the incidence of RPE varies from 0.9% to 29.8% (3-5), the mortality rate associated with RPE can be as high as 20% (6,7). Therefore, early recognition and fast symptom-orientated treatment are necessary for a good outcome. However, RPE usually appears unexpectedly, although several studies about RPE, including investigations of its clinical features, treatment or prevention, have been reported. RPE can occur even when the collapse lasts for less than 3 days (4), although in the comprehensive review of RPE by Mahfood and colleagues (6), 83% of the cases had experienced periods of lung collapse lasting 3 or more days. Ultimately, the risk factors for RPE remain unclear. In this study, we wanted to analyze the clinical characteristics and risk factors of RPE by retrospectively assessing the clinical records of patients with spontaneous pneumothorax who were treated by thoracostomy.

Patients and methods

Patients

We retrospectively reviewed the clinical records of all patients hospitalized in our surgical department after they had undergone drainage for the treatment of spontaneous pneumothorax in our institution between January 2007 and December 2012. Patients with a known history of underlying lung disease (mainly chronic obstructive pulmonary disease) were excluded. All patients underwent erect posteroanterior chest radiography to verify the presence of a spontaneous pneumothorax. Subsequent radiographs and chest computed tomography (CT) scans were obtained within 24 hours of thoracostomy to confirm the lung reexpansion, as well as the presence of complications such as tube malposition, RPE or the presence of bullae. The methods used for the lung expansion included high negative suction with needle aspiration, a chest tube with an underwater seal or suction.

Diagnostic criteria for RPE

A diagnosis of RPE was made on a radiographic basis. The radiographic criteria included a chest radiograph or CT scan with a new finding of focal ground-glass opacity with a vascular distribution (8).

Classification of the pneumothorax sizes

The pneumothorax size was measured according to the method described by Collins *et al.* (9). This method used CT volumetry to derive a formula based on measurements of the interpleural distances on a chest radiograph to estimate the pneumothorax size. The formula requires measurements of the interpleural distance at the apex (A) and the lateral wall at the mid-point of the upper and lower halves of the collapsed lung (B and C).

Estimated pneumothorax size (%) =4.2+ [4.7 + (A + B + C)]

We classified the patients based on the size of their pneumothorax into the following four groups: small, medium, large and tension (5). A small pneumothorax was defined as a pneumothorax that was localized to the apex of the lung on chest radiography. A medium pneumothorax was defined as a pneumothorax that extended beyond one-third of the width of a hemithorax. A large pneumothorax was defined as a pneumothorax leading to complete or nearly complete collapse of the lung parenchyma. A tension pneumothorax was defined as a pneumothorax associated with depression of the diaphragm or a shift of the mediastinum and trachea away from the collapsed lung.

Classification of the chest tube sizes

We also classified the patients based on chest tube sizes used for drainage into the following three groups: small (≤14 Fr), medium (16 to 22 Fr) and large (24 to 36 Fr) (10).

Classification of pleural effusion

In general, pleural effusion can occur coincident with pneumothorax, although it is usually quite small.

The determination of the presence of pleural effusion was made on erect posteroanterior chest radiographs which were performed to confirm the presence of a spontaneous pneumothorax. The patients were also classified into three sub-groups based on the appearance of effusion (11-13):

(I) No effusion or very small effusion: a sharp costophrenic angle;
(II) Small: blunting of the costophrenic angle;
(III) Moderate: the partial outline of the diaphragm on the affected side is lost with the meniscus sign;
(IV) Large: the entire outline of the diaphragm on the affected side is lost.

Statistical methods

The continuous data are presented as means with SDs, and were compared with the independent sample *t*-test or Mann-Whitney U-test, as appropriate. Nominal data are presented as the percentages of the frequency of occurrence and were compared with a χ^2 or Fischer exact test, as appropriate. A univariate analysis of the lesions characteristic was used to calculate the risk and odds ratios (OR) with confidence intervals (CI). A multivariate logistic regression analysis was then performed. Values of P≤0.05 were considered to be statistically significant.

Results

Between January 2007 and December 2012, 40 patients were diagnosed with a spontaneous pneumothorax and treated with tube thoracostomy. The patients ranged in age from 15 to 64 years old (mean, 26.6±12.3 years old) and there were 32 males and 8 females (*Table 1*). The mean duration of symptoms was 5.1±8.4 days. The pneumothorax was located on the right side in 21 patients, on the left

side in 18 and bilaterally in one patient. With regard to the pneumothorax size, 18 patients were classified in the small group, 9 patients were classified as having a medium pneumothorax, 7 were classified as large and 6 patients were classified as having a tension pneumothorax. Of the chest tubes inserted for treatment, 9 were small, 23 were medium sizes and 8 were large. Pleural effusion was not detected in 18 patients, was small in 17 patients, moderate in 5 patients (*Figure 1*), and there were no patients with large effusion.

Table 1 Patient characteristics

Factor	N
Age (mean ± SD) (year)	26.6±12.3
Male/female (n)	32/8
Duration of symptoms (mean ± SD) (day)	5.15±8.43
Location of pneumothorax (right/left/bilateral)	21/18/1
Size of pneumothorax (small/medium/large/tension)	18/9/7/6
Size of chest tubes (small/medium/large) (Fr)	9/23/8
Pleural effusion (not detected/small/moderate/large)	18/17/5/0

RPE developed in 13 (32.5%) of the 40 patients with a spontaneous pneumothorax that was treated by thoracostomy. Four of these patients developed a mild cough and dyspnea, but no patients developed respiratory failure or death, and nine patients were asymptomatic and did not require specific therapy. The CT image findings of RPE were limited to one pulmonary lobe in 8 of 13 patients, two lobes in three and three lobes in two patients. No patients develop RPE in the contralateral lung.

The factors that could have contributed to the RPE were evaluated from a comparison of patients with and without RPE. These factors are shown in *Table 2*. These were followed by a multivariate analysis (*Table 3*). The duration

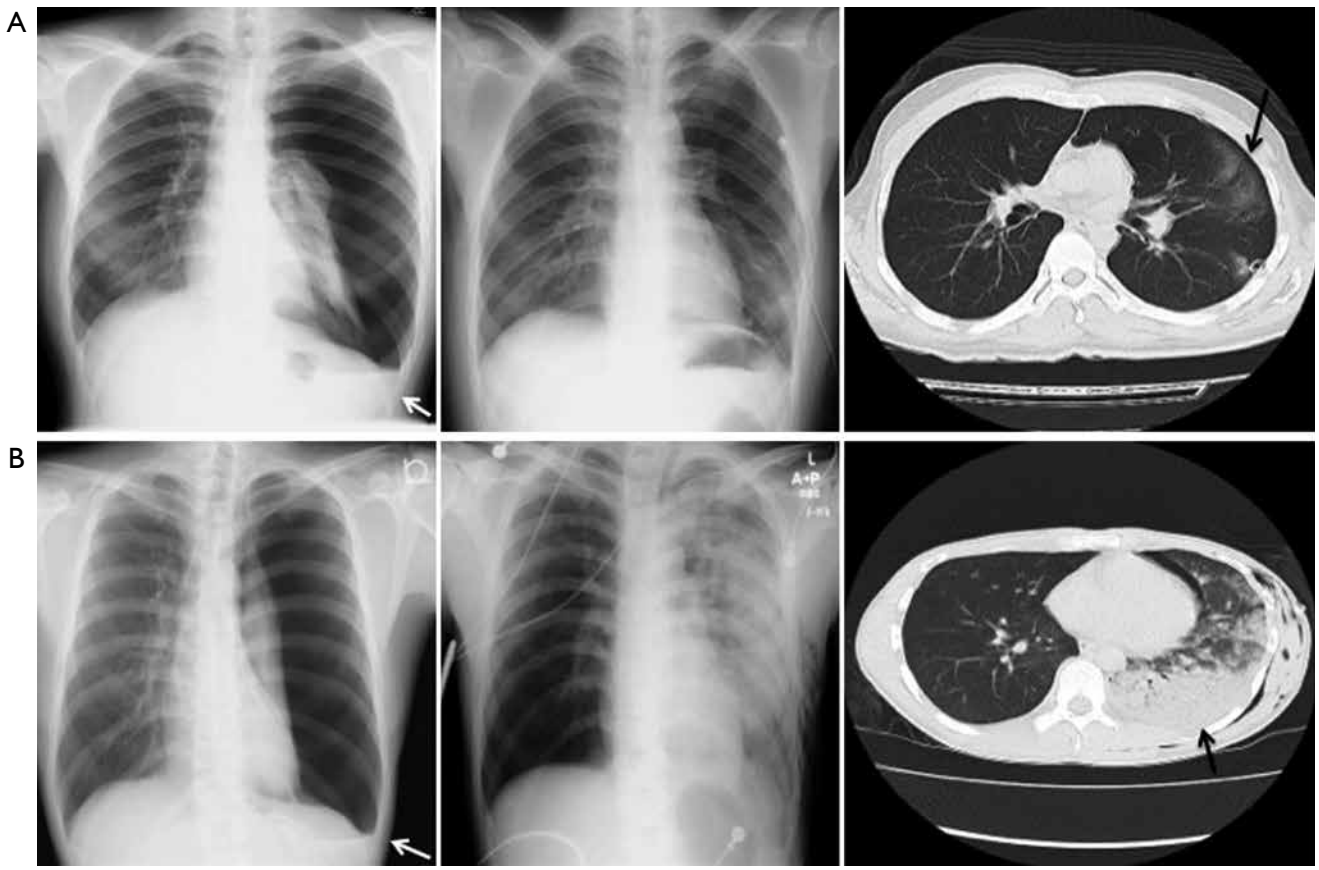

Figure 1 Representative chest radiographs and CT scan of a pneumothorax that was associated with the development of asymptomatic RPE (A) and symptomatic RPE (B). Both figures show X-rays of pleural effusion (white arrow) in addition to pneumothorax (left column). Both of the X-rays taken after tube thoracostomy reveals a hazy ground-glass infiltrate in the left lower-lobe (middle column). Right column indicates CT images of RPE (black allow); RPE, reexpansion pulmonary edema.

Table 2 Comparison of patients with and without RPE

Factor	RPE (n=13)	No RPE (n=27)	P value
Age (mean ± SD) (year)	30.8±16.0	24.7±9.5	0.241
Male/female (n)	12/1	20/7	0.185
Duration of symptoms (day)	9.2±12.8	3.2±3.9	0.037
Location of pneumothorax (right/left/bilateral) (n)	9/3/1	16/11/0	0.903
Size of pneumothorax (%)	70.7±28.2	49.2±5.8	0.025
Size of chest tube (Fr)	18.8±5.43	18.0±4.11	0.620
Pleural effusion (not detected/small/moderate/large) (n)	1/7/5/0	17/10/0/0	<0.001
Size of pneumothorax (small/medium/large/tension)	2/5/2/4	17/5/3/2	<0.001

RPE, reexpansion pulmonary edema.

Table 3 Multivariate analysis of factors contributing to RPE

Factor	OR	95% CI for OR	P value
Pleural effusion	1.557	1.290-1.880	<0.001
Size of pneumothorax	1.004	1.000-1.008	0.004
Duration of symptoms	0.996	0.980-1.011	0.610

OR, odds ratio; 95% CI, 95% confidence intervals; RPE, reexpansion pulmonary edema.

Table 4 Comparison between symptomatic RPE and asymptomatic RPE

Factor	Symptomatic RPE (n=4)	Asymptomatic RPE (n=9)	P value
Age (mean ± SD) (year)	31.8±18.7	30.3±14.7	0.894
Male/female (n)	4/0	8/1	0.147
Duration of symptoms (day)	17.5±19.3	5.4±5.0	0.360
Location of pneumothorax (right/left/bilateral) (n)	3/1/0	5/3/1	0.465
Size of pneumothorax (%)	95.9±5.5	59.5±26.9	0.005
Size of chest tube (Fr)	20.0±4.89	18.3±5.58	0.644
Pleural effusion (not detected/small/moderate/large) (n)	0/3/1	4/2/3	0.485

RPE, reexpansion pulmonary edema.

of symptoms (OR, 1.004; 95% CI, 1.000-1.008) and size of the pneumothorax (OR, 0.996; 95% CI, 0.980-1.011) were not significant risk factors for RPE, but the pleural effusion was found to be a risk factor for RPE (OR, 1.557; 95% CI, 1.290-1.880).

A further analysis was performed to evaluate the risk factors contributing to symptomatic RPE based on a comparison of patients with and without symptoms of RPE (*Table 4*). The size of the pneumothorax was significantly larger in patients with symptomatic RPE than in those with asymptomatic RPE [(95.9±5.5)% *vs.* (59.5±26.9)%; P=0.005], although there were no significant differences in the duration of symptoms, size of the chest tube or volume of pleural effusion between patients with symptomatic RPE and asymptomatic RPE.

Discussion

In our study, the incidence of RPE was much higher (32.5%) than in the series of RPE published to date (3-5), which was probably due to our CT-based diagnosis of RPE according to the criteria as described above, whereas previous studies used a chest radiographic diagnosis of RPE. Indeed, it may be not cost effective to proceed with CT immediately for the diagnosis of pneumothorax. However, CT was needed in order to evaluate the bullas or blebs for treatment options including surgery in our institution. CT imaging is apparently more sensitive than plain radiography

for diagnosing RPE (2). As a result, even small and asymptomatic cases of RPE could be identified in our study. In general, the symptoms of RPE include a new cough, worsening dyspnea, hypoxia, tachypnea, or hemodynamic instability (5,14). The best treatment is thought to be supportive, mainly consisting of the administration of supplemental oxygen and morphine if needed (15). The use of diuretics or steroids may also be effective (16). In our study, there were transient symptoms, such as a mild cough and dyspnea, in some patients, and no respiratory failure or death in any of the patients with symptomatic RPE, and no treatment was necessary for any of the patients with asymptomatic RPE, although RPE had been thought to have a high mortality rate in previous studies (6,7). These findings indicate that RPE is a more common, transient and benign phenomenon than was previously thought.

The radiographic diagnosis of asymptomatic RPE may be clinically insignificant, because it does not require any specific therapy (17). Therefore, it is important to identify risk factors for symptomatic RPE. Several risk factors for RPE have been proposed, including the duration of symptoms (5,18,19), a larger size of the pneumothorax (4,5,19), younger age (4) and a rapid rate of reexpansion (20). However, the duration of symptoms and size of the pneumothorax were not significant risk factors for RPE in our study. On the other hand, we found that the presence of pleural effusion coincident with pneumothorax was associated with the development of RPE. To the best of our knowledge, no previous studies have investigated this association.

In our present study, the size of the pneumothorax was also significantly larger in patients with symptomatic RPE than in those with asymptomatic RPE (6). Mahfood *et al.* reported that 64% of patients exhibited symptoms within 1 hour after reexpansion, and in all cases, the onset occurred within 24 hours (6). Accordingly, physicians should pay particular attention to the clinical course of the patient for 24 hours when the post-procedure images show findings of RPE following the treatment of a large pneumothorax which is coincident with moderate pleural effusion, even if the patient is asymptomatic. Although the exact mechanism(s) underlying the development of RPE is still not completely understood, the possible pathogenic events leading to RPE may include pulmonary vascular injury and an increase in capillary permeability (17,21). The development of pleural effusion which is coincident with the pneumothorax may also be caused by these mechanisms, because the patients with a known history of underlying lung disease were excluded and pleural effusion was associated with RPE in our study.

It may be difficult to prevent the development of RPE even if physicians can predict it based on the risk factors, because the thoracostomy procedure itself, which is an effective method to prevent the development of RPE, tends to be both a complex and difficult procedure to perform. According to previous guidelines (13,22), it has been recommended that the collapsed lung should be reexpanded by using a small-bore catheter (14 Fr) or chest tube (16 to 22 Fr) in clinically stable patients, or by using a larger chest tube (24 to 28 Fr) in unstable patients, and that suction should not be routinely employed. Although the procedure was undertaken in compliance with the guidelines in our cases, we could not prevent RPE. Future studies will hopefully identify a new procedure or type of postoperative care that can be used to prevent RPE.

In conclusion, the incidence of RPE appears to be higher than has been reported in previous studies. Furthermore, it often remains asymptomatic. Of note, the size of the pneumothorax was significantly greater in symptomatic RPE than in asymptomatic RPE. Our findings therefore suggest that the presence of pleural effusion coincidentally with pneumothorax may be a new risk factor for RPE.

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Original Article

Rapid detection of Streptococcus pneumoniae by real-time fluorescence loop-mediated isothermal amplification

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Background and aim of study: A significant human pathogenic bacterium, Streptococcus pneumoniae was recognized as a major cause of pneumonia, and is the subject of many humoral immunity studies. Diagnosis is generally made based on clinical suspicion along with a positive culture from a sample from virtually any place in the body. But the testing time is too long. This study is to establish a rapid diagnostic method to identification of Streptococcus pneumoniae.

Methods: Our laboratory has recently developed a new platform called real-amp, which combines loop-mediated isothermal amplification (LAMP) with a portable tube scanner real-time isothermal instrument for the rapid detection of Streptococcus pneumonia. Two pairs of amplification primers required for this method were derived from a conserved DNA sequence unique to the Streptococcus pneumoniae. The amplification was carried out at 63 degree Celsius using SYBR Green for 60 minutes with the tube scanner set to collect fluorescence signals. Clinical samples of Streptococcus pneumoniae and other bacteria were used to determine the sensitivity and specificity of the primers by comparing with traditional culture method.

Results: The new set of primers consistently detected in laboratory-maintained isolates of Streptococcus pneumoniae from our hospital. The new primers also proved to be more sensitive than the published species-specific primers specifically developed for the LAMP method in detecting Streptococcus pneumoniae.

Conclusions: This study demonstrates that the Streptococcus pneumoniae LAMP primers developed here have the ability to accurately detect Streptococcus pneumoniae infections by real-time fluorescence LAMP.

Keywords: Streptococcus pneumoniae; real-time; loop-mediated isothermal amplification (LAMP)

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Introduction

Streptococcus pneumoniae is a Gram-positive, alpha-hemolytic, aero tolerant anaerobic member of the genus Streptococcus (1). A significant human pathogenic bacterium, S. pneumoniae was recognized as a major cause of pneumonia in the late 19th century, and is the subject of many humoral immunity studies (2).

S. pneumoniae resides asymptomatically in the nasopharynx of healthy carriers. However, in susceptible individuals, such as elderly and immunocompromised people and children, the pathogen can spread to other locations and cause disease. S. pneumoniae is the main cause of community acquired pneumonia and meningitis in

children and the elderly, and of septicemia n HIV-infected persons (3).

Streptococcus pneumoniae is a major cause of diseases such as pneumonia, meningitis and sepsis, though each of these diseases is also caused by other organisms. In the developed world, serious disease occurs mainly in children below 2 years of age and in the elderly. In developing countries, the disease is common in children under 2 years, including newborn infants; rates of the disease in the elderly population are largely unknown (4).

Diagnosis is generally made based on clinical suspicion along with a positive culture from a sample from virtually any place in the body. An ASO titre of >200 units is significant. S. pneumoniae is, in general, optochin sensitive, although optochin resistance has been observed (5).

The microbiological diagnosis made microscopically and culturally. Pneumococci can be well on blood agar plates or in liquid culture media containing blood cultured. However, the period between sample collection and processing be as short as possible, because the cause of the pneumococcal autolytic enzyme system for the rapid death of the pathogen (6).

LAMP is a relatively new DNA amplification technique, which due to its simplicity, ruggedness, and low cost could provide major advantages. In LAMP, the target sequence is amplified at a constant temperature of 60-65 ℃ using either two or three sets of primers and a polymerase with high strand displacement activity in addition to a replication activity. Typically, four different primers are used to identify six distinct regions on the target gene, which adds highly to the specificity (7). Due to the specific nature of the action of these primers, the amount of DNA produced in LAMP is considerably higher than PCR based amplification. The corresponding release of pyrophosphate results in visible turbidity due to precipitation, which allows easy visualization by the naked eye, especially for larger reaction volumes or via simple detection approaches for smaller volumes (8). The reaction can be followed in real-time either by measuring the turbidity or the signals from DNA produced via fluorescent dyes that intercalate or directly label the DNA, and in turn can be correlated to the number of copies initially present. Hence, LAMP can also be quantitative (9). While LAMP is widely being studied for detecting infectious diseases such as tuberculosis, malaria, and sleeping sickness in developing regions, it has yet to be extensively validated for other common pathogens. Our study is to establish a real time LAMP for the diagnosis of Streptococcus pneumoniae.

Methods

Bacterial strains

Bacterial strains were isolated from human clinical samples which were collected following the third affiliated Hospital of Guangzhou Medical University approved procedures. The study was approved by the Ethics Committee of the Third affiliated Hospital of Guangzhou Medical University and all aspects of the study comply with the Declaration of Helsinki.

Streptococcus pneumoniae ATCC 49619

Streptococcus pneumoniae ATCC 49619 was kindly provided by Professor Jia-Yun Liu of the Fourth Military Medical University. The genomic DNA was subjected to serial 10-fold dilutions in sterilized distilled water to produce concentrations ranging from 0.3 ng/uL to 3,000 ng/mL and assess the correlation between time to amplification and amount of target DNA. In addition, to evaluate the specificity of real-amp, DNA extracts from the array of bacterial species were tested.

DNA extraction

DNA was isolated from all the samples using a QIAamp DNA Mini Kit [Qiagen, Valencia, CA (Qiagen method)]. Briefly, each sputum sample was liquefied in an equal volume of sputasol solution, placed 60 minutes at 37 ℃ and incubate until liquifaction is complete. One milliliter of the liquefaction of sputum was moved into a 1.5 mL eppendorf tube, and then centrifuged at 12,000 rpm for 10 minutes and the precipitate collected. The precipitate was washed by one milliliter of 16 TE (Tris-EDTA) buffer once, and then centrifuged at 12,000 rpm for 10 minutes and the precipitate collected. Forty microliters of sterilized distilled water was added to the tube containing the precipitate and mixed. The tube was heated on a heat-block at 100 ℃ for 15 minutes, and then placed on ice for 10 minutes. Finally, the tube was then centrifuged at 12,000 rpm for 10 minutes and the supernatants were collected and used in the real-amp assays.

Design of real-amp primers

The primers forward outer primer (F3), backward outer primer (B3), forward internal primer (FIP), backward internal primer (BIP) and loop backward primer (LB) listed

Table 1 Sequences of primers F3, B3, BIP and LB used in the real-amp assay

Target	Sequences(5'-') of Strep-1	Sequences(5'-') of Strep-2
F3	GGCTCTACTGTGAATTCTGG	GGCTCTACTGTGAATTCTGG
B3	GGCAACTGGTACTGGTTC	GGCAACTGGTACTGGTTC
FIP (F1c + F2)	TATCCAGTCAGCGGACGGACTTGTCTGCCAGTGTTCC	TATCCAGTCAGCGGACGGACTTGTCTGCCAGTGTTCC
BIP (B1c + B2)	GCGCCTTCTTTAGCGTCTAAGTAACGAAGAAGGTGCCATG	GCGCCTTCTTTAGCGTCTAAGTCAACGAAGAAGGTGCCAT
FLP	ACAGGCTGGTACTACCTCA	ACAGGCTGGTACTACCTCA
BLP	GTACTTGACCCAGCCTGTC	GTACTTGACCCAGCCTGTC

F3, forward outer primer; B3, backward outer primer; FIP, forward internal primer; B3, backward internal primer; FLB, forward loop backward primer; BLP, backward loop backward primer.

in *Table 1* for the real-amp test were designed by targeting the conserved regions of the pneumolysin a gene of Streptococcus pneumonia.

Real-amp method

The real-amp method was performed using the commercially available DNA thermostatic amplification kit (Guangzhou Diao Bio-technology Co., Ltd., Guangdong, China) following the manufacturer's instructions. Reactions were performed in 25 mL total volume containing 26 reaction buffer (40 mm Tris-HCl PH 8.8, 20 mm KCl, 16 mm $MgSO_4$, 20 mm $(NH_4)_2SO_4$, 0.2% Tween-20, 0.8M Betaine, 2.8 mm of dNTPs each), 0.5 mL of a 1:100 dilution SYBR green I (Invitrogen), 0.2 mm of each outer primers of F3 and B3, 1.6 mm of each inner primers of FIP and BIP, 0.8 mm of loop primer of LB, and 8 units of Bst polymerase (New England Biolabs, Ipswich, MA). DNA amplification was carried out at 63 ℃ for 60 minutes using the ESE-Quant Tube scanner which was set to collect fluorescence signals. The ESE-Quant Tube scanner used in this study was developed by a company (QIAGEN Lake Constance GmbH, Stockach, Germany). This device has an eight tube holder heating block with adjustable temperature settings and spectral devices to detect amplified product using fluorescence spectra. The unit is completely portable and can be operated with a Li-Ion rechargeable power pack without external power supply. A small liquid crystal display (monitor) is available to display the results (as positive or negative) without the need of a computer. However, the device can also be used together with a computer to generate real time amplification plots as the reaction progresses. In this study, each sample was tested three times.

Results

Real-amp primers designed in this study

The target selection for primer design can be accomplished by using the Primer Explorer (http://Primer Explorer.jp/e/v4manual/Index.html). The primer specificity was checked using the basic local alignment search tool (BLAST) against human DNA and other Streptococcus sequences in the nonredundant GenBank database. And the primers used in this study listed in *Table 1*.

We were able to amplify Streptococcus pneumoniae ATCC 49619 within 60 minutes without loop backward primer. The fluorescence peak typically persisted for about 20 minutes (*Figure 1A,B*). And when we amplify Streptococcus pneumoniae with loop backward primer, the amplification time shorten to 20 minutes, and the fluorescence peak typically persisted for about 10 minutes. No amplification was seen with negative control. The fluorescence in millivolts of Strep-2 is higher than Strep-1, so we chose Strep-2 for the next experiments (*Figure 1C,D*).

Sensitivity of the real-amp method

The limits of detection of real-amp were determined using DNA obtained from Streptococcus pneumoniae ATCC 49619. The DNA was diluted from 0.3 or 3 to 3,000 pg/uL. This assay required at least 300 to 3,000 pg/uL for the detection of Streptococcus pneumoniae ATCC 49619. The fluorescence peak typically persisted for about 10 minutes (*Figure 2A*). More time for amplification was required for samples with lower DNA concentration although no clear correlation was observed between time to amplification and the DNA concentration.

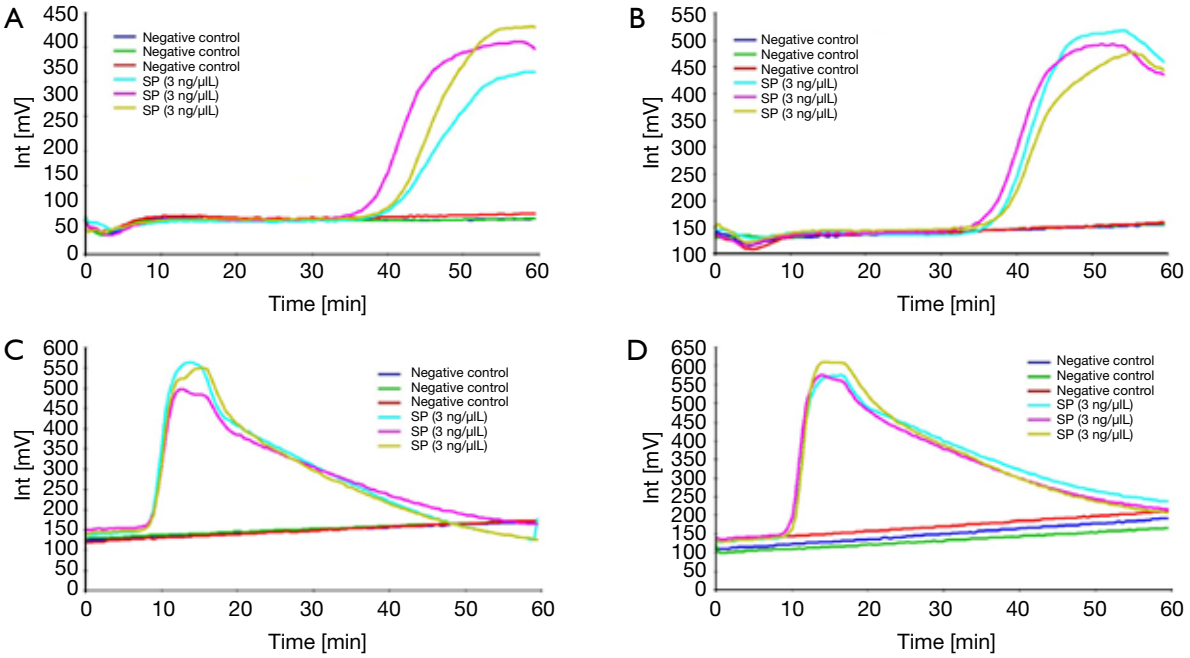

Figure 1 The real-amp primers designed in this study. (A) Real-amp without loop primers (Strep-1); (B) real-amp without loop primers (Strep-2); (C) real-amp with loop primers (Strep-1); (D) real-amp with loop primers (Strep-2).

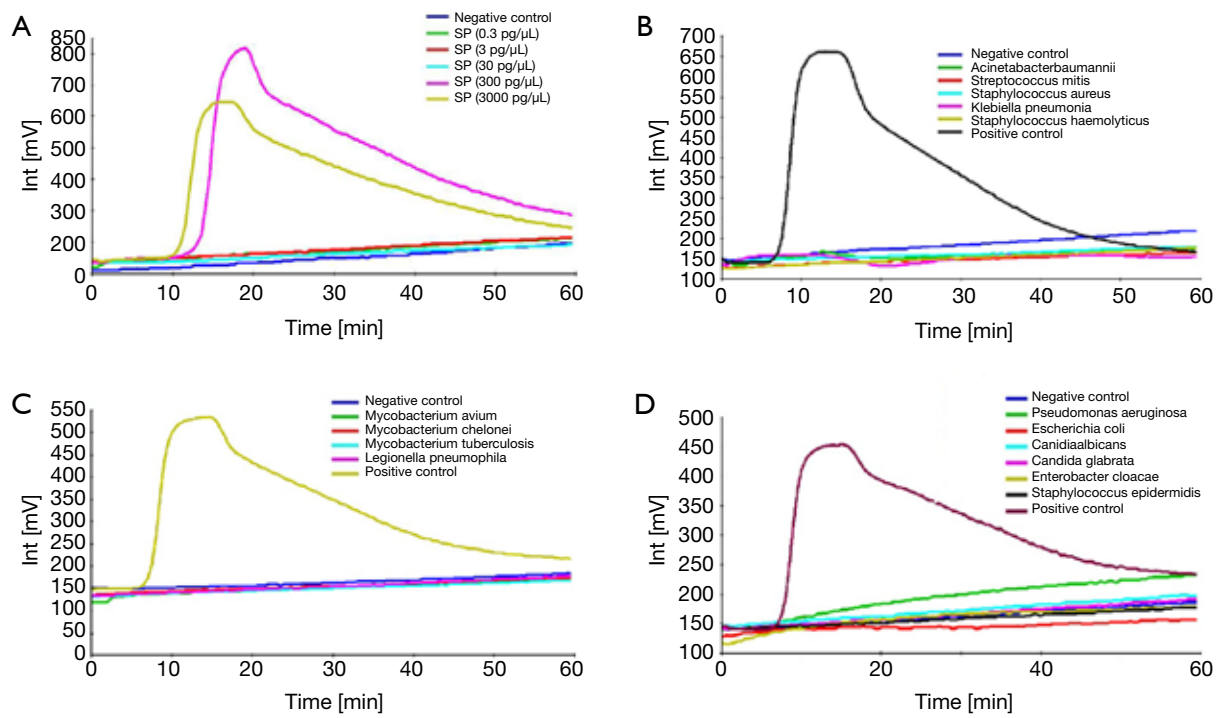

Figure 2 Specificity and sensitivity of the real-amp method. (A) Sensitivity of the real-amp method; (B) specificity of the real-amp method (compared to Acinetobacter baumannii, Streptococcus mitis, Staphylococcus aureus, Klbiella pneumonia and Staphylococcus haemolyticus); (C) specificity of the real-amp method (compared to Mycobacterium avium, Mycobacterium chelonei, Mycobacterium tuberculosis and Legionella pneumophilawere); (D) specificity of the real-amp method (compared to Pseudomonas aeruginosa, Escherichia coli, Canidia albicans, Candida glabrata, Enterobacter cloacae and Staphylococcus epidermidis).

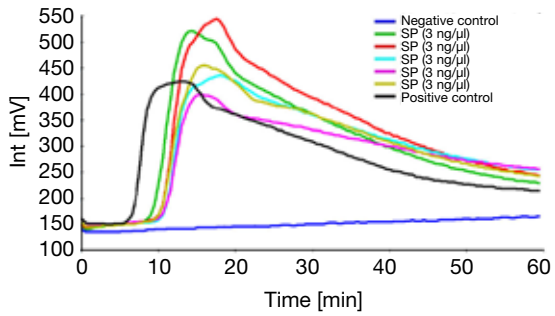

Figure 3 Repeatability of the real-amp method.

Specificity of the real-amp method

Clinical sputum samples were first identificated by VITEK 2 system, and then assessed by real-amp established in this study.

We selected 15 species belong to other genera. The results showed that the Real-Amp assay could effectively differentiate Streptococcus pneumoniae from 15 strains of other non-Streptococcus pneumoniae (*Figure 2B-D*).

Of the 15 species tested in VITEK 2 system, all samples were confirmed to be negative in the real-amp assay. *Figure 2B* shows that Acinetobacter baumannii, Streptococcus mitis, Staphylococcus aureus, Klebiella pneumonia and Staphylococcus haemolyticus were confirmed negative by real-amp assay. *Figure 2C* shows that Mycobacterium avium, Mycobacterium chelonei, Mycobacterium tuberculosis and Legionella pneumophila were confirmed negative by real-amp assay. *Figure 2D* shows that Pseudomonas aeruginosa, Escherichia coli, Canidia albicans, Candida glabrata, Enterobacter cloacae and Staphylococcus epidermidis confirmed negative by real-amp assay.

Repeatability of the real-amp method

The results showed that the repeatability of the real-amp method is good (*Figure 3*).

Discussion

In recent years, molecular biology, especially LAMP, has become the most valuable technology for clinical microbiology diagnosis (10-13). LAMP is an autocycling and strand displacement DNA synthesis method involving the use of the large fragment of Bst DNA polymerase and two pairs of specific inner and outer annular primers designed based on the gene sequence of different purposes. In the LAMP reaction, the design of the inner primer is capable of hybridizing to the DNA region in the target sequence, synthetizing the complementary strand, and producing a type of dumbbell-shaped DNA (14). Then this special structure use itself as a template for DNA synthesis to convert stem-loop DNA, which is the starting configuration of the LAMP cycling reaction. Because the inner primer hybridization in the ring of the stem-loop structure, so after the replacement the primer can produce a gaped stem-loop-like DNA which may be attaching target sequence (15). In the LAMP reaction process, pyrophosphate ions generated from the DNTP may bind to Mg^{2+} in a reaction solution, and became ivory precipitation magnesium pyrophosphate. The results also can be determined under a naked eye by adding fluorescent dye. LAMP reaction can be processed at a constant temperature by using simple devices with no need for temperature cycle, and its rapid and simple features give it an advantage over PCR (16-18).

LAMP is a single tube technique for the amplification of DNA. LAMP is isothermal nucleic acid amplification. Isothermal amplification in general obviates the need for thermal cyclers (10,19,20). Detection of amplification product can be determined via photometry for turbidity caused by an increasing quantity of magnesium pyrophosphate in solution as a byproduct of amplification or with addition of SYBR green, a color change can be seen without equipment. Also in-tube detection of DNA amplification is possible using manganese loaded calcium which starts fluorescing upon compellation of manganese by pyrophosphate during *in vitro* DNA synthesis (21-23).

LAMP has the potential to be used as a simple screening assay in the field or at the point of care by clinicians (16-18,24). As previously mentioned, LAMP is isothermal which eradicates the need for expensive thermo cyclers used in conventional PCR, it may be a particularly useful method for infectious disease diagnosis in low and middle income countries (10,19,20,25,26).

In a conclusion, LAMP is easy to operate and no need of complex instruments. In conclusion, as a quick and easy detection of Streptococcus pneumoniae, real-time Fluorescence Loop-Mediated Isothermal Amplification was successfully established, laid the foundation for the diagnosis and treatment of Streptococcus pneumonia.

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Original Article

Airway bacterial colonization in patients with non-small cell lung cancer and the alterations during the perioperative period

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Background: To observe the alterations in airway bacterial colonization during the perioperative period in patients with non-small cell lung cancer (NSCLC) and evaluate their clinical implications.

Methods: Patients with resectable primary NSCLC were enrolled from October 2011 to April 2012. Airway secretions were harvested for microbiological study after admission, immediately after surgery, and before endotracheal extubation. Spontaneous sputum was collected when patients presented with signs of postoperative pneumonia (POP). Detailed data on the isolated pathogens were carefully recorded. Risk factors for airway colonization and POP were analyzed.

Results: A total of 78 consecutive patients were enrolled. Fourteen patients (17.9%) had airway colonization at admission, including four cases of fungi and ten cases of Gram-negative bacilli (GNB). Five patients (6.4%) had colonized pathogens at the end of surgery, including three cases of GNB and two cases of Gram-positive cocci. Nine (11.5%) patients had positive culture of airway secretions collected before extubation, including seven cases of GNB and two cases of fungi. Eighteen patients (23.1%) had POP, of whom one suffered from bronchopleural fistula and one died of POP. Pathogens of POP were confirmed in 11 patients, including nine cases of GNB and two cases of fungi. Three patients had the same pathogens as preoperative colonization. The proportion of more antibiotic-resistant strains increased gradually. Advanced age [odds ratio (OR), 2.263; 95% confidence interval (95% CI), 1.030-4.970] and smoking (OR, 2.163; 95% CI, 1.059-4.429) were risk factors for airway colonization. Decreased diffusion capacity of the lung for carbon monoxide (OR, 5.838; 95% CI, 1.318-25.854), prolonged operation time (OR, 6.366; 95% CI, 1.349-30.033), and preoperative airway colonization (OR, 9.448; 95% CI, 2.206-40.465) were risk factors of POP.

Conclusions: Airway colonized pathogens altered and more antibiotic-resistant GNB emerged during the perioperative period. These pathogens played an important role in the presence of POP.

Keywords: Airway bacterial colonization; non-small cell lung cancer (NSCLC); operation; pneumonia

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Introduction

Postoperative pneumonia (POP) is one of the most common complications of lung surgery. The incidence of POP is as high as 22% to 25% in patients who underwent major lung resections (1-4). It causes most of the in-hospital deaths after lung surgery (5). In addition, patients who have suffered from POP may have poor prognosis (6). Versatile risk factors, including comorbidity of chronic obstructive pulmonary disease (COPD) (2,3,6), prolonged operative time and postoperative intensive care unit (ICU) admission (2), gender and extent of resection (3), low predicted postoperative forced expiratory volume in

1 second (FEV_1) (7), positive smoking history (8), advanced age and pathologic stage (8,9), and decreased diffusion capacity of the lung for carbon monoxide (DL_{CO}) (10-12), are predictors of patients at high risk of postoperative pulmonary complications. Besides, airway bacterial colonization is also an independent risk factor of POP (13). In contrast to healthy nonsmoking individuals, airway bacterial colonization is frequently seen in patients with chronic pulmonary diseases such as COPD, bronchiectasis, or non-small cell lung cancer (NSCLC) (14). However, little is known on the alterations in the colonization during the perioperative period. This prompted us to perform a pilot prospective observational study, investigating the alterations in the airway flora during the perioperative period in patients with resectable NSCLC, as well as the relationship between the flora and the pathogens of POP. We also investigated the risk factors of airway bacterial colonization and POP.

Materials and methods

Patients

From October 2011 to April 2012, consecutive patients admitted to West China Hospital, Sichuan University for major lung resection were included in this study according to the following criteria: (I) pathologically or clinically diagnosed as NSCLC before surgery; and (II) suitability for surgical treatment using TNM classification and cardiopulmonary assessment. Patients were excluded if they did not fulfill these criteria or if they: (I) suffered from signs of acute infection, including purulent sputum, hyperpyrexia, or leukocytosis within 2 weeks before surgery; (II) had a history of antibiotic medication within 4 weeks prior to surgery; (III) received neoadjuvant chemotherapy or radiotherapy before surgery; (IV) refused to participate in the study; or (V) were finally diagnosed with benign lesions. This study was approved by the Institutional Review Board of our hospital. Informed consent was obtained from each patient.

Data collection

We designed a standard questionnaire for data collection. All data concerning the patient's characteristics, preoperative assessments, surgical procedures, post-operative management, results of microbiological studies, pathological diagnosis, and in-hospital outcome were collected. The questionnaire was divided into three sections, namely, the patient's characteristics and preoperative assessments, operation room events, and post-operative management. These three sections were filled in by the attending doctor, the operation room staff, and the ICU staff, respectively.

Microbiological sampling

All the patients underwent microbiological sampling in the morning of the first three consecutive days after admission. Secretions in the distal airway were brought out by deep cough after gargling thrice with physiological saline and were collected for microbiological study. Surgical procedures were performed under general anesthesia with double-lumen endotracheal intubation. Immediately after the operation, airway secretions were harvested through the endotracheal intubation in the operation room using a sterile suction tube and a sputum container. All the patients were transferred to the ICU with endotracheal intubation after surgery. The intubation was removed once the patient had recovered well from anesthesia. Before removal of the intubation, secretions of the distal airway were also collected with the same method as in the operation room. Postoperatively, repeated spontaneous sputum or bronchial aspirates were collected for microbiological study when patients presented at least one symptom that defined POP. According to the guidelines of the American Thoracic Society, POP is defined by the presence of clinical infectious signs, such as new onset of fever, purulent sputum, leukocytosis, decline in oxygenation, and positive culture of airway secretions, combined with or without new or progressive infiltrative shadows on chest X-ray (15).

Microbiological processing

All samples were delivered to the Clinical Laboratory of Microorganism of our hospital for microbiological study within 10 min after sampling. Antimicrobial susceptibility test was performed for the identified bacterial strains. Anaerobic culture was not routinely performed for these patients. Sputum samples were considered suitable for culture when less than 10 squamous cells and more than 25 leucocytes per low-power magnification field were seen. If contaminated by upper airway secretions, the sample was discarded. Samples were cultured quantitatively in accordance with standard laboratory procedures. Antimicrobial susceptibility test of the isolated Gram-negative bacilli (GNB) was carried out using different representative antibiotics of the selected categorizations, including penicillins, cephalosporins, carbapenems,

Table 1 Patients' characteristics and details of surgery (N=78)

Parameter	Value (%)
Male (n)	57 (73.1)
Age [years]	61.5 [33-78]*
Body mass index (kg/m^2)	23.6±3.2
Body mass index ≥25 (n)	23 (29.5)
Positive smoking history (n)	43 (55.1)
Smoking index ≥400 cigarette-years (n)	35 (44.9)
COPD (n)	17 (21.8)
Hypertension (n)	21 (26.9)
Diabetes mellitus (n)	7 (9.0)
Preoperative laboratory test	
Hemoglobin (g/L)	131.2±14.6
White blood cell count (×10^9/L)	6.2±1.4
Albumin (g/L)	41.2±4.8
Pulmonary function test	
% pre, FEV_1	84.8±17.2
≥80% pre (n)	45 (57.7)
70-80% pre (n)	16 (20.5)
<70% pre (n)	17 (21.8)
% pre, MVV	93.5±23.3
% pre, DLco	90.7±23.3
≥70% pre (n)	62 (79.5)
<70% pre (n)	16 (20.5)
Surgical procedure	
Open lobectomy (n)	57 (73.1)
Duration of operation (min)	192.6±52.5
Duration of operation ≤3 hrs (n)	39 (50.0)
Volume of blood loss (mL)	100 [20-1,500]*
Volume of blood loss ≤300 mL (n)	70 (89.7)
ICU	
Mechanical ventilation (hours)	3.7±2.4
PaO_2 (mmHg)	143.0±56.8
$PaCO_2$ (mmHg)	41.3±5.4
Histology	
Squamous cell carcinoma (n)	27 (34.6)
Adenocarcinoma (n)	34 (43.6)
Adenosquamous carcinoma (n)	13 (16.7)
Others (n)	4 (5.1)

Data are presented as mean ± SD or n (%) unless otherwise stated. *, these data are described with median and range; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; MVV, maximum ventilatory volume; DLco, diffusion capacity of the lung for carbon monoxide; ICU, intensive care unit.

aminoglycosides, and quinolinones. When Gram-positive cocci or *Haemophilus influenzae* were isolated, Penicillins, Quinolinones, Tetracyclines, Macrolides, Clindamycin, Rifampicin and Vancomycin were selected for the antimicrobial susceptibility test.

Strategies of prophylactic antibiotics

The most preferred prophylactic antibiotics for lung surgery in China are first- or second-generation cephalosporins, as recommended by the Surgical Branch of the Chinese Medical Association. With the agreement of our Hospital Nosocomial Infectious Surveillance Committee, we chose cefmetazole as prophylactic medication during the perioperative period. Clindamycin was used as an alternative if there were contraindications for cefmetazole. Prophylactic antibiotics for patients with preoperative airway bacterial colonization were changed according to the antimicrobial susceptibility test. Antibiotic prophylaxis was administered during the induction of anesthesia. Another dose of antibiotics was added if the surgical procedure exceeded 3 hours. Postoperative antibiotic administration was ceased within 24 hours after surgery and may be prolonged in patients presented with clinical signs of POP, which was decided according to the expectoration, body temperature, pulmonary examination, and white blood cell count.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Results are expressed as percentage, mean ± standard deviation (SD) or median and range. Categorical variables were analyzed using χ^2-test, Fisher's exact test, or univariate logistic regression when needed. The quantitative continuous variables were compared using the Student's *t*-test or Mann-Whitney *U* test. All were two-tailed tests with the level of significance set at 0.05. Logistic regression was performed to evaluate risk factors associated with airway bacterial colonization and POP. Variables with P≤0.1 were entered into the multivariate regression analysis.

Results

A total of 78 patients with primary NSCLC were included in this study. Characteristics and preoperative assessments of these patients, details of surgery, and diagnosis are summarized in *Table 1*.

Microbiological study

Fourteen patients (17.9%) were identified with airway bacterial colonization after admission, including four cases of fungi (three cases of *Candida*, one case of *Aspergillus*) and ten cases (12.8%) of GNB. *Klebsiella pneumoniae* was the most frequently involved microorganism (*Table 2*). Samples collected immediately after surgery were isolated with pathogens in five patients (6.4%). There were three strains of GNB and two strains of Gram-positive cocci. Nine (11.5%) patients had a positive culture of airway secretions harvested before removal of the endotracheal intubation, including seven cases of GNB and two cases of *Candida albicans*.

Repeated spontaneous sputum was collected for microbiological study from 32 patients (41.0%) who presented at least one sign indicating POP. Eighteen (23.1%) of these patients were diagnosed with POP, of whom one suffered from bronchopleural fistula and one died of pneumonia. Pathogens of POP were detected in 11 patients, including nine cases of bacteria and two cases of fungi. A total of 22 strains were isolated, including 16 strains of GNB, 2 strains of Gram-positive cocci, and 4 strains of *Candida albicans*. Samples collected immediately after surgery showed that airway colonized pathogens remained unchanged in two patients. Samples collected before removal of endotracheal intubation revealed the same pathogens as preoperative airway colonization in three patients. Postoperatively, five patients had more than one kind of pathogens isolated from the sputum. Pathogens of POP were the same as those of preoperative colonization in three patients. Airway colonization identified during the perioperative period is listed in *Table 2*.

Only 6 (15.0%) of the 40 isolated strains were gram-positive cocci. Antimicrobial susceptibility test was conducted for all of the isolated bacteria strains. Resistance to Penicillins was observed in 30 (75%) of these strains. The proportion of more antibiotic-resistant bacteria strains increased among the four sequential samplings (*Table 3*). At the time of admission, 2 of the 10 isolated strains (2/10) were multi-drug resistant bacteria (MDR). However, bronchial secretions collected after surgery revealed 4 strains (4/5) of MDR, and 3 strains (3/7) of MDR at extubation. Postoperatively, nearly half (8/18) of the isolated strains were MDR.

Risk factors for airway bacterial colonization

Potentially predictive variables of airway bacterial colonization included the following: gender (male or female), age (in years: <60, 60 to 70, or ≥70), body mass index (BMI) (<25 or ≥25), smoking index (in cigarette-years: 0, 0 to 400, or ≥400), comorbidity of COPD, FEV_1 (≥80%, 70% to 80%, or <70%), maximum ventilatory volume (MVV) (≥70% or <70%), and DL_{CO} (≥70% or <70%). After univariate analysis, advanced age and smoking index proved to be statistically significant. Furthermore, the logistic regression model showed that advanced age [odds ratio (OR), 2.263; 95% confidence interval (95% CI), 1.030-4.970] and smoking (OR, 2.163; 95% CI, 1.059-4.429) were independent predictors of airway bacterial colonization in NSCLC patients (*Table 4*).

Risk factors for POP

Several variables were analyzed as potential predictors of POP, including: gender (male or female), age (in years: <60, 60 to 70, or ≥70), BMI (<25 or ≥25), smoking index (in cigarette-years: 0, 0 to 400, or ≥400), FEV_1 (≥80%, 70% to 80%, or <70%), MVV (≥70% or <70%), DL_{CO} (≥70% or <70%), duration of the operation (≤3 or >3 h), blood loss (≤400 or >400 mL), surgical approaches (VATS or open), and preoperative airway colonization. BMI, DL_{CO}, duration of the operation, and preoperative airway colonization were proven to be statistically significant by univariate analysis. The logistic regression model showed that decreased DL_{CO} (OR, 5.838; 95% CI, 1.318-25.854), prolonged operation time (OR, 6.366; 95% CI, 1.349-30.033), and the presence of preoperative airway colonization (OR, 9.448; 95% CI, 2.206-40.465) were risk factors of POP (*Table 5*).

Discussion

The incidence of airway bacterial colonization in lung cancer patients undergoing surgery ranged between 10.5% and 83%, and colonization of potential pathogenic microorganisms ranged between 10.5% and 41% (3,6,16-20). Samples for microbiological study were collected at different time points using various methods in these studies, such as bronchoalveolar lavage (BAL) of resected specimen (16), bilateral bronchoscopic aspirate after endotracheal intubation (3,17,19), preoperative spontaneous sputum (6,18), and preoperative bronchoscopic brushing or BAL (6,20). Present data showed that the incidence of preoperative airway colonization was 17.9% in our patients. In addition to differences of the population studied and heterogeneity of the methodology, versatile

Table 2 Pathogens isolated during the perioperative period

No.	Age	Gender	Smoking	Admission	Completion of surgery	Endotracheal extubation	Post-operation	POP
4	57	M	Yes	*Candida glabrata*	–	–	NS	No
7	63	M	Yes	*Aspergillus*	–	–	*B/h. acinetobacter, Enterobacter Cloacae*	Yes
8	67	M	No	–	–	*Acid producing Klebsiella*	*Candida albicans, B/h. acinetobacter*	Yes
10	65	M	No	*K. pneumoniae*	*K. pneumoniae*	*K. pneumoniae*	*K. pneumoniae*	Yes
11	70	M	Yes	*K. pneumoniae*	–	–	NS	No
15	36	F	No	–	–	–	–	BPF
18	70	M	Yes	*B/h. acinetobacter*	*Enterobacter Cloacae*	*B/h. acinetobacter*	*B/h. acinetobacter, Enterobacter Cloacae*	Yes
20	77	M	Yes	*K. pneumoniae*	–	–	*K. pneumoniae*	Yes
21	62	M	Yes	–	–	*B/h. acinetobacter*	–	No
27	57	M	Yes	*P. aeruginosa*	–	–	NS	No
29	42	F	No	–	–	–	*B/h. acinetobacter*	Yes
30	78	M	Yes	*Acid producing Klebsiella*	*Acid producing Klebsiella*	–	*Candida albicans*	Yes
31	71	M	No	*P. aeruginosa*	–	*P. aeruginosa*	NS	No
42	74	M	Yes	*Candida albicans*	–	–	*P. aeruginosa*	Yes
43	63	F	Yes	*Candida albicans*	–	–	NS	No
52	43	M	Yes	–	*S. pneumoniae*	*S. pneumoniae*	–	Yes
61	59	F	No	–	*Staph. aureus*	–	NS	No
64	75	M	Yes	–	–	*Candida albicans*	*Candida albicans, B/h. acinetobacter*	Death
70	61	M	Yes	*Lwoffii Acinetobacter*	–	*S. pneumoniae*	*S. pneumoniae, H. influenzae*	Yes
73	50	M	Yes	*K. pneumoniae*	–	*Candida albicans*	*Candida albicans*	Yes
78	57	M	No	*K. pneumoniae*	–	–	NS	No

B/h. acinetobacter, Bowman/hemolytic acinetobacter; BPF, bronchopleural fistula; F, female; *H. influenzae*, haemophilus influenzae; *K. pneumoniae*, klebsiella pneumoniae; M, male; NS, not sampled; *P. aeruginosa*, pseudomonas aeruginosa; POP, postoperative pneumonia; *S. pneumoniae*, streptococcus pneumoniae; *Staph. aureus*, staphylococcus aureu.

Table 3 Alterations of the number of resistant bacteria strains isolated during the four sequential microbiological studies

Time of sampling	Antibiotic resistance (No. of resistant strains)						Total
	S	R1	R2	R3	R4	R5	
Admission	0	7	1	1	0	1	10
Completion of surgery	0	1	0	1	1	2	5
Endotracheal extubation	0	3	1	1	2	0	7
Post-operation	2	2	6	3	2	3	18

S, sensitive to all categories of the tested antibiotics; R1-5, resistant to 1 category to 5 categories of the tested antibiotics.

Table 4 Risk factors for airway bacterial colonization

Variables	OR	95% CI	P value
Univariate			
Gender (M/F)	0.169	0.021-1.384	0.131
Age (<60, 60-70, ≥70)	2.175	1.017-4.650	0.045
BMI (<25, ≥25)	1.420	0.419-4.816	0.810
Smoking index (0, 0-400, ≥400 cigarette-years)	2.097	1.043-4.215	0.038
Comorbidity of COPD	2.407	0.682-8.492	0.301
FEV_1 (≥80%, 70-80%, <70%)	1.289	0.651-2.554	0.466
MVV (≥70%, <70%)	2.127	0.247-18.310	0.795
DLco (≥70%, <70%)	2.677	0.751-9.546	0.234
Multivariate			
Age (<60, 60-70, ≥70)	2.263	1.030-4.970	0.042
Smoking index (0, 0-400, ≥400 cigarette-years)	2.163	1.059-4.429	0.034

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DLco, diffusing capacity of the lung for carbon monoxide; F, female; FEV_1, forced expiratory volume in one second; M, male; MVV, maximum ventilatory volume; OR, odds ratio.

diagnostic standards used in different labs could be an important reason for the huge variability of incidence.

The pathogens classically reported for early hospital-acquired pneumonia, such as *Haemophilus influenza*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*, also played an important role in the occurrence of POP (3,6,16-20). Previous studies have shown that these pathogens were also the most commonly identified pathogenic bacteria strains in the distal airways of patients with resectable NSCLC (3,6,16-20). However, the pathogens isolated from preoperative airway secretions in this study were quite different from those previously reported. The main pathogens identified were GNB, such as *Klebsiella pneumoniae*. Focusing on the pathogens of POP, GNB was the most common agents in these patients, similar to those of previous reports (6,18). The reason for this difference is also unclear. Considering the overuse of antibiotics is quite a serious problem in China, we prudently presume that this could be an important reason. However, data on the occurrence of airway colonization in Chinese patients are still rare, and whether this small population represents the real situation is uncertain. Therefore, this presumption needs further confirmation, and we hope that additional data on airway colonization in Chinese patients with NSCLC can be obtained in the future.

The pathogens of POP are frequently different from those in preoperative colonization (6,17). We also observed the same phenomenon in this study. Airway colonization altered during the perioperative period, and the proportion of more antibiotic-resistant pathogens, such as *Acinetobacter baumannii*, increased. The occurrence of more resistant pathogens may be caused by the screening effect of prophylactic antibiotics. The reasons for the alteration have rarely been described. We presume that decreased airway

Table 5 Risk factors for POP

Variables	OR	95% CI	P value
Univariate			
Gender (M/F)	0.323	0.067-1.565	0.253
Age (<60, 60-70, ≥70)	1.654	0.817-3.349	0.162
BMI (<25, ≥25)	0.754	0.215-2.643	0.018
Smoking index (0, 0-400, ≥400 cigarette-years)	1.429	0.787-2.598	0.241
FEV1 (≥80%, 70-80%, <70%)	1.364	0.712-2.611	0.349
MVV (≥70%, <70%)	2.547	0.298-21.737	0.644
DLco (≥70%, <70%)	4.580	1.360-15.428	0.025
Duration of the operation (≤3, >3 hrs)	3.889	1.128-13.411	0.050
Blood loss (≤300, >300 mL)	1.333	0.243-7.329	1.000
Surgical approaches (VATS/open)	0.882	0.250-3.116	1.000
Preoperative airway colonization	9.333	2.564-33.973	0.001
Multivariate			
DLco (≥70%, <70%)	5.838	1.318-25.854	0.020
Duration of the operation (≤3, >3 hrs)	6.366	1.349-30.033	0.019
Preoperative airway colonization	9.448	2.206-40.465	0.002

BMI, body mass index; CI, confidence interval; DLco, diffusing capacity of the lung for carbon monoxide; F, female; FEV_1, forced expiratory volume in one second; M, male; MVV, maximum ventilatory volume; OR, odds ratio; VATS, video assisted thoracic surgery.

colonization during the operation was due to the use of prophylactic antibiotics. However, prolonged endotracheal intubation may increase the risk of bacterial colonization, which is in accordance with the increasing trend as observed of the samples collected before removal of the intubation.

Airway bacterial colonization is a frequent feature in patients with stable chronic lung diseases (14). In previous studies on lung cancer patients, the comorbidity of COPD (6), central location of the tumor, and overweightness (BMI >25 $kg \cdot m^{-2}$) (19) have been described as independent risk factors of airway bacterial colonization. Our data showed that advanced age and smoking were independent risk factors of airway bacterial colonization. Only 21.7% of our patients had COPD, and few of them had severe COPD. The proportion of overweight patients was only 29.5% in this group. Both comorbidity of COPD and overweightness were not identified as independent risk factors of airway bacterial colonization. This may be due to their small proportions in the currently observed group. The incidence rate of postoperative pulmonary complications was 23.1% in the present group, similar to those in previous reports (1-4). Multivariate analysis of our data also revealed that preoperative airway bacterial colonization was an independent risk factor of POP, as well as %Pre DL_{CO} <70% and prolonged operative duration. According to these reasons, NSCLC patients with high risk factors should have microbiological study of the airway secretions before surgery, and this may guide the perioperative preventive measures for POP.

First- or second-generation Cephalosporins, mainly targeting Gram-positive cocci, are the most commonly recommended prophylactic antibiotics for lung surgery (21), but GNB contributed the most towards the occurrence of POP in our patients as well as in some other reports (6,18). Evidence on the constitution of the most appropriate antibiotic prophylaxis for lung cancer surgery is still insufficient, and the implications of preoperative airway colonization on the selection of prophylactic antibiotics are unknown. A further investigation into the airway flora in more patients with NSCLC is needed, and this may help us revise the strategy of perioperative prophylactic medication.

There are also some limitations in this study. We were unable to study the sputum flora after surgery in all patients, but only in patients with signs of POP. Confined to the limitations of clinical practice, the methodology of sample collecting varied among the four sequential time

point. Moreover, the sample size obtained for the study is relatively small.

Conclusions

The airway colonized pathogens changed and more antibiotic-resistant GNB emerged during the perioperative period. Advanced age and smoking are risk factors of airway bacterial colonization in patients with lung cancer. Decreased DL_{CO}, preoperative airway bacterial colonization, and prolonged operation time are risk factors of POP. According to this pilot study, special attention should be paid to GNB when patients suffered from pneumonia after lung cancer surgery.

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Author's contribution: M.J.D. designed and carried out the study, collected and analyzed data, and wrote the paper; L.L.X. designed and carried out the study, interpreted data; T.M.L. carried out the study, collected and analyzed data; X.N.H. carried out the study and collected data; P.Q. analyzed data and revised the paper; L.C.W. revised the paper; M.L. carried out the study and analyzed data; S.H. carried out the study and collected data; C.G.W. designed the overall study and carried out the study, analyzed and interpreted data, and revised the paper.
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Original Article

Corticosteroid therapy against treatment-related pulmonary toxicities in patients with lung cancer

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Background: With the recent increased use of new anti-neoplastic agents, molecular-targeted drugs and radiation in patients with lung cancer, there has been an increase in the occurrence drug-induced or radiation-induced pulmonary toxicities. We conducted this study to evaluate the clinical characteristics of patients with lung cancer who presented with treatment-related pulmonary toxicities and to analyze the dosage pattern of corticosteroid therapy against them.

Methods: To collect the baseline data from the patients with lung cancer who developed treatment-related pulmonary toxicities, we initially selected those who were prescribed corticosteroids between January 1, 2008 and December 31, 2012. Depending on clinical and radiological diagnoses, we classified pulmonary toxicities into drug-induced interstitial lung disease (DILD), radiation pneumonitis, acute exacerbation of chronic obstructive pulmonary disease (AE COPD) and others.

Results: We divided total patients (n=398) into four groups, and these include 88 cases (22%) of DILD, 189 cases (47%) of radiation pneumonitis, 47 cases (12%) of AE COPD and 74 cases (19%) of others. The prescribed rate of pulse or high-dose steroid was measured as 73%, 20%, 40% and 38%, respectively (P<0.001). In DILD radiologic findings, the 2-month mortality was significantly higher in the patients with the diffuse alveolar damage (DAD) pattern (100%) as compared with those with the non-specific interstitial pneumonia (NSIP) or bronchiolitis obliterans with organizing pneumonia (BOOP) one (62% or 42%, respectively) (P=0.032).

Conclusions: This study showed that the natural course of DILD had more unfavorable outcome requiring higher dose steroid therapy as compared with those with radiation pneumonitis or AE COPD. According to a subgroup analysis of the patients with DILD, BOOP and NSIP radiographic patterns showed more favorable outcomes.

Keywords: Corticosteroids; drug-induced interstitial lung disease (DILD); lung cancer; pulmonary toxicity; radiation pneumonitis

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Introduction

Lung cancer has been a leading cause of cancer-related death worldwide including South Korea (1). To date, chemotherapy, molecular-targeted therapy and radiation therapy (RT) have been known to be effective for the treatment of inoperable lung cancer. Still, however, much treatment-related pulmonary toxicity remains fatal (2,3). Currently, new anticancer agents and novel radiation techniques are becoming available for the treatment of lung cancer. This is also accompanied by increased risks of developing pulmonary toxicities in patients with lung cancer (4). It has been reported that the degree of the efficacy of epidermal growth factor receptor (EGFR)

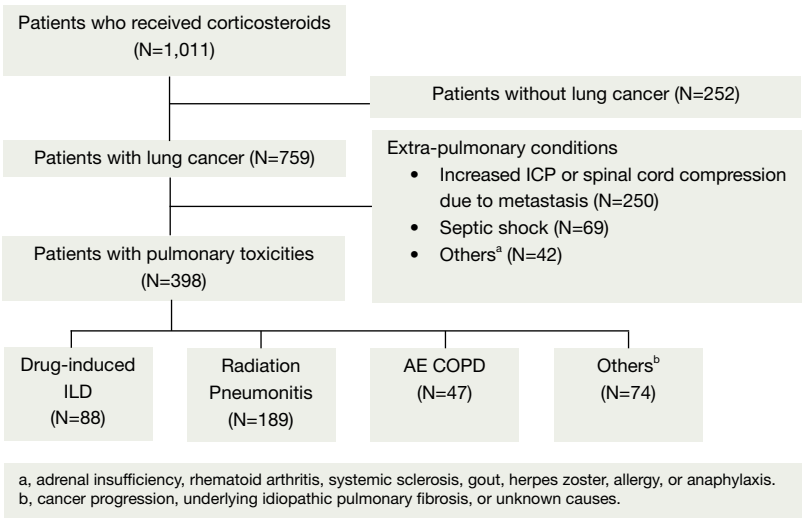

Figure 1 The selection and classification of the patients based on the CONSORT flow chart. Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; ICP, intracranial pressure; ILD, interstitial lung disease; AE COPD, acute exacerbation of chronic obstructive pulmonary disease.

tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, is relatively higher compared with chemotherapy in patients with EGFR mutations (5,6). It remains problematic, however, EGFR-TKIs can cause interstitial lung disease (ILD); overall, the incidence of erlotinib-induced and gefinitib-induced ILD has been reported to reach 0.8% and 1%, respectively. Moreover, the incidence of gefitinib-induced ILD is estimated at 2% in Japan and 0.3% in the United States (7-13). Furthermore, the mortality of gefitinib-induced ILD exceeds 30% (14). The incidence of symptomatic RT-induced lung injury is estimated at 20% in patients with lung cancer who were treated with RT. In patients with severe RT-induced lung injury, the survival period is relatively shorter (2).

To date, there are no established treatment guidelines for patients with pulmonary toxicities due to anticancer therapies. In these patients, however, clinicians have attempted to discontinue the use of the causative agents and to administer systemic corticosteroids on empirical basis (3,4). It has also been reported that corticosteroid therapy is effective against the episodes of acute exacerbation of chronic obstructive pulmonary disease (AE COPD) and ILD; both entities may be concurrently present in patients with lung cancer (15-18). Nevertheless, there is a paucity of data regarding the optimal timing, dosage and duration of corticosteroid therapy in the treatment of patients with lung cancer (19).

Given the above background, we conducted this study to evaluate the clinical characteristics of patients with lung cancer who presented with treatment-related pulmonary toxicities and to analyze the dosage pattern of corticosteroid therapy against them.

Materials and methods

Study population

To collect the baseline data from the patients with lung cancer who developed treatment-related pulmonary toxicities, we initially selected those who were prescribed corticosteroids at Lung and Esophageal Cancer Clinic of Chonnam National University Hwasun Hospital between January 1, 2008 and December 31, 2012.

We excluded the patients without lung cancer and patients who received corticosteroid therapy to control extra-pulmonary conditions like increased intracranial pressure or spinal cord compression, septic shock, adrenal insufficiency, rheumatoid arthritis or systemic sclerosis (*Figure 1*). The current study was approved by the Institutional Review Board (IRB) of Chonnam National University Hwasun Hospital (IRB approval number: 2013-118). Informed consent was waived due to the retrospective nature of the current study.

Classification of pulmonary toxicities

Two chest radiologists comprehensibly reviewed all X-ray and computed tomography (CT) scans, thus attempting to determine the imaging characteristics of pulmonary

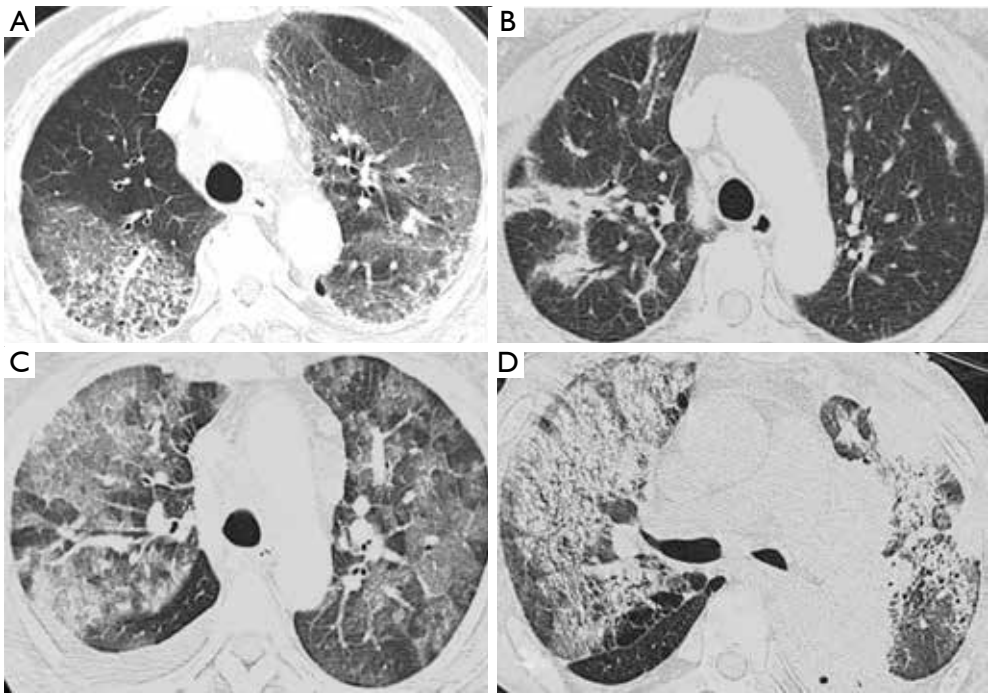

Figure 2 Computed tomography (CT) findings of drug-induced interstitial lung disease. (A) Nonspecific interstitial pneumonia pattern shows bilateral patchy areas of ground glass opacity, accompanied by some thickening of interlobular septa and minimal bronchiectasis; (B) bronchiolitis obliterans organizing pneumonia pattern shows multifocal peripheral areas of peribronchial consolidation and bronchial wall thickening; (C) diffuse alveolar damage (DAD) pattern shows diffuse thickening of interlobular septa, scattered areas of ground glass opacity and right pleural effusion; (D) mixed pattern (diffuse alveolar pattern and radiation pneumonitis) shows bilateral patchy areas of consolidation and perilesional ground glass opacities in both lungs, mixed with volume loss in the left upper lobe.

toxicities. Depending on radiological diagnosis, we classified treatment-related pulmonary toxicities into drug-induced ILD (DILD), radiation pneumonitis, AE COPD and others. In addition, drugs were referred to as those that are used for both conventional chemotherapy and molecular-targeted therapy. In our series, we made a diagnosis of DILD after ruling out other possible diagnoses, such as infection, cancer progression, and acute exacerbation of underlying idiopathic pulmonary fibrosis or unknown conditions. We performed laboratory tests such as C-reactive protein, procalcitonin, serologic tests, sputum and blood cultures to rule out the patients with infection.

Demographics and clinical variables

Baseline demographics and clinical data include age, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), histology, cancer stage and pulmonary function test before corticosteroid treatment. Histology was classified as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC was divided into three categories: squamous cell cancer (SQC), adenocarcinoma (ADC) and others. Cancer stage was presented as non-metastatic or metastatic.

Corticosteroid treatment

We also collected the data about corticosteroid regimen. Corticosteroid treatments include three regimens: pulse, high-dose and low-dose therapy. Pulse was ≥500 mg/day methylprednisolone for 3 days followed by high-dose steroid, high-dose was ≥0.5 mg/kg/day prednisolone and low-dose was <0.5 mg/kg/day prednisolone.

Imaging characteristics of DILD

Chest CT findings of DILD were classified into non-specific interstitial pneumonia (NSIP) pattern, bronchiolitis obliterans organizing pneumonia (BOOP) pattern, diffuse alveolar damage (DAD) pattern and mixed pattern (*Figure 2*).

We examined the number of the involved pulmonary lobes in a total of five lobes.

Outcome measures

The prescribed dosage pattern of corticosteroid was served as the primary outcome measure in the current study, for which we evaluated the patient response to the corticosteroid therapy based on two categories: 'recovered' and 'fatal'. Thus, we defined 'fatal' cases as in-hospital death or death outside hospital and 'recovered' ones as better outcomes at discharge or tapered/discontinued use of corticosteroids in an outpatient setting.

We also performed a subgroup analysis of the patients presenting with DILD, for which we measured the 1-month and 2-month mortality after initiating the corticosteroid therapy.

Statistical analysis

We performed univariate analysis with the χ^2 test to analyze categorical variables. We also performed one-way analysis of variance (ANOVA) to analyze continuous variables. We performed stratified multivariate logistic regression analysis with a backward stepwise procedure to identify the factors that are associated with the fatality of treatment-related pulmonary toxicities. All the tests were two-sided, and a P value of 0.05 was considered statistically significant. Statistical analysis was done using the SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients

We enrolled a total of 398 patients (n=398) in the current study, whose median age was 67 years. Our clinical series of the patients include men (n=340, 85%), thus showing a male predilection. We divided our patients into four groups, depending on the classification of pulmonary toxicities, and these include 88 cases (22%) of DILD, 189 cases (47%) of radiation pneumonitis, 47 cases (12%) of AE COPD and 74 cases (19%) of other conditions (*Table 1*).

In the patients with DILD, age of ≤65 years, female sex, never smokers, ADC histology and metastatic stage were more prevalent. In the patients with acute exacerbation of COPD, the pulmonary function was poor. In the patients with DILD, possible causative agents include gefitinib (n=32), erlotinib (n=27), docetaxel (n=9), gemcitabine (n=5), paclitaxel (n=3), etoposide (n=3), pemetrexed (n=2), afatinib (n=2), belotecan (n=2), vinorelbine (n=2), dacomitinib (n=1) and tegafur-uracil (n=1). In our series, there were 14 patients who underwent platinum combination therapy.

Outcome measures

As shown in *Table 2*, the patients with DILD were mainly treated with pulse (25%) or high-dose (48%) therapy. In addition, the patients with radiation pneumonitis were routinely treated with low-dose steroid therapy (80%). The prescribed rate of pulse or high-dose steroid was measured as 73% in DILD, 20% in radiation pneumonitis, 40% in AE COPD and 38% in others (P<0.001). We evaluated the response of corticosteroid therapy by measuring the rate of fatality and recovery in the patients who were treated with corticosteroids. This showed that the overall rate of fatality was 23% (92/398); the rate of fatality was 35% in the patients with DILD, 13% in those with radiation pneumonitis, 19% in those with AE COPD and 38% in those with other conditions (P<0.001). However, if we compared the number of patients who received pulse or high dose steroid treatment with the number of patients had fatal outcome among the four groups, actually the mortality rate of DILD (31/64, 48.4%) was lower than the radiation pneumonitis (24/38, 63.2%), and others (28/28, 100%) groups.

Odds ratio (OR) for the fatality

On stratified multivariate logistic regression analysis, only the steroid regimen was independently correlated with the fatality of treatment-related pulmonary toxicities (*Table 3*). In addition, such variables as the age, sex, smoking status, histology, cancer stage and ECOG PS had no significant correlation with the fatality of treatment-related pulmonary toxicities. Furthermore, the degree of the fatality of treatment-related pulmonary toxicities was significantly higher in the patients receiving higher-dose regimen (pulse and high-dose therapy) as compared with those doing low-dose one {DILD [OR 8.41, 95% confidence interval (CI), 1.81-39.04]}, radiation pneumonitis (OR 24.44, 95% CI, 7.77-76.90) and others (OR 21.00, 95% CI, 5.63-78.30). But this was not seen in the patients with acute exacerbation of COPD. In the patients with acute exacerbation of COPD, we could not estimate OR for the fatality of treatment-related pulmonary toxicities because of a smaller sample size.

Table 1 Baseline characteristics of patients

Characteristics	Drug-induced ILD (n=88)		Radiation pneumonitis (n=189)		AE COPD (n=47)		Others (n=74)		P[a]
	No.	%	No.	%	No.	%	No.	%	
Age, years[b]									0.009
<65	46	52	74	39	11	23	34	46	
≥65	42	48	115	61	36	77	40	54	
Sex[c]									0.009
Male	70	80	169	89	44	94	57	77	
Female	18	20	20	11	3	6	17	23	
Smoking status[d]									0.019
Never	23	26	25	13	5	11	17	23	
Ever	65	74	164	87	42	89	57	77	
Histology[e]									<0.001
SCLC	3	3	28	15	7	15	10	14	
NSCLC									
SQC	32	37	103	54	30	64	26	35	
ADC	44	50	43	23	9	19	30	40	
Others	9	10	15	8	1	2	8	11	
Cancer stage[f]									<0.001
Non-metastatic	20	23	169	89	33	70	29	39	
Metastatic	68	77	20	11	14	30	45	61	
ECOG PS[g]									<0.001
0-1	71	81	181	96	40	85	51	73	
2	16	18	7	3	6	13	19	26	
3	1	1	1	1	1	2	1	1	
PFT[h], mean ± SD									
FEV_1[i], L	2.0±0.6		1.9±0.6		1.3±0.5		2.0±0.6		<0.001
FEV_1[j], %	78±19		80±23		51±17		78±23		<0.001
FVC[k], %	79±17		87±18		76±18		80±23		0.001
DLco[l], %	83±30		87±23		76±27		86±27		0.035

Abbreviations: ILD, interstitial lung disease; AE COPD, acute exacerbation of chronic obstructive pulmonary disease; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; SQC, squamous cell cancer; ADC, adenocarcinoma; ECOG PS, eastern cooperative oncology group performance status; PFT, pulmonary function test; FEV_1, forced expiratory volume in a second; FVC, forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide. [a]P value was calculated by χ^2 test except PFT. One-way ANOVA was performed for PFT; [b-g]comparison drug-induced ILD with radiation pneumonitis and AE COPD (P=0.04, P=0.026, P=0.008, P<0.001, P<0.001, P<0.001, and P=0.001, P=0.032, P=0.034, P<0.001, P<0.001, P=0.608, respectively); [h]PFT: n=352 for FEV_1 and FVC; n=310 for DLco; [i-l]comparison AE COPD with drug-induced ILD and radiation pneumonitis (P=0.022, P=0.031, P=0.137, P=0.837, and P<0.001, P<0.001, P=0.002, P=0.002, respectively).

Table 2 The response of corticosteroid for the treatment-related pulmonary toxicities

	Drug-induced ILD (n=88)		Radiation pneumonitis (n=189)		AE COPD (n=47)		Others (n=74)		P[a]
	No.	%	No.	%	No.	%	No.	%	
Steroid regimen[b]									<0.001
Pulse	22	25	5	3	0	0	7	10	
High-dose	42	48	33	17	19	40	21	28	
Low-dose	24	27	151	80	28	60	46	62	
Corticosteroid response									<0.001
Fatal	31	35	24	13	9	19	28	38	
Recovered	57	65	165	87	38	81	46	62	

Abbreviations: ILD, interstitial lung disease; AE COPD, acute exacerbation of chronic obstructive pulmonary disease. [a]P value was calculated by χ^2 test; [b]Steroid regimen: Pulse, ≥500 mg/day methylprenisolone for 3 days, followed by high-dose steroid; high-dose, ≥0.5 mg/kg/day prednisolone; low-dose, <0.5 mg/kg/day prednisolone.

Table 3 Odds ratio for fatality of treatment-related pulmonary toxicities

	Steroid regimen (higher dose *vs*. low-dose)		
	OR	95% CI	P[a]
Drug-induced ILD	8.41	1.81-39.04	0.007
Radiation pneumonitis	24.44	7.77-76.90	<0.001
AE COPD	∞	0.00- ∞	0.998
Others	21.00	5.63-78.30	<0.001

Abbreviations: ILD, interstitial lung disease; AE COPD, acute exacerbation of chronic obstructive pulmonary disease; *vs*., versus. [a]P value was calculated by stratified mutivariate logistic regression analysis.

Imaging characteristics and mortality of DILD

The mode and median of the number of involved lobes was 3 and 4, respectively. The 2-month mortality due to treatment-related pulmonary toxicities was higher in the patients where the number of involved lobes was 4-5 as compared with those where it was 1-3. But this was not statistically significant (P=0.090). In our series, the NSIP pattern was the most prevalent; it was seen at a frequency of 51% (45/88). In addition, there were 33 cases (38%) of the BOOP pattern and seven cases (8%) of the DAD one (*Table 4*). But there were only three cases of the mixed pattern; these include one case of the NSIP and BOOP pattern, one case of the BOOP and DAD one and one case of the DAD pattern and radiation pneumonitis. Furthermore, there was a significant correlation between the CT findings and the mortality due to treatment-related pulmonary toxicities. In other words, the 2-month mortality due to treatment-related pulmonary toxicities was significantly higher in the patients with the DAD or mixed pattern (100% or 67%, respectively) as compared with those with the NSIP or BOOP one (62% or 42%, respectively) (P=0.032).

On univariate analysis, the steroid regimen had a significant correlation with the mortality due to treatment-related pulmonary toxicities. In addition, the 2-month mortality due to treatment-related pulmonary toxicities was higher in the patients who received the pulse or high-dose therapy as compared with those who did the low-dose one (82% or 62% *vs*. 29%, P=0.001).

Discussion

With the recent increased use of new anti-neoplastic agents, molecular-targeted drugs and radiation in patients with lung cancer, there has been an increase in the occurrence drug- or radiation-induced pulmonary toxicities. In these patients, we empirically use corticosteroids for disease modulation and symptomatic improvement (4,20,21). Our study documented that the prescribed rate of higher-dose regimen (pulse or high-dose therapy) was higher in DILD (73%) than in radiation pneumonitis (20%) or AE COPD

Table 4 Clinical characteristics and mortality of patients with drug-induced interstitial lung disease

	All cases (n=88)		One month mortality[a] (n=32)		P[b]	Two months mortality[a] (n=51)		P[b]
	No.	%	No.	%		No.	%	
The number of involved pulmonary lobes					0.872			0.090
1-3	43	49	16	37		21	49	
4-5	45	51	16	36		30	67	
CT finding					0.132			0.032
NSIP pattern	45	51	15	33		28	62	
BOOP pattern	33	38	10	30		14	42	
DAD pattern	7	8	5	71		7	100	
Mixed pattern[c]	3	3	2	67		2	67	
Steroid regimen[d]					0.001			0.001
Pulse	22	25	13	59		18	82	
High-dose	42	48	17	41		26	62	
Low-dose	24	27	2	8		7	29	

Abbreviations: CT, computed tomography; NSIP, nonspecific interstitial pneumonia; BOOP, bronchiolitis obliterans organizing pneumonia; DAD, diffuse alveolar damage. [a]One month mortality and two months mortality are defined as numbers of death at the time of one month and two months since starting corticosteroid treatment; [b]P value was calculated by using χ^2 test; [c]Mixed pattern: one case of NSIP plus BOOP; one case of BOOP plus DAD; one case of DAD plus radiation pneumonitis; [d]Steroid regimen: Pulse, ≥500 mg/day methylprenisolone for 3 days, followed by high-dose steroid; high-dose, ≥0.5 mg/kg/day prednisolone; low-dose, <0.5 mg/kg/day prednisolone.

(40%) group. As long as more intensive and higher dose steroid is administered for patients with severer conditions, patients treated with higher dose steroid would show the worse outcome. So our results may reflect the natural course of each disease. However, if we compared the mortality only in patients who received pulse or high dose steroid therapy, the mortality rates of DILD (48.4%) and AE COPD (47.4%) were lower than those of radiation pneumonitis (63.2%) and others (100%) groups. Further prospective studies are therefore warranted to conclude the prognosis and propose the treatment guidelines for the optimal regimen and schedule. Thus, efforts should be made to minimize risk and to maximize benefit of anti-cancer treatment in this series.

In a current clinical setting, drug-induced pulmonary toxicity poses diagnostic challenges for clinicians. It would therefore be mandatory to determine the time course of the disease and the timing of causative drug medication as well as to rule out other possible diagnoses, including infections in particular. In addition, it would also be mandatory to evaluate the degree of the treatment response to the discontinued causative drugs and corticosteroids (4,20). Furthermore, previous studies have shown that radiological findings are a key diagnostic clue (10,22-24). It has been reported that the clinical and radiologic findings due to causative drugs are suggestive of the underlying histopathologic processes (23). Rossi *et al*. classified the radiologic manifestations as DAD, NSIP, BOOP, eosinophilic pneumonia, obliterative bronchiolitis, pulmonary hemorrhage, edema, hypertension, or veno-occlusive disease (23). And knowledge of the drugs most frequently involved, together with an understanding of the typical histopathologic and radiologic manifestations of toxicity are necessary for institution of appropriate treatment (23). In this study, we examined whether CT findings would be a prognostic factor in the patients with DILD. We analyzed chest radiographic images and this led to the clinical and radiologic diagnosis of NSIP, BOOP, DAD, and mixed pattern. Our results showed that the 2-month mortality due to treatment-related pulmonary toxicities was significantly higher in the patients with the DAD as compared with those with the BOOP or NSIP one on univariate analysis. This finding of DILD is not different from various ILD in which NSIP or BOOP have better response to steroid treatment and better outcome than DAD.

There are several limitations of the current study as shown below: (I) we conducted the current study under the retrospective design in the patients with moderate to severe

symptoms who were in need of in-hospital treatment and corticosteroid therapy. Our results cannot be applied to the patients with mild pulmonary toxicities who are not in need of corticosteroid therapy; (II) we classified the patients with pulmonary toxicities into four groups depending on the clinical and radiological diagnoses rather than biopsy and microbiological examinations. But we performed serologic tests and sputum and blood cultures to rule out the patients with infection; (III) we considered the fatality of treatment-related pulmonary toxicities to evaluate the efficacy of corticosteroids against them. But this may be insufficient for the assessment of the treatment response to corticosteroids, as previously shown in a report that a longitudinal data of carbon monoxide diffusing capacity would be a more objective indicator (25); (IV) we failed to identify the significant difference in the degree of treatment-related pulmonary toxicities between the causative drugs because we used many drugs in the treatment of our cases; (V) we failed to consider the accumulated toxicities from the previous several anti-cancer therapies. In other words, we failed to consider radiation recall pneumonitis that may occur during the follow-up chemotherapy after prior radiation therapy. Nevertheless, our study is of significance in that we have evaluated clinical characteristics of treatment-related pulmonary toxicities and the prescribed dosage pattern of corticosteroid therapy through a large-scaled clinical and radiological review of patients with moderate to severe respiratory symptoms.

Conclusions

In conclusion, our results showed that the natural course of DILD had more unfavorable outcome requiring higher dose steroid therapy as compared with those with radiation pneumonitis or AE COPD. And this study suggested that the patients with the BOOP and NSIP pattern on initial chest CT scans of DILD had more favorable outcomes.

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Original Article

Comparison of outcomes of open and minimally invasive esophagectomy in 183 patients with cancer

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Background and objectives: Only few randomized trials or comparative studies with large number of patients have been reported on the outcomes of thoracoscopic and laparoscopic esophagectomy (TLE) with cervical anastomosis and open 3-field esophagectomy (OE) for patients with esophageal cancer. The objective of this study is to compare the safety, feasibility, and short-term outcomes between TLE and OE (via right throax, abdomen, and left neck) for esophageal cancer.

Methods: Clinical and surgical data of patients with esophageal cancer who underwent either TLE or OE between February 2011 and December 2013 were retrospectively analyzed. Demographic characteristics, pathological data, operative procedures, and intraoperative and postoperative outcomes and survival in patients were compared between both groups.

Results: Of the 183 patients included in this retrospective analysis, 94 underwent TLE and 89 underwent OE. Demographics, pathologic data, inpatient mortality, and overall surgical morbidity in both cohorts were almost identical. A significant difference was observed in blood loss (182.6±78.3 *vs.* 261.4±87.2 mL, P<0.001), hospital stay (13.9±7.5 *vs.* 17.1±10.2 days, P=0.017), overall surgical morbidity (25.5% *vs.* 46.1%, P=0.004), and rate of pulmonary and cardiac complication (9.6% *vs.* 27.0%, P=0.002; 4.1% *vs.* 12.4%, P=0.046) between TLE and OE groups; however, no difference in survival period was observed between the groups.

Conclusions: The procedure of TLE for esophageal cancer possesses advantages in intraoperative and postoperative outcomes compared with OE. The TLE procedure results in similar or potentially better outcomes.

Keywords: Thoracoscopic; laparoscopic; esophagectomy; esophageal cancer; pulmonary complication

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Introduction

It is estimated that about 16,980 individuals (13,450 men and 3,530 women) were diagnosed with esophageal cancer and 14,710 were reportedly died in 2011 in the United States of America (1). China is also one of the countries with the highest esophageal cancer risk in the world (2). Esophagectomy is a gold standard in the treatment of patients with localized esophageal carcinoma (3). However, esophagectomy for cancer is considered to be one of the most extensive and traumatic oncological surgeries, which is associated with marked perioperative morbidity and mortality (up to 60% and 14%, respectively) (4-6). Elderly patients and those with comorbid diseases may give up the operation because of this high mortality, which is mainly caused by pulmonary and cardiac complications.

In recent years, the success of minimally invasive surgery has revolutionized the management of the disorders in the gastrointestinal tract. In 2000, Luketich *et al.* (7) first reported the minimally invasive esophagectomy (MIE) and proved that the operation was as good as or better than the open esophagectomy (OE). Reducing the trauma related

to surgical access directly results in lesser tissue injury, blood loss, postoperative pain, analgesic requirements, and impairment of respiratory and cardiac function. This potentially allows a more rapid recovery and helps to return to normal health-related quality of life (3,8).

Only few randomized trials or comparative studies with large number of patients have been reported on the outcomes of these procedures. Most comparative studies showed clinical advantages such as shorter operation times, fewer blood loss, shorter intensive care unit (ICU) and hospital stays, as well as a similar survival (9-11). One of the problems arising when comparing MIE and OE is the effect of selection bias on nonrandomized studies. The aim of the present study was to compare the postoperative outcomes and survival of patients with esophageal cancer who underwent thoracoscopic and laparoscopic esophagectomy (TLE) or OE.

Patients and methods

Patients and clinical data

Clinical and surgical data of 183 patients with esophageal cancer, who underwent TLE or 3-field OE between February 2011 and December 2013, were included in this retrospective study. Diagnosis of all the patients was established by esophagoscopy and biopsies; computed tomography and endoscopic ultrasound scans were used to evaluate the resectability of tumor. Resectable esophageal cancer was defined and patients were included in the study per the following eligibity criteria: cT1-3, N0-1, M0; esophageal cancer involving the gastric cardia was excluded; Eastern Cooperative Oncology Group performance scores of 0-2; tolerable pulmonary function under double lung ventilation for thoracotomy operation; normal functions of vital organs; normal blood detection; no previous thoracic, hiatal, or bariatric surgery; and no history of preoperative neoadjuvant chemotherapy and radiotherapy. All operations performed by a group of surgeons, who worked together for several years with experience in OE and TLE with at least 10 MIEs, were considered. The other criterion of operation was as follows: the gastric tube, as a substitute material of esophagus, was used to reconstruct the upper digestive tract through the mediastinal esophageal bed, and gastroesphageal track was anastomosed in the left neck by hands.

Operative technique

The 3-field OE was performed through an upper midline abdominal incision, right thoracotomy, and left neck incision. The procedure was described in detail by McKeown (12). The surgeons learned the technology and were trained in the TLE procedure as a modification of the original operation described by Luketich's (8) and Dr. Tan's (13). With the control and skill of the technique, a lot of own characteristics were also added to the knowledge on technology to perform surgeries.

TLE with cervical anastomosis

Patients were intubated with a double-lumen endotracheal tube and placed in left lateral semi-prone position. The surgeon stood on the right and the assistant on the left. Four thoracoscopic ports were used. Artificial pneumothorax was established by carbon dioxide (CO_2) (pressure: 12 mmHg and flow velocity: 20 L/min), thus providing downward traction on the diaphragm and allowing good exposure of the distal esophagus.

Thoracoscopic mobilization of the esophagus and systematic lymph node dissection

After mobilizing the inferior pulmonary ligament, the mediastinal pleura overlying the esophagus were divided up to the level of azygos vein by an electrical coagulation hook. After double clipping of the azygos vein by Ham-o-lok at each side, the vessel was divided by ultrasonic coagulation shears. Circumferential mobilization of the entire esophagus was performed up to the thoracic top and down to the plane of diaphragm, with removal of paraesophageal and subcarinal lymph nodes. Bilateral recurrent laryngeal nerve lymph nodes were cleaned by sharp dissections. A chest tube and mediastinal drainage tube were placed. The mediastinal drainage tube was placed along the esophageal bed until to the top of chest; hence, the procedure in the thoracic parts was completed. The lung was allowed to inflate; any air leaks from the trachea, proximal bronchus, and re-expanded lung were carefully observed.

Ligation and transection of the esophagus

The patient was turned to supine position. An incision of 4 cm was cut on the left cervical skin first. The cervical esophagus was exposed directly through a left anterior sternomastoid incision and dissection to the level of the cricoid prior to deliver the gastric conduit. The cervical esophagus was dissected with the fingers, ligated it with two sutures, and transected the esophagus by electrical coagulation knife. Two sutures were tied with another suture to extend the length for pulling out the stomach and

esophagus easily.

Laparoscopic mobilization of the stomach and abdominal lymph node dissection

The patient was kept in a supine position, surgeon stood on the patient's right, and first assistant was standing on the left of the patient. Artificial CO_2 pneumoperitoneum was established (pressure: 15 mmHg and flow velocity: 40 L/min). The laparoscopic ports were little different from Luketich's. A 10 mm camera port was created at the right paraumbilical line with a height of 2 cm. The main operating hole (10 mm) was located at the left paraumbilical line with a height of 2 cm, and the second operating hole (5 mm) was located under the costal margin of the left mid-clavicular line. One of assistant's operation holes (10 mm) was created below the xiphoid process and another (5 mm) was on umbilical level of anterior axillary line. The stomach was mobilized by dividing the short gastric vessels using the ultrasonic coagulating shears. The gastrocolic omentum was carefully divided to preserve the right gastroepiploic arcade. After double clipping of the left gastric artery by Ham-o-lok at each side, the vessel was divided by ultrasonic coagulation shears. Lymph nodes and fat tissues along the left gastric vessels, celiac axis, common hepatic artery, and splenic artery were dissected.

Gastric tube construction and cervical anastomosis

The xiphoid port was extended to 5 cm, along the abdominal midline. The specimens from the mini-incision were then dissociated out. A gastric tube of 5 to 6 cm in diameter was constructed along the great curvature by linear cutter or hand sewing. Then, the specimen and proximal gastric cardia were moved. The gastric conduit was pulled up to the neck under laparoscopic guidance, and esophagogastric anastomoses was performed with the three-leaf clipper-assisted manual layered anastomosis technique (14). A nasojejunal feeding tube was guided into the jejunum, and a gastrointestinal decompress tube was placed through nasal cavity. The surgery was finished after closure of the cervical and abdominal incisions.

The treatment principle in perioperative period was identical between both groups. The patients were transferred to the general ward after awakening from anesthesia, and the patients were transferred to ICU if there were breathing complications. All the postoperative patients were instructed to take a deep breath and assisted cough, and they were given liquid food through a nasal feeding after gastrointestinal exhaust. Gastrointestinal decompression was implemented until day 5-6 after surgery, and the patients were given liquid diet which then was converted to a semi-liquid diet from day 7 after the surgery. The patients were discharged from hospital when they could eat semi-liquid food without any trouble and walk without any discomfort.

Postoperative follow-up

The patients were regularly followed up mainly by outpatient service and telephone after surgery. The outpatient follow-up was performed once in the first month after hospital discharge, once in every 3 months till the first 2 years, and thereafter once every 6 months. Death and lost to follow-up were defined as events and were recorded.

Statistical analysis

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS version 17.0). Comparison of data between TLE and OE was done using the Student's *t*-test for continuous data and the chi-square tests for categorical data. Survival was calculated with the Kaplan-Meier method. A value of $P<0.05$ was considered to be statistically significant.

Results

This retrospective study included a total of 183 patients who received either OE or MIE. There were no significant differences in demographic and pathologic characteristics of patients (*Tables 1*,*2*).

The intraoperative and postoperative outcomes are shown in *Table 3*. The TLE group had significantly less blood loss, and fewer patients underwent blood transfusion. The total dissection number of lymph nodes in these two groups was 1,527 *vs.* 1,548 (mean: 16.2 *vs.* 17.4), respectively. The mean number of positive lymph node is 0.67% *vs.* 1.15%, respectively ($P>0.05$). Nine (9.6%) patients of TLE group and 13 (14.6%) patients of OE group required to send to ICU as a consequence of complications. Mean hospital stay was significantly shorter in TLE group than OE group.

The overall surgical morbidity in the TLE group was significantly lower compared with the OE group. There was a significantly lower rate of pulmonary complications and cardiac arrhythmia in the TLE group. There was no statistical significance with the disparity of anastomotic leak and recurrent laryngeal nerve injury between the two groups. Other complications like chylothorax and diaphragmatocele were similar between the two groups. Unfortunately, one patient in TLE group and four patients in OE group died

Table 1 Demographic data

Variables	TLE (n=94) (%)	OE (n=89) (%)	P value
Sex distribution (male/female)	65/29	63/26	0.809[a]
Mean weight (kg)	59.5±8.3	59.9±8.5	0.818[b]
Age			
Range (yrs)	31-79	41-78	0.364[b]
Mean ± standard deviation (yrs)	59.7±9.3	61.1±6.7	
Carcinoma location			0.909[a]
Upper	13 (13.8)	11 (12.4)	
Middle	61 (64.9)	57 (64.0)	
Lower	20 (21.3)	21 (23.6)	
Comorbidity			
Cardiac			0.428[a]
Yes	11 (11.7)	14 (15.7)	
No	83 (88.3)	75 (84.3)	
Respiratory			0.375[a]
Yes	27 (28.7)	31 (34.8)	
No	67 (71.3)	58 (65.2)	
Diabetes			0.750[a]
Yes	12 (12.8)	10 (11.2)	
No	82 (87.2)	79 (88.8)	

TLE, thoracoscopic and laparoscopic esophagectomy; OE, open esophagectomy; SCC, squamous cell carcinoma; [a], χ^2 test; [b], student's *t*-test; yrs, years.

Table 2 The pathologic data

Variables	TLE (n=94) (%)	OE (n=89) (%)	P value
Histology			0.883[a]
Adeno	3 (3.2)	5 (5.6)	
Squamous	87 (92.5)	80 (89.9)	
Undifferentiated	1 (1.1)	1 (1.1)	
Other	3 (3.2)	3 (3.4)	
UICC stage			0.909[a]
0	5 (5.3)	4 (4.5)	
IA	8 (8.5)	6 (6.7)	
IB	11 (11.7)	12 (13.5)	
IIA	13 (13.8)	12 (13.5)	
IIB	19 (20.2)	16 (18.0)	
IIIA	28 (29.8)	26 (29.2)	
IIIB	10 (10.6)	11 (12.4)	
IIIC	0	2 (2.2)	
G stage			0.914[a]
Well differentiated	12 (12.8)	10 (11.2)	
Moderately differentiated	35 (37.2)	32 (36.0)	
Poorly differentiated	46 (48.9)	45 (50.6)	
Undifferentiated	1 (1.1)	2 (2.2)	
Lymph node harvested	16.2±3.1	17.4±3.4	0.132[b]

TLE, thoracoscopic and laparoscopic esophagectomy; OE, open esophagectomy; UICC, Union for International Cancer Control; [a], χ^2 test; [b], student's *t*-test.

within 30 days. The patient died after TLE was due to acute gastrointestinal bleeding, which was also the reason for one of the four patients died in the OE group. Other patients died in the OE group because of pulmonary complications (n=1) and chest infection as anastomotic leak (n=2).

The follow-up of two groups ranged from 6 to 40 months. The Kaplan-Meier survival curve is shown in *Figure 1*. Four patients in the OE group and three in the TLE group were lost to follow-up. Median follow-up was 28 months (standard error 2.4; 95% CI, 23.3-32.7). The log-rank test showed no difference between the two groups (P=0.993). Median survival for patients in OE was 28 months (standard error 3.2; 95% CI, 21.8-34.2) compared with 26 months (standard error 2.6; 95% CI, 20.8-31.2) in the TLE group.

Discussion

The present retrospective study has shown that TLE and OE are both safe and feasible for esophagogastric cancer with comparable morbidity, surgical outcomes, and overall survival. These findings are consistent with other reported studies (8-11). In the present study, the TLE procedure resulted in similar or potentially better outcomes, although the survival was not different between the TLE and OE groups.

The advantages of position and incisions in operation had been reported in previous literatures (15). With the continuous search of optimal operation technology, the cutting of esophagus in the neck was replaced as it was not only convenient for operation, but it could also decrease the cost and chance of contamination and could ensure the integrity of tumor. As the chest incision was only about 1 cm in the TLE group, it could avoid the shortcomings

Table 3 Intraoperative and postoperative outcomes

Variables	TLE (n=94) (%)	OE (n=89) (%)	P value
Operating time (min)	251.3±45.4	247.8±44.1	0.617[b]
Blood loss (mL)	182.6±78.3	261.4±87.2	<0.001[b]
Transfusion (No. of patient)	5 (5.3)	14 (15.7)	0.021[a]
Reoperations	2 (2.1)	3 (3.4)	0.951[a]
Overall surgical morbidity	24 (25.5)	41 (46.1)	0.004[a]
Overall pulmonary complication	9 (9.6)	24 (27.0)	0.002[a]
Anastomotic leakage	6 (6.4)	7 (7.9)	0.696[a]
RLN*-injury	4 (4.3)	4 (4.5)	0.937[a]
Chylothorax	3 (3.2)	4 (4.5)	0.646[a]
Diaphragmatocele	2 (2.1)	0 (0)	0.501[a]
Cardiac arrhythmia	4 (4.1)	11 (12.4)	0.046[a]
Delayed gastric emptying	2 (2.1)	2 (2.2)	1.000[a]
Post-operative mortality[†]	1 (1.1)	4 (4.5)	0.155[a]
ICU stay (No. of patient)	9 (9.6)	13 (14.6)	0.295[a]
Hospital stay (day)	13.9±7.5	17.1±10.2	0.017[b]

RLN*, recurrent laryngeal nerve injury; [†], death within 30 days following the operation; [a], χ^2 test; [b], student's *t*-test.

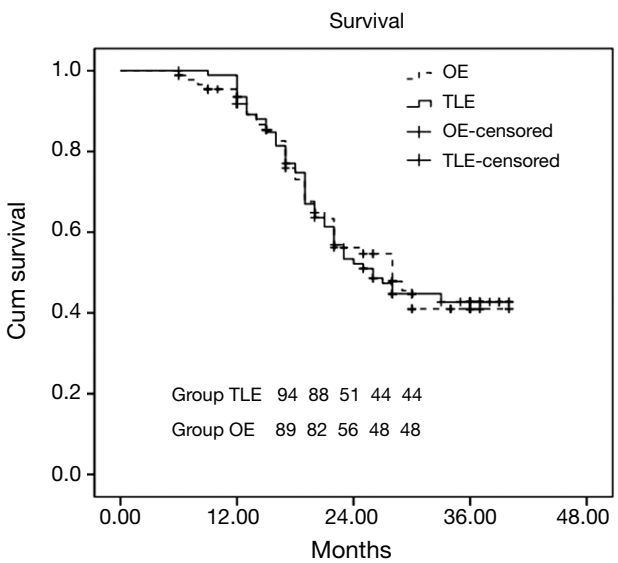

Figure 1 Kaplan-Meier analysis of survival. TLE, thoracoscopic and laparoscopic esophagectomy; OE, open esophagectomy.

of traditional OE such as large incision, ribs distraction, and destruction of the abdominal wall integrity. The blood loss was significantly lower in the TLE group, which was consistent with the literature (3,7,8). Due to the lower blood loss, only fewer patients required blood transfusion. Postoperative mortality and ICU stay did not differ significantly; however, the overall surgical morbidity was significantly lower in TLE, suggesting TLE as a safer procedure with acceptable complication rates.

The most common complications after the surgery mainly include anastomotic fistula, pulmonary complications, arrhythmia, delayed gastric emptying, chylous leakage, and recurrent laryngeal nerve injury. Currently, it is still controversial that the thoracoabdominal endoscopic esophageal resection can reduce the postoperative pulmonary complications. Smithers *et al*. and some others researches (16,17) suggested that the thoracoabdominal endoscopic esophageal resection did not reduce the incidence of postoperative pulmonary complications, but it even increased the incidence of postoperative pulmonary complications. However, some studies have shown that the MIE can significantly reduce postoperative pulmonary complications in patients (8,18-20). Recently, Sihag *et al*. (21) have found that MIE is the only relevant factor in significantly reducing pulmonary complications. In the present study, the incidence of complication in the TLE group was significantly lower compared with the OE group, which was mainly attributed to the obvious decrease in the complications of heart and lung.

Lymph nodes around the recurrent laryngeal nerve are the positions where transfer of esophageal cancer could easily occur, leading to worse disease-specific survival (22). In addition, the damage of recurrent laryngeal nerve will lead to a series of complications and poor prognosis (23,24). Hence, it

is important to pay attention to the protection of the recurrent laryngeal nerve at lymph node dissection, while carefully identifying and preventing accidental injury and taking care of the injuries caused by the ultrasonic scalpel heat conduction. There is a higher difficulty for cleaning the left recurrent laryngeal nerve lymph node using a thoracoscope. In addition to preventing accidental injury of the recurrent laryngeal nerve, the membrane departments of trachea also need much attention. In the present study, there was no significant difference between groups with respect to recurrent laryngeal nerve injury, suggesting TLE as a safer procedure.

With the development of surgical techniques, the occurrence of postoperative anastomotic fistula is significantly reduced. In the present study, there was no significant difference in the incidence of anastomotic leakage, chylothorax, diaphragmatocele, and delayed gastric emptying. However, pleural mediastinal infection caused by the anastomotic fistula is also very dangerous in postoperative patients. At present, the key treatment of this condition is drainage; therefore, mediastinal drainage tube should be conventionally placed before closing the chest in patients undergoing surgery for esophageal cancer (25). Mediastinal drainage tube is placed in the mediastinal esophageal bed, while the upper end directly gets to the chest top and the lower end is fixed in the seventh intercostal space. The vacuum extractor plays a role in drainage, but it can also act as a role of wash pipe, if necessary. Therefore, if the drainage volume is not large after the surgery, the chest tube can be removed on 2-3 days after surgery. Thus, the pain of patient can be reduced as soon as possible. The patients should be encouraged to get out of bed early to accelerate the functional recovery. Nasojejunal tube was also used as opposed to a transcutaneous jejunal tube to reduce the trauma as much as possible in both groups. In the present study, the hospital stay of TLE group was 3 days shorter than OE group. This finding shows that TLE has an obvious advantage than traditional methods.

Rough comparisons with recent reports on OE suggest that reduced perioperative morbidities, especially cardiopulmonary complications and blood loss, plus a shorter postoperative hospital stay are areas in which MIE might prove to be superior. However, surgeons are more concerned about the possibility to enhance long-term survival after the surgery. The patients were followed up for 6-40 months in this study, and the median follow-up was 28.0±2.4 months (95% CI, 23.3-32.7); in which, the median follow-up in the TLE and OE groups were 26.0±2.6 months (95% CI, 20.8-31.2) and 28.0±3.2 months (95% CI, 21.8-34.2), respectively. The survival rates in the both the groups were 42.7% and 41% (Log-rank test: P=0.993), respectively (*Figure 1*). There was no significant difference in survival time, which was consistent with published literature (3,9,11).

Conclusions

In summary, the thoracoabdominal endoscopic esophageal resection is not only technically feasible and safe, but it can also achieve the same radical effect of tumor as the conventional three incisions surgery. The more important is that the surgical method can significantly reduce the bleeding amount, reduce the incidence of perioperative cardiopulmonary complication, and reduce postoperative hospital stay. Although it has not fount to extend the time of the long-term survival in the patients with esophageal cancer, the endoscopic technology still has a potential advantage and is a treatment method worthy to be popularized.

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Original Article

Is video-assisted thoracic surgery lobectomy in benign disease practical and effective?

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Background: The aim of this study was to analyze the surgical outcomes of video-assisted thoracic surgery (VATS) lobectomy for benign pulmonary disease and to propose surgical guidelines based on the retrospective cohort study.

Methods: From January 2004 to December 2009, all lobectomies performed in a university-based tertiary care hospital were analyzed. The inclusion criteria were as follows: (I) VATS lobectomy for benign disease; (II) thoracotomy conversion cases initially approached by VATS lobectomy. All malignant cases were excluded. Electronic medical records were retrospectively analyzed and patients were divided into two groups: with infection and without infection. The primary outcomes were the thoracotomy conversion rate, length of hospital stay, period of thoracic drainage and complications.

Results: VATS was performed in 163 (42%) of 385 patients who underwent lobectomy for benign disease. There were 68 in the infection group and 95 in the group without infection. VATS lobectomy was successful in 157 (96%) patients while 6 were converted into thoracotomy. The mean operation time and blood loss were 160 minutes and 326 mL. Comparing two groups, operation time and blood loss were not statistically different (P value =0.92, 0.63). Moreover conversion rate, length of hospital stay, period of thoracic drainage and complications (P value =0.67, 0.18, 0.25, and 0.50) were not different.

Conclusions: VATS lobectomy for benign disease is practical and effective in selected cases regardless of the presence of infection. However, because various technical obstacles may be encountered during the procedure, therefore, careful patient selection is needed.

Keywords: Minimally invasive surgery; lobectomy (lung); lung benign or congenital lesions

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Introduction

Lobectomy can be performed in both malignant and benign disease. It can be applied in localized or medically-resistant pulmonary tuberculosis or in pulmonary nodules to confirm histologic features (1-4). It is also necessary in the treatment of pulmonary sequestration or congenital cystic adenomatoid malformation (5-8).

Video-assisted thoracic surgery (VATS) had been widely accepted because of its low complication rate, tolerable postoperative pain and early recovery of pulmonary function (9-12). However it still remains controversial whether it is recommendable in benign diseases or not. Because benign disease tends to have pulmonary adhesion, lymph node enlargement, and neovascularization (2,3), these inhibit successful VATS procedure and sometimes require conversion to thoracotomy (2,3). However, little is known about its ideal role because of the paucity of thorough

studies of VATS lobectomy for benign disease compared to for malignant disease (11,13).

Therefore, the aim of this study was to analyze the surgical outcomes of VATS lobectomy for benign pulmonary disease and to gain insight into the most suitable surgical conditions for this approach.

Methods

Patient enrollment

From January 2004 to December 2009 a total of 3,476 (1,067 by VATS, 2,409 by thoracotomy) lobectomies were performed at a university-based tertiary care hospital in Seoul, Korea. Inclusion criteria were (I) patients who had benign disease treated by VATS lobectomy; and (II) thoracotomy conversion cases initially approached by VATS lobectomy. Thoracotomy conversion was defined as a procedure that started with VATS for lobectomy, but was ultimately converted to thoracotomy for any reason. The exclusion criteria were as follows: (I) not a lobectomy; (II) lobectomy undergone by thoracotomy without any attempt at VATS; or (II) a VATS lobectomy for malignant disease. This study was reviewed and approved by the Institutional Review Board of Samsung Medical Center.

Technique

A 15-mm trocar for the 10-mm 30-degree thoracoscope was placed through the sixth intercostal space. A 4- to 5-cm utility incision was made through the fourth or fifth intercostal space in the anterior axillary line without rib spreading. Subsequently, an additional 5- to 10-mm trocar was placed through the sixth or seventh intercostal space in the posterior scapular line. Individual dissection of pulmonary vessels and bronchi was attempted, and they were divided by endoscopic staplers (or surgical clips for vessels). Thoracotomy conversion was performed by extending the utility incision or by connecting two separate VATS ports.

Analysis

We retrospectively analyzed the electronic medical records to analyze gender, age, and surgical information including diagnosis, pleural adhesion, operation time, and blood loss and thoracotomy conversion. Then, we compared the data according to the disease entity, defined as follows: (I) infection group—patients who were diagnosed as having any kind of infection; pulmonary tuberculosis, non-tuberculous mycobacteria, and fungus; (II) non-infection group—congenital disease including congenital cystic adenomatoid malformation or pulmonary sequestration, benign nodule, or bronchiectasis. Primary outcomes were the thoracotomy conversion rate, period of thoracic drainage, length of hospital stay, and complications. Complications were divided into three categories: (I) none-no complications; (II) fatal-acute lung injury, acute respiratory distress syndrome, and bronchopleural fistula; (III) mild-others not including (I) or (II). Subsequently the results were compared between the two groups and follow-up results were also analyzed.

Descriptive statistics were used to describe patient characteristics and outcomes. Continuous variables were manifested as means and standard deviations and categorical variables were presented as numbers and proportions. Student's *t*-test and the chi-square or Fisher's exact tests were used to compare the continuous and categorical variables, respectively. P values less than 0.05 were considered statistically significant. SPSS 12.0K Windows software was used for the analyses.

Results

Basic demographics and surgical information

VATS lobectomy for benign disease was performed in 163 patients. There were 385 lobectomies for benign disease within the study period. Therefore 42% (163 of 385) lobectomies for the benign disease were performed by VATS. Of these, 60% (n=99) were women, and the mean age was 44 years old. Pleural adhesion was seen in half of the patients. Mean operation time and blood loss were 160 minutes and 326 mL, respectively. Thoracotomy conversion was necessary in 6 (4%) patients, with difficulty in hilar dissection being the most common reason (n=4).

There were 68 cases with infection (pulmonary tuberculosis 31, fungal infection 37) and non-infection was recognized in 95 (congenital disease 25, bronchiectasis 29, and benign nodule 41). Age and gender were similar between them. Pleural adhesion was more frequent in the infection group, but the operation time and blood loss was slightly higher in the non-infection group. However, there was no statistically significant difference (P value =0.40, 0.92, 0.63). Thoracotomy conversion was necessary in 2 (3%) of the infection group, and 4 (4%) in the group without infection. Detailed information was written in *Table 1*.

Table 1 Basic demographic and surgical information

	Overall	Infection	Non-infection	P value
Number	n=163	n=68 [42]	n=95 [58]	
Gender				
Male	64 [40]	22 [32]	42 [44]	0.12
Female	99 [60]	46 [68]	53 [56]	
Age	44±15	46±17	44±16	0.52
Surgical information				
Pleural adhesion	80 [49]	36 [53]	44 [46]	0.40
Operation time (min)	160±66	160±66	161±66	0.92
Blood loss (mL)	326±266	314±245	334±282	0.63
Thoracotomy conversion	6 [3.7]	2 [3]	4 [4]	0.67
Difficult hilar dissection	4 [2]	2 [3]	2 [2]	
Indistinct anatomy	1 [<1]		1 [1]	
Bleeding	1 [<1]		1 [1]	

Continuous variables were manifested as means and standard deviation and categorical variables were shown as numbers and proportions.

Table 2 Surgical outcomes

	Overall	Infection	Non-infection	P value
Number	n=163	n=68	n=95	
Thoracic drainage (days)	4.8±3.2	4.4±2.3	5.1±3.7	0.18
Hospital stay (days)	7.3±8.6	8.2±12	6.7±4.8	0.25
Complications				0.50
No	128 [79]	51 [75]	77 [81]	
Mild	30 [18]	14 [21]	16 [17]	
Fatal	5 [3]	3 [4]	2 [2]	
Follow-up results				0.17
Cured	161 [99]	66 [97]	95 [100]	
Recurred	2 [1]	2 [3]	0 [0]	

Continuous variables were manifested as means and standard deviation and categorical variables were shown as number and proportions.

Surgical outcomes

The thoracotomy conversion rate was similar between the two groups (P value =0.67). Mean duration of a thoracic drainage and length of the hospital stay were about 5 and 7 days, respectively (P value =0.18, 0.25). Complications developed in 35 patients but 5 were fatal (3%). They were more in the infection group but there statistical difference was not seen (P value =0.50). On follow up 161 patients were cured (99%) and recurrence was seen in 2 (1%) patients. All recurrences developed in the infection group (pulmonary tuberculosis) and treated by medication. Detailed information was written in *Table 2*.

Comment

We set out to determine the role of VATS lobectomy in benign diseases. While there are many reports about VATS lobectomy for malignancy (9,10,13-15) there is a paucity of reports on VATS lobectomy for benign disease (2,3).

Because benign diseases requiring lobectomy tend to have infection or inflammation, some surgeons choose open thoracotomy rather than VATS. The present study clearly demonstrates that VATS lobectomy is a practical and viable option, and is effective in selected benign disease cases. The thoracotomy conversion rate was low (3.7%) and the cure rate was high (98%). Moreover clinical outcomes were similar regardless of the presence of infection or not. Although the slightly long operation time and hospital stay was minor drawbacks, it is certain that many lobectomies for benign disease can be performed successfully by VATS.

However, careful attention is required in case selection. Half of the patients showed pleural adhesion and six patients required thoracotomy conversion. Moreover, the operation time and blood loss was about 160 minutes and 320 mL, respectively. Considering that these results were from a high-volume hospital, it is possible that these statistics could be poorer in other institutions. Moreover, the surgery was performed in selected cases. VATS was not attempted if severe pleural adhesion was suggested by preoperative chest computed tomography (CT) scan findings and thoracotomy was the first approach of choice if tight hilar adhesion was found on initial thoracoscopic exploration. In other words, VATS lobectomy for benign disease is feasible in selected cases but the choice can be difficult.

This study has some limitations. First, since it was a long-term study, the indication of VATS was extended during the study period. Therefore in some candidates VATS lobectomy were excluded in the early study period. Moreover technical developments could have enhanced results to some extent later in the study period. Second, multiple disease entities were included. For example, pulmonary tuberculosis and fungal infection may be similar in terms of being infectious diseases but clinicopathologic features and treatment strategies can be different. It is therefore difficult to draw categorical conclusions from this study. However, the aim of this study was not a mere comparison of the surgical results for different benign diseases, but to show the practicality and effectiveness of VATS lobectomy for benign disease. We believe this study achieved this goal, based on a substantial number of patients in a single institution.

Conclusions

In conclusion, VATS lobectomy for benign disease is feasible and effective in selected cases, regardless of the presence of infection. However, there various technical obstacles may be present during the procedure, therefore, careful patient selection and meticulous operation are both required.

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Original Article

Risk factors for postoperative complications after lung resection for non-small cell lung cancer in elderly patients at a single institution in China

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Objective: The purpose of this study was to assess the postoperative complications after lung resection for non-small cell lung cancer (NSCLC) in elderly patients and to identify possible associated risk factors.

Methods: All patients aged 70 years or older who underwent pulmonary resection for NSCLC by either an open approach or by a thoracoscopic approach between January 2003 and December 2013 at our institution were reviewed. Postoperative events were divided into minor and major complications. Risk factors for complications were assessed by univariate and multivariate logistic regression analysis. A matched case-control study was performed to determine if the utilization of video-assisted thoracic surgery (VATS) for lung resection for NSCLC in elderly patients' results in decreased complications compared with thoracotomy.

Results: During the study period, 476 consecutive patients (410 thoracotomy, 66 thoracoscopy) older than 70 years underwent resection for NSCLC. Postoperative complications occurred in 169 patients (35.5%) and the overall operative mortality was 2.3% (11 patients). Univariate predictors of complications included history of smoking (P=0.032), CCI scores ≥3 (P<0.001), pneumonectomy (P=0.016), as well as the duration of surgery (P=0.003). After multiple logistic regression analysis, CCI scores ≥3 [odds ratio (OR) =29.95, P<0.001], pneumonectomy (OR =2.26, P=0.029) and prolonged surgery (≥180 min) (OR =1.93, P=0.003) remained the only independent risk factors. After matching based on age, gender, the Charlson Comorbidity Index (CCI), pathologic stage, and the type of resection, there were 60 patients in each group. Patients had similar preoperative characteristics. A VATS approach resulted in a significantly lower rate of complications (25.0% *vs.* 43.3%, P=0.034) and a shorter median length of stay (19 days, range, 12 to 35 *vs.* 21 days, range, 13 to 38, P=0.013) compared with thoracotomy.

Conclusions: Pulmonary resection for NSCLC in patients older than 70 years shows acceptable morbidity and mortality. Postoperative complications are more likely to develop in patients with CCI scores ≥3, those who undergo pneumonectomy, and those with a prolonged surgery. Thoracoscopic minimally invasive surgery for NSCLC in elderly patients is associated with fewer complications as well as a shorter hospital stay compared with thoracotomy.

Keywords: Non-small cell lung cancer (NSCLC); elderly patient; postoperative complications

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Introduction

Lung cancer remains the most frequent cancer worldwide with an estimated 1.8 million new cases (13% of total cancer incidence) and 1.6 million deaths (20% of total cancer mortality) in 2012 (1). Non-small cell lung cancer (NSCLC) constitutes roughly 80% of all lung cancer cases, and more than 50% of NSCLC patients are older than 65 years while over 30% are at least 70 years old at diagnosis (2). According to the statistics from the International Agency for Research on Cancer (IARC), the morbidity and mortality rates of lung cancer in China are highest in the world (1). In addition, the World Health Organization estimates that the annual lung cancer mortality rate in China may reach 1 million by 2025 (3).

Resection still represents the main curative treatment modality for patients with NSCLC. Recent data suggest that pulmonary resection for lung cancer is justified in elderly patients and that age itself is not a contraindication for surgical intervention (4,5), even in octogenarians (6). However, morbidity and mortality rates after pulmonary resections increase with increasing age, especially in elderly patients with severe comorbidities (7,8). As a consequence of growing and ageing populations in China, reducing postoperative complications and mortality is a major issue and still represents a clinical challenge frequently-faced by the thoracic surgeon.

The aim of the present study is to perform a statistical assessment of risk factors for postoperative complications after pulmonary resection for NSCLC in elderly patients at our institution by conducting a retrospective review.

Materials and methods

Approval for the study was obtained and the need for individual patient consent was waived by the Institutional Review Board. A prospectively maintained database of all patients undergoing thoracic surgery for lung cancer, approved by the Institutional Review Board, was used to identify those patients greater than or equal to 70 years of age who underwent pulmonary resection for NSCLC by either an open approach or by a thoracoscopic approach between January 2003 and December 2013 in the Department of Thoracic Surgery at Beijing Chest Hospital. Excluded patients included those who underwent an exploratory thoracotomy or a wedge biopsy; those with a history of preoperative chemotherapy or radiotherapy; histologic diagnosis of small cell carcinoma; and those with incomplete data.

Demographic, clinical variables, preoperative functional status, tumor characteristics, intraoperative details, and postoperative course were obtained from the institutional database that included all patients who had undergone thoracic surgery. The following risk factors were evaluated: gender, smoking history, a history of previous thoracic surgery, previous diseases, pulmonary functions, patient health status, pathologic stage, type of surgery, and duration of surgery. The postsurgical (pathologic) stages of the patients were based on the seventh TNM Classification of Malignant Tumors. Those patients who were diagnosed and treated before 2009 were re-staged according to the revised TNM Staging System (9). Histologic typing occurred according to The World Health Organization Histologic Typing of Lung Tumors (10). In classifying the severity of patient comorbidities, each patient was scaled objectively on the Charlson Comorbidity Index (CCI) based on information collected from the patient medical records (11). Hypertension was not classified as co-morbidity. The five-grade classification of the American Society Anesthesiology (ASA) was used as a composite index of a patient's overall health status. Never-smokers were defined as patients who had never smoked or had smoked fewer than 100 cigarettes in their lifetime. Postoperative complications were classified as minor (non-life-threatening) and major (potentially life-threatening), occurring within 30 days of surgery. Hospital mortality included all deaths during the first 30 days after operation, or during the postoperative hospital stay (12).

All patients were performed either by VATS or standard posterolateral thoracotomy under general anesthesia with single lung ventilation. Thoracoscopic lobectomy was performed without any rib spreading with the thoracoscope placed in the eighth intercostal space in the midaxillary line and a 3-4 cm anterior utility incision in the fifth intercostal space. The detailed technique of VATS lobectomy employed at our institution has been previously described elsewhere (13). Posterolateral thoracotomy in most patients was performed with division of the latissimus dorsi muscle and sparing of the serratus anterior muscle. All operations were performed by the same surgical team with extensive experience in thoracoscopic and open procedures. The decision to employ either a VATS or thoracotomy approach was made by the surgeon. The extended operation was defined as the resection of a pulmonary lobe associated with chest wall resection, additional parenchyma from an adjacent lobe, major vascular resection, or bronchoplastic procedure. After pulmonary resection, a complete systemic mediastinal lymph node dissection or sampling is

performed. Patient controlled intravenous analgesia (PCIA) for postoperative pain relief was offered to all patients regardless of the planned operative approach.

To determine if the utilization of VATS for lung resection for NSCLC in elderly patients' results in decreased complications compared with thoracotomy, we then performed a matched case-control study to evaluate the perioperative outcomes after pulmonary resection by VATS versus thoracotomy. Cases were defined as patients undergoing VATS pulmonary resection, while controls were those patients having a traditional thoracotomy. Controls were individually matched to cases according to five baseline variables by ratio 1:1. (I) Age: up to 2 years older or younger; (II) gender: male, female; (III) the CCI: 0, 1, 2, 3; (IV) pathologic stage: I, II, IIIa; (V) pulmonary resection types: wedge resection or segmentectomy, lobectomy, bilobectomy, extended resection. The perioperative outcomes of two groups were compared.

A logistic regression model was used in univariate and multivariate analyses to identify risk factors for postoperative complications. The data are presented as frequency and percentage for categoric variables and as median and range for continuous variables. The Wilcoxon rank test were used to compare continuous variables and the χ^2 or Fisher exact tests were used for categorical variables and a P value less than 0.05 was considered to be significant. Variables with a P value less than 0.2 in univariate analysis were entered into a multivariate analysis. The statistical software SPSS 13.0 (SPSS Inc, Chicago, IL, USA) was used for all analyses.

Results

Review of the prospective database of thoracic surgical cases performed from January 2003 to December 2013 identified 476 patients who were greater than or equal to 70 years old at the time of surgery and underwent lung resection for NSCLC. Of these 410 patients ultimately underwent thoracotomy, and 66 patients had a successful VATS approach. There were 376 males and 100 females, ranging in age from 70 to 87 years (median age of 73). Nineteen (4.0%) patients were octogenarians.

Demographic and preoperative clinical characteristics are shown in *Table 1*. There were 299 (62.8%) smokers or ex-smokers and 177 (37.2%) non-smokers. The comorbidity rate was 53.4% (254 of 476 patients) and CCI scores of 1, 2, 3, or 4 were assigned to 143, 82, 25 and 4 patients, respectively. Operative characteristics are listed in *Table 2*. Squamous cell carcinoma was the most common histologic type of cancer (48.3%), followed by adenocarcinoma (42.2%). Pulmonary resection was performed mainly for early disease stages (stage I, 44.1%; stage II, 26.7%; stage III, 26.3%; stage IV,

Table 1 Preoperative clinical characteristics

Characteristic	Number of patients (n=476)	Percentage
Gender		
Male	376	79.0
Female	100	21.0
Smoking		
Yes	299	62.8
Present	121	25.4
Past	178	37.4
No	177	37.2
Preoperative weight loss	40	8.4
Previous thoracic surgery	4	0.8
Hypertension	183	38.4
Coronary artery disease	95	20.0
Diabetes mellitus	69	14.5
History of CVA/TIA	31	6.5
COPD	57	12.0
BMI		
<30	450	94.5
≥30	26	5.5
Pulmonary function (FEV1%)		
<70	178	37.4
≥70	298	62.6
ASA score		
1-2	296	62.2
3-4	180	37.8
CCI		
0	222	46.6
1	143	30.0
2	82	17.2
3	25	5.3
4	4	0.8

CVA, cerebrovascular disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV1%, forced expiratory volume as a percentage of forced vital capacity; ASA, American Society of Anesthesiology; VATS, video-assisted thoracic surgery; CCI, Charlson comorbidity Index.

Table 2 Operative characteristics

Characteristic	Number of patients (n=476)	Percentage
Tumor histologic type		
Squamous cell carcinoma	230	48.3
Adenocarcinoma	201	42.2
Adenosquamous carcinoma	16	3.4
Bronchoalveolar carcinoma	15	3.2
Large-cell carcinoma	3	0.6
Others[a]	11	2.3
Pathologic stage		
I	210	44.1
II	127	26.7
III	125	26.3
IV	14	2.9
Type of resection		
Wedge/segment	49	10.3
Lobectomy	300	63.0
Bilobectomy	39	8.2
Extended[b]	53	11.1
Pneumonectomy	35	7.4
Surgical side		
Right	290	60.9
Left	186	39.1
Surgical approach		
VATS	66	13.9
Thoracotomy	410	86.1
Duration of surgery, min		
<180	349	73.3
≥180	127	26.7

[a], Carcinoid, carcinosarcoma, neuroendocrine carcinoma; [b], lobectomy plus wedge, chest wall, major vascular resection or bronchoplastic; VATS, video-assisted thoracic surgery.

Table 3 Complication (deaths excluded) profile[a]

Type, n	VATS (15/60)	Thoracotomy (26/60)	All patients (169/476)
Minor	8	16	105
Supraventricular arrhythmia	4	9	71
Delirium[b]	6	5	24
Prolonged air leak (>7 days)	2	4	29
Atelectasis	4	6	31
Wound infection	0	1	4
Major	7	10	64
Pneumonia	6	7	51
ARDS	0	1	2
MODS	0	1	2
Stroke	0	1	1
Stress ulcer	0	1	3
Myocardial infarction	0	1	2
Circulatory failure	0	1	8
Respiratory failure	1	5	26
Toxic shock	0	1	1
Pulmonary embolus	0	1	4
Reoperation for bleeding	0	1	2
Bronchopleural fistula	0	0	4
Chylothorax	0	0	1

[a], some patients had >1 complication; [b], all 24 patients in our study were in a mild or moderate acute confusional state based on the CAM-ICU, Confusion Assessment Method-Intensive Care Unit; VATS, video-assisted thoracic surgery; ARDS, adult respiratory distress syndrome; MODS, multiple organ dysfunction syndrome.

2.9%). The following types of pulmonary resections were performed: wedge resections or segmentectomies (10.3%), lobectomies (63.0%), bilobectomies (8.2%), extended resections (11.1%), and pnumonectomies (7.4%).

Overall operative mortality was 2.3% (11 patients). The causes of death were respiratory failure (4 patients), circulatory failure (3 patients), pulmonary embolus (3 patients), and toxic shock (1 patient). The mortality rate for lobectomy was 1.0% (3 of 300 patients), extended 7.5% (4 of 53 patients), and pneumonectomy 11.4% (4 of 35 patients, two left sided and two right sided). The number of deaths was too low to identify any significant risk factors. Postoperative complications are demonstrated in *Table 3*. The overall morbidity was 35.5% (169 patients). Minor complications occurred in 105 patients (22.1%) and major complications developed in 64 patients (13.4%). Two complications were seen in 41 patients (8.6%), and 20 patients (4.2%) developed three or more complications. The most common complications were supraventricular arrhythmia (14.9%) and pneumonia (10.7%). Only two patients underwent reoperation for postoperative bleeding.

On univariate analysis using the predictors listed in *Table 4*, smokers (P=0.032), CCI scores of 3-4 (P=0.001), pneumonectomy (P=0.016), and a prolonged surgery (P=0.003) were significantly associated with the occurrence

Table 4 Univariate and multivariate analysis of risk factors for postoperative complications

Variable	Category	OR	95% CI	P value
Univariate				
Gender	Male	0.69	0.43-1.11	0.13
Smoking	Yes	1.55	1.04-2.30	0.032
Previous thoracic surgery	Yes	0.60	0.06-5.84	1.00
Hypertension	Yes	1.26	0.86-1.86	0.24
Coronary artery disease	Yes	1.39	0.87-2.22	0.17
Diabetes mellitus	Yes	0.96	0.56-1.65	0.89
History of CVA/TIA	Yes	1.32	0.57-3.03	0.52
COPD	Yes	1.27	0.72-2.23	0.42
FEV1%	<70/≥70	0.93	0.63-1.37	0.72
BMI	≥30/<30	1.14	0.51-2.58	0.75
ASA	3-4/1-2	1.27	0.86-1.86	0.23
CCI	3-4/0-2	29.00	6.80-123.62	<0.001
Pathologic stage	III-IV/I-II	0.86	0.57-1.31	0.48
Pneumonectomy	Yes	2.30	1.15-4.61	0.016
Duration of surgery, min	≥180/<180	1.89	1.24-2.86	0.003
Multivariate				
Gender	Male	0.80	0.45-1.43	0.45
Smoking	Yes	1.38	0.89-2.21	0.19
Coronary artery disease	Yes	1.25	0.74-2.11	0.41
CCI	3-4/0-2	29.95	6.91-129.88	<0.001
Pneumonectomy	Yes	2.26	1.09-4.71	0.029
Duration of surgery, min	≥180/<180	1.93	1.24-3.00	0.003

OR, odds ratio; CI, confidence interval; CVA, cerebrovascular disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; FEV1%, forced expiratory volume as a percentage of forced vital capacity.

of complications. Gender, previous thoracic surgery, hypertension, diabetes, congestive heart failure, coronary artery disease, history of cerebrovascular disease (CVA)/transient ischemic attack (TIA), chronic obstructive pulmonary disease (COPD), pulmonary functions, body mass index (BMI), ASA, and pathologic stage were not significant predictors of complications. After multiple logistic regression, three independent risk factors for postoperative complications were identified: CCI scores ≥3 (OR =29.95, 95% CI, 6.91-129.88), pneumonectomy (OR =2.26, 95% CI, 1.09-4.71), and prolonged surgical time (OR =1.93, 95% CI, 1.24-3.00).

After matching for age, gender, the CCI, pathologic stage, and the type of resection, there were 120 patients eligible for analysis, 60 patients in each group. There were no conversions to thoracotomy in the VATS group. The patients in each group were well-matched with respect to preoperative characteristics (*Table 5*). The median age of patients was 75 years, and there were a higher proportion of men (70%). With respect to smoking status, previous diseases, pulmonary functions, ASA, histologies, and tumor size, no significant difference was noted (*Table 5*).

Perioperative outcomes are listed in *Table 5*. Patients in the VATS group had a shorter length of stay compared with those in the thoracotomy group (median 19 days, range 12 to 35 days versus median 21 days, range 13 to 38 days, P=0.013). In addition, the VATS group had a significantly lower rate of complications compared with the thoracotomy group (25.0% *vs.* 43.3%, P=0.034). When separated into severity of complications, VATS patients had a decreased incidence of major complications (13.3%) compared with open thoracotomy patients (26.7%). There

Table 5 Patient characteristic and perioperative outcome

Characteristic	VATS (n=60)	Thoracotomy (n=60)	P value
Age [range], yr	75 [70-83]	75 [70-83]	[a]
Gender, n (%)			[a]
Female	18 (30.0)	18 (30.0)	
Male	42 (70.0)	42 (70.0)	
CCI, n (%)			[a]
0	27 (45.0)	27 (45.0)	
1	16 (26.7)	16 (26.7)	
2	15 (25.0)	15 (25.0)	
3	2 (3.3)	2 (3.3)	
Pathologic stage, n (%)			[a]
I	49 (81.7)	49 (81.7)	
II	8 (13.3)	8 (13.3)	
III[a]	3 (5.0)	3 (5.0)	
Type of resection, n (%)			[a]
Wedge/segment	19 (31.7)	19 (31.7)	
Lobectomy	36 (60.0)	36 (60.0)	
Bilobectomy	2 (3.3)	2 (3.3)	
Extended[b]	3 (5.0)	3 (5.0)	
Smoking, n (%)	33 (55.0)	37 (61.7)	0.459
Hypertension, n (%)	27 (45.0)	25 (41.7)	0.715
Coronary artery disease, n (%)	15 (25.0)	10 (16.7)	0.265
Diabetes mellitus, n (%)	6 (10.0)	9 (15.0)	0.412
History of CVA/TIA, n (%)	4 (6.7)	8 (13.3)	0.227
COPD, n (%)	11 (18.3)	6 (10.0)	0.194
FEV1% [range]	76 [51-95]	76 [52-95]	0.933
ASA, n (%)			0.543
1	4 (6.7)	3 (5.0)	
2	30 (50.0)	36 (60.0)	
3	26 (43.3)	21 (35.0)	
Histology, n (%)			0.824
Adenocarcinoma	31 (51.7)	34 (56.7)	
Squamous	19 (31.7)	18 (30.0)	
Others[c]	10 (16.7)	8 (13.3)	
Tumor diameter (range), cm	2.5 (0.5-7.0)	2.7 (0.5-8.0)	0.760
Perioperative outcome			
Conversions, n (%)	0	–	–
Length of stay [range], days	19 [12-35]	21 [13-38]	0.013
Complications, n (%)	15 (25.0)	26 (43.3)	0.034
Death, n (%)	0	2 (3.3)	0.159

[a], used as matching variable; [b], bronchoplasty and pulmonary artery reconstruction in one case and bronchial sleeve lobectomy in two cases; [c], adenosquamous carcinoma, bronchoalveolar carcinoma, large-cell carcinoma and carcinosarcoma; VATS, video-assisted thoracic surgery; CCI, Charlson Comorbidity Index; CVA, cerebrovascular disease; TIA, transient ischemic attack; COPD, chronic bstructive pulmonary disease; FEV1%, forced expiratory volume as a percentage of forced vital capacity; ASA, American Society of Anesthesiology.

was no significant difference in the incidence of minor complications. There were no perioperative deaths in the VATS group, whereas there were two deaths (3.3%) in the thoracotomy group although this difference was not statistically significant (P=0.159). One patient died of toxic shock and one died of respiratory failure.

Discussion

This study demonstrates that pulmonary resection can be performed for NSCLC in patients older than 70 with acceptable overall morbidity and mortality (2.3% and 35.5%, respectively). These results are in the range of those published from other multiinstitution and single-institution series (14-16).

Our findings support those of previously published reports that have suggested that age should not be the sole determinant when considering surgery as a treatment option for lung cancer (4,5). In addition, chronologic age is not an absolute risk factor for morbidity and mortality after lung resection. In the present study age was also not a significant risk factor for complications. A number of recent studies have indicated that in carefully selected elderly patients, pulmonary resection can be performed safely with mortality rates similar to that seen in their younger counterparts (14,16-18) The favorable data demonstrated that elderly lung cancer patients should not be denied the curative surgery based on their chronologic age.

The most common reported complications are arrhythmia (range, 4% to 14%) and air leak (range, 7% to 11%) (4,14,17,19), while the most frequently complications in our study were arrhythmia (14.9%) and pneumonia (10.7%). The incidence of air leak lasting more than 7 days was 6.1%. The different diagnostic criteria may partially explain the difference. According to previous literature, prolonged air leakage was defined as that persisting for more than 5 days (17) or 14 days (20), whereas the criteria for persistent air leak in our study was more than 7 days. Extreme variability in terms of incidence of pneumonia after lung resection was reported in both retrospective and prospective studies, with values ranging from 2% to 40% (21). The incidence of postoperative pneumonia in our series was in agreement with the previously published studies. Such variability probably depends on the characteristics of studied populations, antibioprophylaxis, the type of resection, and postoperative management.

The operative mortality rate of 2.3% is well within the range published by other investigators, who reported a hospital mortality ranging from 1.2% to 12.8% (14,17,19). The number of deaths was too low to identify any significant risk factors. We consider that selection bias may have played a role in our favorable results. That is because patients who had a history of neoadjuvant therapy were excluded and these patients most probably represent a group with advanced stage non-small lung cancer.

The CCI in general has been found to be an important prognostic factor in patients operated for cancer (11). Several studies have demonstrated that a Charlson comorbidity grade of 3 to 4 was significantly associated with major complications of surgery in NSCLC patients (7,17). In this study we also found that the CCI is a strong predictor of complications of surgery than individual risk factor in NSCLC elderly patients.

The present study demonstrated that the duration of surgery was one independent significant risk factor for complications. Licker *et al*. showed that prolonged surgery (≥120 min) was independently associated with an increased risk for postoperative complications (22). In our series, the morbidity rate was higher in patients with surgery time ≥180 min (46.5%) than in patients with surgery time <180 min (31.5%). Surgery time can be influenced by the patient's status, the complexity of surgery, the surgical approach, and the surgeon's skill-level. In addition, patients with severe adhesions or incomplete fissures would require longer operating times. We therefore suggest that operations for elderly patients should be performed by a skillful and experienced surgical team and the surgery duration should be limited to the shortest possible time.

The incidence of postoperative complications and the mortality rate in patients who underwent pneumonectomies (morbidity rate, 54.3%; mortality rate, 11.4%) were clearly more than patients who had undergone lesser lung resections (wedge resections and segmentectomies), lobectomies, bilobectomies, or extended resections. Several previous studies have reported that pneumonectomy, especially right-sided pneumonectomy, is associated with higher incidence of postoperative complications when compared with limited resections (12,23). However, Ginsberg *et al*. (24) showed a lower mortality rate in pneumonectomies in elderly patients (5.9%) compared with lobectomies (7.3%). Also in our series no significant difference was observed between right-sided pneumonectomy and left-sided pneumonectomy. Patient selection bias and low statistical power may account for this observation. Thus, it is still advisable that pneumonectomy should be undertaken with caution, but not avoided if a curative resection can be achieved.

VATS has been proven to be associated with low morbidity and mortality (25). In addition, some authors have reported that postoperative pulmonary function after VATS is better compared with the traditional thoracotomy (26). However, relatively few studies have been done to evaluate the use of VATS in elderly patients (27), or in octogenarians (28). Few studies have showed that a minimally invasive surgery to pulmonary resection results in fewer complications in elderly patients (29), or in octogenarians (30). In the present study we observed that the VATS group had a lower rate of complications and a shorter median length of stay compared with the thoracotomy group. Moreover, VATS patients had a decreased incidence of major complications compared with patients undergoing thoracotomy. However, Koizumi and his colleagues failed to show any difference in morbidity or mortality between VATS and standard thoracotomy in elderly patients (28). This was partially due to a low statistical power (17 thoracoscopy, 15 thoracotomy).

There are strengths and limitations to every study. The main strength of this study is that, compared with other studies, we performed a matched case-control study to eliminate selection bias as rigorously as possible outside of the setting of a randomized, prospective study. Although it is impossible to completely control selection bias in a retrospective study, we attempted to control for all knows contributors. The main limitation of this study is the retrospective nature. Although the data in this study were collected prospectively, the analysis was performed retrospectively. Therefore, unknown confounding variables and inherent selection biases could exist.

Conclusions

In conclusion, pulmonary resection for non-small cell lung carcinoma is justified in patients older than 70 years and its morbidity and mortality are acceptable. On the basis of our findings we concluded that those patients with CCI scores ≥3, those who undergo pneumonectomy, and those with a prolonged surgery are more likely to suffer postoperative complications and therefore need to be closely monitored. Compared with standard thoracotomy, a thoracoscopic approach is associated with a lower incidence of postoperative complications and may prove to be preferable for the elderly patients.

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Original Article

Impact of EGFR mutation status on tumor response and progression free survival after first-line chemotherapy in patients with advanced non-small-cell lung cancer: a meta-analysis

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Objectives: Non-small-cell lung cancer (NSCLC) patients harboring sensitive epidermal growth factor receptor (EGFR) mutations derive greater benefits from EGFR-tyrosine kinase inhibitors (EGFR-TKIs) than those with wild type tumors. However, whether EGFR mutation status is associated with the efficacy of cytotoxic chemotherapy or prognosis in advanced NSCLC patients remained controversial. Thus, we sought to conduct a meta-analysis to answer this question.

Methods: Electronic databases were searched for eligible literatures. The primary outcomes were objective response rate (ORR) and 6-month progression-free survival (PFS) rate. The pooled odds ratio (OR) was calculated using random-effects model. Subgroup analyses stratified by study types, EGFR mutation detection methods, chemotherapy regimens, and patient origins were proposed.

Results: A total of 14 studies involving 1,772 advanced NSCLC patients with known EGFR mutation status who had received first-line chemotherapy were included. Patients with positive EGFR mutation had numerically higher ORR than wild type patients (36.2% *vs*. 30.1%) without significant differences (OR 1.24, 95% CI, 0.90 to 1.70; P=0.19). However, patients with EGFR mutants had significantly superior 6-month PFS rate than wild-type patients (58.6% *vs*. 47.2%; OR 1.88, 95% CI, 1.33 to 2.65; P=0.0003). Results of the subgroup analyses were concordant with the overall ones.

Conclusions: This comprehensive analysis revealed that advanced NSCLC patients with sensitivity EGFR mutation had higher 6-month PFS rate and potentially greater ORR compared with wild-type patients after first-line chemotherapy. It suggested that EGFR mutation status should be considered a significant factor for patient stratification in evaluating the efficacy of antitumor agents in addition to EGFR-TKIs.

Keywords: Non-small-cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR) mutation; first-line chemotherapy; meta-analysis

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Introduction

Lung cancer, predominantly non-small-cell lung cancer (NSCLC), is the leading cause of cancer-related mortality worldwide (1). The majority of patients are diagnosed at advanced stages in which there are few treatment options (2). Despite the limited efficacy, platinum-based doublet chemotherapy remains the standard first-line treatment for advanced NSCLC in recent years (3,4). Advances in genetic testing allowed the discovery of existence and clinical significance of driver oncogenes which could be selected as a therapeutic target, such as activated epidermal growth factor receptor (EGFR) mutations (5). It has been

extensively proved that NSCLC patients who harbor sensitive EGFR mutations (exon 19 deletion or L858R mutation in exon 21) derive greater benefits from EGFR-tyrosine kinase inhibitors (EGFR-TKIs), such as erlotinib and gefitinib, than those with wild type tumors (6,7). The predictive value of EGFR mutation status for EGFR-TKIs efficacy has been substantially confirmed.

In contrast, people used to believe there is no correlation between EGFR mutation status and cytotoxic chemotherapy. Data from some previous studies suggested that Asians represented higher response rate than Caucasians in receiving chemotherapy (8). From the present point of view, the most prominent intrinsic genetic variance between these two races is the proportion of patients with EGFR mutations. Considering the huge differences in tumor biology between EGFR mutation-positive and -negative NSCLC, it is interesting to investigate whether EGFR mutation status also influence chemotherapy efficacy. Several recent studies revealed that advanced NSCLC patients with positive EGFR mutation had favorable response to first-line cytotoxic chemotherapy compared with wild type patients (9,10), while another study showed contrary results (11). In addition, another clinical research reported that there was no obvious association between EGFR mutation status and first-line chemotherapy response in NSCLC (12). Therefore, whether EGFR mutation status is associated with responsiveness to front-line chemotherapy in advanced NSCLC is still not clear. A comprehensive analysis of the various outcomes is warranted. Thus, we sought to perform a meta-analysis incorporating all available evidences to evaluate the clinical outcome according to the EGFR mutation status in patients with advanced NSCLC treated with front-line conventional chemotherapy.

Methods

Literature search

All relevant articles were retrieved by searching PubMed, Embase and the Central Registry of Controlled Trials of the Cochrane Library using a combination of the terms "EGFR", "epidermal growth factor receptor", "mutation", "lung", "non-small-cell lung cancer", "NSCLC" and "chemotherapy". An additional search through Google Scholar and a manual search through reference lists of relevant reviews and included studies were additionally performed. Two authors (ZY and KS) carried out the search independently. No restriction by language or year was set in the search.

Inclusion and exclusion criteria

Eligible studies should meet the following criteria: (I) studies which investigate or report a subset of patients with first-line chemotherapy without combination of EGFR inhibitors (e.g., TKIs or monoclonal antibodies) or other agents potentially targeting the EGFR pathway (e.g., multitargeted antiangiogenic TKIs) in patients with local advanced or metastatic (IIIB or IV) NSCLC; (II) prior neoadjuvant or adjuvant chemotherapy in patients with recurrence after surgery was permitted if it had elapsed from last administration to relapse at least 6 months; (III) EGFR mutation analysis was performed on available tumor tissue samples instead of circulating free DNA in serum in first-line chemotherapy treatment cohort; (IV) at least one primary outcomes was available. Studies failed to meet the inclusion criteria will be excluded.

Outcomes measures, data extraction and quality assessment

Primary outcomes for this meta-analysis were objective response rate (ORR), namely partial response (PR) plus complete response (CR), and 6-month progression-free survival (PFS) rate. The data collection and assessment of methodological quality followed the QUORUM and the Cochrane Collaboration guidelines (http://www.cochrane.de). The data on study type, treatment regimens, major clinical features, ORR and 6-month PFS rate were extracted by two investigators (FW and PH) independently. Figures were electronically digitized and Kaplan-Meier curves were downloaded by appropriate software (Engauge Digitizer, ver 2.12, Mark Mitchell, 2002, free software down loaded from http://sourceforge.net). Two reviewers (SW and DQ) used a JADAD score to evaluate the quality of randomized controlled trials (RCTs) and a modified Newcastle-Ottawa scale to assess the quality of non-RCT studies (13). Discrepancies were discussed by all investigators to reach consensus.

Statistical analysis

In consideration of any potential heterogeneity, we conducted this meta-analysis with a random-effect model in order to avoid any potential heterogeneity. The results were reported as pooled odds radios (ORs) with the corresponding 95% confidence interval (CI). Subgroup and sensitivity analysis were stratified for literature type, EGFR mutation analysis method, therapeutic regimen, patient

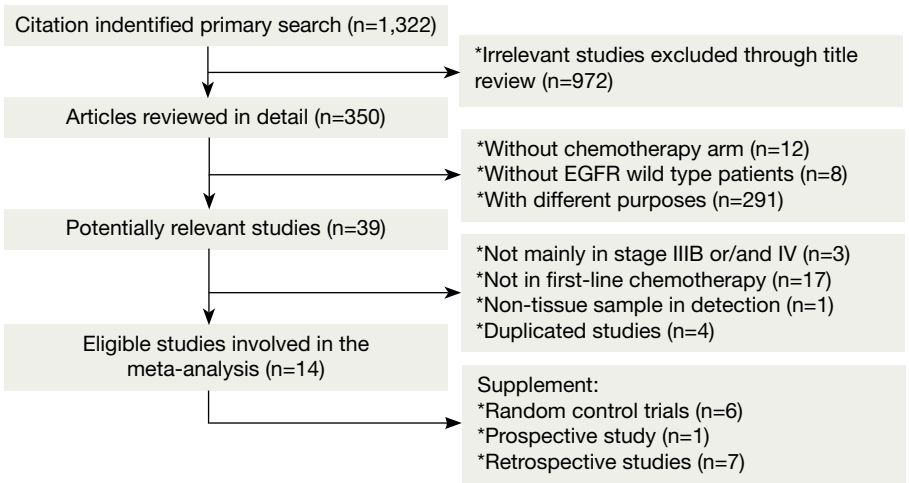

Figure 1 Profile summarizing the trial flow.

origins. An OR greater than one reflected a better ORR or 6-month PFS rate in the EGFR mutant arm. Statistical heterogeneity across studies was assessed with a forest plot and the inconsistency statistic (I^2). Statistical significance was considered at P<0.05. All calculations were performed using REVIEW MANAGER (version 5.0 for Windows; the Cochrane Collaboration, Oxford, UK).

Publication bias

An extensive search strategy was made to minimize the potential for publication bias. Graphical funnel plots were generated to visually assess a publication bias (14). The statistical methods to detect funnel plot asymmetry were the rank correlation test of Begg and Mazumdar and the regression asymmetry test of Egger (14,15).

Results

Eligible studies

We identified 1,322 records according to the search strategy and finally included 14 studies (six RCTs, one prospective study and seven retrospective studies) involving 1,772 advanced NSCLC patients who had been tested for EGFR mutations in first-line chemotherapy treatment cohort (9-12,16-25). *Figure 1* summarized the flow chart. Among these studies, chemotherapy regimens were platinum-based doublets at standard dose, namely cisplatin/carboplatin plus one of the third generation agents (including gemcitabine, paclitaxel, docetaxel, vinorelbine, and pemetrexed), or some non-platinum based regimens. Regimens were not specific in five retrospective studies (10,21-24) so that they were excluded in subgroup analysis stratified for therapeutic regimen. Detecting approaches for EGFR mutation included direct sequencing, nested polymerase chain reaction (PCR), amplification refractory mutation system (ARMS), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP); real time-quantitative PCR (RT-qPCR), denaturing high-performance liquid chromatography (DHPLC), which were also a sub-grouping factor. We considered time to progression (TTP) as PFS in studies by Eberhard (11) and Lee (21). *Table 1* summarized the characteristics of all involved studies.

Objective response rate and six-month PFS rate

According to all literature with available data, patients with positive EGFR mutation had higher pooled ORR than wild type patients (35.8% *vs.* 30.1%), but there was no significant difference between the two groups (OR 1.24, 95% CI, 0.90 to 1.70; P=0.19; heterogeneity: Chi^2 =17.47, P=0.13, I^2 =31%; *Figure 2A*). Subgroup analyses stratified by study type (RCT *vs.* non-RCT), EGFR mutation detecting method (direct sequencing *vs.* non-sequencing methods), therapeutic regimen (gemcitabine-based *vs.* non-gemcitabine-based regimens and cisplatin-based *vs.* carboplatin-based regimens) and patient origin (Asians *vs.* non-Asians) consistently revealed no significant difference between the mutant group and wild type group (*Table 2*). EGFR mutants had higher 6-month PFS rate than wild type patients (62.1%

Table 1 Characteristics of included studies

Lead author [year]	Country	Study category (phase)	Therapeutic regimen [cases in total]	Age, median [range] [y]	Female (%)	Non-smoker (%)	Adenocarcinoma (%)	Evaluable cases for EGFR mutation	EGFR mutation analysis method	EGFR exons identified as mutant	EGFR mutation status	ORR (%)	Six-month PFS rate (%)
David A. Eberhard [2005]	USA	RCT (III)	Paclitaxel 200 mg/m^2 BSA, d1, q3w + carboplatin (AUC =6), d1, q3w ×6 cycles [540]	NA	100 (18.5)	20 (3.7)	105 (19.4)	113	Nested PCR	18, 19, 20, 21	Positive	3/14 (21.4)	10/14 (71.43)
											Negative	27/99 (27.3)	78/99 (78.79)
Tony S. Mok [2009]	Asia	RCT (III)	Paclitaxel 200 mg/m^2 BSA, d1, q3w + carboplatin (AUC =5-6) d1, q3w ×6 cycles [608]	57.0 [25-84]	481 (79.1)	569 (93.6)	591 (97.2)	214	DxS ARMS	18, 19, 20, 21	Positive	61/129 (47.3)	64/129 (49.61)
											Negative	20/85 (23.5)	35/85 (41.18)
Shirin Khambata-Ford [2010]	USA	RCT (III)	Paclitaxel 225 mg/m^2 BSA or docetaxel 75 mg/m^2 BSA, d1, q3w + carboplatin (AUC =6) d1, q3w ×6 cycles [338]	65.0 [34-85]	134 (39.6)	25 (7.4)	NA	87	Direct sequencing	18, 19, 20, 21	Positive	1/9 (11.1)	7/9 (77.78)
											Negative	17/78 (21.8)	25/78 (32.05)
Ji-Youn Han [2012]	Asia	RCT (III)	Gemcitabine 1,250 mg/m^2 on d1 and 8+ cisplatin 80 mg/m^2 on d1 q3w × ≤9 cycles [150]	56.5 [19-74]	134 (89.3)	150 (100.0)	NA	43	Direct sequencing	19, 20, 21	Positive	6/16 (37.5)	9/16 (56.25)
											Negative	14/27 (51.9)	15/27 (55.56)
Cesare Gridelli [2012]	International	RCT (III)	Gemcitabine 1,200 mg/m^2 BSA, d1, 8, q3w + cisplatin 80 mg/m^2 BSA, d1, q3w × ≤6 cycles [380]	62.0 [34-81]	128 (33.7)	79 (20.8)	212 (55.8)	137	PCR-RFLP	19, 21	Positive	5/20 (25.0)	14/20 (70.00)
											Negative	NA/117 (NA)	45/117 (38.46)
Yi-Long Wu [2013]	Asia	RCT (III)	Gemcitabine 1,250 mg/m^2 BSA, d1, 8, q4w + carboplatin (AUC =5) or cisplatin 75 mg/m^2 BSA, d1, q4w + placebo d15-28, q4w ×6 cycles [225]	57.3 [37-88]	85 (38.0)	107 (48.0)	168 (75.0)	115	RT-qPCR	18, 19, 21	Positive	7/48 (14.6)	27/48 (56.25)
											Negative	13/67 (19.4)	26/67 (38.81)
Yuko Kawano [2013]	Japan	Prospective (II)	Pemetrexed 500 mg/m^2 BSA, d1, q3w + cisplatin 75 mg/m^2, d1, q3w × ≤4 cycles [50]	60.0 [28-74]	14 (28.0)	14 (28.0)	41 (82.0)	33	RT-qPCR	19, 21	Positive	6/9 (66.7)	3/9 (33.33)
											Negative	11/24 (45.8)	5/24 (20.83)
Kyung-Hun Lee [2006]	Korea	Retrospective	Platinum-based regimen [75]	NA	NA	NA	NA	75	Direct sequencing	18, 19, 21	Positive	6/14 (42.9)	11/14 (78.57)
											Negative	21/61 (34.4)	31/61 (50.82)
Katsuyuki Hotta [2007]	Japan	Retrospective	Platinum-based regimen [35] or non-platinum-based regimen [19]	NA	NA	NA	NA	54	Direct sequencing	19, 21	Positive	3/14 (21.4)	7/14 (45.80)
											Negative	6/40 (15.0)	9/40 (21.90)

Table 1 (*continued*)

Table 1 (*continued*)

Lead author [year]	Country	Study category (phase)	Therapeutic regimen [cases in total]	Age, median [range] [y]	Female (%)	Non-smoker (%)	Adenocarcinoma (%)	Evaluable cases for EGFR mutation	EGFR mutation analysis method	EGFR exons identified as mutant	EGFR mutation status	ORR (%)	Six-month PFS rate (%)
Meina Wu [2009]	China	Retrospective	Platinum-based regimen [132] or non-platinum-based regimen [13]	61.0 [21-78]	66 (45.5)	NA	106 (73.1)	145	DHPLC	19, 21	Positive	19/55 (34.5)	NA
											Negative	30/90 (33.3)	NA
Aristea Kalikaki [2010]	Greece	Retrospective	Platinum-based regimen [79]	NA	30 (23.4)	39 (30.5)	96 (75.0)	79	Direct sequencing	18, 19, 20, 21	Positive	5/8 (62.5)	NA
											Negative	17/71 (23.9)	NA
			Non-platinum-based regimen [49]					49			Positive	0/1 (-)	NA
											Negative	9/48 (18.8)	NA
Jin Hyun Park [2012]	Korea	Retrospective	Gemcitabine + cisplatin/ carboplatin [131]	59.0 [26-82]	120 (55.3)	144 (66.4)	174 (80.2)	131	RT-qPCR	18, 19, 20, 21	Positive	26/85 (30.6)	23/85 (27.06)
											Negative	16/46 (34.8)	13/46 (28.26)
			Paclitaxel + cisplatin/ carboplatin [86]					86			Positive	20/52 (38.5)	25/52 (48.08)
											Negative	12/34 (35.3)	15/34 (44.12)
M. Takeda [2012]	Japan	Retrospective	Platinum-based regimen [200]	63.0 [29-81]	73 (36.5)	65 (32.5)	178 (89.0)	182	ARMS/the PCR-Invader method	NA	Positive	14/31 (45.2)	16/31 (51.61)
											Negative	59/151 (39.1)	57/151 (37.75)
Xiao-Peng Dong [2013]	China	Retrospective	Gemcitabine + cisplatin [81]	57.0	17 (42.5)	57	24 (60.0)	81	Direct sequencing	18, 19, 20, 21	Positive	13/40 (32.5)	36/40 (90.00)
				61.0	19 (46.3)	61	21 (51.2)				Negative	13/41 (31.7)	35/41 (85.37)
			Docetaxel + cisplatin [77]	62.0	19 (43.2)	62	24 (54.5)	77			Positive	16/44 (36.4)	42/44 (95.45)
				58.0	15 (45.5)	58	19 (57.6)				Negative	12/33 (36.4)	28/33 (84.85)
			Vinorelbine + cisplatin [71]	60.0	16 (44.3)	60	22 (61.1)	71			Positive	13/36 (36.1)	35/36 (97.22)
				63.0	16 (45.7)	63	20 (57.1)				Negative	13/35 (37.1)	26/35 (74.29)

RCT, random control trial; AUC, area under the concentration time curve; BSA, body-surface area; ADK, adenocarcinoma; EGFR, epidermal growth factor receptor; ORR, objective response rate; TTP, time to progression; PFS, progression-free survival; PCR, polymerase chain reaction; ARMS, amplification refractory mutation system; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; RT-qPCR, real time-quantitative PCR; DHPLC, denaturing high-performance liquid chromatography; NA, not available.

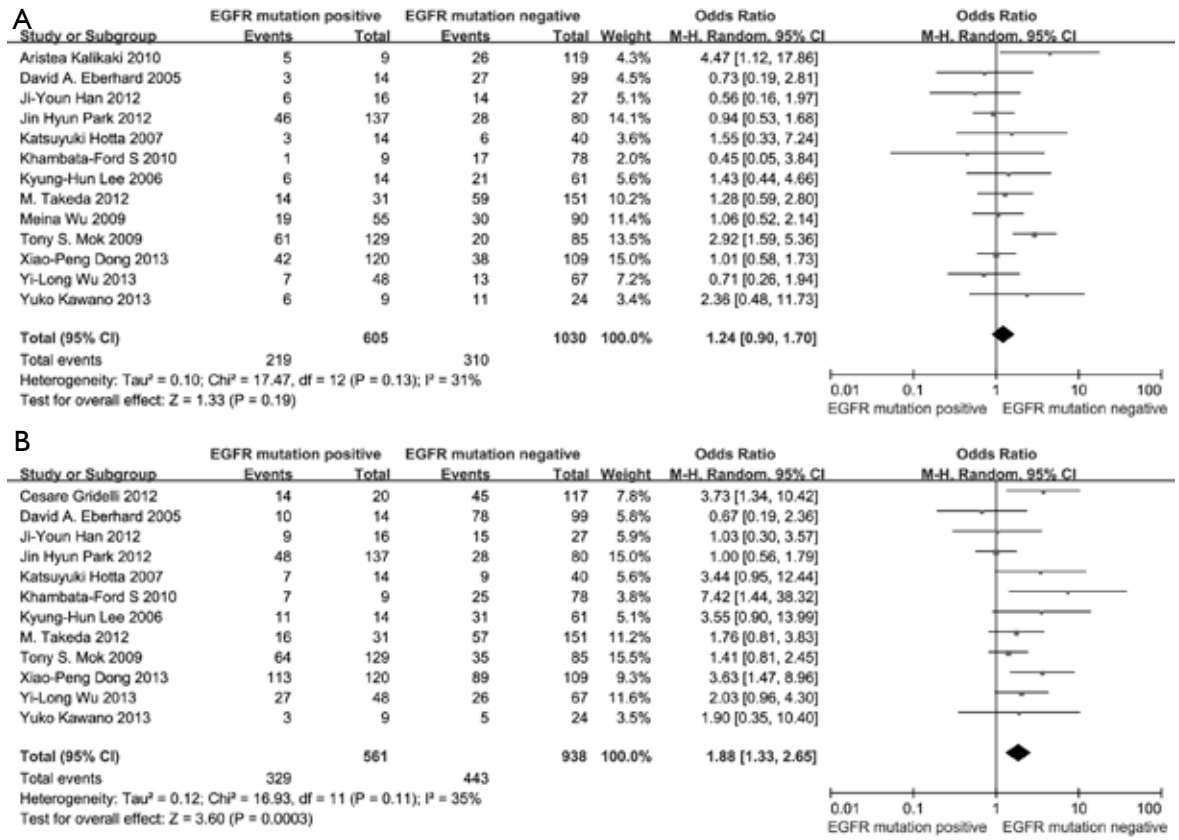

Figure 2 (A) Meta-analysis on objective response rate among advanced NSCLC patients receiving first-line chemotherapy according to EGFR mutation status; (B) meta-analysis on 6-month PFS rate among patients receiving first-line chemotherapy according to EGFR mutation status. NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; PFS, progression-free survival; CI, confidence interval; I^2, inconsistency statistic.

vs. 45.1%) with significance (OR 1.88, 95% CI, 1.33-2.65; P=0.0003; heterogeneity: Chi^2 =16.93, P=0.11, I^2 =35%; *Figure 2B*). Subgroup analyses also revealed similar tendency of significantly superior 6-month PFS of EGFR mutants, regardless of study types, methods of EGFR mutation detection, chemotherapy regimens and patient origins (*Table 3*). Additionally, we pooled the results of DCR although only five studies reported this data. No differences between EGFR mutation positive and negative groups were observed (OR 1.33, 95% CI, 0.93-1.91; P=0.11; heterogeneity: Chi^2 =2.23, P=0.69, I^2 =0%; *Figure 3*).

Assessment of heterogeneity and publication bias

As described above, the statistical heterogeneity was moderate. Any potential clinical heterogeneity was examined and subsequently excluded by subgroup analyses. In addition, sensitivity analysis by leaving any study out did not alter the general results. There was no publication bias for both outcome measures, with asymmetrical appearance on funnel plot analysis (*Figure 4*) and all P values greater than 0.05 in Begg's test and Egger's test.

Discussion

The association of EGFR mutation status with the responsiveness or prognosis in patients with advanced NSCLC after first-line chemotherapy was controversial based on previous small-size reports. A meta-analysis that could incorporate all available results, including subgroup data from RCTs as well, is a good way to address our concerns. In the current study, we found that 6-month PFS rate was significantly higher in EGFR mutants than in wild type patients after first-line chemotherapy, while the ORR and DCR appeared to be higher but the difference did not reach significance. These results admit of two

Table 2 Subgroup analysis on objective response rate among advanced NSCLC patients receiving first-line chemotherapy according to EGFR mutation status

Categories of included studies	Number of included studies	Objective response rate (event/total)		Test of heterogeneity			Test of effect size	
		EGFR mutation positive	EGFR mutation negative	Chi^2	P value	I^2 (%)	OR (95% CI)	P value
Total	13	219/605	310/1,030	17.47	0.13	31	1.24 (0.90-1.70)	0.19
Literature type								
Random control trial	5	78/216	91/356	11.36	0.02	65	0.97 (0.41-2.29)	0.94
Non-random control trial	8	141/389	219/674	5.56	0.59	0	1.17 (0.88-1.56)	0.28
EGFR mutation analysis method								
Direct sequencing method	6	63/182	122/434	6.20	0.29	19	1.17 (0.70-1.96)	0.56
Non-direct sequencing methods[1]	7	156/423	188/596	10.95	0.09	45	1.27 (0.83-1.95)	0.28
Therapeutic regimen								
Gemcitabine based regimens	4	52/189	56/181	0.67	0.88	0	0.80 (0.50-1.28)	0.36
Non-gemcitabine based regimens	6	120/293	112/388	9.11	0.10	45	1.36 (0.78-2.38)	0.28
Therapeutic regimen								
Cisplatin based regimens	3	54/145	63/160	1.93	0.38	0	1.00 (0.62, 1.61)	0.99
Carboplatin based regimens	3	65/152	64/262	5.49	0.06	64	1.27 (0.38, 4.32)	0.70
Patient origin								
Asia	10	210/573	240/734	12.72	0.18	29	1.22 (0.89-1.68)	0.21
Non-Asia area	3	9/32	70/296	4.75	0.09	58	1.27 (0.31-5.20)	0.74

[1]Non-direct sequencing methods included Nested PCR, ARMS, PCR-RFLP, RT-qPCR, and DHPLC. NSCLC, non-small-cell lung cancer; PCR, polymerase chain reaction; ARMS, amplification refractory mutation system; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; RT-qPCR, real time-quantitative PCR; DHPLC, denaturing high-performance liquid chromatography; EGFR, epidermal growth factor receptor; I^2, inconsistency statistic; OR, odds radio; CI, confidence interval.

Table 3 Subgroup analysis on six-month PFS rate among advanced NSCLC patients receiving first-line chemotherapy according to EGFR mutation status

Categories of included studies	Number of included studies	Six-month PFS rate (event/total)		Test of heterogeneity			Test of association	
		EGFR mutation positive	EGFR mutation negative	Chi^2	P value	I^2 (%)	OR (95% CI)	P value
Total	12	329/561	443/938	16.93	0.11	35	1.88 (1.33-2.65)	0.0003
Literature type								
Random control trial	6	131/236	224/473	8.74	0.12	43	1.80 (1.06-3.05)	0.0300
Non-random control trial	6	198/325	219/465	8.18	0.15	39	2.01 (1.20-3.36)	0.0080
EGFR mutation analysis method								
Direct sequencing method	5	147/173	169/315	4.27	0.37	6	3.04 (1.73-5.37)	0.0001
Non-direct sequencing methods[1]	7	182/388	274/623	7.37	0.29	19	1.50 (1.07-2.11)	0.0200
Therapeutic regimen								
Gemcitabine[2] based regimens	5	109/209	134/298	5.16	0.27	23	1.63 (0.99-2.68)	0.0500
Non-gemcitabine[3] based regimens	6	186/293	212/388	10.66	0.06	53	1.88 (0.97-3.62)	0.0600
Therapeutic regimen								
Cisplatin based regimens	4	178/286	167/330	3.26	0.35	8	2.61 (1.44, 4.71)	0.0020
Carboplatin based regimens	3	81/152	138/262	5.27	0.07	62	1.65 (0.59, 4.65)	0.3400
Distribution area of patients								
Asia	9	298/518	295/644	9.46	0.31	15	1.71 (1.25-2.33)	0.0008
Non-Asia area	3	31/43	148/294	6.48	0.04	69	2.53 (0.66-9.63)	0.1700

[1]Non-direct sequencing methods included Nested PCR, ARMS, PCR-RFLP, RT-qPCR, and DHPLC; [2]We defined gemcitabine + platinum-based regimen as gemcitabine + cisplatin/carboplatin; [3]We defined non-gemcitabine + platinum-based regimen as taxane/paclitaxel/docetaxel + cisplatin/carboplatin or vinorelbine/pemetrexed + cisplatin. NSCLC, non-small-cell lung cancer; PCR, polymerase chain reaction; ARMS, amplification refractory mutation system; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; RT-qPCR, real time-quantitative PCR; DHPLC, denaturing high-performance liquid chromatography; EGFR, epidermal growth factor receptor; PFS, progression-free survival; I^2, inconsistency statistic; OR, odds radio; CI, confidence interval.

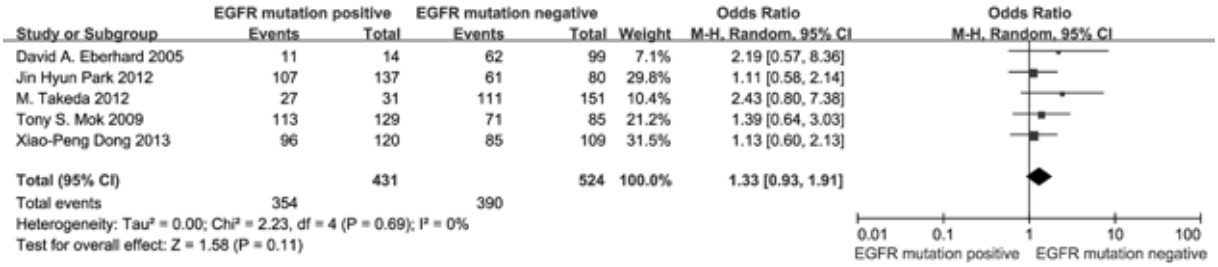

Figure 3 Meta-analysis on disease control rate among advanced NSCLC patients receiving first-line chemotherapy according to EGFR mutation status. NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; CI, confidence interval; I^2, inconsistency statistic.

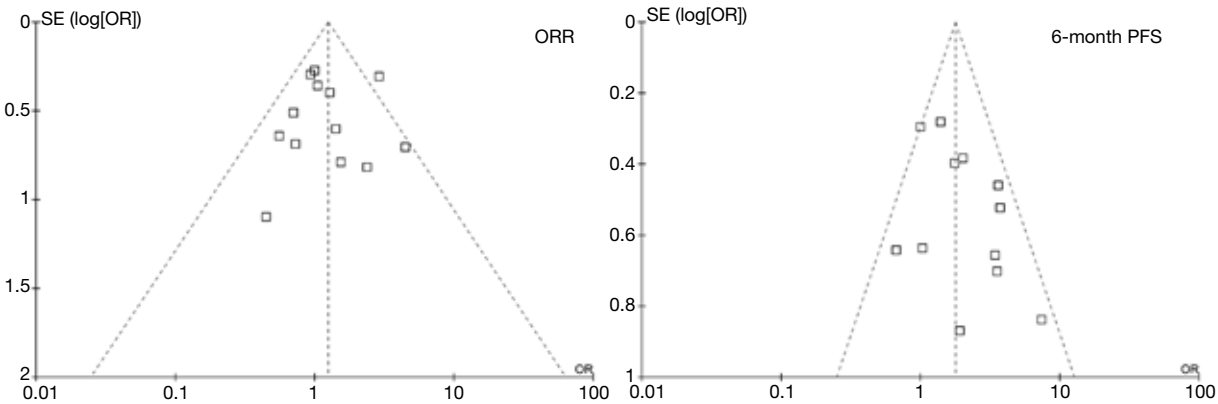

Figure 4 Funnel plots of ORR and 6-month PFS. OR, odds radio; ORR, objective response rate; PFS, progression-free survival.

interpretations.

Firstly, EGFR mutation might indeed be a predictor to the efficacy of cytotoxic chemotherapy. Activation of EGFR-dependent pathway plays an important role in the proliferation and aggressive phenotype transition of epithelial cells especially EGFR-mutated tumors (26,27). Moreover, a prior research indicated that a critical level of EGFR signaling was necessary for cisplatin-mediated apoptosis in tumor cells and suggested an inhibitory effect of this pathway on the repair of cisplatin-damaged DNA (28). Therefore, it was reasonable to hypothesize that tumor cells harboring EGFR mutation are more sensitive to cytotoxic chemotherapy. The hypothesis for selective killing of EGFR+ cells was supported by a clinical observation which showed a reduced plasma EGFR mutation frequency after chemotherapy in patients with NSCLC (29). By selectively eliminating or suppressing the 'seeds', tumor growths were persistently restricted, which translated into prolonged PFS as our result indicated. On the other hand, EGFR mutants did have higher pooled response rate although the magnitude of benefit was not as great as that of PFS. We suspected that the magnitude difference was attributed to the intratumoral heterogeneity. A recent study demonstrated that approximately 30% of patients presented intratumoral EGFR mutational heterogeneity through microdissection of the tumor samples (30). Therefore, tumors detected as EGFR mutated not necessarily contain pure EGFR+ cells. In other words, the intratumoral abundace of EGFR+ cells might be small in some patients. Thus, selective killing of EGFR+ cells was probably not associated with significant tumor shrinkage. As a result, patients intrinsically 'responded' to the chemotherapy might fail to meet the criteria for ORR (at least a 30% decrease in the sum of diameters of target lesions) according to Recist 1.1 criteria (31). However, direct evidence to confirm this mechanism requires real-time re-biopsy after treatments, which seems to be an impossible mission considering ethics. Secondly, we can not rule out the possibility that the improved PFS was merely the underlying prognostic effect of EGFR mutation since there was evidence showing that EGFR mutation was likely to be a favorable prognostic factor (32). However, the prognostic value of EGFR

mutation itself in NSCLC was still controversial (33).

Nonetheless, regardless of what the true causes are, this comprehensive analysis confirmed the association between EGFR mutation and PFS. This was highly concordant with an important report this year that among the patients treated with non-targeted therapy, those with a driver mutation detected had a longer median overall survival than those without identified driver mutations (2.4 *vs.* 2.1 years) (34). All these results gave us some important hints. Firstly, we strongly suggested that investigators should consider the proportion of EGFR mutation patients as a stratification factor in designing or reviewing clinical studies regarding chemotherapy regimen or other non-targeted agents. Second, it might partially explain why some clinical trials on chemotherapy in Asia reported higher response rate than those in Europe-American, and similarly, explain the negative results of combination of gefitinib with chemotherapy in patients with EGFR mutation compared with chemotherapy alone in some previous studies (35). In addition, the response to chemotherapy in EGFR wild type patients or projectively driven mutation 'pan-negative' patients was worse than what we acknowledged. Therefore, more efforts should be made to improve the prognosis of this population.

Notably, we only focused on first-line chemotherapy in this analysis in order to minimize the crossover effects. Some previous investigations suggested an inferior response from EGFR-TKIs following treatment of chemotherapy (36). Consistently, the study by Bai *et al*. also showed that the overall incidence of EGFR mutation was lower in plasma DNA after first-line chemotherapy (29). Thus, getting second-line or third-line chemotherapy involved will tangle the discussion.

This is the first study to comprehensively answer the impact of EGFR mutation on chemotherapy, addressing the confusion from inconsistent conclusions of current studies. However, there are several limitations. First, our meta-analysis was based on non-randomized studies and sub-group data extracted from RCTs, which somehow compromised the evidence level. Second, EGFR exons identified as mutant were heterogeneous among included articles but we were unable to assess whether 19 or 21 exon alterations had different impact on chemotherapy. Finally, we failed to investigate different first-line regimens separately with limited data. In addition, we cannot differentiate the respective impact of EGFR mutation on cell-cycle nonspecific antineoplastic agents (platinum) and specific agents (third-generation agents). For clinical practice, after all, it is essential to determine the optimal regimen for EGFR mutant NSCLC patients, especially who have failed front-line EGFR-TKIs or have no access to these agents. Further studies are warranted.

In conclusion, this meta-analysis showed that advanced NSCLC patient with EGFR mutation had significantly higher 6-month PFS rate and potentially higher ORR than wild type patients after first-line chemotherapy. We suggest that EGFR mutation status should be considered a stratification factor not only in studies regarding EGFR-targeted agents but also in those regarding non-EGFR-targeted drugs.

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Original Article

Lesion with morphologic feature of organizing pneumonia (OP) in CT-guided lung biopsy samples for diagnosis of bronchiolitis obliterans organizing pneumonia (BOOP): a retrospective study of 134 cases in a single center

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Background: Small biopsy samples are generally considered inconclusive for bronchiolitis obliterans organizing pneumonia (BOOP) diagnosis despite their potential to reveal organizing pneumonia (OP) pathologically, necessitating risky invasive tissue biopsy during surgery for reliable confirmation.

Objective: OP by CT-guided lung biopsy was to evaluate the role in the diagnosis of BOOP.

Methods: A retrospective review of 134 cases with the OP feature in the CT-guided lung biopsy samples between 2004 and 2011 at a single center was conducted. Diagnostic accuracy of OP by CT-guided lung biopsy and clinical-radiographic data alone were compared.

Results: After exclusion of 11 cases due to pathology with others besides OP and 15 cases for loss to follow-up, 108 were included. Of these, 95 cases and 13 cases were classified as BOOP and non-BOOP group, respectively. Among BOOP group, only 30 were initially diagnosed as BOOP according to the typical clinical and radiographic features. The other 65 cases with atypical features were diagnosed as BOOP mainly based on OP by CT-guided lung biopsy. Among non-BOOP group, one was misdiagnosed as BOOP, and others were not BOOP according to clinical and radiographic findings. Thus, OP by CT-guided lung biopsy produced a diagnostic accuracy of 87.96% (95/108), much higher than 31.25% (30/96) observed using clinical and radiographic data alone. Combined, these techniques produced diagnostic accuracy of 98.96% (95/96).

Conclusions: OP by CT-guided lung biopsy can be effectively used as the pathological evidence for BOOP diagnosis and reducing unnecessary surgery.

Keywords: Bronchiolitis obliterans organizing pneumonia (BOOP); organizing pneumonia (OP); CT-guided lung biopsy; diagnosis; retrospective study

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Introduction

Bronchiolitis obliterans organizing pneumonia (BOOP) occurs when bronchiolar inflammation rapidly progresses and disrupts areas of the airways due to organizing pneumonia (OP), characterized by loose plugs of granulation tissue (Masson bodies) within bronchioles or alveoli (1-3). Since BOOP was first described by Epler *et al.* (4) in 1985, it has been reported worldwide as a distinct clinicopathological entity (2). In modern literature, BOOP is distinguished from bronchiolitis obliterans by assignment of the terms cryptogenic (COP) or secondary organizing pneumonia (SOP), based on clinical presentation guidelines (2,5). The term BOOP is used here, as no clear proof exists that COP and SOP represent two distinct clinical entities (6-8).

Since over 80% of BOOP cases are curable (1), accurately distinguishing BOOP from other interstitial lung diseases and pulmonary infectious diseases is critical. However, the BOOP diagnosis as other interstitial pneumonia requires the clinic-radiologic-pathologic data (2) for the typical symptoms and radiographic features are nonspecific, and the pathological hallmark of OP can occur in a variety of other infectious diseases, lung cancer, vasculitis and so on (3,9). Since the OP is nonspecific, a rather large piece of lung tissue is required (2,5). The surgical lung biopsy is recommended by 2002 ATS/ERS Consensus Classification of the Idiopathic Interstitial Pneumonias for the diagnostic accuracy is about 90% (2,5,9-14). Such specimens, however, require general anesthesia and cases incur substantial morbidity and mortality risks (13-15). Safer and more effective methods for identifying BOOP-associated OP are urgently needed.

Though transbronchial lung biopsy (TBLB) is an important minimally invasive lung biopsy method, only 7-37% of patients are revealed in these samples (5,10). Thus, TBLB may be of limited use in BOOP diagnosis (5,10). Alternatively, several recent studies (16-18) have applied CT-guided lung biopsy for diagnosis of lung lesions, producing acceptable results with relatively lower costs and complication rates. CT-guided lung biopsy for BOOP has been reported in isolated cases (19-21); however, no broad clinical assessments of accuracy in small biopsy specimens with non-specific OP have been conducted (5).

To investigate the effectiveness of diagnosing BOOP using specimens produced by CT-guided lung biopsy in patients with non-specific OP, a retrospective analysis was conducted. These findings allow for the evaluation of OP in CT-guided lung biopsy specimens, as a reliably pathological evidence for BOOP.

Materials and methods

The study protocol was approved by the Drum Tower Hospital Institutional Review Board of the Medical School of Nanjing University (Nanjing, China) prior to beginning the study. Patient consent was not required for the retrospective study. The diagnostic pathology archives of the Drum Tower Hospital were searched for cases in which the terms "OP" and "CT-guided lung biopsy" were present. A total of 134 cases from 1 January 2004 to 31 December 2011 were identified. The morphologic feature of OP using published histological criteria (2,3,5) was confirmed by two independent and experienced pathologists. Eleven patients were excluded from the 134 cases due to the OP was not the only finding in the tissue: vasculitis (three cases), suspected pulmonary abscess (one patient), pulmonary tuberculosis (one patient), cryptococcus pneumonia (two cases), pulmonary aspergillosis (two cases), pulmonary infarction (one patient), and low-grade pulmonary lymphomas (one patient).

Then clinical data were collected by computerized searching in the Patient Record database and image database. The data were made up by the demographic data; symptoms and signs; routine laboratory tests including full blood cell counts, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP); re-biopsy findings from surgery, TBLB, or CT-guided lung biopsy; prescribed medications and images (or reports) of plain chest radiographs and/or CT findings. A minimum 3 months follow-up record was needed for the improvement either by spontaneous, surgery or treatment.

Of the 123 patients, 15 patients were excluded due to an absence of the minimum follow-up of 3 months for review. Accordingly, 108 cases with exclusive OP finding, complete patients' notes, radiographic imagines or reports, and follow-up data made up the final study group. The patients data were reviewed by five pulmonologists using published criteria of BOOP (2,22). In brief: (I) radiographic abnormalities ranging from multiple acinar/nodular shadows to solitary pneumonia-like or nodular shadows; (II) exclusive OP findings-masson bodies were apparent in alveoli and chronic inflammatory cell infiltration in the mesenchyme (*Figure 1*)—in the CT-guided lung biopsy samples; (III) negative microbiological analysis or no response to standard antibiotic therapy; (IV) rapid clinical and imaging improvement following corticosteroid treatment (or spontaneous in cases not prescribe these medications). Cases consistent with BOOP were assigned for BOOP group, or they were assigned for non-BOOP group.

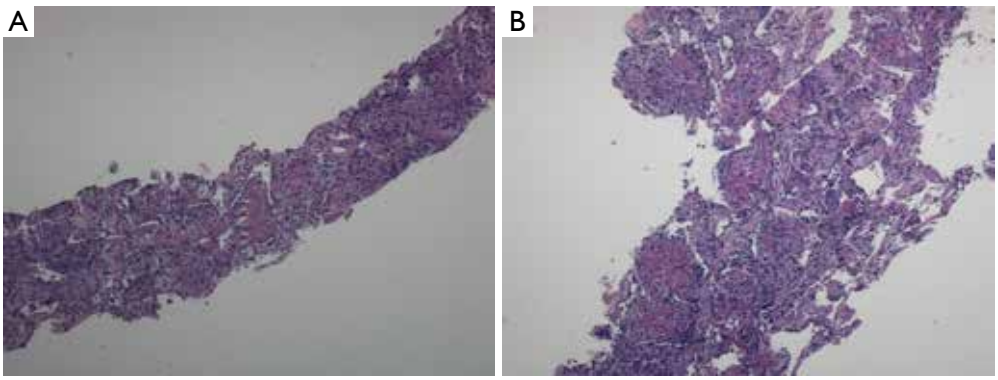

Figure 1 Organizing pneumonia (OP) identified by CT-guided lung biopsy in a 53-year-old female. (A) Pathological changes were evenly distributed (HE staining, 50×); (B) masson bodies apparent in the alveoli, showing chronic inflammatory cell infiltration in the mesenchyme (HE staining, 100×).

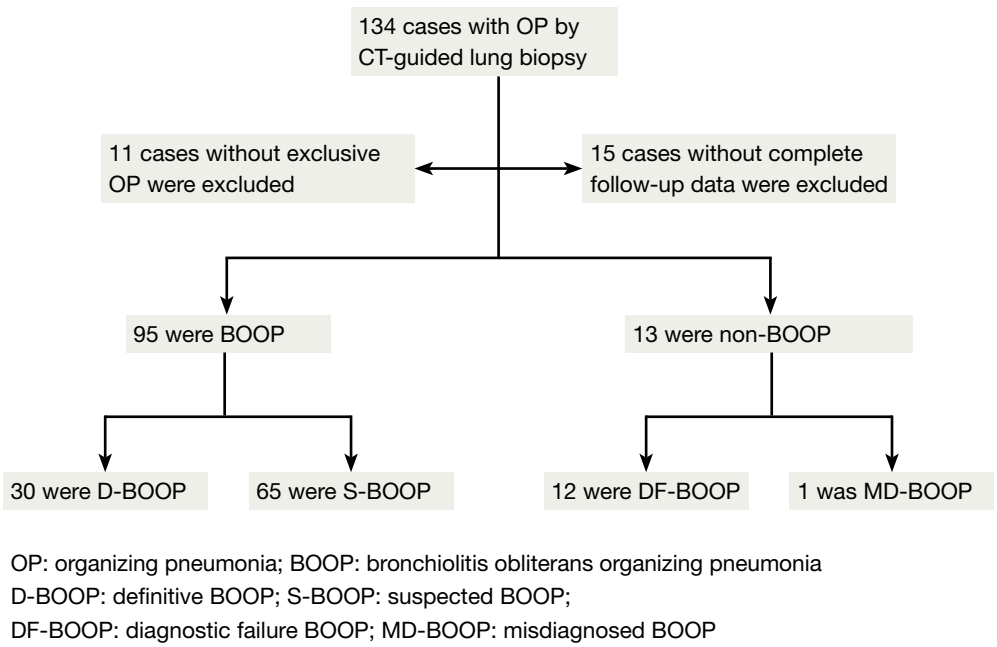

Figure 2 Study profile.

To evaluate the role of the nonspecific OP findings by CT-guided lung biopsy, BOOP patients were assigned for definitive BOOP (D-BOOP) and suspected BOOP (S-BOOP) group when the patients were initially diagnosed as probable, possible BOOP according to the clinical and radiographic data alone, respectively. Non-BOOP patients were assigned for diagnostic failure BOOP (DF-BOOP) and misdiagnosed BOOP (MD-BOOP) group. DF-BOOP patients were initially diagnosed as other diseases and the exclusive OP by CT-guided lung biopsy confused the diagnosis and need re-biopsy. MD-BOOP patients were misdiagnosed according to the clinical, radiographic, exclusive OP by CT-guided lung biopsy (*Figure 2*).

Statistical analysis

All statistical analyses were conducted using SPSS version 17.0 for Windows (IBM Inc., Chicago, IL, USA). Patient characteristics were expressed as means ± SD or number and frequency percentages. Group differences were tested by *t*-tests or χ^2 tests. P values less than 0.05 were considered significant (P<0.05).

Table 1 Clinical parameters

	BOOP (n=95) (%)			Non-BOOP (n=13) (%)			P value
	All patients	D-BOOP	S-BOOP	All patients	MD-BOOP	DF-group	
Sex, M/F	61/34	16/14	45/20	9/4	1/0	8/4	0.318
Age, mean ± SD, years	58.42±12.11	58.00±12.88	58.46±11.84	54.08±11.02	40	55.25±10.63	0.69
Cough	81 (85.26)	23 (76.67)	58 (89.23)	10 (76.92)	1	9 (75.00)	0.195
Sputum	59 (62.11)	15 (50.00)	44 (67.69)	8 (61.54)	1	7 (58.33)	0.22
Dyspnea	37 (38.95)	14 (46.67)	23 (35.38)	3 (23.08)	1	2 (16.67)	0.182
Fever	61 (64.21)	17 (56.67)	44 (67.69)	7 (53.85)	0	7 (58.33)	0.45
Flu-like symptoms	33 (34.73)	15 (50.00)	18 (27.69)	3 (23.08)	1	2 (16.67)	0.045
Chest pain	14 (14.74)	3 (10.00)	11 (16.92)	1 (7.69)	0	1 (8.33)	0.555
Hemoptysis	12 (12.63)	1 (3.33)	11 (16.92)	3 (23.08)	1	2 (16.67)	0.175
Weight loss	10 (10.53)	2 (6.66)	8 (12.31)	1 (7.69)	0	1 (8.33)	0.683
Crackles or wheeze	37 (38.95)	22 (73.33)	15 (23.08)	5 (38.46)	0	5 (41.67)	<0.01
Leukocytes >10,000/mm^3 or neutrophil >70%	52 (54.74)	10 (33.33)	42 (64.62)	9 (69.23)	0	9 (75.00)	0.07
ESR	71 (74.74)	19 (63.33)	52 (80.00)	10 (76.92)	0	10 (83.33)	0.171
CRP	59 (62.11)	16 (53.33)	43 (66.15)	6 (46.15)	0	6 (50.00)	0.355
Bilateral alveolar infiltrates	58 (61.95)	27 (90.00)	31 (47.69)	8 (61.54)	1	7 (58.33)	<0.01
Single consolidation	12 (12.63)	3 (10.00)	9 (13.85)	1 (7.69)	0	1 (8.33)	0.791
Massive or nodular opacity or obstructive atelectasis	25 (26.32)	0	25 (38.46)	5 (38.46)	0	5 (41.67)	<0.01
Pleural effusion	27 (28.42)	9 (30.00)	18 (27.69)	4 (30.77)	1	3 (25.00)	0.944
Mediastinal lymphadenopathy	9 (9.47)	1 (3.33)	8 (12.31)	4 (30.77)*	0	4 (33.33)	0.027

Note: BOOP, bronchiolitis obliterans organizing pneumonia; D-BOOP, definitive BOOP; S-BOOP, suspected BOOP; MD-BOOP, Misdiagnosed BOOP; DF-BOOP, diagnostic failure BOOP; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. *t*-tests and χ^2 tests were used to compare BOOP and non-BOOP group, only mediastinal lymphadenopathy differences were noted (*P=0.048). An χ^2 test was used to compare D-BOOP, S-BOOP, and DF-groups; due to limited patient numbers (one patient) in the MD-group, this group was not considered in these analyses.

Results

Clinical data

Clinical data are summarized in *Table 1*. A total of 108 patients finally fulfilled the inclusion criteria, with follow-up times ranging from 3-51 months (mean 9.86±6.23 months) with intervals of 1-12 months (mean 3.45±1.81 months). Of the108 cases, 95 (87.97%) cases and 13 (12.03%) cases were classified as BOOP and non-BOOP group, respectively. In the BOOP group, 61 (64.21%) were male and the mean age was 58.42±12.11 years (range, 22-77 years). Presenting symptoms and signs included cough, sputum, dyspnea, fever, flu-like symptoms, chest pain, hemoptysis, weight loss and crackle or wheeze and the laboratory data are no significant differences between the BOOP and non-BOOP group (P>0.05). The difference of the imaging features between the two groups was the mediastinal lymphadenopathy (P=0.048).

The BOOP group included 30 (31.58%) D-BOOP and 65 (68.42%) S-BOOP cases. The non-BOOP group included 1 (7.70%) MD-BOOP and 12 (92.30%) DF-group cases (*Figure 2*). As there was only one patient in the MD-BOOP group, no comparison with other groups was performed.

Observations in D-BOOP group

D-BOOP patients who were firstly diagnosed as probable BOOP only according to the clinical and radiographic data were supported by the OP feature in the CT-guided

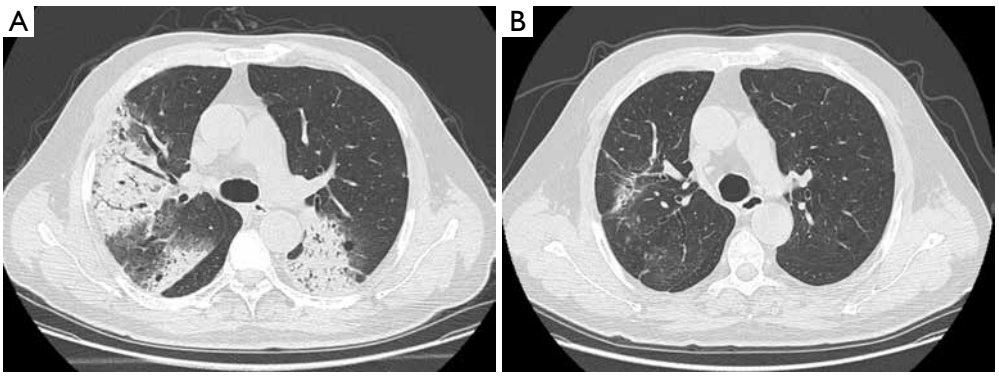

Figure 3 A 45-year-old male with BOOP by CT-guided lung biopsy showing resolution on follow-up computed tomography (CT) scans. (A) Chest CT showing bilateral alveoli filled with consolidation and ground glass opacities; (B) chest CT at the same level after 3 months of glucocorticoid treatment, showing bilateral blotchy consolidation, ground glass opacities absorbed strips and traction bronchiectasis. BOOP, bronchiolitis obliterans organizing pneumonia.

lung biopsy samples and verified by the rapid improvement after treatment. It seems that those patients' data including symptoms and signs and imaging features are more typical than other groups. It was well known that BOOP begin with a mild flu-like illness with fever, cough, malaise, dyspnea, weight loss and others (2,5,9). In this study, flu-like illnesses, fever, cough and crackles were presented more than 50% of D-BOOP cases. Only flu-like symptoms and crackles were significantly more common in the D-BOOP group than in the S-BOOP or DF-BOOP groups ($P<0.05$). Other manifestations such as mild dyspnea, anorexia, and weight loss were no significant differences between them (*Table 1*).

Twenty-seven (90%) of D-BOOP cases exhibited multiple alveolar filling shadows in both lungs with densities ranging from ground-glass to consolidation ranging several centimeters to a full lobe (*Figure 3*). Most were peripheral and some exhibited migratory patterns. Air bronchograms were visible among consolidation. Notably, these were assigned for the typical BOOP imaging features and less in either the S-BOOP group or DF-group in this study (47.7% and 58.3%, respectively; $P<0.01$). Additionally, three cases exhibited unilateral opacities firstly diagnosed as BOOP based on clinical manifestations along (no obvious fever; normal WBC count, ESR, and CRP level; present cough, dyspnea, and auscultation crackles).

With corticosteroid therapy, D-BOOP cases, including relapsed cases, exhibited overall positive treatment outcomes. A total of 30 D-BOOP cases exhibited lesions with rapid resolution following glucocorticoid treatment. There were no residues in 23 cases, and only 7 cases exhibited apparent traction bronchiectasis or bands of fibrous tissue (*Figure 3*).

Observations in S-BOOP group

S-BOOP patients who were as possible BOOP based on the clinical and radiographic data alone were confirmed by the pathological hallmark in CT-guided lung biopsy specimens and reinforced by the rapid improvement with corticosteroid therapy.

Of the 65 cases, 25 (38.46%) cases were suspected as tumor for radiographic features with single or multiple nodules (*Figure 4*) and obstructive pneumonia-like structural abnormalities. Forty cases (61.54%) were initially diagnosed as bacterial or fungal infections or tuberculosis that did not respond to antibiotic treatment. Fortunately, 51 patients were established the diagnosis of BOOP according to the OP findings in the CT-guided lung biopsy tissues and avoid the surgical lung biopsy. In view of small biopsy sample limitations and non-specific OP change, 14 cases with atypical imaging findings were required the re-biopsy, either with bronchoscope, secondary CT-guided lung biopsy, or surgical lesion excision.

The S-BOOP group as in the D-BOOP group, lesions rapidly regressed in most cases with corticosteroid treatment (64 cases), with minimal bands or streaks remaining in only 19 cases. One patient with OP by CT-guided lung biopsy was initially suspected as lung cancer by CT scanning. Though this patient voluntarily rejected further diagnosis and treatment, the lesion resolved spontaneously within 32 months, confirming a correct diagnosis of BOOP rather

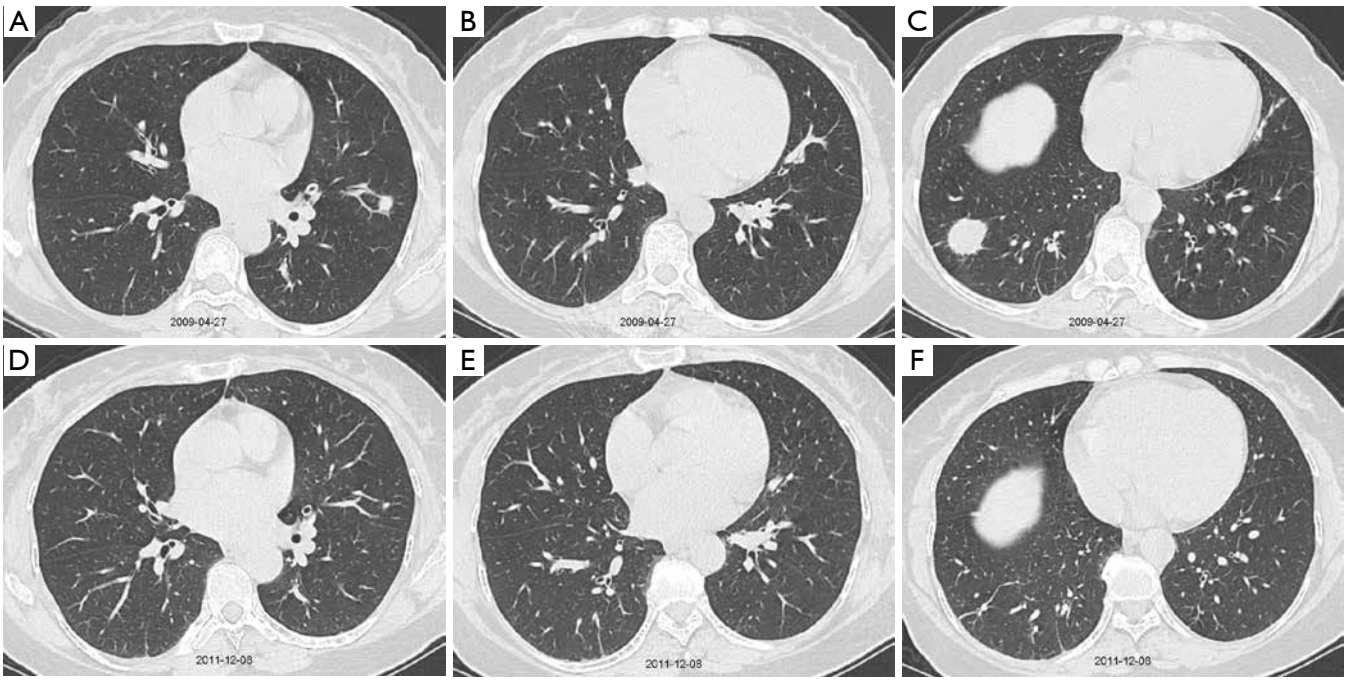

Figure 4 Suspected lung cancer in a 57-year-old female with bilateral multiple lung nodules revealed by CT scanning. Nodules in the lower right lung were diagnosed as OP by CT-guided lung biopsy. The patient voluntarily refused treatment. Follow-up at 32 months revealed that nodules were absorbed, confirming BOOP. Initial chest CT scans showed (A) nodules in the left upper lung with vessel convergence signs; (B) a nodule in the middle lobe of right lung adjacent to the cardiac border; (C) a 2.5 cm nodule in the right lower lung with sentus and strip shadow in the upper lobe of left lung. During follow-up, chest CT scans showed (D) left upper lobe nodule (see in A) was absorbed; (E) the nodule adjacent to the cardiac border (seen in B) was absorbed; and (F) the nodule in the right lower lung and the strip shadow in the left lung were absorbed, with the only remaining strip shadows in the right lower lung. OP, organizing pneumonia.

than cancer (*Figure 4*).

Observations in MD-BOOP group

One patient, a 40-year-old male, was misdiagnosed with BOOP based on symptoms of dry cough and shortness of breath after activity, and radiography of multiple alveolar infiltrates and OP by biopsy. Rapid clinical and imaging improvement at rest was improperly regarded as the effect of corticosteroid treatment at the first 3 months period (*Figure 5*). When migratory lesions appeared, the final confirmed diagnosis of cardiac tumor was established.

Observations in DF-group

Of the 12 cases, no clear clinical manifestations implied BOOP. Radiography revealed suspect masses in five cases, and seven cases exhibited multiple opacities accompanied by cavity-like changes. Pleural effusion was observed in three cases, two cases exhibited moderate pleural effusion. Four cases exhibited enlarged lymph nodes, and four cases were diagnosed with other diseases, including vasculitis, occult nephritis, leukemia, and diabetes. Moreover, one patient exhibited eosinophil levels >30%.

The OP by CT-guided lung biopsy confused the diagnosis. As in the S-BOOP group, further confirmation by biopsy was required for ten cases. A total of 12 DF-group cases were finally diagnosed with pneumonia (four cases), tuberculosis (three cases), and pulmonary fungal infections (two cases), lung cancer (one patient) (*Figure 6*), lung abscess (one patient), and eosinophilic pneumonia (one case). All cases exhibited good recovery with appropriate treatment.

OP by CT-guided lung biopsy versus clinical and radiologic data alone for BOOP diagnosis

Based on clinical and radiologic data alone, BOOP was

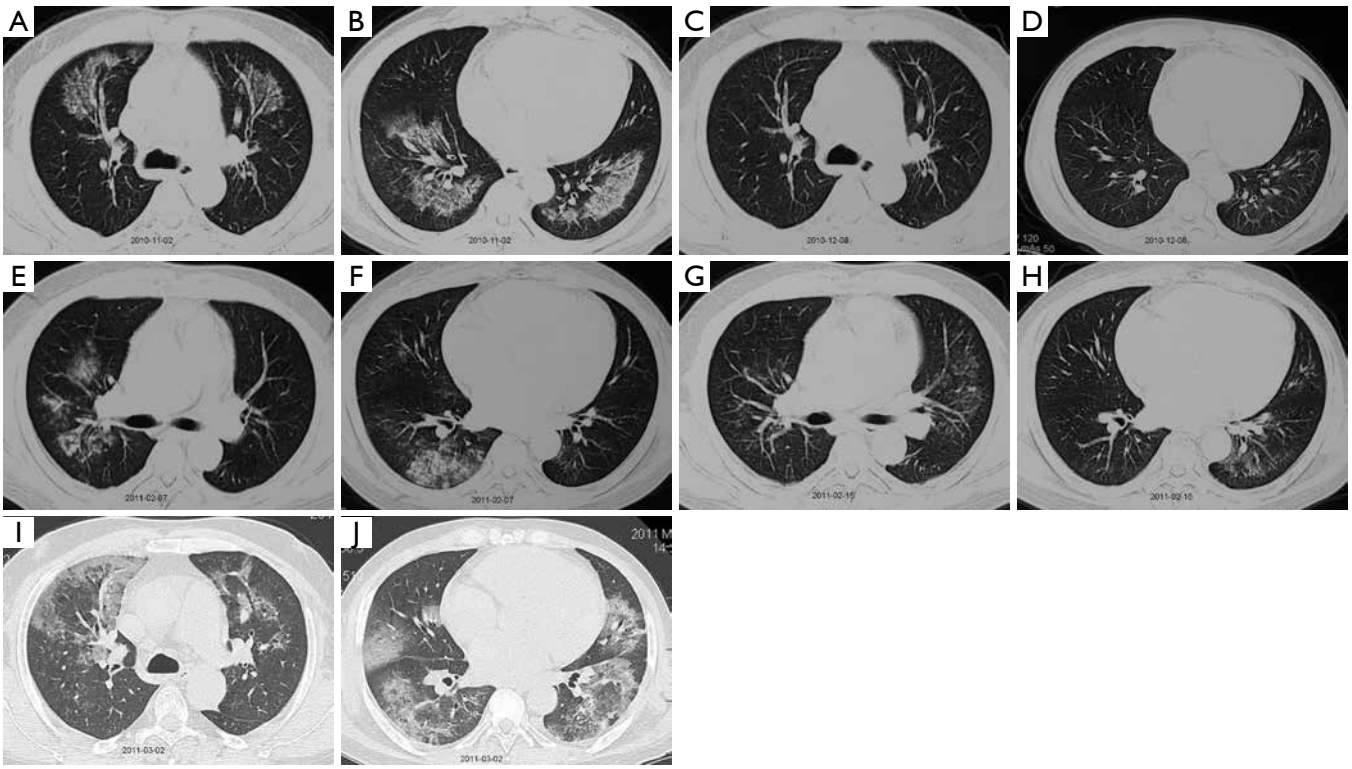

Figure 5 A 40-year-old male with intracardiac tumor was misdiagnosed as BOOP. (A,B) Initially, bilateral multiple alveoli filling was apparent; (C,D) chest CT after one month of glucocorticoid treatment showed complete absorption of alveoli fillings in the (C) bilateral upper lungs (see in A) and (D) in the bilateral lower lungs (seen in B); (E,F) chest CT after three months glucocorticoid treatment showing symptom deterioration with reduced dosage with (E) alveoli fillings around the bronchus in the upper lobe of right lung and unremarkable left lung combined with (F) alveoli fillings in the right lower lung and unremarkable left lung; (G,H) chest CT following increased glucocorticoid treatment 1 week after symptom deterioration onset showing lesion migration with (G) absorption of alveoli fillings in the right upper lung but not in the left upper lung (seen in E) combined with (H) absorption of lesions in the right lower lung but not in the left lower lung (seen in F); (I,J) chest CT scan during a period of symptomatic chest tightness and shortness of breath following activity, (I) revealing blotchy consolidation and ground glass opacities and (J) multiple blotchy consolidation and ground glass opacities in the upper and lower lobes of the left lung and middle and lower lobes of the right lung. BOOP, bronchiolitis obliterans organizing pneumonia.

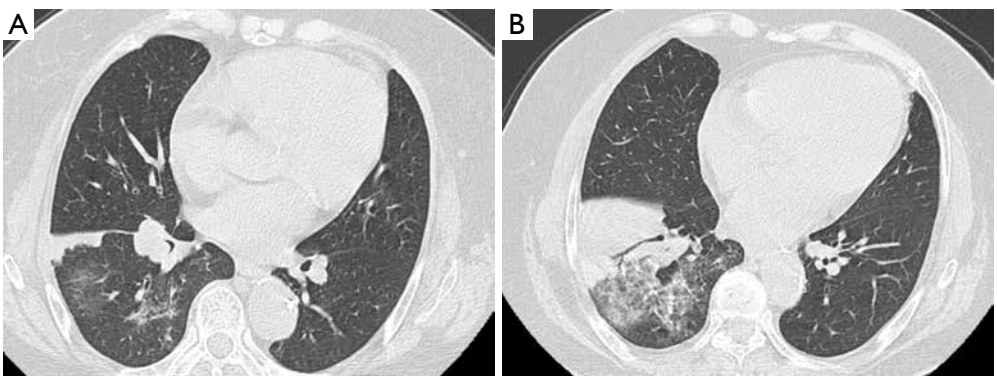

Figure 6 A 75-year-old female using clinical manifestation and radiographic imaging was finally diagnosed lung cancer although OP was given by CT-guided lung biopsy. (A) Soft tissue mass located in the bronchus of the right lower lung, indicating potential lung cancer; (B) consolidation and ground glass opacities apparent in the right lower lung. Air bronchogram signs were also apparent in the consolidation. lung biopsy on this region revealed OP pathologically. OP, organizing pneumonia.

only diagnosed correctly in 30 (31.25%) out of 96 cases (BOOP and MD-BOOP) and was excluded in 12 (11.11%, DF-BOOP) out of 108 cases. Application of the exclusive OP by CT-guided lung biopsy alone, the diagnostic accuracy of BOOP was 87.96% (95/108). As the recommended diagnostic process of 2002 ATS/ERS Consensus Classification of the Idiopathic Interstitial Pneumonias (2), combined clinical, radiographic, and pathological findings- the exclusive OP by CT-guided lung biopsy instead of surgical lung biopsy-produced an amazing diagnostic accuracy of 98.96% (95/96).

Discussion

The current study demonstrated that the exclusive OP finding by CT-guided lung biopsy could be used as a reliably pathological evidence for BOOP diagnosis, especially combined with clinical and radiographic data could further increase the diagnostic accuracy.

The diagnostic process of the interstitial pneumonias is an integrated clinic-radiologic-pathologic approach (2). The clinical manifestations including symptoms and signs and imaging features between BOOP and non-BOOP are not highly differences; however, they are the good preliminary indicators. As in the D-BOOP group and DF-BOOP, the typical imaging features could distinguish BOOP from non-BOOP at initial diagnostic process. Notably, the typical BOOP imaging features and crackle are the confident evidence for pulmonologists, but the diagnostic accuracy in the present study was 31.25% (D-BOOP), more patients were often compounding initial diagnoses and needed further evidence to establish the diagnosis (S-BOOP). Though significantly higher reports have been published, indicating up to 79% diagnostic accuracy (23), these discrepancies may be due to better identification of BOOP in idiopathic interstitial pneumonia using CT imaging features.

Widely accepted surgical lung biopsy is a costly procedure that may unnecessarily increase the risk of serious complications in some cases. Alternatively, Jara-Palomares *et al.* (22) reported that high resolution CT findings and bronchoalveolar lavage could be used in cases with suspicious clinical presentations. However, no extensive clinical trials have assessed these techniques in BOOP cases. OP by CT-guided lung biopsy produced a current diagnostic accuracy for BOOP of 87.96%, much higher than that of TBLB reported to range from 7% to 37% (10). Especially in cases with non-specific clinical and radiological features as in the S-BOOP group, commonly misdiagnosed as lung cancer, risky and unnecessary surgery is often performed (24). The current findings clearly demonstrate that OP by CT-guided lung biopsy can obviate the need for surgery lung biopsy, although some cases still required additional OP using more invasive techniques. Thus, OP by CT-guided lung biopsy is an acceptable result for BOOP diagnosis that may increase the accuracy of BOOP patient diagnosis and facilitate early intervention. In view of CT-guided lung biopsy is much more affordably and safer method than conventional invasive surgical biopsy in the previous reports (2,10-15,17,18) and has been proved the feasibility in early diagnosis of BOOP in some cases reports (19,20), our findings suggested that CT-guided lung biopsy could be as a reasonable alternative to lung biopsy for practically effective early diagnosis of BOOP.

Notably, identification of OP is the predominant diagnostic criteria for BOOP; however, OP changes were not always related to BOOP as previously believed (2,3,5,25) and in current study (11 patients were excluded from the 134 cases due to the OP was not the only finding in the tissue and 12 patients with OP in the DF-BOOP were finally diagnosed the other diseases). Because of the misdiagnosing alternative conditions that may mimic BOOP (3,5), our observations highlight some key concepts regarding integration of radiographic characteristics, symptomatic manifestations, OP by CT-guided lung biopsy, proper treatment, and observation to avoid the misdiagnosis. In current study, one patient in MD-BOOP with carefully follow-up was finally corrected diagnosis as cardiac tumors. The combined diagnostic accuracy of BOOP reaches 98.96% (95/96).

Additionally, not all BOOP cases presenting typical imaging features, such as bronchocentric patterns and reversed halo signs (3,26-28), were considered in the present study due to ineligibility of for CT-guided lung biopsy, potentially limiting the applicability of these results to broader patient populations. Further, limitations of this study are its retrospective nature, but we believe that the largest in literature to date, confirms the OP by CT-guided lung biopsy as a reliable evidence for BOOP.

Conclusions

The current retrospective analysis indicated that the diagnostic accuracy of OP by CT-guided lung biopsy for BOOP was 87.96%, a value slightly lower than previously reported using surgical lung biopsy techniques but

higher than that reported using TBLB. Thus the OP by CT-guided lung biopsy can aid in early detection of BOOP, particularly when combined with clinical and radiological data. In view of CT-guided lung biopsy is affordably and safe method, it can be used to confirm OP pathology reliably and reduce unnecessary surgery.

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Original Article

Elevated pretreatment serum globulin albumin ratio predicts poor prognosis for advanced non-small cell lung cancer patients

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Background: The aim of the present study was to explore the association between the pretreatment globulin albumin ratio (GAR) and the survival of advanced non-small cell lung cancer (NSCLC) patients.

Methods: Patients hospitalized between January 2007 and December 2010 were enrolled and eliminated according to the inclusion and exclusion criteria. GAR was defined as the absolute globulin value divided by the absolute albumin value. Chi-squared test was performed to compare clinical characteristics in different groups. Kaplan-Meier and Cox regression model were used to determine independent prognostic factors. A P value of ≤0.05 was considered to be statistically significant.

Results: Total 316 patients were finally enrolled. The median progression free survival (PFS) and overall survival (OS) were 210.0 and 430.0 days, respectively. The statistical analyses indicated that pretreatment GAR >0.58 [hazard ratio (HR) =1.52, 95% confidence interval (95% CI): 1.12-2.08, P=0.008 for PFS, HR =1.65, 95% CI: 1.20-2.26, P=0.002 for OS], and pretreatment albumin ≤35 g/L (HR =2.09, 95% CI: 1.20-3.65, P=0.003 for PFS, HR =1.92, 95% CI: 1.10-3.36, P=0.022 for OS) were independent prognostic factors for both PFS and OS.

Conclusions: Our study first established a connection between pretreatment GAR and advanced NSCLC patients, suggesting that GAR was an independent prognostic factor and could be the biomarker for prognosis.

Keywords: Globulin albumin ratio (GAR); prognostic factor; non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is still the leading cause of cancer death in the world, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer (1). The majority of NSCLC patients are diagnosed at advanced stage, which is thought to be one important reason for the short survival of lung cancer. To prolong the survival of advanced NSCLC patients, sensitive and specific factors for classifying cancer risk and predicting survival are always desired in clinic to help guiding treatment, and several prognostic factors have been identified in previous studies (2,3). However, some factors have limitations in clinical application because of their tissue-specific expression and high cost of testing, making the efficiency and accuracy of the existing factors need to be improved. There is still need for a promising predictive factor that can be simply detected and closely linked to survival for advanced NSCLC patients.

Serum albumin is generally applied to assess the nutritional status and severity of disease and also used to evaluate the progression and prognosis of some disease, such as operable colorectal cancer, and hepatic disease (4). Previous studies observed that serum albumin is a prognostic factor for various cancers including lung cancer (5-8). Low albumin predicates a poor survival of cancer patients, and high level of albumin is associated with a better survival (8). However, as an index of serum biochemistry, albumin level can be interfered by many factors, which limit its application and credibility in clinic (9).

Another biochemistry index, globulin is demonstrated in research to be interfered by the body status and several disease. One type of globulin, sex hormone-binding globulin (SHBG), is suggested to be associated with the poor survival of hormone related cancer (10-13). Previous studies also demonstrated that hormone was involved in NSCLC. Estrogen receptor β, a hormone receptor, is one of the factors which involved in promoting the development of NSCLC (14,15). Thus it can be seen that globulin may be one prognostic factor for NSCLC patients.

Here we gave a hypothesis that since globulin and albumin are both serum chemistry indexes, taken these two together, globulin albumin ratio (GAR) could reduce the influence to least and may be an effective prognostic factor for advanced NSCLC patients. The aim of the present study was to investigate the association between the pretreatment GAR and the response to treatment, and survival of patients with advanced NSCLC.

Patients and methods

Patients

Patients first hospitalized in the department of respiratory medicine signed a written informed consent which demonstrated that the results of examinations in hospital may be used in respective studies in future. The informed consent and research proposal of this respective study was approved by chairman of the ethics committee of Jinling Hospital (Nanjing, China). Patients hospitalized between January 2007 and December 2010 consecutively enrolled into the present retrospective study. The inclusion criteria are: (I) patients were hospitalized for the primary diagnosis, therapy-naïve; (II) patients were histologically diagnosed primary NSCLC; (III) patients were staged according to the Tumor-Node-Metastasis (TNM) criteria (AJCC criteria 2009) and in stage IIIB and IV, including those in stage IIIA but not able to surgery or not accept the operation; (IV) if took chemotherapy, patients had at least two cycles of first-line platinum-based combination chemotherapy and a response evaluation after treatment; (V) all clinical data was available. Patients were excluded if they had clinical evidence of inflammation in nearly one month, immunity disease, hematology disease or end-stage liver disease.

Clinical and laboratory data collection

Clinical characteristics including gender, age, smoke status, histology, differentiation, TNM stage, metastasis organ, metastasis number, metastasis symptom, and the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) were recorded for all patients. First-line platinum-based chemotherapy was consisted of platinum with third-generation chemotherapy agent and therapy response evaluation by whole body tumor scanning was taken after two cycles of treatment. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was applied for the evaluation of response. The response was assessed by radiologist and treating physician, and reviewed by the investigator Yanwen Yao. The response of treatment was also collected as a clinical characteristic. During the data collection, all the investigators were set blinded to the GAR value of the patients.

Follow-up time was defined as the interval time from diagnosis to 31 May 2012. Progression free survival (PFS) was defined as the time from diagnosis until disease progressed or death of any cause. If the patients were dead during the follow-up time, overall survival (OS) was defined as the interval between the date of diagnosis and the date of death. Otherwise, OS time was defined as the interval time between the date of diagnosis and 31 May 2012.

For all study subjects, the value of albumin and globulin testing 1 day before diagnosis were recorded. GAR was defined as the absolute globulin value divided by the absolute albumin value.

Statistical analysis

Data was summarized with the number of subjects and median value, and the optimal cutoff value of pretreatment GAR was estimated by receiver operating characteristics (ROC) curve, as the value at the largest Youden Index. Chi-squared test and RIDIT analysis were performed to compare baseline clinical characteristics in different groups. Mann-Whitney U test or Kruskal-Wallis H test was used to compare categorical end-points and two-sample *t*-test was used to compare continuous variables after data transformation.

Univariate analysis was performed to determine the significance of variables using logistic regression model for response rate and Cox regression model was performed for PFS and OS. Survival curve was estimated by Kaplan-Meier analysis and the log-rank test was utilized to examine the significance of the differences of survival distributions between groups. Subsequently, the variables with $P \leq 0.05$ enter into multivariate analysis. Cox proportional hazards regression model was used to determine the independent

Table 1 Clinical characteristics of all 316 advanced NSCLC patients

Characteristic	Data
No. of patients	316
Age (mean ± sd, years)	61.8±11.3
Gender (female/male)	99/217
Smoke status (never/ever)	135/181
Histology (non-squamous/squamous)	206/110
Differentiation (well and moderate/poor)	72/244
TNM stage (III/IV)	81/235
Tumor stage (T1/T2/T3/T4)	41/107/33/135
Node stage (N0/N1/N2/N3)	44/30/168/74
Metastasis stage (none/regional/distant)	81/80/155
Metastasis organ (none/bone/brain/ intra-lung/liver/adrenal gland/others)	81/109/58/ 80/13/13/10
Metastasis number (none/single/multiple)	81/187/48
Metastasis symptom (never/ever)	211/105
ECOG PS ≤1/>1	242/74
Chemotherapy (CR + PR + SD/PD)	117/36

TNM stage, Tumor-Node-Metastasis stage; ECOG PS, the Eastern Cooperative Oncology Group Performance Status Scale; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NSCLC, non-small cell lung cancer.

prognostic factor. Generally, a P value of ≤0.05 was considered to be statistically significant for all analyses. All statistical analyses were performed using the Statistical Package for the Social Sciences software program version 18.0 (SPSS Inc., Chicago, IL, USA).

Result

Baseline patient characteristics

According to the inclusion criteria, total 420 NSCLC patients at stage III and IV entered in the present study. Final 316 patients were finally enrolled into the study by further referring to the exclusion criteria, excluding seven patients with clinical evidence of anemia and three patients with hepatic disease before diagnosis, 52 patients who had took single agent chemotherapy or targeted therapy, 42 patients did not take at least two cycles of therapy or have a response evaluation.

Baseline characteristics are presented in *Table 1*. In all patients, the mean age was 61.8 years, 217 were males (68.7%), 135 patients (42.7%) were never smokers and 242 patients had ECOG PS score ≤1. The number of patients in stage III and IV was 81 and 235, respectively. In 235 patients with metastasis, the most common metastatic site was bone [109], followed by intrapulmonary metastasis including pleura [80], brain [58], liver [13], adrenal gland [13] and other sites [10]. Forty two patients had two or more metastatic sites including 19 patients had both bone and brain metastases. A total of 105 patients ever had symptom caused by metastasis, such as pain, dizziness and vomit.

In all study subjects, 153 patients received platinum-based chemotherapy and took a clinical response evaluation. Chemotherapy was chosen according to the tumor histology and patient's intention. Among these patients, 107 had docetaxel and platinum combined therapy, 17 had pemetrexed and platinum combination, and 29 had gemcitabine and platinum combination. One (0.7%) patients got complete response (CR), 37 (24.7%) patients had partial response (PR), 79 (51.6%) patients had stable disease (SD) and 36 (23.5%) patients had progressive disease (PD), as shown in *Table 1*.

A total of 107 (40.2%) patients survived till 31 May 2012. The median PFS of these survived patients was 276.0 days (mean ± sd, 330.76±20.3) and the median OS was 516 days (mean ± sd, 590.7±21.9). The median PFS of all 316 patients was 180 days (mean ± sd, 228.25±11.2) and the median OS was 376.5 days (mean ± sd, 408±14.9).

Separate globulin and albumin analysis

Separate globulin and albumin was respectively analyzed. The cut-off value for globulin and albumin were chosen according to the normal range of these two indexes in serum biochemistry test and were 35 and 27 g/L, respectively.

Patients with pretreatment globulin <27 g/L had a higher prevalence of young patients (age <65 years) (P=0.001), histology of non-squamous (P=0.003), poor differentiation (P=0.021), metastasis stage (P=0.035), while patients with pretreatment albumin >35 g/L had more ever smokers (P=0.014).

GAR analysis

The best cut-off value of GAR was chosen at 0.58 according to the ROC curve (*Figure 1*). The area under curve (AUC) of GAR was 0.600 [95% confidence interval (95% CI): 0.536-0.664, P=0.003]. Patients who had an elevated pretreatment GAR (>0.58) were identified as high GAR

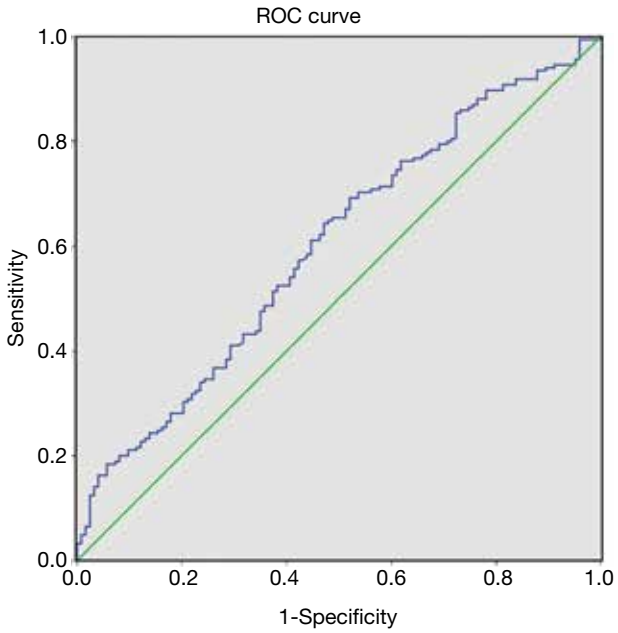

Figure 1 Receiver operating characteristics (ROC) curve of pretreatment globulin albumin ratio.

group and 181 patients (57.3%) were in this group. The left 135 patients (42.7%) were identified as low GAR group.

The distribution of clinical characteristics in GAR subgroup is shown in *Table 2*. Patients with pretreatment GAR >0.58 had a higher prevalence of high age (P=0.004), histology of squamous carcinoma (P=0.000) and poor differentiation (P=0.025). GAR had no significant difference in PS, TNM stage and reaction of chemotherapy.

Median PFS in patients with pretreatment GAR ≤0.58 was 360.0 days (mean ± sd, 569.0±55.6) compared with 180.0 days (mean ± sd, 310.4±28.1) in patients with GAR >0.58 (P=0.001). Median OS in GAR ≤0.58 group and GAR >0.58 group was 619.0 days (mean ± sd, 851.8±68.9) and 343.0 days (mean ± sd, 468.6±31.2), respectively (P=0.000). The Kaplan-Meier curves of PFS and OS stratified by pretreatment GAR are respectively shown in *Figures 2,3*.

Univariate response rate and survival analysis

Poor differentiation [odd ratio (OR) =3.137, 95% CI:

Table 2 Distribution of clinical characteristics stratified by pretreatment GAR

Characteristic	GAR ≤0.58	GAR >0.58	P value
Patients	135	181	
Age (years)			
Mean ± sd (range)	60.2±10.7	63.0±11.6	
<65/≥65	90/45	91/90	0.004
Gender (female/male)	44/91	55/126	0.676
Smoke status (never/ever)	66/69	69/112	0.056
Histology (non-squamous/squamous)	103/32	103/78	0.000
Differentiation (well and moderate/poor)	39/96	33/148	0.025
TNM stage (III/IV)	36/99	45/136	0.716
Tumor stage (T1/T2/T3/T4)	22/46/9/58	19/61/24/77	0.156
Node stage (N0/N1/N2/N3)	23/13/70/29	21/17/98/45	0.552
Metastasis stage [none (M0)/regional (M1a)/distant (M1b)]	36/36/63	45/44/92	0.763
Metastasis organ (none/bone/brain/intra-lung/others)	36/48/23/26/15	45/61/35/54/21	0.359
Metastasis number (none/single/multiple)	36/84/15	45/103/33	0.218
Metastasis symptom (never/ever)	94/41	117/64	0.352
ECOG PS (≤1/>1)	108/27	134/47	0.215
Chemotherapy	77	76	
CR + PR + SD/PD	58/19	59/17	0.737

TNM stage, Tumor-Node-Metastasis stage; ECOG PS, the Eastern Cooperative Oncology Group Performance Status Scale; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; GAR, globulin albumin ratio.

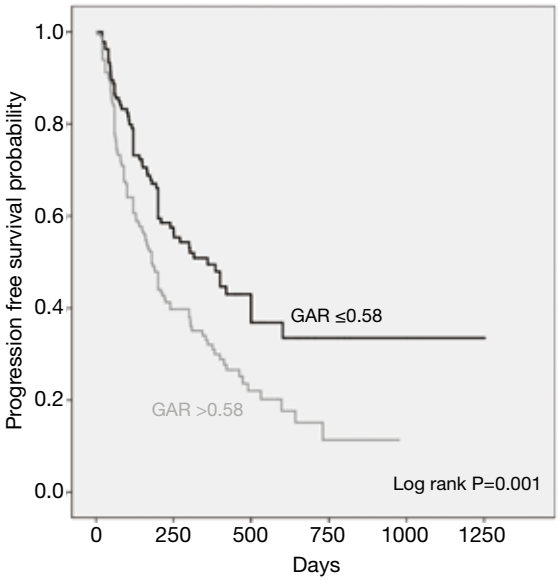

Figure 2 Kaplan-Meier curves showing progression free survival (PFS), stratified by the pretreatment globulin albumin ratio.

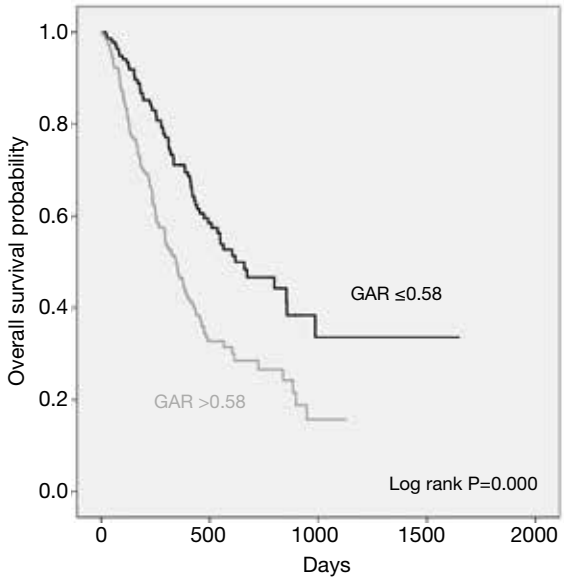

Figure 3 Kaplan-Meier curves showing overall survival (OS), stratified by the pretreatment globulin albumin ratio.

1.029-9.565, P=0.044] and multiple metastasis sites (OR =5.278, 95% CI: 1.586-17.564, P=0.007) were associated with poor response to first-line platinum-based combination chemotherapy (PD versus CR, PR, SD) at first evaluation. As shown in *Table 3*.

Result of univariate survival analysis demonstrated that GAR was a prognostic predictor. A high pretreatment GAR >0.58 was associated with worse PFS [hazard ratio (HR) =1.664, 95% CI: 1.233-2.247, P=0.001]. Other PFS prognostic variables were male (HR =1.408, P=0.039), TNM stage IV (HR =1.718, P=0.003), distant metastasis stage M1b (HR =2.061, P=0.000), single metastasis site (HR =1.557, P=0.017), multiple metastasis sites (HR =2.648, P=0.000), ECOG PS >1 (HR =1.657, P=0.001), and low albumin ≤35 g/L (HR =2.458, P=0.001), shown in *Table 3*.

Pretreatment GAR >0.58 (HR =1.959, P=0.000), age <65 years (HR =1.553, P=0.003), male (HR =1.566, P=0.007), ever smokers (HR =1.603, P=0.002), TNM stage IV (HR =1.630, P=0.007), single metastasis site (HR =1.502, P=0.028), multiple metastasis sites (HR =2.283, P=0.000), ECOG PS >1 (HR =1.654, P=0.001), albumin ≤35 g/L (HR =2.750, P=0.000) and globulin >27 g/L (HR =1.471, P=0.009) was associated with OS (*Table 3*).

Multivariate response rate and survival analysis

The significant factors in univariate survival analysis were enrolled into a multivariate Cox proportional regression for the test of independent factors. The statistical analysis data indicated that pretreatment GAR >0.58 (HR =1.524, P=0.008), pretreatment albumin ≤35 g/L (HR =2.093, P=0.003), ECOG PS >1 (HR =1.607, P=0.003), TNM stage IV (HR =3.235, P=0.000), distant metastasis (HR =1.600, P=0.018), and male (HR =1.439, P=0.032) were independent prognostic factors for PFS. Pretreatment GAR >0.58 (HR =1.651, P=0.002) was also associated with OS independently.

Other independent factors were pretreatment albumin ≤35 g/L (HR =1.922, P=0.022), ECOG PS >1 (HR =1.614, P=0.003), TNM stage IV (HR =3.371, P=0.000), distant metastasis (HR =1.515, P=0.031), age ≥65 years (HR =1.555, P=0.005) and ever smokers (HR =1.651, P=0.002) (*Table 4*).

Sensitivity and specificity analysis

According to ROC curve shown in *Figure 4*, AUCs of GAR and albumin were 0.600 (95% CI: 0.536-0.664, P=0.003) and 0.397 (95% CI: 0.333-0.460, P=0.002), respectively. The sensitivity and specificity of GAR at 0.58 were 62.2% and 53.7%, while those of albumin at 35 were 89.7% and 4.1%.

Discussion

In our study, pretreatment GAR was demonstrated to be

Table 3 Univariate analysis of clinicopathological factors, serum biochemical index and response rate, PFS and OS in 316 patients

Parameter	Response rate			PFS			OS		
	OR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age									
<65	1			1			1		
≥65	0.649	0.285-1.476	0.302	1.263	0.948-1.681	0.110	1.553	1.165-2.070	0.003
Gender									
Female	1			1			1		
Male	1.119	0.498-2.513	0.786	1.408	1.018-1.947	0.039	1.566	1.131-2.169	0.007
Smoke status									
Never	1			1			1		
Ever	0.924	0.434-1.967	0.838	1.317	0.979-1.770	0.069	1.603	1.189-2.161	0.002
Histology									
Non-squa	1			1			1		
Squamous	0.547	0.219-1.366	0.197	1.135	0.846-1.524	0.398	1.313	0.978-1.763	0.070
Differentiation									
Non-poor	1			1			1		
Poor	3.137	1.029-9.565	0.044	1.296	0.908-1.850	0.153	1.232	0.863-1.759	0.251
TNM stage									
III	1			1			1		
IV	2.296	0.879-5.997	0.090	1.718	1.207-2.446	0.003	1.630	1.145-2.321	0.007
Tumor stage									
T1	1			1			1		
T2	1.000	0.269-3.724	1.000	0.902	0.547-1.489	0.688	1.057	0.641-1.743	0.828
T3	4.000	0.733-21.838	0.109	2.128	1.202-3.767	0.010	2.957	1.666-5.248	0.000
T4	1.792	0.543-5.919	0.338	1.313	0.813-2.121	0.265	1.351	0.836-2.181	0.219
Node stage									
N0	1			1			1		
N1	2.000	0.334-11.969	0.448	1.953	1.072-3.557	0.029	2.143	1.174-3.909	0.013
N2	1.406	0.366-5.399	0.619	1.495	0.924-2.417	0.101	1.626	1.005-2.631	0.048
N3	3.111	0.781-12.384	0.108	1.890	1.116-3.200	0.018	1.764	1.042-2.986	0.035
Metastasis stage									
M0	1			1			1		
M1a	1.705	0.514-5.656	0.384	1.198	0.773-1.858	0.419	1.195	0.770-1.855	0.426
M1b	2.580	0.955-6.969	0.061	2.061	1.428-2.976	0.000	1.887	1.308-2.721	0.001
Metastasis number									
None	1			1			1		
Single	1.770	0.651-4.810	0.263	1.557	1.082-2.240	0.017	1.502	1.044-2.161	0.028
Multiple	5.278	1.586-17.564	0.007	2.648	1.669-4.201	0.000	2.283	1.443-3.612	0.000
Metastasis symptom									
Never	1			1			1		
Ever	0.692	0.243-1.975	0.492	1.157	0.783-1.711	0.464	1.209	0.817-1.787	0.342
ECOG PS									
≤1	1			1			1		
>1	1.160	0.468-2.876	0.748	1.657	1.216-2.257	0.001	1.654	1.213-2.256	0.001

Table 3 (*continued*)

Table 3 (*continued*)

Parameter	Response rate			PFS			OS		
	OR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Albumin									
>35	1			1			1		
≤35	0.141	0.012-1.604	0.114	2.458	1.442-4.192	0.001	2.750	1.614-4.684	0.000
Globulin									
≤27	1			1			1		
>27	0.650	0.279-1.517	0.319	1.266	0.948-1.691	0.109	1.471	1.101-1.965	0.009
GAR									
≤0.58	1			1			1		
>0.58	0.814	0.382-1.735	0.594	1.664	1.233-2.247	0.001	1.959	1.449-2.649	0.000

OR, odd ratio; HR, hazard ratio; CI, confidence interval; TNM stage, Tumor-Node-Metastasis stage; ECOG PS, the Eastern Cooperative Oncology Group Performance Status Scale; GAR, globulin albumin ratio; PFS, progression-free survival; OS, overall survival.

Table 4 Result of multivariate analysis regarding PFS and OS in 316 advanced NSCLC patients

Variable	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
GAR						
≤0.58	1			1		
>0.58	1.52	1.12-2.08	0.008	1.65	1.20-2.26	0.002
Albumin						
>35	1			1		
≤35	2.09	1.20-3.65	0.003	1.92	1.10-3.36	0.022
ECOG PS						
≤1	1			1		
>1	1.61	1.18-2.19	0.003	1.61	1.18-2. 20	0.003
Metastasis stage						
M0	1			1		
M1b	1.60	1.06-2.42	0.018	1.51	1.04-2.21	0.031
TNM stage						
III	1			1		
IV	3.23	1.99-5.24	0.000	3.37	2.05-5.55	0.000
Gender						
Female	1			–		
Male	1.44	1.03-2.01	0.032	–	–	–
Age						
<65	–			1		
≥65	–	–	–	1.55	1.14-2.12	0.005
Smoke status						
Never	–			1		
Ever	–	–	–	1.65	1.20-2.26	0.002

HR, hazard ratio; CI, confidence interval; ECOG PS, the Eastern Cooperative Oncology Group Performance Status Scale; GAR, globulin albumin ratio; PFS, progression free survival; OS, overall survival; NSCLC, non-small cell lung cancer; TNM stage, Tumor-Node-Metastasis stage.

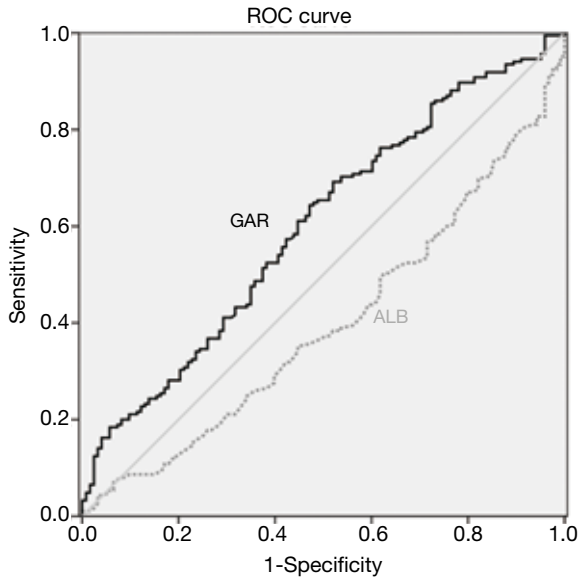

Figure 4 Comparison of receiver operating characteristics (ROC) curve of pretreatment globulin albumin ratio and albumin level.

associated with PFS and OS for advanced NSCLC patients for the first time. Patients with pretreatment GAR >0.58 had worse PFS and OS. In multivariate survival analysis, after adjusting to age, gender, smoke status, TNM stage and ECOG PS, GAR remained to be an independent factor associated with PFS and OS. Besides GAR, albumin was also proven to be an independent prognostic factor for worse survival in the present study.

Albumin, which is produced by liver, helps to maintain intravascular oncotic pressure and acts as a free radical scavenger (8). The association between albumin and cancer was reported in a large investigation that serum albumin and body mass index were significantly lower in cancer than in non-cancer subjects (16). And in patients with advanced or terminal cancer, it was found that low baseline serum albumin level (<3.7 g/dL) predicted shorter survival (17). Previous studies successively proved that low albumin level was associated with malignant disease and was related to poor prognosis in many cancers, such as breast cancer, ovarian cancer, bladder cancer and lung cancer (7,9,18-21). Our observation also observed an independent association between low pretreatment serum albumin level and poor survival in advanced NSCLC patients.

The role of serum albumin in predicting prognosis may be due to the metabolic which is a reflection of both malignancy of cancer and status of body (9). However, albumin may also be related to metabolic changes caused by many factors, such as stress, illness, hepatic insufficiency, and depletion of visceral protein mass or synthesizing ability (22,23). The volatility of albumin limits the application in clinic.

To avoiding the limitation of albumin, our present study gives a hypothesis that taking albumin and globulin together, the GAR would be a predicting factor associated with prognosis of NSCLC. The result of our study supported this hypothesis and GAR was proved to be a strong factor than albumin in predicting survival for advanced NSCLC patients. The reason for this may be that globulin was not only another protein produced by liver, but also associated with cancer survival. Several studies suggested that globulin especially SHBG was a biomarker for cancer risk in breast cancer and prostate cancer patients (10,11,13,24). Löfgren *et al*. suggested that SHBG was associated with estrogen receptor which was also related to initiation and development of NSCLC (25-27).

Our present study was a single-institution retrospective study with limited number of included patients. However, this study focused on the advanced NSCLC patients, and more than 300 patients were finally enrolled in this study. Compared with other existing factors, GAR also has some advantages: it can be simply obtained rather than other invasive operation, low costing and efficiency. The association between GAR and worse prognosis of NSCLC patients is confirmed in our study, proving the accuracy of GAR as a biomarker in clinic.

Taken together, our study first established a connection between pretreatment GAR and advanced NSCLC patients, suggesting that GAR was an independent prognostic factor and could be the biomarker for prognosis. The clinical utility of GAR still needs to be confirmed with prospective analysis.

Conclusions

In summary, the results provide novel evidence that pretreatment serum GAR serves a useful prognostic predictor for advanced NSCLC patients. Accordingly, GAR could be used in clinic to better define the baseline risk in cancer patients.

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Original Article

Effects of different LAD-blocked sites on the development of acute myocardial infarction and malignant arrhythmia in a swine model

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Objective: To explore the effects of various left anterior descending (LAD) artery-blocked sites on the development of acute myocardial infarction (AMI) and malignant arrhythmia in a swine model.

Methods: Twenty-two pigs underwent occlusion of the coronary artery with balloon angioplasty were randomly divided into three groups according to the blocked site of the balloon: middle-site-blocked LAD group, bottom-third-blocked LAD group and control group. Then, the development of AMI and malignant arrhythmia, including ventricular tachycardia and ventricular fibrillation during the process of model creation, were recorded. Changes of the hemodynamics, blood gas analysis, electrocardiography, and myocardial enzymes were analyzed in each group before and after occlusion.

Results: Middle-site-LAD blockage resulted in a larger infarction size and the corresponding incidence of ventricular fibrillation was significantly higher than that of the bottom-third-blocked group ($P<0.05$). After the occlusion, the QTc interval of the Middle-site-blocked LAD group was significantly longer than that in the other groups ($P<0.01$). Moreover, mean arterial blood pressure (MAP), left ventricular ejection fraction (LVEF), and partial pressure of oxygen (PaO_2) were significantly lower, but partial pressure of carbon dioxide ($PaCO_2$) increased, in the Middle-site-blocked-LAD group compared with that in the bottom-third-blocked group ($P<0.01$). Compared with the control group, the two LAD-blocked groups showed significantly higher levels of Mb, CK-MB, LDH, AST and cTnT ($P<0.01$) four hours after the artery occlusion. However, these indexes were not significantly different between the two LAD-blocked groups ($P>0.05$).

Conclusions: Location of LAD blockages in swine models may affect the development of AMI and malignant arrhythmia.

Keywords: Acute myocardial infarction (AMI); malignant arrhythmia; left anterior descending (LAD); swine

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Introduction

Acute myocardial infarction (AMI) is a common cardiovascular disease characterized by rapid and sudden morbidity and high mortality (1). The occlusion positions of the coronary artery are closely correlated with the prognosis, among which the left anterior descending (LAD) is the most commonly blocked (2). LAD block can result in infarctions of the left anterior ventricular wall, cardiac apex and lateral wall. The prognosis varies because of different infarction areas in distinct LAD occlusion locations (3). AMI is often accompanied by malignant arrhythmia, such

as ventricular tachycardia (VT) and ventricular fibrillation (VF), which account for 60-100% of deaths during the acute phase of AMI (4,5). Identification of the culprit vessel and blockage sites of AMI with malignant arrhythmia is one of the most heated research subjects.

Animal models provide opportunities for clinically study the pathophysiology and pathogenesis of AMI. The swine's heart anatomy and coronary artery are close to those in humans (6,7), and great similarity exists between the swine AMI model established by blocking the coronary artery branch and AMI in humans (8). This present study employed the swine AMI model established by blocking the LAD through balloon angioplasty to explore the influence exerted by different LAD occlusion sites on the morbidity of AMI and malignant arrhythmia.

Materials and methods

Tested animals

Twenty-two male swine, weighing 26.32±2.15 kg and 3-4 months of age, were purchased from Jiangsu Academy of Agricultural Sciences and successfully passed inspection and quarantine.

Materials

Experimental equipment included an ECG monitor (V24E, Philips), a Labsystem electrical physiology recorder (Bard, USA), a VIVID 7 heart color ultrasonic diagnostic apparatus (GE, USA), a digital cardiovascular imaging system (Siemens, Germany), a cardiac reader analyzer (Roche, Switzerland), an i-STAT blood gas analyzer (Abbott, USA), a Vitros 5.1 FS automatic biochemical analyzer (Johnson & Johnson, USA), a Judkins Right 4.0 catheter, a guide wire for occlusion of the coronary artery with balloon angioplasty (Cordis, USA), a second catheter, a second guide wire for the punctuation of femoral artery, an artery sheath and a pressure pump (Medtronic).

Acute myocardial infarction model establishment

Twelve hours after a preoperative preparation, animals received oxygen inhalation (3 L/min), an intramuscular injection of ketamine (20-25 mg/kg) and atropine (0.5 mg) to induce anesthesia as described by our group previously (9,10). Swine were fixed in a supine position on the workstation, and access to the marginal ear vein was established. Pentobarbital sodium (3% solution; 60 mg/kg) was intravenously injected into the swine to induce a deep anesthetic state. During the operation, ketamine (100 mg) was injected intravenously every 20-30 min according to body motion to maintain anesthesia. After injection with 2% lidocaine for local anesthesia of the right groin of the swine, the right femoral artery was punctured to create AMI (11). Continuous ECG monitoring and vital sign changes were monitored during the procedure.

The animals were randomly divided into three groups according to the blocked sites of the balloon: group 1, control group (n=4), with catheter balloon inserted into the LAD, but without LAD occlusion; group 2, the bottom-third-blocked LAD group (n=9); and group 3, middle-site-blocked-LAD group (n=9). The femoral artery was punctured and a sheath was implanted with a guide wire inside. Diluted heparin (6,000 u) was injected intravenously and an additional 2,000 u was given every 1 h during the operation. The imaging tube was sent retrograde through the sheath to the coronary opening for angiography. The position for blocking was determined according to the imaging results for the bottom-third-blocked and middle-site-blocked-LAD groups. The balloon catheter (2.5-3.5 mm × 15 mm) with the guide wire was inserted through the sheath. The balloon was opened with six atmospheres to block the LAD for 90 minutes (12-14). Then the blood perfusion was restored. Continuous 12-lead ECG monitoring was applied during the whole procedure. If premature ventricular contractions (PVCs) were observed, the lidocaine and amiodarone dosage was increased. If VT was shown, intravenous lidocaine and amiodarone were given immediately. If VF appeared, an immediate 360 J external defibrillation and external chest compression was given until the restoration of sinus rhythm (15). Before and after the model creation, indexes including hemodynamics, ECG, myocardial enzymology and artery blood gas were collected to confirm the establishment of the model. The establishment of the model was assessed by ST elevation and the occurrence of pathologic Q wave, and confirmed by the pathological analyses of the hearts after the animals were sacrificed.

Arrhythmia monitoring and evaluation of AMI and ventricular fibrillation-cardiac arrest

Intra-operative continuous ECG monitoring was performed and the occurrence of ventricular arrhythmia was recorded. According to the international standard of arrhythmia (16), more than three continuous PVCs was defined as VT, less

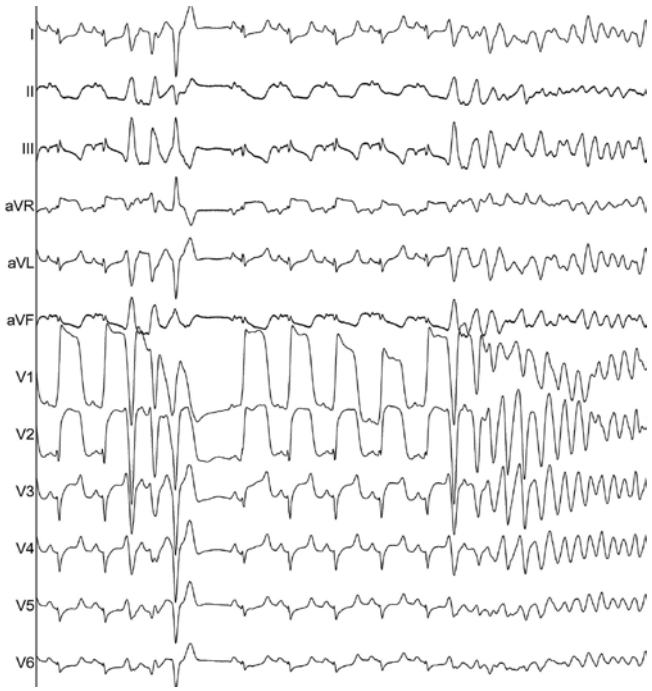

Figure 1 ECG showed that ST segment was elevated and VT and VF occurred following 30 min of LAD occlusion. VT, ventricular tachycardia; VF, ventricular fibrillation; LAD, left anterior descending.

than 30 seconds VT was defined as non-sustained VT, and more than 30 seconds was defined as persistent VT; the disappearance of the equipotential line was defined as VF, which would lead to cardiac arrest if not treated promptly. Continuous VT and VF were defined as malignant arrhythmia.

Mean arterial blood pressure (MAP), left ventricular ejection fraction (LVEF), partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in arteries were recorded before establishment of the model and 2 h after model establishment. Myoglobin (Mb), CK-MB, LDH, AST and cTnT were also collected 4 h after model establishment. Also, the QT and QTc intervals in each animal were measured and compared among three groups.

Statistical analyses

Statistical tests were performed in SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean ± SD and compared using an unpaired Student's *t*-test or ANOVA test. Kruskal-Wallis H tests and Mann-Whitney U tests were used when the data did not met the normal distribution criteria or homogeneity of variance. Qualitative variables were compared using the χ^2-test, unless otherwise indicated. A two-tailed P value of less than 0.05 was considered statistically significant.

Results

Model establishment of AMI and malignant arrhythmia

During the occlusion, the incidence of PVCs (88.89% *vs.* 100%, P=0.999) and VT (44.44% *vs.* 88.89%, P=0.134) were not significantly different between the bottom-third-blocked LAD group and the middle-site-blocked group, whereas the incidence of VF (33.33% and 100%, respectively, P=0.012) was significantly higher in the middle-site-blocked group. During the procedure, ECG showed that the ST segment was elevated and VT and VF occurred after LAD occlusion (*Figure 1*).

QTc interval comparisons

Compared with the Control group, QTc intervals in the Bottom-third-blocked LAD group and the middle-site-blocked group were significantly longer and the difference was statistically meaningful (bottom-third-blocked LAD group *vs.* control group, 425.56±21.96 *vs.* 357.00±14.49, P<0.01; middle-site-blocked group *vs.* control group, 462.67±27.55 *vs.* 357.00±14.49, P<0.01); QT intervals were statistically different between the middle-site-blocked group and the control group (362.00±29.18 *vs.* 319.75±17.63, P<0.05). The QTc interval was significantly increased in the middle-site-blocked LAD group when compared with that of the bottom-third-blocked LAD group (462.67±27.55 *vs.* 425.56±21.96, P<0.01), while QT intervals were not statistically different between these two groups (P>0.05) (*Table 1*).

Comparison of hemodynamic and artery blood gas indexes before and after model establishment

Hemodynamic and artery blood gas indexes recorded after the model establishment suggested that MAP, LVEF and PaO_2 indexes in the Bottom-third-blocked group and in the middle-site-blocked group were significantly lower than that before the model establishment, while $PaCO_2$ was significantly higher. The differences in MAP, LVEF, PaO_2 and $PaCO_2$ indexes among the three groups before the model establishment were not statistically significant (P>0.05). However, after the occlusion, MAP in the middle-

Table 1 Comparison of QT and QTc intervals among three groups

ECG indexes	Control group	Bottom-third-blocked LAD group	Middle-site-blocked LAD group
QT interval (ms)	319.75±17.63	336.78±20.65	362.00±29.18*
QTc interval (ms)	357.00±14.49	425.56±21.96$^{\Delta}$	462.67±27.55$^{\Delta,\star}$

LAD, left anterior descending; compared with the control group, *, P<0.05, $^{\Delta}$, P<0.01; compared with the Bottom-third-blocked LAD group, *, P<0.01.

Table 2 Comparison of hemodynamic and artery blood gas indices among three groups

Indexes	Control group	Bottom-third-blocked LAD group	Middle-site-blocked LAD group
MAP (mmHg)			
Pre-establishment	78.50±7.59	78.44±7.73	77.56±7.89
Post-establishment	77.49±7.33	69.67±8.22*	57.89±7.10$^{\Delta,\star}$
LVEF (%)			
Pre-establishment	63.50±6.25	62.89±5.16	64.11±7.42
Post-establishment	62.67±5.96	45.00±6.08$^{\Delta}$	41.56±4.75$^{\Delta}$
PaO_2 (mmHg)			
Pre-establishment	198.50±18.91	195.22±18.04	205.00±30.78
Post-establishment	196.33±17.89	84.22±13.94$^{\Delta}$	78.22±25.77$^{\Delta}$
$PaCO_2$ (mmHg)			
Pre-establishment	39.50±2.65	38.78±2.82	39.22±3.90
Post-establishment	39.09±2.52	46.89±4.20$^{\Delta}$	48.33±2.87$^{\Delta}$

MAP, mean arterial blood pressure; LVEF, left ventricular ejection fraction; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; compared with that before model establishment, *, P<0.05, $^{\Delta}$, P<0.01; compared with the Bottom-third-blocked LAD group, *, P<0.01.

Table 3 Comparison of myocardial enzymology among three groups

Myocardial enzyme	Control group	Bottom-third blocked LAD group	Middle site-blocked LAD group
Mb (μg/L)	42.00±15.43	647.33±334.19$^{\Delta}$	864.22±487.77$^{\Delta}$
CK-MB (U/L)	19.75±6.65	6,242.22±2,701.60$^{\Delta}$	7,796.00±3,558.92$^{\Delta}$
LDH (U/L)	195.00±77.09	1,443.89±471.24$^{\Delta}$	1,707.11±646.35$^{\Delta}$
AST (U/L)	39.25±18.41	325.67±156.95$^{\Delta}$	433.89±243.31$^{\Delta}$
cTnT (ng/mL)	<0.01	0.47±0.37$^{\Delta}$	0.76±0.64$^{\Delta}$

Mb, myoglobin; compared with the control group, $^{\Delta}$, P<0.01.

site-blocked group was significantly lower than that in the Bottom-third-blocked group (P<0.01), while LVEF, PaO_2 and $PaCO_2$ were not statistically different between the two groups (P>0.05) (*Table 2*).

Myocardial enzymology

Myocardial enzymology indexes recorded 4 h after the model establishment indicated that Mb, CK-MB, LDH, AST and cTnT in both the Bottom-third-blocked LAD group and the middle-site-blocked group were statistically higher than that in Control group (P<0.01) (*Table 3*). These indexes were not significantly different between the bottom-third-blocked LAD group and the middle-site-blocked group (P>0.05), which suggested that the difference in occlusion sections of LAD would not influence myocardial

enzymology after AMI.

Discussion

Malignant arrhythmias are the main causes of sudden cardiac death following AMI. To predict the severity and the prognosis of an AMI, changes in hemodynamics, ECG and myocardial enzymology indexes are usually observed in the clinic (17).

The structure, size and coronary circulation of the swine heart are similar to that of humans. It is very similar to pathological changes of AMI in humans to block the swine coronary artery branches to induce myocardial infarction, and this has significant implications for research on the pathological physiology and the treatment of AMI. Since there are few branches of the swine coronary artery, it is hard to establish collateral circulation. A swine's cardiac conduction system also has a poor tolerance to ischemia and hypoxia. Therefore, large infarction area and various malignant arrhythmias can occur easily when the main coronary arteries, especially LAD, are occluded (18). The occlusion of LAD not only leads to massive myocardial ischemia and necrosis, but also influences the cardiac conduction system. Cardiac cell membrane potential decreases and creates the conduction abnormality such as VT and VF, which have lead to extremely high mortality rates (19,20). The main reasons for VF include formation of the turn-back ring following acute myocardial ischemia and an increase in automaticity as the base of ventricular arrhythmia, and the low threshold of the ventricular fibrillation in swine, which is easily induced by ischemia and reperfusion (21).

In the present study, an AMI model was created by occluding the bottom-third-site or the middle-site of LAD through balloon angioplasty, suggesting that VT incidence was not statistically different between the two infarction groups. However, the incidence of VF in the middle-site-blocked group was significantly higher than that of the bottom-third-blocked group. This offers a good reference for further studies on prediction indexes of malignant arrhythmia after AMI occurrence.

A previous study showed that QT interval and QTc interval prolongation after AMI can lead to a longer period of phase ventricular vulnerability, followed by an increased susceptibility to rapid ventricular arrhythmia, as well as VT and VF (22). The present study showed that, compared with the control group, QTc interval was significantly prolonged in the Bottom-third-blocked LAD group and the middle-site-blocked group. QT interval extension in the middle-site-blocked LAD group was significantly different compared with that in the control group. QTc interval in the middle-site-blocked LAD group was significantly longer than that in bottom-third-blocked LAD group. Therefore, QTc interval was more sensitive than QT interval after AMI which could result a significantly longer QTc interval. The longer of QTc interval, the more likely to induce malignant arrhythmia (23,24). For those who have a marked extension of QTc interval, more attention should be paid to the possible occurrence of VT and VF. Prolonged QTc interval might be perceived as an independent prediction factor to assess the AMI prognosis.

The location of AMI is correlated with blood supply area of coronary artery branches. A large area infarction caused by LAD occlusion is usually accompanied by shock, left ventricular dysfunction, severe hemodynamic disorder and ventricular arrhythmia. This would lead to an increase in left ventricular end diastolic pressure and pulmonary venous pressure, and to pulmonary interstitial and alveolar edema, decrease in lung compliance and in alveolar ventilation volume, resulting in disorders of ventilation and blood flow, abnormality of diffusion function, the decrease of PaO_2 and in the increase of $PaCO_2$ (25). This study indicated that serious hemodynamic disorder existed in both groups after the AMI model establishment with significant MAP and LVEF decrease. MAP in the middle-site-blocked LAD group was significantly lower than that in bottom-third-blocked-LAD group. In addition, compared with that before model establishment, PaO_2 decreased significantly while $PaCO_2$ had a marked increase. Consequently, hemodynamic and blood gas analyses may, to some extent, reflect the AMI severity and its prognosis.

AMI affects the heart by exerting direct damage on the myocardial cells, which can be assessed by the serum myocardial enzymes test. In this study, compared with control group, Mb, CK-MB, LDH, AST and cTnT were significantly higher in the Bottom-third-blocked LAD group and the middle-site-blocked group while these indexes were not statistically different between the two AMI groups. This suggested severe myocardial damage brought by AMI whereas the difference in occlusion positions had no significant influence on the change of myocardial enzymology indexes. Necrosis of cardiac cells induced by AMI can lead to the aggregate release of myocardial enzymes, which are later flushed from the infarcted myocardium into blood because of the flushing effect of the opened epicardial vessel, resulting in an early rapid rise

in enzyme concentration (26). Myocardial enzyme index was recorded 4 h after AMI. The myocardial enzyme level of this study may not the maximal, and also the rise of myocardial enzyme level might not reflect the infarction area.

Conclusions

In conclusion, LAD occlusion positions affected the occurrence of malignant arrhythmia in an AMI model established by blocking swine LAD through balloon angioplasty. The changes of hemodynamic, ECG, myocardial enzymology and artery blood gas indexes may help us to predict the severity and prognosis of AMI. Since the present study is based on animal experiments, it may not fully reflect the pathophysiological characteristics of clinical patients. Large-scale and multi-center studies of clinical application are needed to confirm the results and to provide more valuable evaluating indicators for risk stratifications of early AMI patients.

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Original Article

Adiponectin protects rat heart from left ventricular remodeling induced by chronic intermittent hypoxia via inhibition of TGF-β/smad2/3 pathway

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Objective: Obstructive sleep apnea syndrome (OSAS) is associated with many cardiovascular disorders. Chronic intermittent hypoxia (CIH) is the primary player in OSAS of the many associated factors. This study was in order to investigate the effects of the Adiponectin (Ad) on left ventricular remodeling induced by CIH.

Methods: Forty-five rats were randomly divided into three groups: normal control (NC) group, CIH group and CIH plus Ad supplemented (CIH + Ad) group. After 35 days' CIH exposure, masson analysis was used to detect the left ventricular fibrosis and western blot was used to measure the protein expression of collagen I, collagen III and TGF-β/smad2/3 pathway. Gene analysis by RT-PCR was used to study the MMP2 and TIMP2.

Results: After CIH exposure, the fibrosis of left ventricular in CIH group was significantly remarkable than that in both NC and CIH + Ad groups ($P<0.05$), although statistical difference existed between NC and CIH + Ad groups ($P<0.05$). In addition, the protein expression of collagen I as well as collagen III and the ratio of mRNA levels of MMP2/TIMP2 were the highest in CIH group but the lowest in NC group, with CIH + Ad group in between. There was a significant difference among three groups (all $P<0.05$). The TGF-β/smad2/3 pathway was activated obviously in CIH group, but less noticeably in CIH + Ad group ($P<0.05$) with a significant difference in the two groups.

Conclusions: The present study showed that Ad could ameliorate the left ventricular remodeling induced by CIH via inhibition of the expression of TGF-β/smad2/3 pathway.

Keywords: Chronic intermittent hypoxia (CIH); left ventricular remodeling; adiponectin

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Introduction

Obstructive sleep apnea syndrome (OSAS), as a common health disorder, is characterized by repeatedly upper airway collapse, resulting in chronic intermittent hypoxia (CIH) within the body. It has been detected OSAS is associated with cardiac dysfunction, which can be improved by positive airway pressure ventilation (CPAP) treatment (1-3). However, the correlation mechanisms between OSAS and associated cardiac damage are still under investigation and more effective treatments are desired for clinical practice since CPAP are not well tolerated by all OSAS patients. Chika Matsumoto *et al.* reported that intermittent hypoxia

could induce left ventricular remodeling (4). Other report showed that oxidative stress, TGF-β and inflammatory cytokines might play important roles in left ventricular remodeling (5). Seong-Man Kim *et al.* reported that the severity of OSA was correlated with left artricular structural and functional remodeling (6).

Adiponectin (Ad) as a protein derived by the adipose tissue, is abundantly presents in plasma and displayed in three major forms in plasma: trimer, hexamer, and a high-molecular-weight form (7,8). Globular adiponectin (gAd), a proteolytic cleavage product of Ad, also exists in plasma (9). It is reported that Ad has the cardioprotective effect (10) and gAd is significantly more potent in reversing insulin resistance than uncleaved Ad (11). Koichi Fujita *et al.* reported that Ad protected cardiac from fibrosis induced by Ang II through Activation of PPAR-α (12). However, it remains to be elucidated about the relationship between CIH and left ventricular remodeling as well as the possible intervention role of Ad *in vivo*. In current study, the CIH model was established to investigate the possible association among them.

Materials and methods

Procedures of this study were approved by the Animal Ethic Committee of Nanjing Medical University.

Animals

Forty-five male Wistar rats (specific pathogen free) 8 weeks of age were purchased from Shanghai Silake Ltd. Inc. The rats were housed in Animal Care Center under the 12:12 hour light-dark cycle and allowed free access to standard chow and tap water, which were randomly divided into three groups with 15 in each group: normal control (NC) group, CIH group, CIH plus Ad supplement (CIH + Ad) group. The method of CIH has been reported previously (13,14). The rats were housed in a cage placed in the chamber of the OxyCycler Oxygen Profile Controller (BioSpherix). The inspired oxygen fraction was changed from ~21% to ~5-6% every 2 min with sustained for 15~20 s. The intermittent hypoxia events persisted 35 days. Rats in NC group were treated with ambient 21% O_2 in a separate chamber. Rats in CIH + Ad group were also received the injection of Ad with intravenous at the dosage of 10 μg per time, twice a week for 5 weeks. A similar injection of saline (0.5 mL per time) was carried out in NC group and CIH group. Data were collected at the end of 5th week (day 35).

Tissue processing

After 35 days of experiment, the rats were anesthetized using pentobarbital. The chest was opened for collecting the heart tissue. The heart tissue was quickly isolated and part was stored at –70 ℃ while part was infused into 4% paraformaldehyde.

Masson analysis

Masson analysis was used to detect the cardiac fibrosis, according to the instruction of manufacturer. After deparaffinization and rehydration, the section incubated in R1 for 1 min, then immersed in R2 for 30 s. The sections were treated with R3 for 8 min. Then R4 was used to incubate the slides for 5 min. The section was analyzed by microscope. To evaluate the fibrosis index of heart tissues, ten random heart fields per tissue section were captured at the 400× magnification.

Quantitative real-time RT-PCR analysis

Total RNA (1 μg) extracted from left ventricular by using the TRIzol reagent (Invitrogen, USA) was reverse transcribed to complementary DNA using Transcriptor First Strand cDNA Synthesis Kit (Roche, Germany). Real-time QPCR was performed by using Power SYBR Green QPCR Master Mix (Applied Biosystems, Foster City, California, USA). The primer for rat MMP2 (Invitrogen, USA): forward (5'-AGGGCACCTCTTACAACAGC-3'); reverse (5'-CCCGGTCATAATCCTCGG TG-3'). The primer for rat TIMP2 (Invitrogen, USA): forward (5'-CAACCCCATCAAGAGGATTC-3'); reverse (5'-CGCAAGAACCATCACTTCTC-3'). The primer for rat β-actin (Invitrogen, USA): forward (5'-CAGGGTGTGA TGGTGGGTATGG-3'); reverse (5'-AGTTGGTGACAATGCCGTGTTC-3'). The cycling parameters were set as follows: 95 ℃, 10 minutes and 40 cycles of 95 ℃ for 15 seconds and 60 ℃ for 1 minute. A single product obtained was proved by the dissociation curves. The PCR fluorescent signals of all genes were standardized to the β-actin. Comparative and relative quantifications of these gene products normalized to β-actin and the control group were calculated by the $2^{-\Delta\Delta Ct}$ method.

Western blot analysis

Left ventricular was homogenized using Tissue Protein

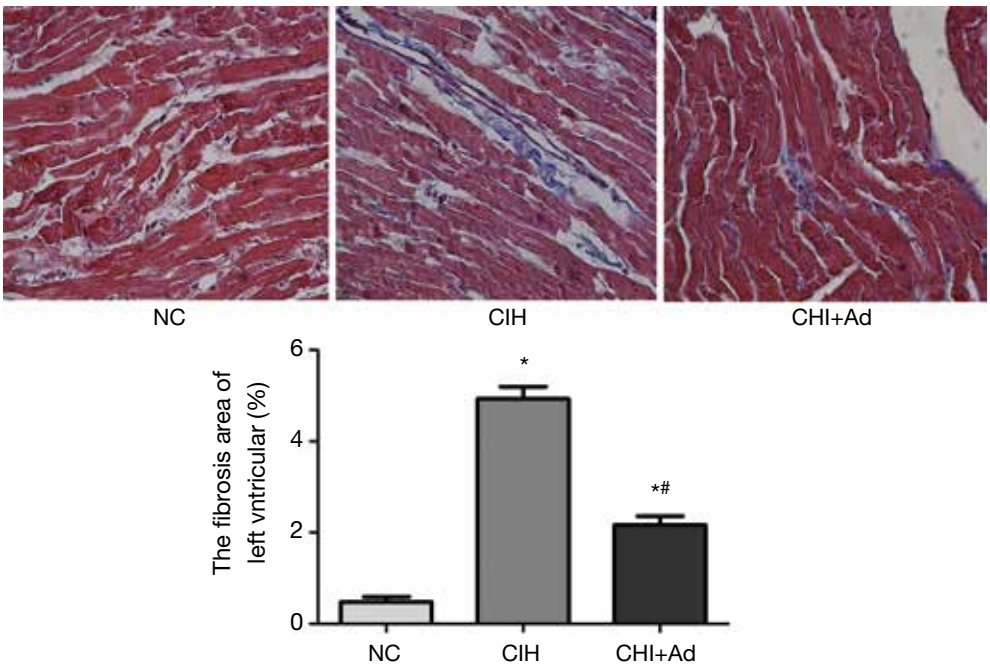

Figure 1 The Masson analysis of the left ventricular. The blue represented the fibrosis and the red represented the normal myocardium. *P<0.01 versus NC group; #P<0.05 versus CIH; NC, normal control; CIH, chronic intermittent hypoxia; CIH + Ad, chronic intermittent hypoxia and adiponectin supplement.

Extraction Reagent (Thermo scientific, USA) containing 1 mM of PMSF and phosphatase inhibitor cocktail (Roche, Germany). Then the homogenates were centrifuged at 10,000 ×g for 5 minutes and the supernatants were collected. The protein assay kit (Thermo Scientific, Rockford, USA) was used to detect the protein concentration (bicinchoninic acid method). Total left ventricular lysates were used to quantify proteins of TGF-β (Abcam Ltd, USA), smad2/3 (Cell Signaling Technology, USA), collagen I (Abcam Ltd, USA) and collagen III (Abcam Ltd, USA) by western blot. Equal protein amounts (30 μg) of left ventricular lysates were subjected to electrophoresis on 10% sodium dodecyl sulfate PAGE, which transferred to polyvinylidene fluoride membranes (Roche, USA). The 5% bovine serum albumin in TBS with 0.1% Tween-20 at pH 7.6 was used to blot the membranes for 1 h at room temperature, then the membranes were incubated with primary antibodies diluted in 5% bovine serum albumin in TBS with 0.1% Tween-20 at pH 7.6 at 4 ℃ for one night with gentle shaking, followed by incubation with a peroxidase-labeled secondary antibody diluted in 5% bovine serum albumin in TBS with 0.1% Tween-20 at pH 7.6 for 1 h at 37 ℃. The membranes were detected by using enhanced ECL kit (Thermo Scientific, USA) and exposed using the digital imaging system (Molecular Imager® ChemiDocTM XRS + System), which offered sensitive chemiluminescent detection (Bio-Rad Laboratories Inc, Hercules, CA, USA). The intensity of band was normalized to β-actin analyzed using Image Lab 2.0 Software (Bio-Rad Laboratories Inc, USA).

Statistical analysis

Values are presented as means ± SD in three independent experiments. Significant differences between all groups were computed by one-way analysis of variance (ANOVA) using the Student-Newman-Keuls post hoc test for multiple group comparisons. Statistical difference was accepted at P<0.05.

Result

The cardiac fibrosis after CIH

After 35 days' exposure of CIH, Masson analysis showed the area of cardiac fibrosis of the left ventricular in the CIH group were significantly higher than that in NC and CIH + Ad groups (P<0.05), although there was difference still statistical difference between NC and CIH + Ad groups (P<0.05) (*Figure 1*). The expression of collagen I and

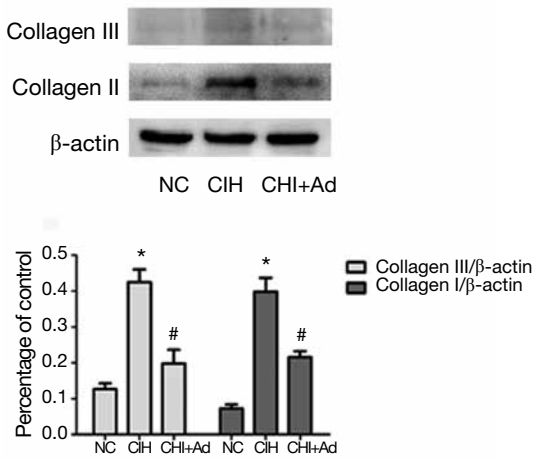

Figure 2 The protein levels of collagen I and collagen III. The protein levels of collagen I and collagen III. Western blot bands of collagen I and collagen III were normalized to β-actin. *P<0.05 versus NC group; #P<0.05 versus CIH group. NC, normal control; CIH, chronic intermittent hypoxia.

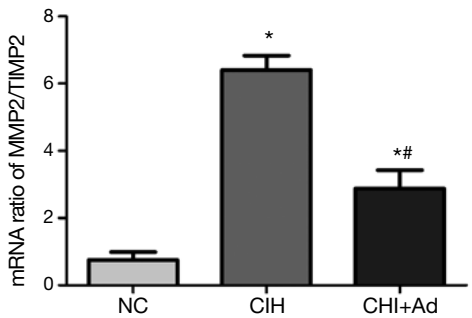

Figure 3 The ratio of mRNA levels of MMP2 and TIMP2. The mRNA expressions of MMP2/TIMP2 in heart of three groups; PCR fluorescent signals for MMP2, TIMP2 were standardized to PCR fluorescent signals obtained from an endogenous reference (β-actin). *P<0.01 versus NC group; #P<0.05 versus CIH. NC, normal control; CIH, chronic intermittent hypoxia.

collagen III measured with western blot was the highest in the CIH group but the lowest in the NC group, with the CIH + Ad group in between. There was a significant difference among all the three groups (all P<0.05) (*Figure 2*).

Expression of molecules related to CIH-induced cardiac fibrosis

Apart from the finding of the cardiac fibrosis from the myocardium of left ventricle after CIH exposure, a

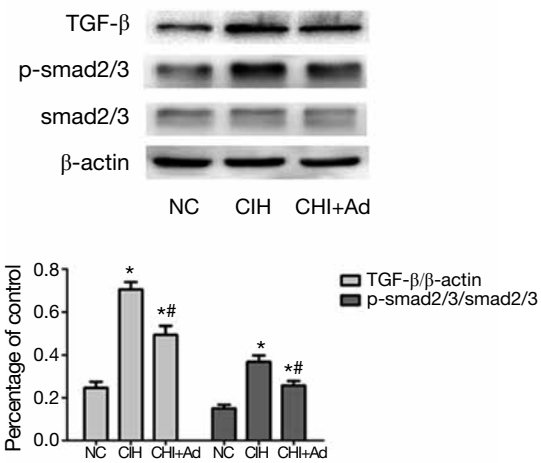

Figure 4 The protein levels of TGF-β/smad2/3 pathway. The protein levels of TGF-β and smad2/3. Western blot bands of TGF-β and smad2/3 were normalized to β-actin. *P<0.05 versus NC group; #P<0.05 versus CIH group. NC, normal control; CIH, chronic intermittent hypoxia.

significantly higher ratio of mRNA levels of MMP2/TIMP2 was also detected in CIH group than those in NC group (P<0.05), although there was still a markedly difference between the NC and CIH + Ad groups (P<0.05) (*Figure 3*).

Since the TGF-β/smad2/3 pathway which is associated with the fibrosis, our further investigate into this pathway revealed that the expression of TGF-β and phosphorylation smad2/3 detected by western blot were significantly enhanced in the CIH group, compared with both NC group and CIH + Ad groups (P<0.05), even though there was a statistical difference between the NC and CIH + Ad groups (P<0.05) (*Figure 4*).

Discussion

In order to study the effects of Ad on left ventricular remodeling induced by CIH, we established an animal model to mimic CIH. In this study, we found that after 35 days CIH exposure, the CIH could induce the left ventricular remodeling represented by the area of fibrosis and the protein expression of collagen I and collagen III. With Ad supplement, the left ventricular remodeling was ameliorated and the possible mechanism was the inhibition of TGF-β/smad2/3 pathway.

It is well known that OSAS is one of the important risks for several cardiovascular diseases (15). It has been reported that CIH could induce the left ventricular remodeling in

mice (4) or rat (14,16,17). Our findings were consisted with them. In the present study, the enhanced fibrosis of left ventricular was also founded in CIH group. Our previous study demonstrated that CIH could induce oxidative stress and myocardium apoptosis (13) and it has been reported that oxidative stress is important for left ventricular remodeling (18). So we speculate that CIH induced the left ventricular remodeling through oxidative stress. However, when Ad was supplemented, we found, the index of the fibrosis was ameliorated. Our findings were consisted with many studies (19). It is well reported that Ad has the effect of cardiac protection (10,20,21). And Koichi Fujita *et al.* found Ad could protect against cardiac fibrosis induced by angiotensin II (12). Shimano, M's study showed that Ad-KO mice exhibited greater left ventricular (LV) interstitial fibrosis after the TAC surgery compared with the WT mice (22). So we suggested that Ad could ameliorate the cardiac fibrosis.

MMPs, a family of the proteolytic enzymes for extracellular matrix protein (ECM) degradation, are key players in cardiac matric remolding (23). TIMPs, the tissue inhibitors of metalloproteinases, synthesized proteins which bind to the active MMPs to regulate net proteolytic activity (24). MMPs and TIMPs regulate the matrix degradation which determines the cardiac fibrosis (25). MMP2 is a crucial protein in the process of tissue fibrosis and TIMP2 is the main inhibitory factor of MMP2 in tissue (26). The increased MMP activity and the imbalance between MMP2 and TIMP2 have been implicated in pathological processes (23). Recent study showed that MMP2 activity was responsible for the development of left ventricular hypertrophy in a two kidney, one clip hypertensive rat model (27). In accordance with these reports, we found the elevated ratio of mRNAs levels of the MMP2/TIMP2 were induced by CIH, which represents the imbalance between MMPs and TIMPs. And when the Ad was added, the change of MMP2/TIMP2 was partially improved. This suggested that Ad may protect the myocardium against the fibrosis through regulating the balance between MMPs and TIMPs.

In the present study, we found Ad could improve the left ventricular remodeling induced by CIH and the imbalance between MMPs and TIMPs. TGF-β, as a pleiotropic cytokine, is involved in lots of biological processes such as cell growth and differentiation, embryonic development, fibrosis, cell proliferation and survival and regulation of the inflammatory response (28). The TGF-β signals via the receptors of trans-membrane to activate Smad2/3 phosphorylation, and then the pSmad2/3 complex translocates into the nucleus and induces the pro-fibrotic target genes expression (28-30). It has been reported that the TGF-β signal was an important role in cardiac remodeling (28) and the overexpression of TGF-β could enhance the extracellular matrix protein synthesis (31,32). And in the hypertensive rats induced by one kidney clip, the increased expression of TGF-β, along with temporal changes of MMP2 activity, was associated with simultaneous cardiac remodeling (33). According to these studies, in the present study, we found that the TGF-β pathway was activated by CIH and the supplement of Ad reduced the overexpressions of the TGF-β and Smad2/3.

In conclusion, our results suggested that Ad could protect the myocardium from left ventricular modeling induced by CIH through inhibition of TGF-β/smad2/3 pathway. However, further investigation is still needed to further explore the detailed cardioprotective mechanisms of Ad during CIH.

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Disclosure: The authors declare no conflict of interest.

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Original Article

FDG PET-CT combined with TBNA for the diagnosis of atypical relapsing polychondritis: report of 2 cases and a literature review

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Objective: To explore the value of ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) combined with transbronchial needle aspiration (TBNA) in diagnosing atypical relapsing polychondritis (RP).

Methods: Data from two patients with atypical RP, which had been diagnosed in our hospital using FDG PET-CT combined with TBNA, were retrospectively analyzed. A review of the relevant literature was also performed.

Results: Consistent with the previously reported 20 cases of RP that had been diagnosed using FDG PET-CT, the two patients in the present study showed the involvement of multiple organs, including the nose, throat, trachea, bronchi, costicartilage and joint cartilages, and increased FDG uptake was found in these areas. The mean value of SUVmax was 5.14. PET-CT revealed that 86.4% of the patients with RP had airway involvement. TBNA technique was used for biopsy of the hypermetabolic lesions, and pathologic examinations confirmed the diagnosis of RP. The time to diagnosis in these two patients and the 20 cases reported previously was about 6.9 months, significantly shorter than the average diagnosis time (20 months).

Conclusions: FDG PET-CT has several advantages for diagnosing RP, especially atypical RP. TBNA is a minimally invasive and safe technique for obtaining airway cartilage. Combining PET-CT with TBNA may play an important role in shortening the time to diagnosis in patients with RP involvement of airway.

Keywords: Relapsing polychondritis (RP); positron emission tomography-computed tomography (PET-CT); transbronchial needle aspiration (TBNA); cartilage; fluorodeoxyglucose (FDG); standard uptake value (SUV)

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Introduction

Relapsing polychondritis (RP) is a disease of unknown etiology characterized by recurrent non-infectious inflammation of cartilaginous and connective tissues. Previous studies have shown that autoimmunity may play a role in the pathogenesis of this disease (1,2). Clinical presentations of RP vary considerably from patient to patient, and the involvement of multiple organs has been reported. However, there is currently no specific diagnostic method available; as a result, the rates of misdiagnosis and missed-diagnosis are very high, particularly with regard to the early diagnosis of atypical RP.

To date, very few studies have reported the use of ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) combined with transbronchial needle aspiration (TBNA) for the diagnosis of RP. Here, we have analyzed the clinical features of two cases of atypical RP that had been diagnosed in our hospital using FDG PET-CT combined with TBNA, and performed a literature review to evaluate the value of this approach in diagnosing RP and in shorting the time to diagnosis in patients with RP.

Methods

Data from two patients with atypical RP, which had been diagnosed in our hospital using FDG PET-CT combined with TBNA, were retrospectively analyzed. Articles published up to June 2014 were searched for in several databases, including the Cochrane Library, PubMed and EMBASE, using "RP" and "PET-CT" as keywords. Duplicated articles were excluded. Information concerning the patient's age, sex, clinical symptoms, PET-CT features [abnormal uptake sites and the maximum standard uptake value (SUV_{max})], and biopsy sites was extracted and analyzed.

Results

Case 1

A 42-year-old male patient was admitted to our hospital in 2012 with symptoms of cough and intermittent fever for more than 2 months. The patient had not been diagnosed with any previous disorders, and reported no alcohol consumption or tobacco smoking. The patient had been experiencing cough, expectoration and fever during the preceding 2 months, without obvious predisposing causes. The highest temperature of the patient had been recorded as 39.0 ℃. No other symptoms, including chest congestion and shortness of breath, were reported. After a trial of anti-inflammatory medication had resulted in no improvement, the patient had been admitted to our hospital for further diagnosis and treatment. On admission, the temperature of the patient was 36.7 ℃, the heart rate 82 beats/minute, respiration 16 times/minute, and blood pressure 115/85 mmHg. No enlargement of the superficial lymph nodes was detected, and breath sounds were clear in the bilateral lungs. CT scanning of the chest was performed, and no abnormalities were found. Routine blood tests revealed a white blood cell count of 5.44×10^9/L, a neutrophil count of 3.33×10^9/L, a hemoglobin level of 99 g/L, and a platelet count of 305×10^9/L. Examination of a panel of tumor biomarkers showed that the levels of neuron-specific enolase, tumor specific growth factor (TSGF) and ferritin were 21.8 ng/mL, 72.4 U/mL and 811.6 ng/mL, respectively. Examination of a panel of lupus, blood transfusion and antineutrophil cytoplasmic antibodies identified no abnormalities. Blood culture, mycobacterium tuberculosis-specific gamma interferon release assays (T-spot), and ultrasound examination of the heart were also performed, and no abnormalities were detected. Increases in erythrocyte sedimentation rate (ESR, 124 mm/h) and C-reactive protein level (CRP, 14.89 mg/L) were found, while assessment of pulmonary function suggested an obstructive disturbance of ventilatory function. A bone marrow biopsy was performed, but the bone marrow smear and culture showed no abnormalities. As the underlying disease could not be diagnosed, FDG PET-CT scanning was performed. There were no abnormalities in the density and distribution of the radioactivity in the bilateral lungs, and no enlargement of the mediastinal and hilar lymph nodes. In addition, no lesions showing abnormal FDG uptake were found in the neck or the organs of the abdominal and pelvic cavities. In contrast, a symmetric increase in uptake was found in the costicartilage, trachea and bilateral bronchial walls, while no enhancement of uptake was identified in the skeletal system of other sites (*Figure 1A*), suggesting the possibility of chondritis. Therefore, tracheoscopic examination was performed; these revealed mucosal hypertrophy and slight bronchial stenosis, particularly stenosis of the bronchus in the right upper lobe (*Figure 1B*). The TBNA technique was used to obtain cartilage biopsies, and these showed infiltration of neutrophils, lymphocytes and plasma cells around hyaline cartilage (*Figure 1C*). These findings helped us to diagnose RP in this patient. Careful re-taking of the medical history revealed that the hearing of the patient had deteriorated during the past 6 months; a hearing test was then performed, and this showed moderate neural hearing loss in both ears. No symptoms or signs of chondritis were evident in the ears and nose, and pain was not elicited by pressure on the costicartilage. Intravenous injections of methylprednisolone (40 mg, qd) were given for 7 days; at the end of this treatment, the temperature of the patient had returned to a normal level, only an occasional cough remained. Intravenous methylprednisolone was then replaced by oral prednisone (10 mg, tid); no fever was identified, and the patient was discharged showing substantial improvement. Follow-up assessments were performed 6 weeks after discharge: no symptoms or discomfort were reported, and tracheoscopic examination showed substantial improvement of the mucosal congestion and edema, with no tracheal stenosis (*Figure 1D*). In addition, endobronchial ultrasound examination demonstrated normal cartilaginous rings and no thickening of the bronchial wall (*Figure 1E*).

Case 2

A 51-year-old male patient was admitted to our hospital in 2013, with symptoms of a relapsing cough, expectoration

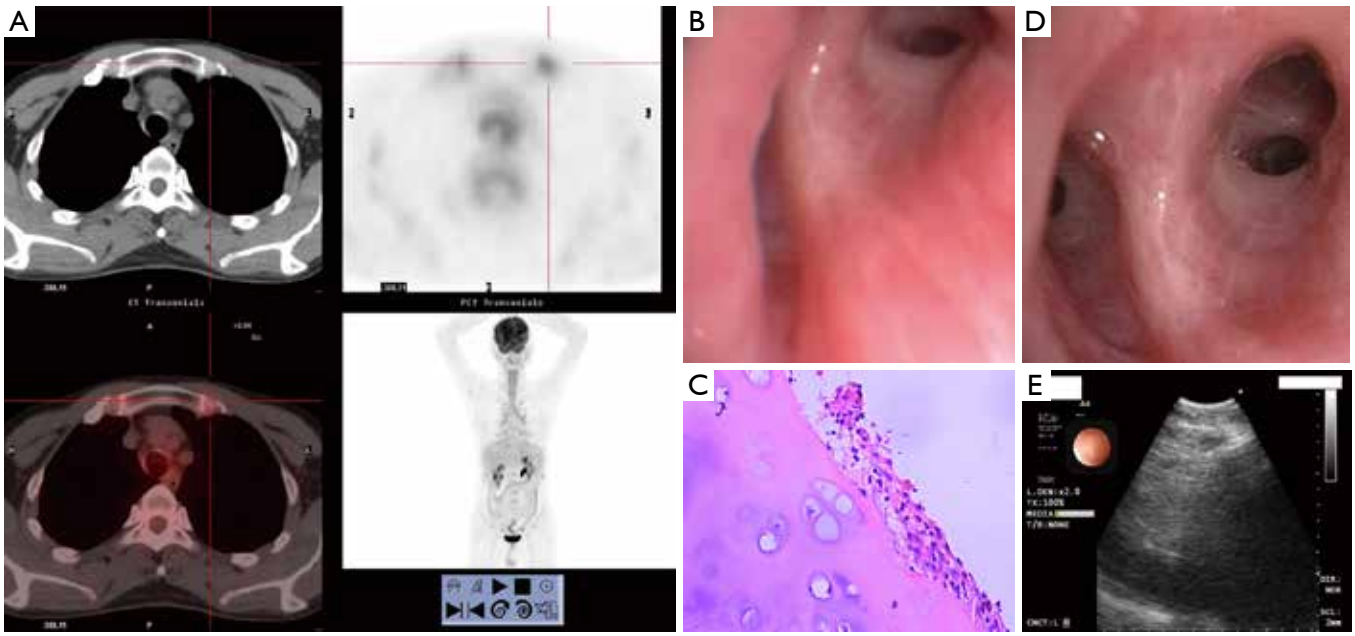

Figure 1 (A) FDG PET-CT images showing symmetric increases in FDG uptake in the bilateral costicartilage and the walls of the trachea and bronchi; (B) before treatment, there was congestion and edema of the walls of the bronchus in the right upper lobe, as well as slight stenosis of the bronchus; (C) TBNA biopsy showed an infiltration of neutrophils, lymphocytes and plasma cells around the hyaline cartilage (HE staining, ×200); (D) after treatment, tracheoscopic examination showed no congestion or edema of the walls of the bronchus in the right upper lobe, and the diameter of the bronchus was normal; (E) after treatment endobronchial ultrasound examination showed no thickening of the walls of the trachea and no cartilage ring abnormalities. FDG PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; TBNA, transbronchial needle aspiration.

and fever for more than 1 month. Prior to admission, the patient had not been diagnosed with any previous disorders, and no predisposing causes for the symptoms had been identified. The patient had a 20-year history of smoking approximately 1 pack per day. The highest temperature of the patient had been recorded as 38.5 ℃. No other symptoms, including chest tightness and shortness of breath, were present. The patient had been admitted to our hospital after the failure of anti-infectious treatments administered in a local hospital. On admission, the temperature of the patient was 37.0 ℃, the heart rate 84 beats/minute, respiration 18 times/minute, and blood pressure 110/74 mmHg. There was no enlargement of the superficial lymph nodes, and the breath sounds were clear in the bilateral lungs. CT scanning of the chest demonstrated increased lung markings and enlarged mediastinal lymph nodes. The white blood cell count was 10.64×10^9/L, the neutrophil count 6.36×10^9/L, the hemoglobin level 129 g/L, and the platelet count 419×10^9/L. Abdominal ultrasound examination suggested the presence of a hepatic cyst and gallbladder polyps. Ultrasound examination of the heart found no abnormalities. Other investigations were also performed to evaluate the levels of rheumatoid factor, serum procalcitonin, anti-tuberculosis antibody and 24-hour urinary calcium, but the results were negative. Examinations of panels of blood transfusion, thyroid function, lupus, and antineutrophil cytoplasmic antibodies showed no abnormalities. Blood culture and T-spot also showed no abnormalities. The ESR (57 mm/h) and CRP (15.06 mg/L) of the patient were increased. Examination of the levels of a panel of tumor biomarkers demonstrated that the ferritin level was 697.8 ng/mL. FDG PET-CT scanning was performed to further clarify the diagnosis. No lesions showing abnormal uptake were found in the neck, and the density and distribution of the radioactivity in the bilateral lungs was not abnormal. Although the mediastinal lymph nodes were enlarged, no abnormal uptake of radioactivity was found. In addition, no lesions showing abnormal uptake were found in the organs of the abdominal and pelvic cavities. Increased uptake was found in costicartilage near the xiphisternum, the trachea, and the walls of the bilateral main bronchi. No enhancement of uptake was evident in the

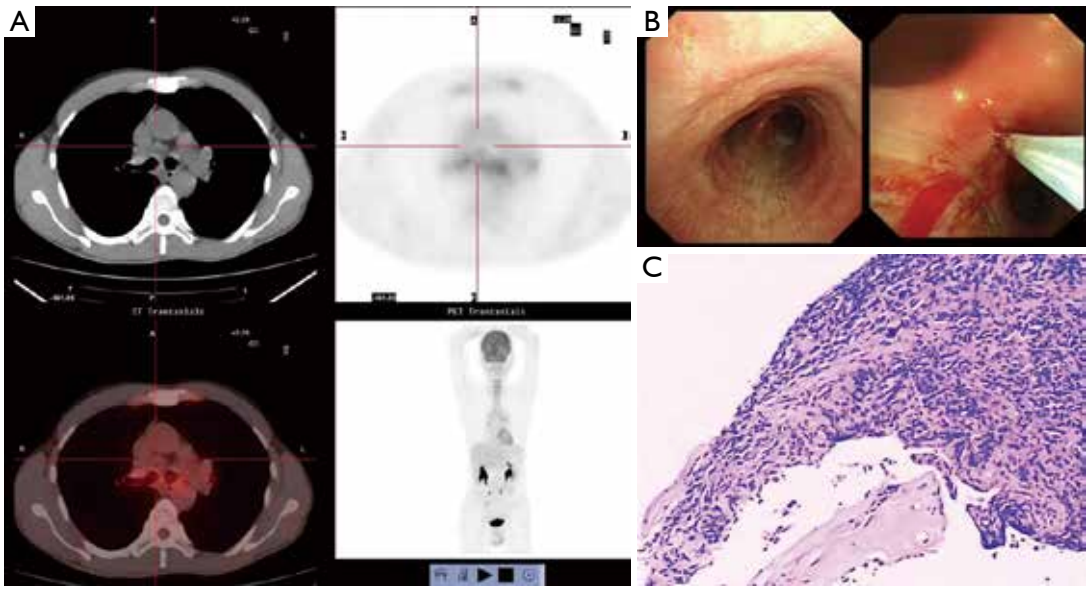

Figure 2 (A) FDG PET-CT images showing a symmetric increase in FDG uptake in the walls of the trachea and bilateral main bronchi, as well as in the costicartilage near the xiphisternum. An enlarged mediastinal lymph node was also shown; however, it did not exhibit an increase in FDG uptake; (B) tracheoscopic examination showed congestion and edema of the tracheal walls but no abnormality of the cartilage ring; airway collapse was not evident, while the carina was widened. TBNA was then used for biopsy of the S8 lymph nodes; (C) pathologic examination of the TBNA biopsy revealed a small amount of hyaline cartilage with infiltration of a large number of neutrophils, lymphocytes and plasma cells. No tumor cells were found (HE staining, ×200). FDG PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; TBNA, transbronchial needle aspiration.

skeletal system of other sites. These findings suggested the possibility of chondritis (*Figure 2A*). As the symptoms of the patient were atypical, and enlargement of the mediastinal lymph nodes was found, bronchoscopic biopsy was performed to exclude malignancy: there were no obvious abnormalities in the cartilaginous rings, whereas congestion and edema of the tracheal mucosa was found, as well as slight bronchial stenosis. The TBNA technique was used to biopsy the S8 lymph nodes (3) (*Figure 2B*): inflammatory cell infiltration was evident around the cartilage, but tumor cells or granulomatous inflammation were not found (*Figure 2C*). On the basis of the findings, the patient was diagnosed with RP. The medical history of the patient was carefully re-visited, and additional physical examinations performed; however, no other positive signs were found. After a 10-day course of oral prednisone (10 mg, qd), the temperature of the patient had returned to a normal level, although an occasional cough remained. Follow-up assessments performed 6 months later found no positive signs.

The clinical manifestations of both patients were fever, cough and expectoration, while no other symptoms were reported. Hearing loss was identified in one patient after the medical history was carefully re-taken. Increases in ESR, CRP and ferritin were found in both patients, while the other examinations demonstrated no abnormalities. In both patients, FDG PET-CT revealed increased FDG uptake in costicartilage and/or the trachea, as well as in the walls of the bilateral main bronchi. Although enlargement of the mediastinal lymph nodes was also found in the second case, FDG PET-CT scanning did not show evidence of enhanced FDG uptake in these lymph nodes. The findings of these two cases demonstrate that targeted biopsy of the lesion with TBNA, performed after FDG PET-CT scanning, could facilitate the diagnosis of RP. The time to final diagnosis in these two patients was about 1.5 months.

Twelve articles (4-15), involving 20 cases, were identified that reported the diagnosis of RP using PET-CT. Thus, a total of 22 cases (15 males and 7 females; mean age, 55.5 years) of RP, diagnosed using PET-CT, have been reported, including the two cases described in the present study. The main clinical symptoms of these patients included fever and cough. Common features of the PET-CT images included symmetric involvement of cartilage and joints, evident as ^{18}F-FDG hypermetabolic lesions. The SUV_{max}

Table 1 Clinical and PET-CT characteristics of RP patients

Patient No.	Age	Gender	Symptoms	Uptake focuses of PET-CT	SUV_{max}	Biopsy
P1 (4)	47	M	1, 2, 3, 4	16, 17, 18, 19	6.25	Tracheal mucous membrane
P2 (5)	67	M	1, 2, 3, 5	16, 17, 20, 21	NR	Costicartilage
P3 (6)	60	M	1, 2, 3, 6	16, 21	NR	Aurical cartilage
P4 (7)	59	F	1, 2, 4, 5, 7, 8	16, 17, 20, 21, 22	6.41	Undone
P5 (8)	77	M	3, 5, 8, 9, 10, 11, 12	22, 23, 24	NR	Undone
P6 (9)	57	M	1, 6	18, 20, 21, 25, 26	4.5	Undone
P7 (10,14)	37	M	1, 2, 7	16, 17, 20, 21, 27	NR	Costicartilage
P8 (11)	55	F	1	16, 21	4.5	Undone
P9 (12)	50	F	2, 3, 5, 7	16, 17	NR	Undone
P10 (13)	79	F	3, 4, 8, 10, 11, 12, 13	20, 24, 28	3.38	Undone
P11 (13)	61	M	1, 4, 6, 10, 11, 14	19, 22, 24, 29	6.44	Undone
P12 (13)	74	F	7, 8, 12	17, 18, 19, 21, 25, 30	13.03	Nasal cartilage
P13 (13)	66	M	1, 2, 3, 6	16, 17, 19, 21	4.75	Laryngeal cartilage
P14 (13)	44	F	2, 3, 5	17	1.93	Undone
P15 (14)	38	M	2, 15	16, 17, 20, 21, 27	4	Aurical cartilage
P16 (14)	55	M	1, 2	20, 21, 24, 27	4.8	Costicartilage
P17 (14)	66	F	2, 3	21	3.6	Aurical cartilage
P18 (14)	41	M	2, 3	16, 17, 20, 22, 24	5	Aurical cartilage
P19 (14)	55	M	2	16, 17, 24	4.2	Aurical cartilage
P20 (15)	39	M	2, 3, 5, 6	16, 17, 21, 22	NR	Lymph node, trachea and tonsils
P21 (16)	42	M	1, 2, 8	16, 17, 20	3.73	Tracheal rings
P22	51	M	1, 2	16, 17, 20	5.04	Tracheal rings and lymph nodes

P, patient; M, male; F, female; 1, fever; 2, cough; 3, chest tightness; 4, hoarseness; 5, sore throat; 6, weight loss; 7, arthralgia; 8, hearing loss; 9, headache; 10, conjunctivitis; 11, swelling and redness of the aurical; 12, swelling and redness of the nasal bridge; 13, dizziness; 14, shoulder pain; 15, chest pain; 16, trachea; 17, bronchus; 18, wrist joint; 19, shoulder joint; 20, costicartilage; 21, throat; 22, lymph nodes; 23, auditory canal; 24, auricle; 25, elbow joint; 26, sternum; 27, nose; 28, annular cartilage; 29, aorta; 30, sinus and paranasal sinus; NR, not record; SUV_{max}, maximum standard uptake value.

was recorded for 16 of the 22 cases; it ranged from 1.93 to 13.03, with a mean value of 5.14. *Table 1* showed the clinical characteristics and PET-CT features of the 22 patients.

Discussion

RP is a relapsing degenerative disease of cartilaginous tissues characterized by the involvement of multiple organs and vessels, including the nose, ears, throat, trachea, eyes, joints and cardiac valves; however, the etiology of RP is still not fully understood. Previous studies have suggested that autoimmunity may be associated with the pathogenesis of RP. No ethnicity, sex or age differences have been reported for RP, but most patients with RP are between 40 and 60 years of age (1,2). Currently, most medical practitioners and researchers apply the criteria proposed by Damiani *et al.* (17) for the diagnosis of RP.

As RP is a rare disease with clinical manifestations that vary from patient to patient, it is very hard to diagnose, especially in patients with atypical symptoms. The early diagnosis of RP is even more challenging (1). The clinical symptoms of the two cases reported here were fever and cough, and no other abnormalities were found. After the diagnosis of RP, the clinical history of each patient was carefully re-taken. In the first case, hearing loss was identified as an additional symptom in the first patient, but there was no involvement of the cartilage of the ears, joints, nose and eyes. FDG PET-CT scanning showed inflammation of the costicartilage, trachea and bilateral main bronchi. In the second case, no involvement of the

cartilage of the ears, joints, nose and eyes was identified, and there were no lesions in the cochlea and ear vestibules. FDG PET-CT scanning suggested inflammation in the costicartilage near the xiphisternum, as well as in the trachea and the walls of the bilateral main bronchi. TBNA was used for biopsy of the sites showing increased FDG uptake in FDG PET-CT scans; the results obtained helped to determine the final diagnosis, and no obvious complications occurred. Glucocorticoids were used to treat both of the patients, and effectively alleviated the symptoms. The findings in these two patients suggested that FDG PET-CT could play an important diagnostic role in patients with atypical RP.

Laboratory investigations in these two cases revealed increased ESR and CRP, in accordance with previous studies (18); interestingly, we also found an increased ferritin level in both patients, consistent with the findings of Fujiki *et al.* (19) In addition, an elevated ferritin level had been found in 4 other cases of RP diagnosed recently in our hospital. These findings suggested that an increased ferritin level could also be valuable in the diagnosis of RP.

Previous studies have shown that FDG PET-CT is of great value in diagnosing diseases presenting as fever of unknown origin, with a sensitivity and specificity of 92% and 94%, respectively (20). FDG is a non-specific imaging agent that can be taken up by tumor tissues to result in an increased SUV; thus, FDG can play an important role in the diagnosis and staging of tumors, the planning of therapeutic strategies, the prediction of prognosis, and the evaluation of treatment efficacy in patients with cancer (21,22). FDG can also accumulate in tissues showing infective or non-infective inflammation, due to their high glucose metabolism and expression of cell surface glucose transporters; the resulting increase in SUV can play a critical role in diagnosing such inflammatory diseases (23-25). In our literature review, 12 articles were identified that described the diagnosis of RP with FDG PET-CT. The first case of RP diagnosed with FDG PET-CT was reported by Nishiyama *et al.* in 2007 (4); in 2013, we also reported the use of FDG PET-CT for the diagnosis of RP in a patient (16). In the cases reported previously, symmetric, multiple, hypermetabolic lesions were found in the cartilages of the trachea, bronchi, costicartilage, throat and lymph nodes. PET-CT revealed that 86.4% (19/22) of the patients with RP had airway involvement. The SUV_{max} was reported in 16 of these cases, and ranged from 1.93 to 13.03, with a mean of 5.14. These findings suggested the existence of chondritis, which had been acknowledged to be a reliable indicator of RP. Therefore, FDG PET-CT played an important role in the diagnosis of RP in all 22 of these cases.

Both of the cases reported here were diagnosed within 1.5 months of disease onset. Complete medical records were available in 17 of the 22 cases (including the present 2 cases) diagnosed using FDG PET-CT; the time to diagnosis in these 17 patients was within 6.9 months of onset, significantly shorter than the average time to diagnosis of 20 months (26). Such earlier diagnosis could potentially decrease the risk of the development of late complications. These findings demonstrated that FDG PET-CT could potentially play an important role in the diagnosis of RP, especially atypical RP, and effectively shorten the time to diagnosis.

In 10 of the 22 reported cases, FDG PET-CT was used for re-examination of the patient after treatment had been administered; these assessments showed that FDG uptake had decreased substantially or disappeared after treatment, and that no other hypermetabolic lesions were evident (5-8,11,14). This indicated that FDG PET-CT could also play an important role in the evaluation of treatment efficacy.

For atypical RP patients, the main biopsy sites are costicartilage, aurical cartilage and nasal cartilage. And the primary complication is infection and collapse of auricles (27). However, TBNA, as a minimally invasive and safe technique, has never presented with obvious complication in both adults and children (28,29). The clinical symptoms of the two cases reported here were not typical, and only a limited number of organs (including the cartilage of the trachea and bronchi) were involved. TBNA was used for biopsy of cartilage from the sites with increased FDG uptake, and yielded satisfactory pathologic results with minimal trauma and no complications. This would suggest that combining FDG PET-CT with TBNA could be an effective means with which to diagnose RP. In particular, TBNA might show particular promise for the diagnosis of RP in patients with atypical symptoms, especially those with airway involvement. To our limited knowledge, the present study is the first to report the application of TBNA for pathologic examinations of patients with RP, and the first to report the use of endobronchial ultrasound to examine the tracheal walls after treatment (this showed normal cartilaginous rings and no thickening of the tracheal wall). However, endobronchial ultrasound examination (30) was not performed in these two cases before treatment. In the second case reported here, there was enlargement of the mediastinal lymph nodes, a very rare finding in previous studies (7,14,15); moreover, biopsy of the mediastinal

lymph nodes using TBNA technique played an important role in the differential diagnosis. In addition, the use of tracheoscopic examination to observe the airway and obtain biopsies of the tracheal mucosa may also prove valuable for the differential diagnosis of RP from bronchial asthma and other trachea-involving diseases (31,32). Besides bronchoscope and TBNA technique, the dynamic expiratory CT and three-dimensional image reconstructions are valuable for diagnosis and following up of RP involved bronchotracheal (33).

In summary, FDG PET-CT scanning was able effectively to display increased FDG uptake in the trachea, bronchi, costicartilage and joints; these findings could be used as reliable signs of joint cartilage involvement in RP. PET-CT revealed that 86.4% of the patients with RP had airway involvement, so we recommend that clinicians should improve their understanding of RP, and apply TBNA and targeted biopsy in the diagnosis of this disease in order to shorten the time to diagnosis.

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Original Article

Construction and management of ARDS/sepsis registry with REDCap

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Objective: The study aimed to construct and manage an acute respiratory distress syndrome (ARDS)/sepsis registry that can be used for data warehousing and clinical research.

Methods: The workflow methodology and software solution of research electronic data capture (REDCap) was used to construct the ARDS/sepsis registry. Clinical data from ARDS and sepsis patients registered to the intensive care unit (ICU) of our hospital formed the registry. These data were converted to the electronic case report form (eCRF) format used in REDCap by trained medical staff. Data validation, quality control, and database management were conducted to ensure data integrity.

Results: The clinical data of 67 patients registered to the ICU between June 2013 and December 2013 were analyzed. Of the 67 patients, 45 (67.2%) were classified as sepsis, 14 (20.9%) as ARDS, and eight (11.9%) as sepsis-associated ARDS. The patients' information, comprising demographic characteristics, medical history, clinical interventions, daily assessment, clinical outcome, and follow-up data, was properly managed and safely stored in the ARDS/sepsis registry. Data efficiency was guaranteed by performing data collection and data entry twice weekly and every two weeks, respectively.

Conclusions: The ARDS/sepsis database that we constructed and manage with REDCap in the ICU can provide a solid foundation for translational research on the clinical data of interest, and a model for development of other medical registries in the future.

Keywords: Acute respiratory distress syndrome (ARDS)/sepsis registry; research electronic data capture (REDCap); data quality; data management

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Introduction

Sepsis is a systemic response to infection that can result in severe complications such as organ dysfunction and septic shock (circulatory failure despite fluid resuscitation) (1). Further, it is the most common etiology of acute respiratory distress syndrome (ARDS) (2). ARDS and sepsis are currently the leading causes of death among critically ill patients, with reported case-fatality rates ranging from 25% to nearly 50% for ARDS, up to 30% for sepsis, 50% for severe sepsis, and 80% for septic shock (3-7).

We have been assisting several large-scale global clinical trials to collect clinical data of our patients with ARDS and sepsis for a long time. However, a special electronic database to manage these precious clinical resources has never been established. Although our in-clinic diagnoses and treatments are in accordance with international guidelines, some excellent clinical findings by senior doctors could not be published owing to lack of clinical evidence. Further, because a large number of ARDS/sepsis patients

are registered to the intensive care unit (ICU) every year, it has proved necessary to establish a special ARDS/sepsis registry to collect and manage the data comprising the daily diagnosis and treatment of the patients in the ICU. Our objective is to establish a database that can serve as a convenient and reliable tool in data collection, storage, and management, and to facilitate clinical research aimed at improving diagnosis and treatment, exploring the biomarkers of the diseases, and proposing helpful suggestions for public health decision makers.

We worked with the Applied Health Research Centre (AHRC), a leading academic research organization at St. Michael's Hospital, Canada, to build and manage our ARDS/sepsis registry. The workflow methodology and software solution of research electronic data capture (REDCap), an NIH-sponsored, HIPAA compliant, free, and secure web-based application designed for data collection and management to support clinical and translational research, was used to construct the registry (8,9). REDCap was originally developed at Vanderbilt University by Paul A. Harris and colleagues in 2004 and is continuously updated and enhanced by the Project REDCap Team at Vanderbilt. Currently, it is being used in more than 111,000 projects by over 143,000 users across the world, including extensive usage by Clinical and Translational Science Awards (CTSAs) and other institutions such as Harvard, Mayo Clinic, and Massachusetts Institute of Technology (MIT) (10). It provides multiple studies and case report forms (CRFs) and very effectively supports data capture for small and medium scale study and is capable of supporting prospective and retrospective studies, as well as multicenter clinical trials. Data collections in microsoft excel and microsoft access can be easily converted to REDCap. The methodology used to construct our ARDS/sepsis registry with REDCap and utilization of the registry for submission, storage, and management of the data of ARDS/sepsis patients for clinical and translational research are presented in this paper. The data presented here are part of a long-term study of ARDS/sepsis patients registered to the ICU.

Methods

REDCap application

REDCap is not an open-source software, but it is available free of charge to institutional partners. It is not difficult to support; however, infrastructural requirements such as a web server that supports PHP, a MySQL database server, and secure sockets layer (SSL) connections need to be satisfied (10). On signing a valid end-user license agreement with Vanderbilt University to become a consortium partner, we obtained access to the software and help resources. It is now hosted on a local server at The First Affiliated Hospital of Guangzhou Medical University.

ARDS/sepsis patients

ARDS/sepsis patients registered to the ICU at The First Affiliated Hospital of Guangzhou Medical University between June and December 2013 were enrolled the project. We define ARDS using the Berlin definition (11), and sepsis in accordance with the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (1). Patients were eligible for enrollment if they fulfilled the criteria for ARDS or sepsis within 24 hours after ICU admission. Any patient who was pregnant, below 18 years old, had a life expectancy of less than 48 hours, had a history of bone marrow or liver transplantation, had been receiving chemotherapy or radiation therapy within the previous eight weeks, or was positive for the human immuno-deficiency virus was excluded. Clinical data collection began immediately following ICU admission. From each enrolled patient, 5 mL of venous blood was drawn and centrifuged, and the plasma aliquots (200 μL) stored at –80 ℃ for further analysis.

The study protocol was approved by the Ethics Committee of The First Affiliated Hospital, Guangzhou Medical University. Written informed consent was also obtained from all participants in the study.

Registry description

The research team worked with clinicians to design our discipline-specific, comprehensive registry, which consists of six parts: demographic characteristics, medical history, clinical interventions, daily assessments, clinical outcome, and follow-up. In addition to collecting the clinical data of the patients, we observed the changing state of their illnesses 1, 3, 5, 7, 14, 21, and 28 days after admission. We created a large, prospective, non-interventional database in the registry to collect data describing the management and outcomes of ARDS/sepsis patients in the ICU. All data met accepted clinical standards governing the usage of existing standard terminology concerning ARDS and sepsis. Consistent and comparable formats were also adopted whenever possible. Original clinical data were abstracted from the electronic and written medical records of the patients for 28 days from the day of ICU admission or until

discharge, if earlier, and recorded on a CRF. To ensure that the clinical data were collected in the appropriate format necessary for essential analysis, a statistician was assigned to review the database planning process.

Creation process

The ARDS/sepsis registry was designed and implemented on the REDCap platform, which provides (I) an intuitive interface for validated data entry; (II) audit trails to track the history of data entry and revision; (III) procedures for importing data from external sources; (IV) data downloads to Excel, PDF, SAS, SPSS, Stata, and R; and (V) a built-in scheduling calendar, ad hoc reporting tools, and advanced features such as branching logic and calculated fields (8,10).

No formal programming, networking, or database experience was needed to use REDCap because training videos and help resources were available on the REDCap consortium website to familiarize users with REDCap. However, to ensure that the database was information security compliant and aligned with standard operating procedures, an AHRC IT specialist was assigned to assist with project programming. The implementation steps comprised (I) logging in to our hospital network to access REDCap; (II) creating a new project by navigating to the "Create New Project" tab and completing and submitting all required information about the main project settings; (III) creating data collection instruments by defining data variables and their properties; (IV) previewing and testing data entry screens to ensure appropriate dataset yields for planned statistical analyses; (V) configuring study member permissions and user rights; and (VI) moving the project from development to production to ensure data accuracy and integrity after actual collection of clinical data started.

Data entry and quality control

It is important to have a mechanism to reduce the possibility of data entry errors. With REDCap, we restricted data format/type, set ranges for date and numeric fields, and allowed data validation. Data consistency problems such as incorrect data type, values out of range, and outliers for numerical fields can be reported using the data quality module. Further, we applied pre-defined rules that facilitated determination of whether a specific data value might be discrepant, which is very important because our project contains many fields and has many records. Two trained medical staff members worked together on data extraction

Figure 1 Schematic diagram of the registry management methodology. CRFs, case report forms; REDCap, research electronic data capture.

and the data were cross-checked during the input process. The project director reviewed all the medical records of the first 50 patients to ensure that standard operating procedures, including data collection and entry, were adhered to. Spot checks were also conducted by a statistician every two months. Only five entry mistakes or less per 100 were acceptable, failing which all clinical data underwent a full-scale review or were re-entered and reassessed.

Database management

A project director, a research team, clinicians, an IT specialist, and a statistician worked together to manage the ARDS/sepsis registry. The project director, who was also the project administrator, coordinated the activities of all personnel associated with the database. The database structure was designed based on discussions held with practicing clinicians and the research team. Electronic CRFs were developed by the IT specialist using REDCap and reviewed by the statistician. ICU clinicians identified subjects for the study according to the eligibility and exclusion criteria. Demographic and clinical data capture, entry, and analysis were performed by the research team. The project director and the statistician supervised all data activities to assure quality control (*Figure 1*).

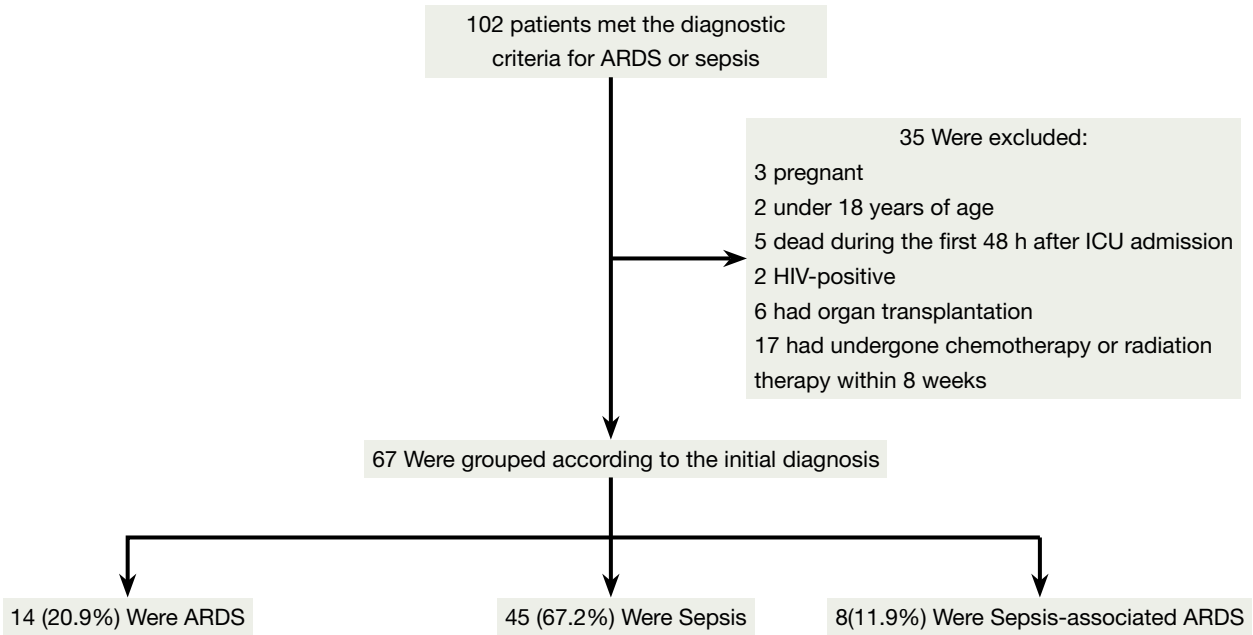

Figure 2 Patient inclusion/exclusion flow diagram. ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Results

Inclusion and exclusion of patients

A total of 102 ARDS/sepsis patients registered to the ICU between June and December 2013 were assessed for inclusion in the study. Of this total, 35 were excluded and the remaining 67 eligible patients were enrolled in the registry. Among the eligible patients, 45 (67.2%) were diagnosed with sepsis, 14 (20.9%) with ARDS, and eight (11.9%) with sepsis-associated ARDS at the time of ICU admission (*Figure 2*).

Structure of the registry

The registry comprises six categories, demographic characteristics, medical history, clinical interventions, daily assessments, clinical outcome, and follow-up, which are sub-divided into 121 items and 186 variables (*Table 1*).

Data storage

As shown in *Figure 3*, the record status dashboard of the registry is a table listing all existing records and their status for every data collection instrument. The data collected at the various points in time are categorized accordingly for storage and management.

Table 1 ARDS/sepsis registry structure

Entries	Variables
Demographics	Study ID, gender, date of birth, marital status, height, weight, address, smoking, junior physician of ICU, senior physician of ICU, hospital admission date, ICU admission date
Medical history	Co-morbidities, surgery history, lung Injury cause
Clinical interventions	ARDS/sepsis screening, mechanical ventilation, fluid balance, nutritional support, analgesia, sedation, neuromuscular blockade, transfusion, chest tube, RRT, PICCO, ECMO, IABP, antibiotics, vasopressor, corticosteroids, immunoglobulin
Daily assessments	Patient disposition, vitals, lab results, glasgow coma score, SOFA score, APACHE II score, pathogens and sources, chest X-ray, CT scan
Clinical outcome	ICU outcome, date of death, cause of death, ventilator on days, ICU expenses, hospitalization expenses
Follow-up	30-, 60-, 90-, 180-, 365-day survival

ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

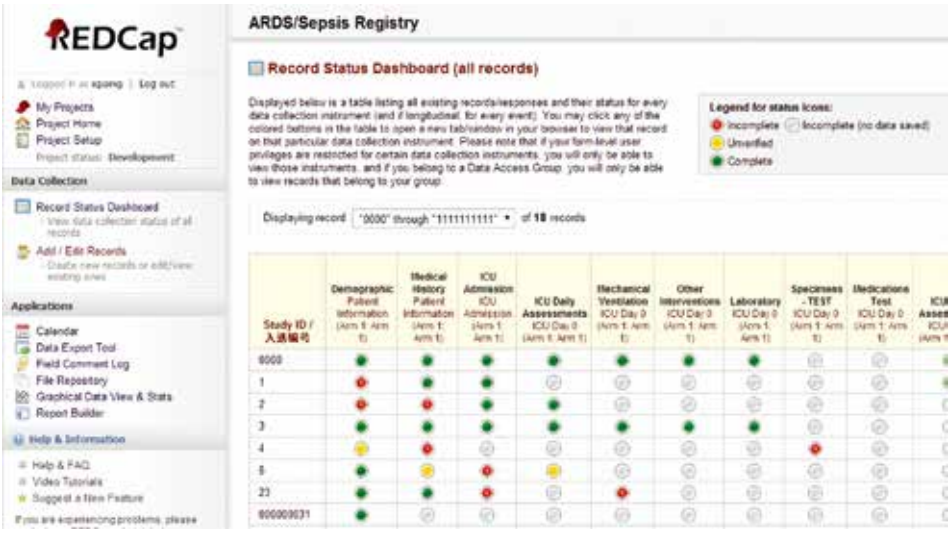

Figure 3 Record status dashboard of the ARDS/sepsis registry. ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

The red, grey, yellow, and green icons signify incomplete, blank, unverified, and complete records, respectively. Clicking any of the colored buttons in the table automatically activates the associated data collection instrument.

Security of the data

The clinical data maintain full patient confidentiality since they are SSL encrypted and stored on a secure server. Every interaction with the data is logged, creating an audit trail. The project director can also lock the data after all finalization checks have been completed. Researchers can access the database from multiple sites and institutions only with their own unique usernames and passwords. Different levels of data access rights can also be assigned by the project administrator to different users, depending on their roles in the project. These rights include logging, data entry rights, managing survey participants, calendar, data export tool, data import tool, file repository, data quality, project design, and setup (*Figure 4*).

Enhanced efficiency in data collection to support research

Data were collected and entered into the database twice weekly and every two weeks, respectively, by trained medical staff. It took a trained medical worker approximately 30 minutes per subject to convert clinical data to the eCRF format used in the REDCap platform. The frequent collection ensured timely and efficient acquisition of the clinical data of the patients of interest, significantly reducing the traditional data collection workload and facilitating future clinical research. Moreover, since the data collected can be easily converted to formats used by microsoft excel, microsoft access, SPSS, and SAS, they are convenient to transfer and share.

Discussion

A high quality medical registry can help to monitor and improve the health of ARDS/sepsis patients by facilitating description of the epidemiologic and clinical characteristics of the diseases and evaluation of the effectiveness of interventions. One notable example is the surviving sepsis database of the surviving sepsis campaign (SSC), which contains ten measures of the routine care process and one outcome measure of sepsis patients. It remains the core measurement strategy for the SSC. The SSC was developed in an attempt to increase early recognition and improve outcome in severe sepsis and septic shock patients (12,13). Since proposal of the SSC guidelines in 2004 and their subsequent updating in 2008 and 2012, the survival rate of patients with severe sepsis and septic shock has been significantly improved. Levy *et al*. found that the hospital mortality decreased significantly from 37% to 30.8% (P=0.001) within 2 years (14). Castellanos-Ortega *et al*. reported that the hospital mortality in the historical group was significantly higher than in the intervention group (57.3% *vs*. 37.5%, P=0.001) (15). Miller *et al*. reported that severe sepsis and septic shock bundle compliances reduced hospital mortality from 21.7% in 2004 to 9.7% in

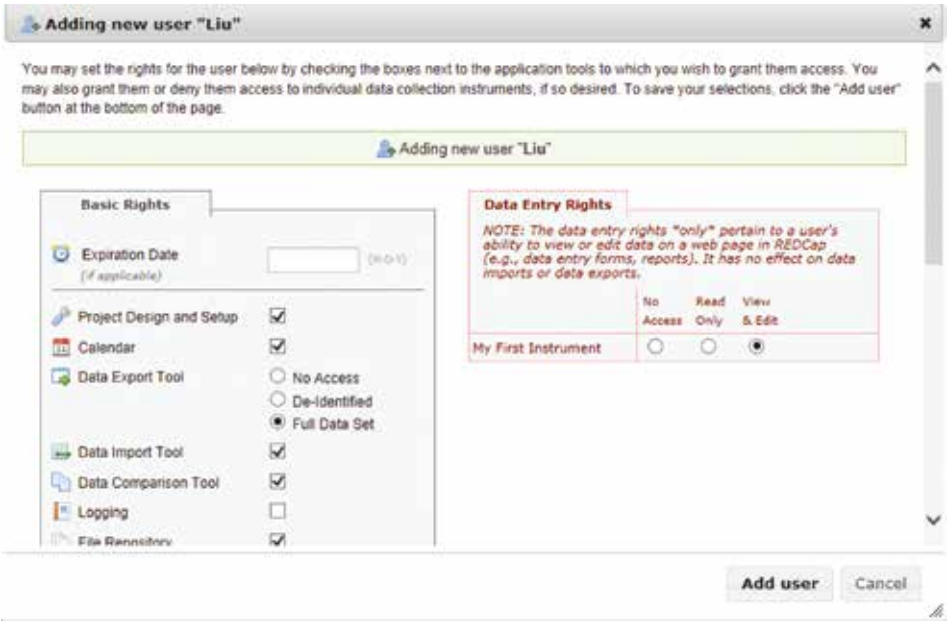

Figure 4 User rights that can be granted or restricted.

2010 (16). Significant achievements of ARDS Networks, such as the ALVEOLI Study, and the Fluid and Catheter Treatment Trial (FACTT) study, have also benefitted from comprehensive patient information (17-19).

Although the SSC database is reasonable in design, it is aimed at early recognition and treatment of sepsis patients. Clinical data collection is primarily focused on the characteristics of early condition changes in sepsis patients and the efficacy of initial interventions (like fluid resuscitation, and 3- and 6-hour bundles). Our ARDS/sepsis registry, established using the REDCap platform, facilitates collection and management of the clinical data of patients with ARDS and sepsis in a more comprehensive manner.

The ARDS/sepsis registry collection demographics, diagnoses, interventions, medications, and laboratory data of ARDS/sepsis patients are valuable for clinical research. They can be used to identify patients for clinical research, analyze disease-specific practice patterns, and aid in the development of potential treatment strategies (20,21). In addition, the plasma samples obtained from our patients at ICU admission and stored, frozen at –80 ℃, can be analyzed. Combinations of clinical data with biological specimens enhance a better understanding of pathophysiological mechanisms of ARDS and sepsis and help determine biomarkers to improve diagnostic and prognostic accuracy (22).

This ARDS/sepsis registry has several limitations. Although many clinically important variables are included in the database, the data cannot be automatically transferred from the Hospital Information System to REDCap. Therefore, much time and labor are expended collecting and inputting these data into our registry. Although REDCap provides automatic data validation and popup warnings regarding out-of-range values, it does not prevent invalid data from being entered. Consequently, efforts to minimize the possibility of incorrect data being inputted and to control data quality are especially important.

Conclusions

This paper described the infrastructure of our ARDS/sepsis registry and the approach taken to its construction and management with REDCap. Construction of the ARDS/sepsis registry facilitates better translation from clinical practice to scientific research. This methodological study is an effort to fully utilize daily clinical data of ARDS/sepsis patients and to implement a reproducible research system for clinical data integration. Such an effort can be generalized to other medical registries.

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Author contributions: Xiaoqing Pang, Sulong Wu, Yongbo Huang and Pu Mao designed the registry, collected and entered the clinical data. Xiaoqing Liu and Weiqun He designed the registry and identified eligible subjects. Mei Jiang reviewed the registry. Chaoyi Huang developed the eCRFs. Natascha Kozlowski coordinated the activities between Guangzhou and Toronto. Yimin Li and Haibo Zhang supervised all data activities and coordinated the activities of all members.

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Disclosure: The authors declare no conflict of interest.

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Original Article

Application of piezoelectric nanogenerator in medicine: bio-experiment and theoretical exploration

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Background: A large number of wearable and implantable electronic medical devices are widely used in clinic and playing an increasingly important role in diagnosis and treatment, but the limited battery capacity restricts their service life and function expansion. Piezoelectric nanogenerators can convert mechanical energy into electrical energy. Our experiment tries to find out if the piezoelectric nanogenerator fixed to the surface of the heart can convert the natural contractions and relaxations of the heart into stable electric energy for electronic medical devices such as pacemakers.

Methods: We used Chinese miniature pig and prepared with standard open chest procedure. Then we fixed two opposite edges of the rectangular nanogenerator at the following three positions of the heart respectively to detect the electric voltage output: Position A, right ventricular surface, near the atrioventricular groove, parallel to the long axis of the heart; Position B, right ventricular surface, parallel to the atrioventricular groove; and Position C, left ventricular surface, near cardiac apex, parallel to the left anterior descending branch. Then we selected the place which has the highest voltage output to fix both ends of the nanogenerator and closed the chest of pig. We recorded the voltage output of nanogenerator under closed chest condition (natural condition) and compared the result with open chest condition. Finally we used Dopamine (positive inotropic agents) and Esmolol (negative inotropic agents) respectively to detect the relation between voltage output of nanogenerator and myocardial contractility.

Results: With its both ends fixed on the surface of the heart, the piezoelectric nanogenerator produced stable voltage output from the mechanical contractions of the heart. Piezoelectric nanogenerator which was fixed at Position A produced the highest voltage output (3.1 V), compared with those fixed at Position B or Position C. The voltage is enough for the pacemaker's operation. The voltage output of piezoelectric nanogenerator at the natural condition (closed chest) was the same as the open chest condition and made a light emitting diode (LED) light continue to shine, which further confirmed its clinical application value. The voltage output of piezoelectric nanogenerator is positively correlated with the myocardial contractile force. The voltage output increased after we used positive inotropic agents and decreased after we used negative inotropic agents.

Conclusions: Piezoelectric nanogenerators can convert the kinetic energy of the heart during the contractions and relaxations of the muscles to electric energy. The output voltage was stable in three positions on the surface of the heart. The highest voltage appeared on the surface of right ventricle, near atrioventricular groove, parallel to the long axis direction of the heart, which can be the potential new energy source for pacemakers. Piezoelectric nanogenerator can be used as cardiac function monitor in the future for its voltage output is positively correlated with myocardial contractile force.

Keywords: Implantable medical electronic device; wearable medical electronic device; piezoelectric nanogenerator; body mechanical energy; biomechanical energy harvester; new power source

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Introduction

Implantable and wearable medical electronic devices such as cardiac pacemakers, implantable cardioverter defibrillators (ICD), left ventricular assist devices (LVAD), and total artificial hearts (TAH), etc. are more and more widely used in medicine. They can allow *in situ*, real-time biomedical detection, monitoring and treatment. However, traditional lithium batteries with limited electric power storage capacity cannot satisfy the function expansion of these devices. When the battery exhausts, patients have to receive surgical operations again to replace the battery of a device, causing the patients' physical and mental pain and the huge waste of medical resources (1). We hope that one day medical devices can be self-powered without batteries. A living human body produces kinetic energy (from its heart beating, joint movement, muscle stretching, blood vessel contraction and blood flow) and chemical energy (from glucose), etc. These power sources are inexhaustible and non-polluting. The key point is how to convert them into electric energy efficiently.

Zhong-Lin Wang has reported an approach to convert kinetic energy into electric power with the use of aligned zinc oxide (ZnO) nanowires (2). Its mechanism is the combination of semiconducting and piezoelectric nature of ZnO as well as the Schottky barrier formed between the metal and ZnO contacts (3-6). Piezoelectric nanogenerator belongs to the flexible electronic materials, thin and soft, and can convert kinetic energy from muscle contraction and joints movement to electric energy output (7,8). That is to say it has the potential for harvesting mechanical energy from the environment for self-powered electronic medical devices. Our experiment tried to explore if a piezoelectric nanogenerator can be a stable and reliable energy source for implantable electronic medical devices.

Materials and methods

Rectangular piezoelectric nanogenerators (9,10) were provided by Engineering Mechanics and Materials Lab of Tsinghua University (*Figure 1*). We have performed five animal implants, at the first and second animal implants we tested the nanogenerator at the open chest condition, at the other animal implants we tested the nanogenerator at the closed chest condition. We used Chinese miniature pigs of 30 kg weight with the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health, prepared with general anesthesia, supine position, median thoracotomy, suspended pericardium and exposed the heart. Then we fixed two opposite edges of a rectangular piezoelectric nanogenerator with 4-0 Prolene (ETHICON) on the surface of the heart at the following positions of the heart (according to the movement style of the heart) (11) respectively to detect the voltage output:

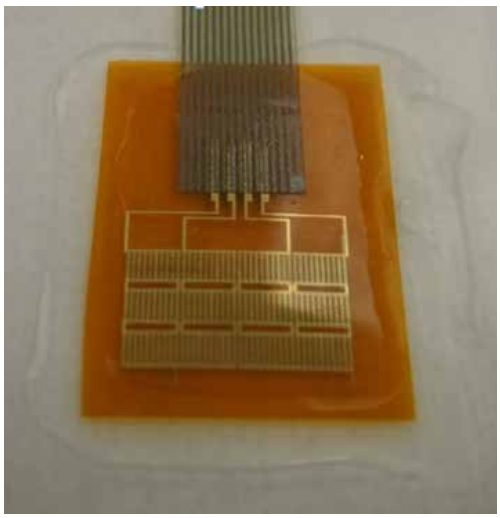

Figure 1 Piezoelectric nanogenerator with size of 5 cm (length) × 2 cm (width) × 7.5 μm (thickness) provided by Center for Mechanics and Materials and Department of Engineering Mechanics, Tsinghua University.

- Position A, right ventricular surface, near the atrioventricular groove, parallel to the long axis of the heart (*Figure 2*);
- Position B, right ventricular surface, parallel to the atrioventricular groove (*Figure 3*);
- Position C, left ventricular surface, near cardiac apex, parallel to the left anterior descending branch (*Figure 4*).

Then we selected the place which has the highest voltage output to fix both ends of the nanogenerator and closed the chest of pig. We recorded the voltage output of nanogenerator under closed chest condition (natural condition) and compared the result with open chest condition (*Figure 5*). Finally we used Dopamine (positive inotropic agents) and Esmolol (negative inotropic agents) respectively to detect the relation between voltage output of nanogenerator and myocardial contractility.

Results

With its both ends fixed on the surface of the heart, a

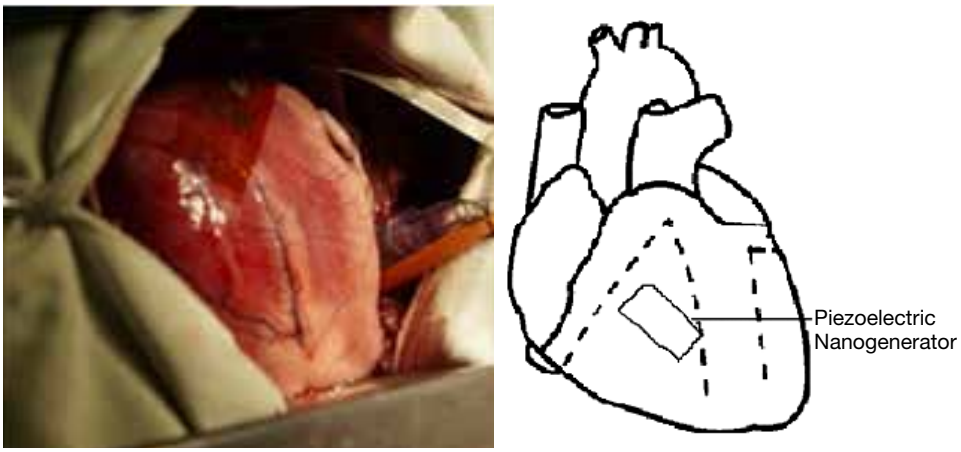

Figure 2 Position A, piezoelectric nanogenerator fixed on the right ventricular surface, near the atrioventricular groove, parallel to the long axis of the heart.

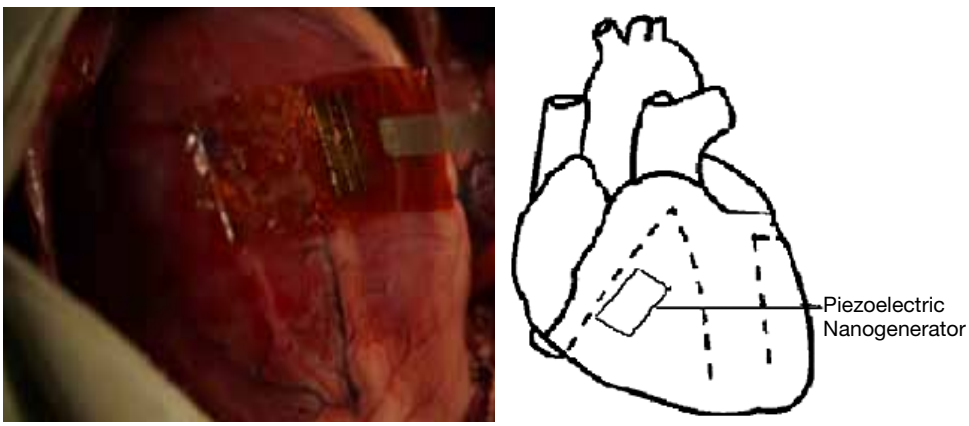

Figure 3 Position B, piezoelectric nanogenerator fixed on the right ventricular surface, parallel to the atrioventricular groove.

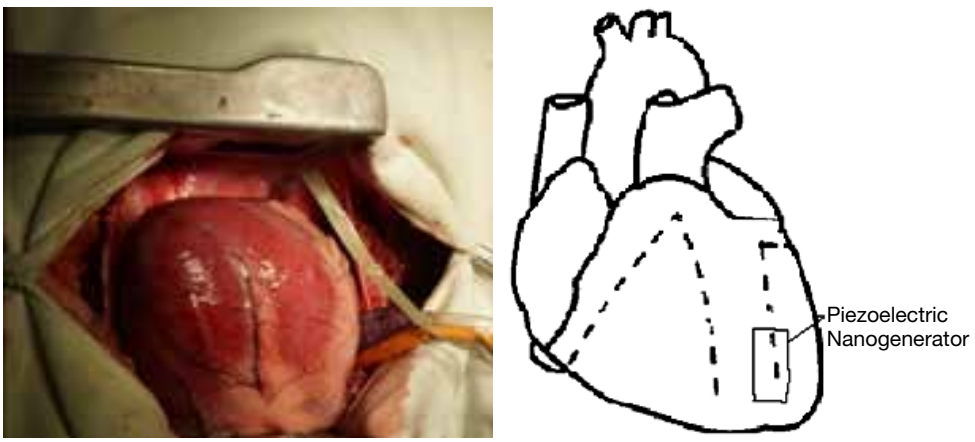

Figure 4 Position C, piezoelectric nanogenerator fixed on the left ventricular surface, near cardiac apex, parallel to the left anterior descending branch.

piezoelectric nanogenerator can produce stable voltage output from the contraction and relaxation kinetics of the heart. The piezoelectric nanogenerator fixed on the surface of the right ventricle, near atrioventricular groove, parallel to the long axis direction of the heart produced the highest voltage output stably (3.1 V), compared with those fixed on the surface of right ventricle, parallel to the atrioventricular groove or on the surface of left ventricle, near cardiac apex, parallel to the left anterior descending branch (*Figure 6*). The voltage is enough for the pacemaker's operation. The voltage output of the piezoelectric nanogenerator in the natural condition (closed chest) is the same as that in the open chest condition and can make a light emitting diode (LED) light continue to shine, which further confirmed its clinical application value (*Figure 7*). The voltage output of piezoelectric nanogenerator is positively correlated with myocardial contractile force. The voltage output increased after we used positive inotropic agents (*Figure 8*) and decreased after we used negative inotropic agents (*Figure 9*). Experiment process is shown in *Figure 10*.

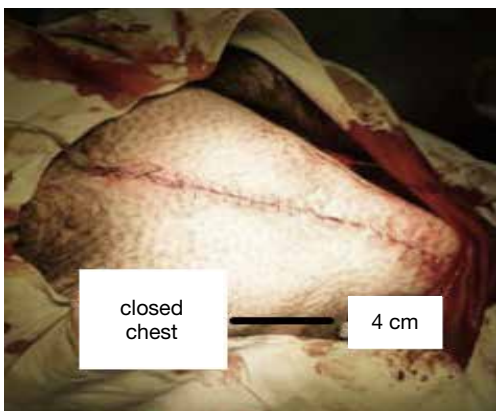

Figure 5 Closed chest condition (natural condition) with piezoelectric nanogenerator fixed on the surface of the heart and the wire went through the skin.

Discussion

Wearable and implantable electronic medical devices such as pacemakers, heart rate monitors, ICD, implantable drug pumps, and brain pacemaker play an important role in continuous clinic and family diagnostics and treatment. Although these electronic medical devices have huge potential application value in medicine, the biggest limitation of them is operational lifetime due to the limitation of battery storage, which rarely exceeds five years for implants and five days for wearable devices. Surgical procedures have to be done to replace the exhausted batteries of implantable medical devices every few years, which may increase the patients' operative complications, morbidity and potential mortality. To minimize the necessity for surgical operations and contain the medical costs, we try to find alternative ways to overcome batteries' limitations.

Zurbuchen reported that mass imbalance oscillation generator could be an energy harvester to convert cardiac wall motion to electrical energy (12), but the device was too big for clinical application. John A. Rogers and his team reported that piezoelectric nanogenerators could produce significant electrical power from motions of internal organs (10). The human's kinetic energy can be converted into electric energy by with the help of piezoelectric ZnO nanowire arrays (13-15). This method has the ability of converting mechanical, hydraulic and vibrational energy into electricity to power electronic medical devices and to monitor physical signs. ZnO combines the properties of piezoelectric and semiconducting. When it is bended, ZnO can create a strain field and charge separation across the

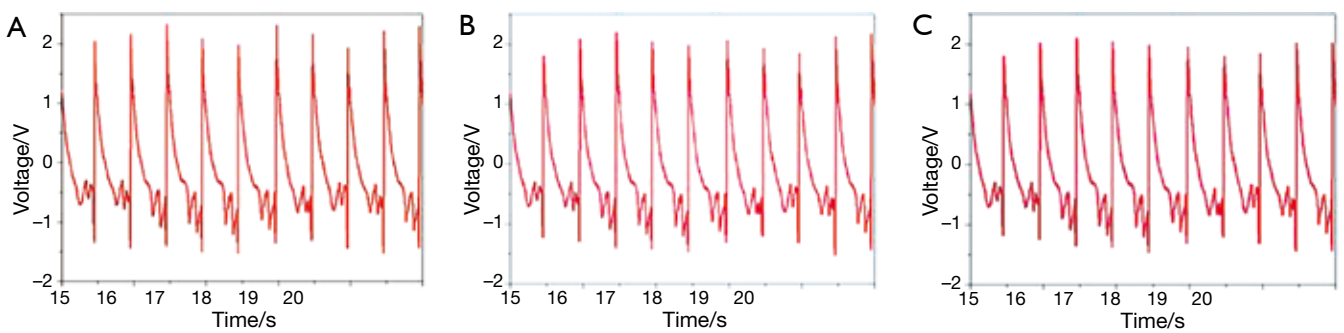

Figure 6 The voltage output of piezoelectric nanogenerator was 3.1 V at position A, 2.9 V at position B and 2.7 V at position C.

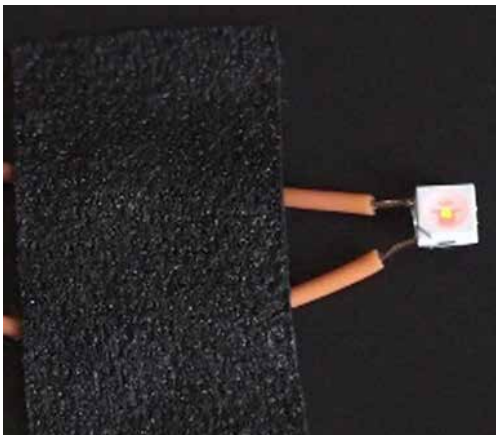

Figure 7 The voltage output of piezoelectric nanogenerator at the natural condition (closed chest) can make LED light continue to shine. LED, light emitting diode.

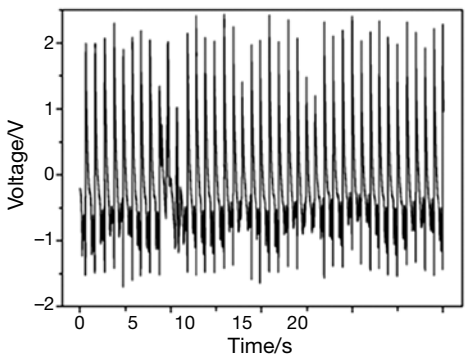

Figure 8 The voltage output of piezoelectric nanogenerator at natural condition increased to 3.3 V after we used positive inotropic agents.

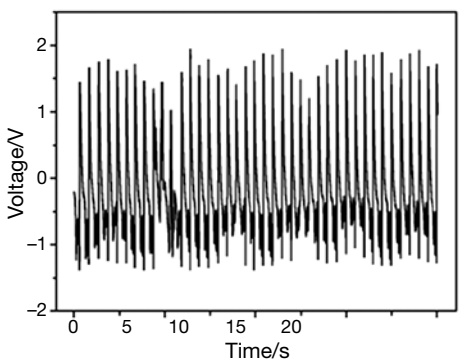

Figure 9 The voltage output of piezoelectric nanogenerator at natural condition decreased to 2.6 V after we used negative inotropic agents.

nanowire which leads to electric current generation.

The piezoelectric nanogenerator used in this experiment was provided by Xue Feng *et al.* from Tsinghua University. The nanogenerator is a kind of slice with length of 5 cm, width of 2 cm and thickness of 7.5 μm, combined with piezoelectric materials and micro storage battery. The slice is conformal and can be bended and stretched within certain limits, it can produce voltage output as it deforms and the deformation extent and the voltage output are positively correlated. We encapsulated its surface to avoid corrosion from the body fluid and to minimize its influence on the body's internal environment.

Our experiment shows that a piezoelectric nanogenerator with its both ends fixed on the surface of the heart can convert kinetic energy from heart beat to electric energy stably. From the comparison of the results from three different positions, we find that the piezoelectric nanogenerator output the highest voltage on the surface of right ventricular, near atrioventricular groove and parallel to long axis of the heart.

Shapes and contraction patterns of the muscles of the left ventricular wall and right ventricular wall resulted in different deformations of the piezoelectric nanogenerator, hence different electric voltage output. The left ventricular wall is generally 9-11 mm thick is thicker than right ventricular wall (3-5 mm). It is roughly cylindrical and contracts in a torsional or twisting pattern with three spiraling layers of wall muscles, it ejects blood by reducing its diameter and circumference whereas wall thickening (16). The right ventricular wall is generally 3-5 mm thick and is wedge shaped with a concave free wall attached to the convex interventricular septum (17) and ejects blood by contracting its free wall (18). The contraction pattern of right ventricular by shortening the free wall results in enhanced wall motion and increased bending of the piezoelectric nanogenerator than the twisting contraction pattern of the left ventricular. At the same time, the longitudinal deformation amplitude of right ventricular free wall is greater than the transverse deformation amplitude, so the position at right ventricular free wall and parallel to the heart long axis (Position A) has the highest voltage output (3.1 V).

Further experiments shows that the voltage output of piezoelectric nanogenerator is uninfluenced under closed chest (natural) condition and can keep an LED light steadily glowing. The voltage produced by nanogenerator can meet the needs of most implantable and wearable medical electronic devices. This discovery provides a new

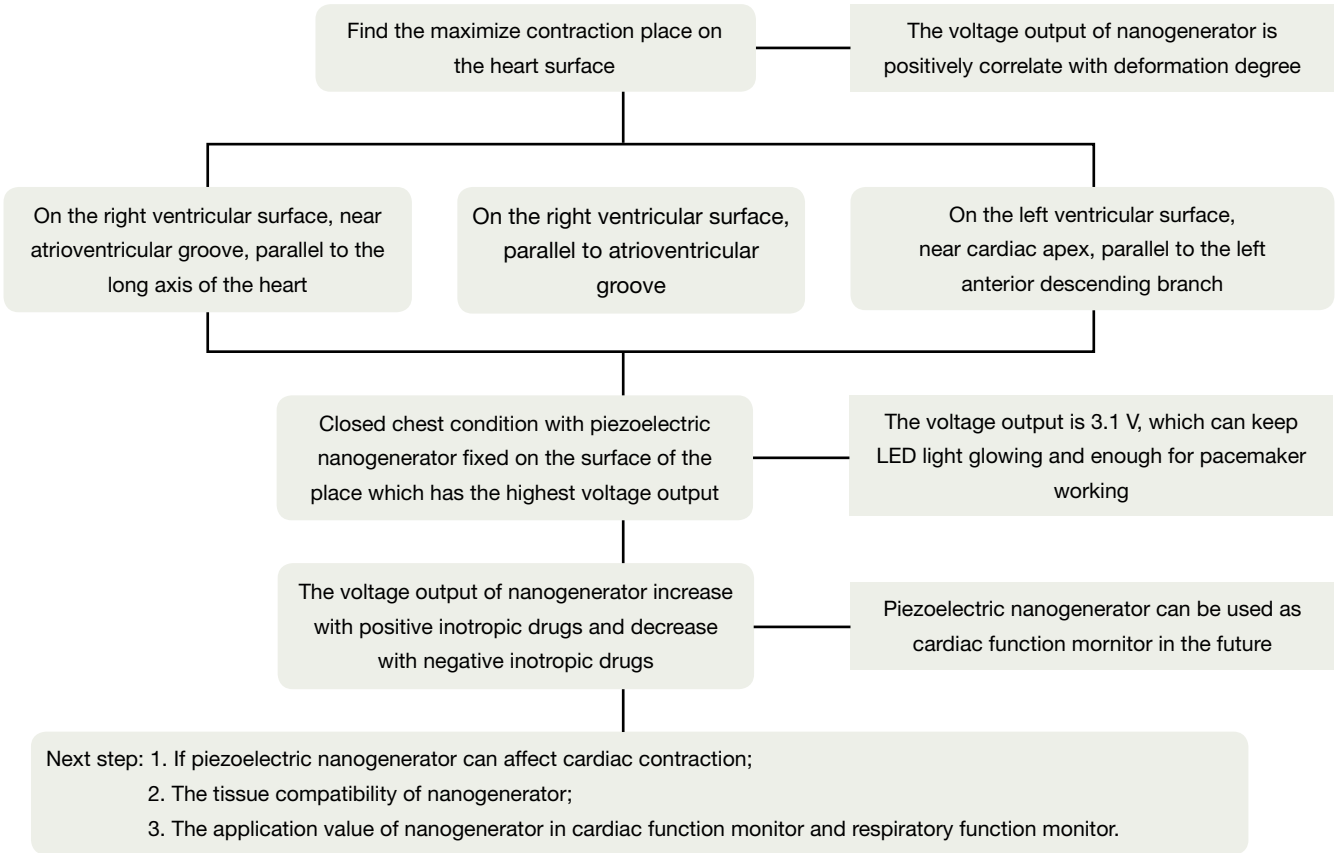

Figure 10 Experiment process. LED, light emitting diode.

sustainable and non-polluting energy source for medical electronics and make them more miniaturization which will reduce the patients' wounds eventually.

Besides generating electric energy to power the medical devices, piezoelectric nanogenerators can also be a kind of monitor to cardiac contraction force, heart rate, blood pressure (19), breathing state, diaphragmatic muscle movement, etc. as its voltage output is positively correlated with muscle contraction force and motion state (20). For example, we can make piezoelectric nanogenerator in the shape of a conductor and combine it with pacing leads so that surgeons can monitor cardiac function directly while pacing the heart. At present, doctors can only monitor cardiac function by Swan-ganz catheter or cardiac ultrasound indirectly. In the future, we also can realize accurate, noninvasive and real time arterial pressure monitor by putting the piezoelectric nanogenerator on the surface of the skin (21). With the help of computer and three dimensional (3D)-printing, we can even build the mechanical model of cardiac contraction by nanogenerator to provide guidance in ventricular reconstruction surgery.

In our next step, we plan to test if piezoelectric nanogenerator itself will affect cardiac contraction and its tissue compatibility, we will implant our nanogenerator in the chest and on the surface of heart, lung, diaphragm of pig at least 6 months (chronic animal implant) to test the efficacy, security and compatibility of nanogenerator. In summary, with the development of material science, flexible electronics such as piezoelectric nanogenerator will play a more and more important role in clinical diagnosis and treatment, and they will further reduce patients' pain and provide convenience to the doctors.

Conclusions

Piezoelectric nanogenerator can convert kinetic energy from contraction of muscle to electrical energy for implantable electronic medical devices. Piezoelectric nanogenerators can output steady voltage on the surface of right ventricle, near atrioventricular groove, parallel to the long axis direction

of the heart, which can be the new potential energy source for pacemakers. Piezoelectric nanogeneratosr can be used as cardiac function monitor in the future for its voltage output is positively correlated with myocardial contractile force.

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Brief Report

Malignant giant cell tumor of the rib with lung metastasis in a man

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Abstract: Malignant giant cell tumor of bone (MGCTB) accounts for 0.07% of all cases of primary bone tumor. The rarity and complexity of this tumor give rise to some arguments about its histological differentiation, diagnosis, treatment and prognosis. In this paper, we present a 57-year-old man who has a large MGCTB in his rib with lung-targeted metastasis at the time of initial diagnosis. He underwent an operation followed by radiotherapy. The man has been free of recurrence or metastasis for 18 months.

Keywords: Chest wall; malignant giant cell tumor of bone (MGCTB); metastasis

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Introduction

Giant cell tumor of bone (GCTB) usually appears as a benign tumor with local aggressiveness. GCTB mainly invades the end of long bones but rarely the ribs (1). Only 2% of all cases may evolve into a malignant one, and most of these malignancies occur in GCTB patients who underwent radiotherapy. In this paper, we present the imaging and clinicopathologic findings of a 57-year-old man with primary malignancy in GCTB (PMGCTB) and superior lobe of right lung metastasis.

Patients and methods

Our study was approved by the West China Hospital Ethics Committee and the patients signed an informed consent form. The patient underwent operation and radiation treatment in our hospital. The sample was confirmed with immunohistochemistry. All the regents were kindly provided by the pathology department of our hospital.

Results

The 57-year-old male went to our hospital with the chief complaint of chest pain on the right side for about half a year. He denied tuberculosis and had no history of surgery or trauma. His medical history was unremarkable.

Physical examination showed nothing remarkable and no thoracocyllosis. Contrast-enhanced computed tomography (CT) showed a large nearly ovoid mass on the right side of the chest wall with corresponding rib destruction (*Figure 1*). The mass showed dense soft tissue and obvious strengthening. Some nodules were found in the right lung. A little of pleural effusion was seen in the right thoracic cavity. Both sides of pulmonary lobes show mild chronic inflammation. Single photon emission tomography computed tomography (SPETCT) scan showed a mass on the right side of the third rib. The adjacent ribs, the second and the fourth ribs were also damaged. To identify the pathologic type of this mass, a fine needle biopsy was performed and the result was giant cell tumor. Laboratory tests including serum calcium, serum phosphorus, acid phosphatase, and alkaline phosphatase tests were unremarkable. Neither contrast-enhanced CT nor SPETCT found other metastasis except the right lung. The patient had no obvious contraindication. He received operation and the tumor was resected en bloc with 13-cm-long part of the involved ribs (including the third and the fourth ribs on the right sides). Surgical margin was 4 cm far away from the mass. The superior lobe of the right lung was also resected and the chest wall was reconstructed using Dacron patch (*Figure 2*). A cystic zone (6 cm × 4 cm × 3 cm) with hemorrhagic necrosis was found in this lesion. Histopathologic examination confirmed the complete

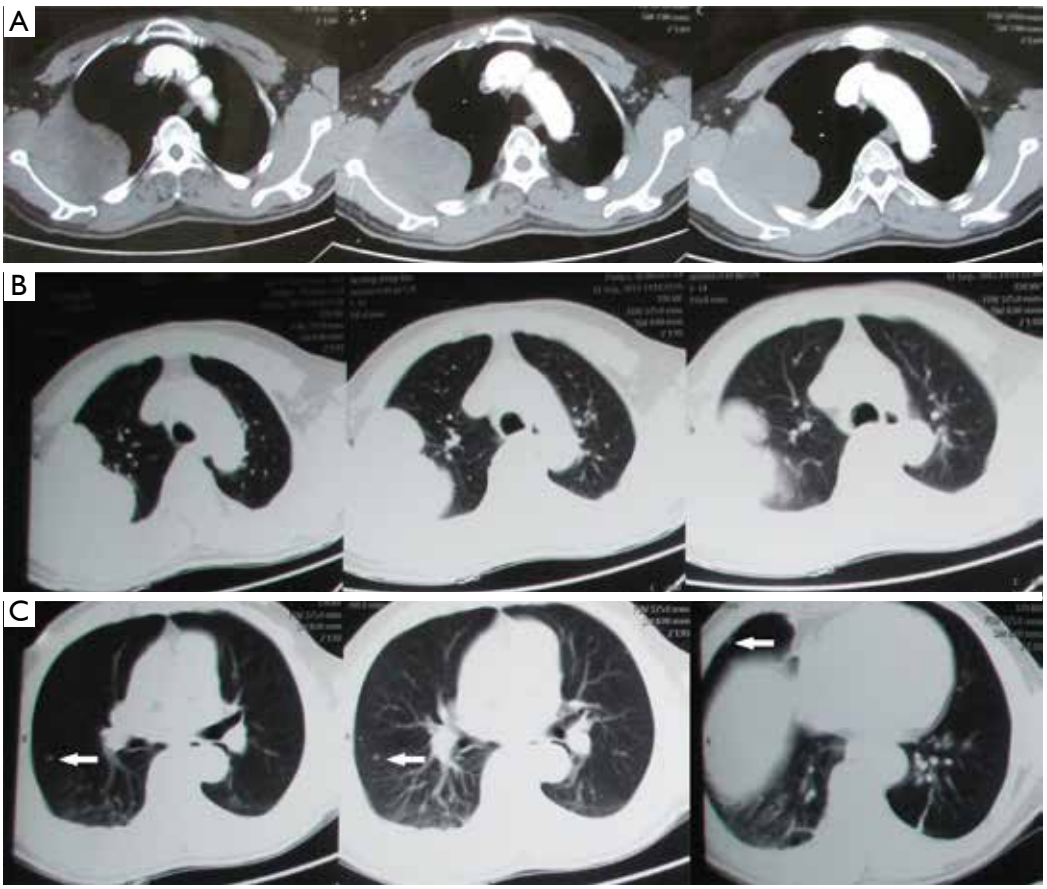

Figure 1 CT scan. Contrast-enhanced computed tomography (CT) showed that there was a large, nearly ovoid mass with dense soft tissue on the right side of the chest wall (A and B); some nodules were found and indicated using arrows in the right lung (C).

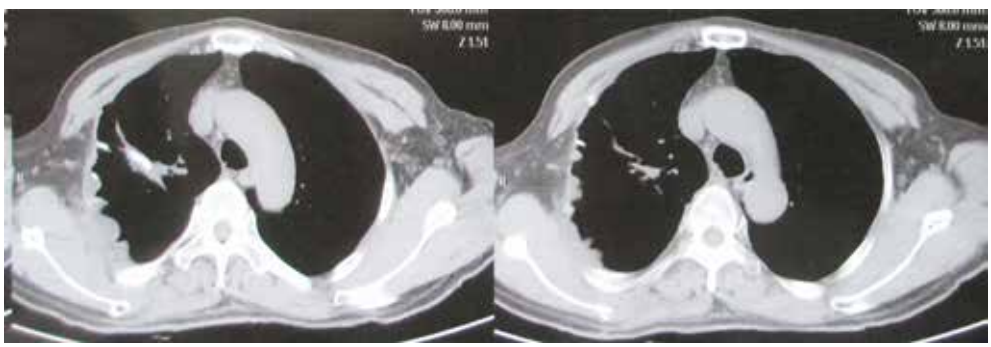

Figure 2 Post-operative CT scan. Computed tomography (CT) showed that the large mass was already resected and the chest wall was reconstructed using synthetic material.

resection of the lesion, which was measured to be 10 cm × 6.5 cm × 4.8 cm and diagnosed to be PMGCTB with aneurysmal bone cyst. Immunohistochemical examination (IHC) showed that P63 and Ki-67 were stained positive (about 30-40%), while smooth muscle actin (SMA), S-100, CR, HBME1, Desmin, Caldesmon, PCK and CD31 were stained negative. The IHC results not only confirmed the diagnosis of MGCTB but also ruled out the possible mesothelioma of pleura or muscle-derived tumors (*Figure 3*). Besides, no positive cytological results were found in

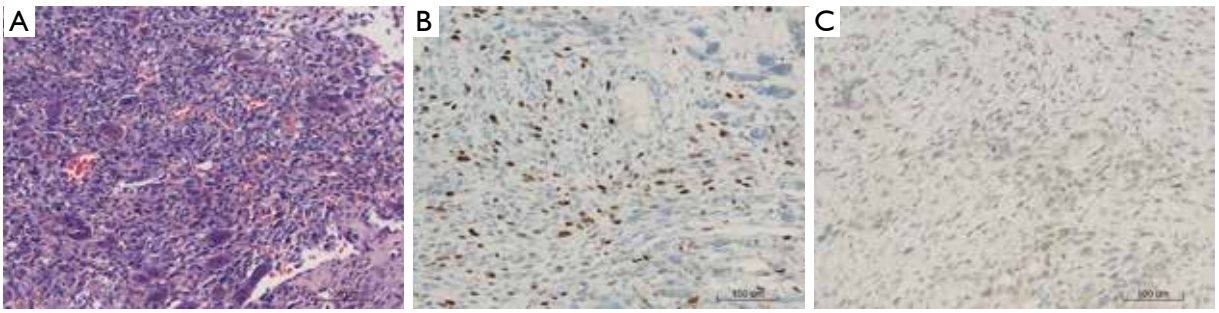

Figure 3 HE and IHC staining. HE (A) showed that the benign GCTB features were obvious in PMGCTB as the multinuclear giant cells were seen; IHC showed that P63 (B) and Ki67 (C) were stained positive (20×). IHC, immunohistochemical examination; GCTB, giant cell tumor of bone; PMGCTB, primary malignancy in GCTB.

the pleural effusion. Subsequently, this man underwent radiation treatment to reduce the high rate of recurrence and metastasis. Follow-up was performed with CT every three months. Since the operation and radiotherapy, the man has been free of recurrence or metastasis for 1.5 years.

Discussion

MGCTB is a very rare subtype of GCTB and only accounts for 1-2% of all reported cases (2). This disease was previously called malignant giant cell tumor which includes giant cell—rich osteosarcomas, malignant fibrous histiocytoma, locally aggressive giant cell tumor of bone, and metastatic benign giant cell tumor. This tumor was renamed malignancy in giant cell tumor by Dahlin *et al*. and divided into primary and secondary malignancies (3). Of which, PMGCTB is extremely rare.

We reported a 57-year-old man suffering from PMGCTB in his rib. Unni (4), who also took part in defining and describing this disease, considered that patients suffering from MGCTB were older than those suffering from benign giant cell tumors. Our finding is consistent with Domovitov *et al*. (5). Like benign GCTB, the malignancies preferentially invade the ends of long bone including distal femur, proximal tibia and distal tibia. Pelvis and sacrum are also common invading sites.

The clinical manifestation of PMGCTB is always nonspecific. The most common symptoms are pain and swelling, which may last for months (average 12 months; median 6 months) (2). Radiologic findings may show osteolytic lesions with well-circumscribed margins that are similar to those of conventional GCTB (6). We could not easily distinguish malignancies from the benign ones even when the former has a metastasis or a soft tissue invasion, because the benign ones also have the capacity of local invasion.

The diagnostic criteria of MGCTB were first made by Jaffe *et al*. (6). The MGCTB contained a giant-cell lesion and sarcomatous stroma. Hutter *et al*. (7) and Dahlin *et al*. (3) further elaborated the criteria. Briefly, MGCTB had plump spindle or ovoid shaped stromal cells with multinucleated giant cells intermingling. The nuclei were elongated and vesicular. The cytoplasm was pink and has distinctly circumscribed borders. Most cells had hyperchromatic nuclei and their nucleoli were prominent. Mitotic activity could be always present with atypical mitosis. Usually, there was almost no intercellular substance. The case in our study suited all the MGCTB characteristics mentioned above. According to the definition by Dahlin *et al*. (3), MGCTB is a high-grade sarcoma since it contains both giant-cell lesion and sarcomatous stroma (8). Almost all lesions of PMGCTB contain many conventional giant cells. Except for benign GCTB, the differential diagnosis can be made difficult and confusing by osteosarcoma, fibrosarcoma and undifferentiated high-grade pleomorphic sarcoma which also contain giant cells. MGCTB is quite different from the benign ones in terms of treatment and prognosis, and thus, pathological diagnosis is of great importance. We suggest that more samples should be obtained when using biopsy. Other than pathological examinations, immunohistochemistry argument is also as helpful and important. P53 was a tumor suppressor gene, the expression of which would be very strong in secondary MGCTB and play a role in the malignant transformation of benign GCTB (9,10). P63, one kind of P53 family, is considered to be a special mark of GCTB (11). Besides, we doubt whether the cell-cycle-associated proteins, such as P63 and Ki67 that reflect cell proliferation, may help with differential diagnosis (9).

In addition to correct diagnose, resection and reconstruction of the chest wall is another important thing. Different views are existent referring to the extension of resection and 4 cm is selected as a common distance between surgical margin and malignant lesions (12). Chest wall reconstruction is thought to be necessary if the defect is wide and located in anterior or lateral chest wall (13). Dacron patch, medical polymethacrylate and metallic material are commonly used. Marlex and polypropylene net are popular in recent years (14).

The treatments of PMGCTB include surgery, chemotherapy, radiotherapy, and surgery combined with chemotherapy. Previous studies show that patients treated by surgery combined with chemotherapy had a significantly higher one-year survival rate than those treated by surgery alone, but the five-year survival rates were almost the same. Since radiotherapy alone was not recommended (8) and Ki67-positive cells are chemo-resistant (9), we chose surgery combined radiotherapy according to the National Comprehensive Cancer Network Guideline. The prognosis of this disease is controversial. But Stepan thought that PGMCTB had a high survival rate of 50-70% (5).

In summary, PMGCTB is a confusing disease, since its clinical manifestation and radiologic findings were nonspecific and similar to that of benign GCTB. Even pathological examination as the gold standard may make a mistake. We know the secondary MGCTB is derived from surgery or radiotherapy-treated benign ones, but the origination of PMGCTB is still unknown though P53 may play a role in this progress (10). We reported a person suffering from PMGCTB in ribs and treated by combining surgery with radiotherapy. The patient has been free of recurrence or metastasis for 18 months. From this result we could learn that an operation followed by radiotherapy was effective for the patients suffered from Ki67-positive-PMGCTB. Follow-up should continue and more samples should be collected to further study this disease.

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Brief Report

Calcified amorphous tumor in left atrium presenting with cerebral infarction

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Abstract: Calcified amorphous tumor (CAT) of the heart is an extremely rare cardiac mass. We describe a case of cardiac CAT in a 70-year-old Korean female who presented with acute onset dysarthria and right side weakness. Echocardiography and chest computed tomography revealed a left atrial mass that originated from the interatrial septum. The patient underwent surgical resection and pathologic examination demonstrated CAT. Postoperative course was uneventful and she was followed without recurrence.

Keywords: Calcification; cardiac tumor; cerebral complication

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Introduction

Calcified amorphous tumor (CAT) is a non-neoplastic tumor composed of calcified nodules on a background of amorphous fibrous material and it can cause symptoms of embolization or obstruction of calcified fragments. Herein, we describe a patient with CAT that was presented with cerebral infarction.

Case report

A 70-year-old Korean female with a history of hypertension and diabetes mellitus was referred to our hospital. She complained of abruptly developed dysarthria and right side weakness. Her blood pressure, pulse rate, and body temperature on presentation were 140/90 mmHg, 87 beats/min and 36.7 ℃. Laboratory findings showed white blood cell count of 8,700/L, blood urea nitrogen of 28.4 mg/dL, creatinine of 0.77 mg/dL and serum calcium of 9.4 mg/dL. Brain magnetic resonance imaging showed acute infarction in pons and multiple high signal intensities in both cerebral subcortical white matter and periventricular white matter on FLAIR images. Her symptoms were improved after medical treatment and echocardiography revealed a hyperechoic and calcified mass in the left atrium (*Figure 1*). The mass originated from the interatrial septum 2 cm above the foramen ovale. Mitral regurgitation and mitral annular calcification were not found and left ventricular function was preserved. Chest computed tomography was performed and approximately 2 cm-sized, oval shaped ring like calcified mass in the left atrium was noted in the non-enhanced and enhanced imaging (*Figure 2*).

The patient underwent cardiac exploration and the mass was noted in the left atrium and that was attached to the interatrial septum (*Figure 3*). The cardiac mass was completely resected and postoperative course was uneventful. On the basis of the pathological examination (*Figure 4*), the cardiac mass was demonstrated with CAT of the heart. The patient was doing well with no evidence of the recurrence of the tumor and cerebral infarction 14 months after operation.

Discussion

Primary cardiac tumors are not so frequent and 75% of primary cardiac tumors are benign and 25% are malignant.

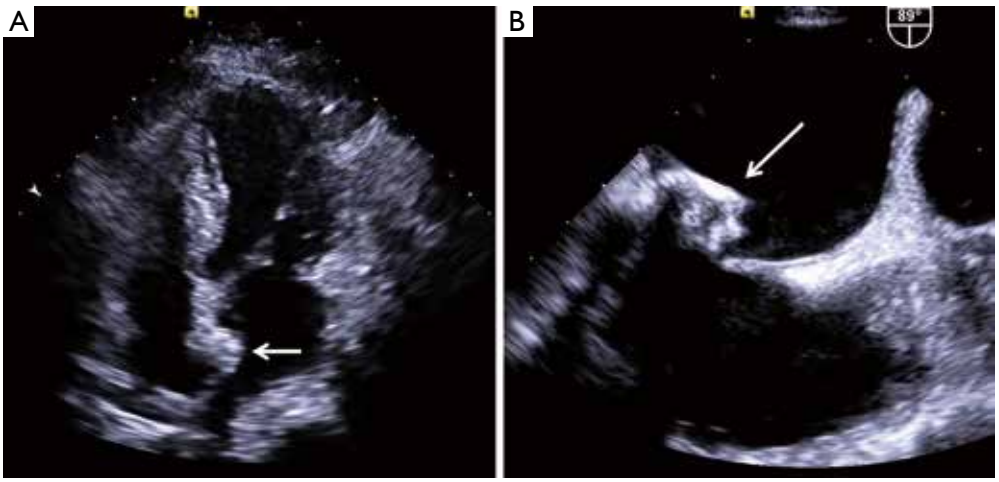

Figure 1 (A) Transthoracic (B) and transesophageal echocardiography revealed a calcified mass in the left atrium. White arrow indicates the mass.

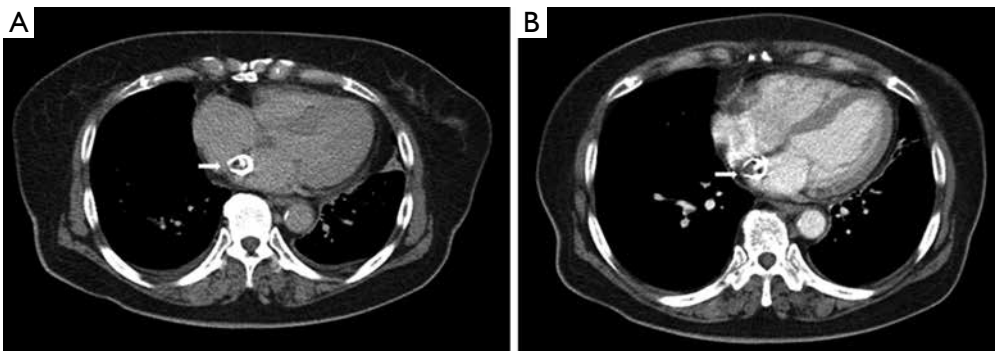

Figure 2 Chest computed tomography demonstrating approximately 2 cm-sized, calcified mass in the left atrium which was attached to the interatrial septum. (A) Non-enhanced image; (B) enhanced image.

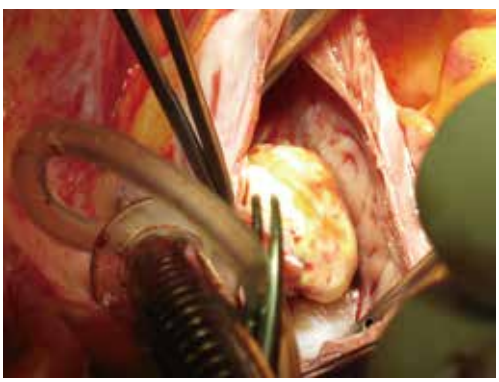

Figure 3 Operation field shows oval and yellowish glistening mass.

Most common benign cardiac tumors are myxoma and they occupy 50% of all benign cardiac tumors. Systemic embolization is the second most common presentation of myxoma, comprising 30% to 40 % of patients.

CAT of the heart is a rare non-neoplastic cardiac mass that mimics malignancy and causes symptoms of obstruction or embolization (1) and diffuse calcific involvement of myocardium rarely elicits congestive heart failure symptoms (2). Fifty percent of embolic episodes of myxoma were occurred in the central nervous system. Retinal artery embolization had been described in patient with myxoma and visual loss due to cardiac CAT was also reported (1). However, pontine infarction caused by cardial CAT has not been reported.

Previously it was named "pseudotumors" and had represented organized thrombi (3). In 1997, Reynolds *et al.* first reported 11 cases of CAT of the heart during 30 years (4). From these Mayo clinic's series, CAT can originate in any of cardiac chambers and the distribution of age and predilection of sex, tumor size and configuration are variable and most of the tumors were located intracavitary and motionless.

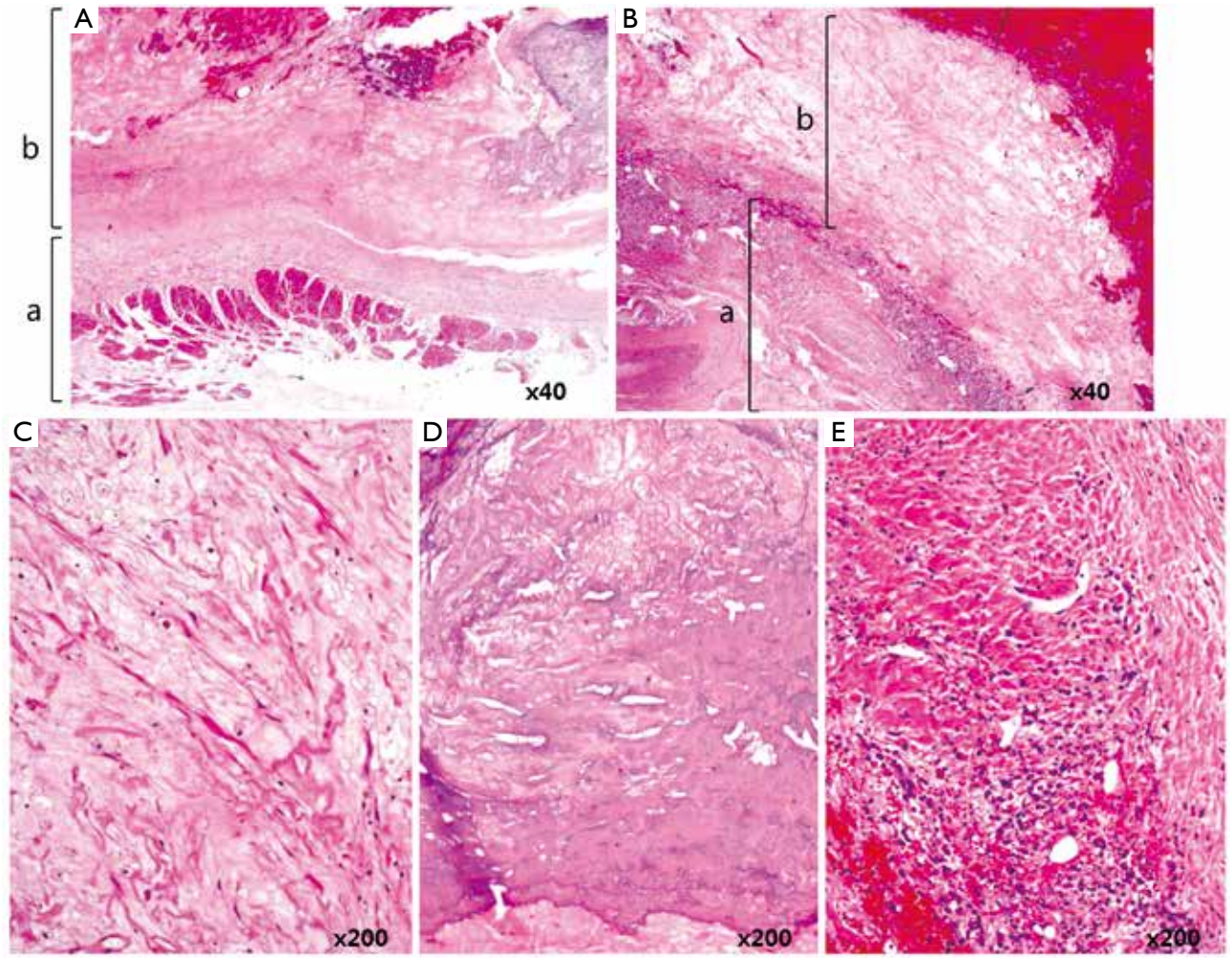

Figure 4 Cardiac calcified amorphous tumor after decalcification. Intracavitary cardiac mass composed of dense calcification in a background of amorphous degenerating fibrinous material and chronic inflammation. (A) Cardiac wall (Hematoxylin and eosin; ×40); (B) intracavitary mass with hemorrhage and calfication (Hematoxylin and eosin; ×40); (C) amorphous degenerating fibrinous material (Hematoxylin and eosin; ×200); (D) dense calcification (Hematoxylin and eosin; ×200); (E) chronic inflammation (Hematoxylin and eosin; ×200).

CAT is a nonneoplastic cardiac tumor and has characteristic histologic features which include the presence of calcified nodules in an amorphous background of fibrin with degeneration and focal chronic inflammation (4). Although pathogenesis of cardiac CAT has been unknown, association with organized thrombi, primary or secondary hypercoagulability (5), or abnormal calcium-phosphorous metabolism especially in hemodialyzed patients (6,7) were suggested.

CAT should be differentiated with calcified myxoma or fibroma, calcified cardiac tuberculoma, vegetation as well as intracardiac carcinosis, especially in patients with hemodialysed end stage renal disease and abnormal calcium metabolism (7,8).

Surgical excision is mandatory for diagnosis and treatment. Resection of the lesion usually curative, but postoperative recurrence of CAT has been rarely reported and postoperative regular follow-up with cardiac imaging studies is recommended, especially in case of incomplete resection (5).

Cardiac CAT is a rare benign condition in the heart and it can be mimicked with benign and malignant cardiac tumors, predominantly myxomas, and nonneoplastic processes that include thrombi, emboli, and vegetations. Therefore, it has to be considered in the differential diagnosis prior to surgery.

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Brief Report

Single-staged uniportal VATS major pulmonary resection for bilateral synchronous multiple primary lung cancers

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Abstract: It is difficult to make diagnosis and treatment decision for patient with bilateral multiple pulmonary foci. Surgical resection can offer sufficient specimens for diagnostic differentiation and the greatest chance for long-term survival in patient with presumptive synchronous multiple primary lung cancers (SMPLC). Since uniportal video-assisted thoracoscopic surgery (VATS) is a less invasive technique and has been attempted in lung cancer surgery, we transferred it into the management of SMPLC. In this paper, we report two cases of bilateral SMPLC managed through single-staged uniportal VATS with major pulmonary resection. This successful attempt provides an optimized idea to accomplish simplified mini-invasive diagnosis and synchronous treatment using the less invasive uniportal VATS technique for the management of SMPLC, especially for those with multiple bilateral lesions.

Keywords: Synchronous multiple primary lung cancers (SMPLC); video-assisted thoracoscopic surgery (VATS); single-port; ground glass opacity (GGO); diagnosis; treatment

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Introduction

Difficulty in diagnosis and treatment decision making for patient with bilateral multiple pulmonary foci usually raises a clinical dilemma for clinicians. An aggressive surgical approach can offer sufficient specimens for diagnostic differentiation and the greatest chance for long-term survival in patient with presumptive synchronous multiple primary lung cancers (SMPLC) (1,2). In such situation, mini-invasive technique of video-assisted thoracoscopic surgery (VATS) has been reported to be effective (1,3,4). Since uniportal VATS has been attempted as a less invasive technique (5), we transferred it into the management of presumptive SMPLC. Here, we present two cases of bilateral SMPLC managed through single-staged uniportal VATS with major pulmonary resection, which provides simplified mini-invasive diagnosis and synchronous treatment.

Cases report

Patient 1 was a 67-year-old female, who was presented with chest pain for about 2 months. Preoperative high-resolution computed tomography revealed four ground glass opacity (GGO) lesions (two in the right upper lobe, each in the left upper and lower lobe, respectively, *Figure 1A-D*). Patient 2 was a 53-year-old female, who was admitted with a mass in the right upper lobe (*Figure 1E*) and a GGO lesion in the superior segment of the left lower lobe (*Figure 1F*). Both of them were presumptively diagnosed with bilateral SMPLC. The preoperative staging work-up indicated no sign of lymphadenopathy or distal metastasis. Given no surgical contraindication, single-staged uniportal VATS for bilateral pulmonary foci was planned for each of them with written informed consent.

General anesthesia with double-lumen endotracheal intubation was administered to each of them. A 5 mm 30° thoracoscope was used for inspection. Patient 1 was firstly placed in a right lateral decubitus position. On the left, a 3.5 cm incision was made in the fourth intercostal space at the anterior axillary line. Each of the two lesions was identified through digital palpation and the surface of the lung right on the top of each lesion was marked

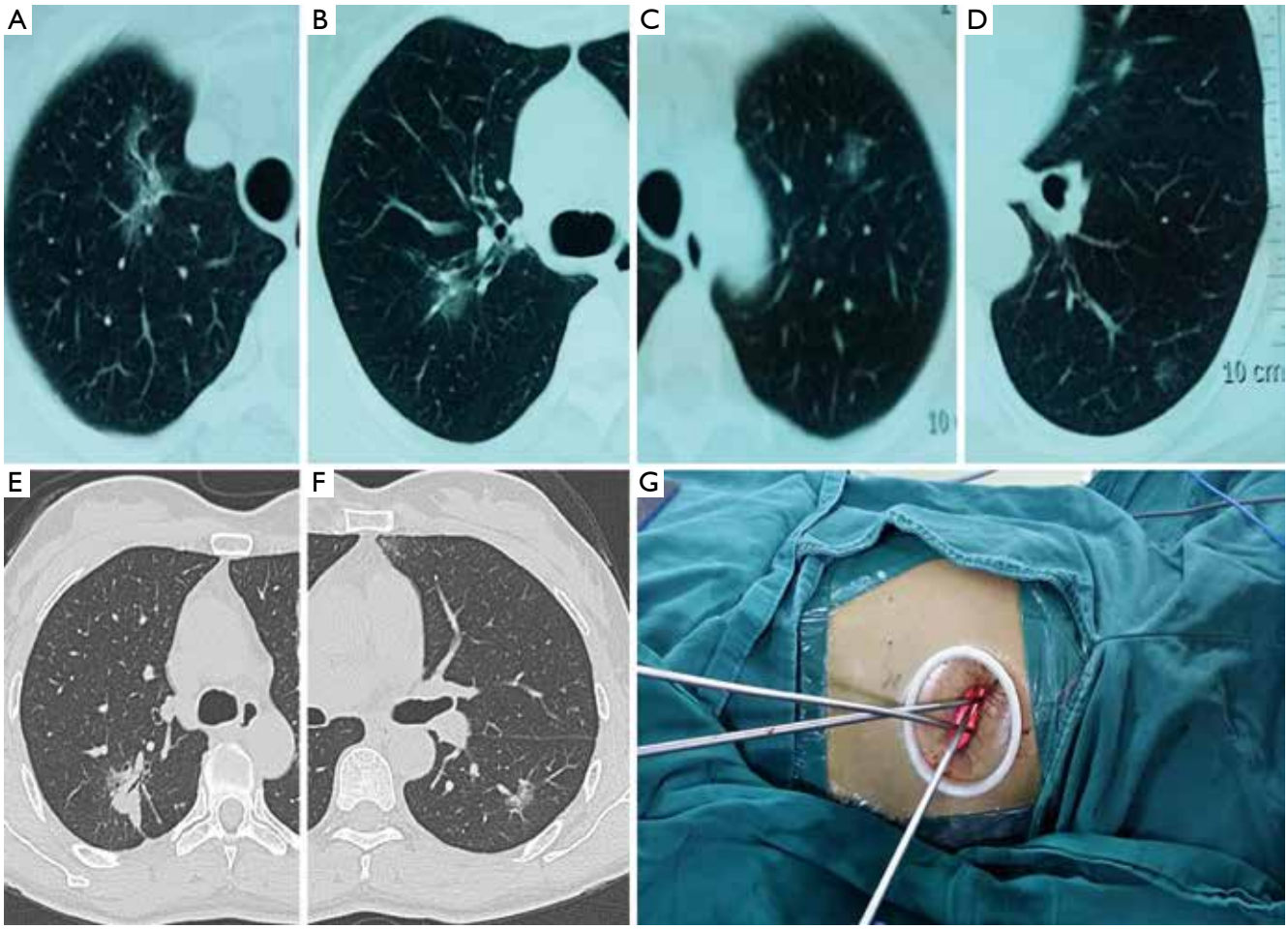

Figure 1 (A-D) High-resolution computed tomography (HRCT) reveals four ground glass opacity (GGO) lesions of patient 1 (a 3.2×1.5 cm lesion located at the apical segment of the right upper lobe, a 1.3×1.0 cm lesion located at the posterior segment of the right upper lobe, a 1.0×0.8 cm lesion located at the apical segment of the left upper lobe, and a 0.8×0.8 cm lesion located at the posterior basal segment of the left lower lobe); (E,F) HRCT reveals two tumor-like lesions of patient 2 (a 3.0×2.5 cm mass located at the posterior segment of the right upper lobe and a 1.6×0.9 cm GGO lesion located at the superior segment of the left lower lobe); (G) surgical image of instrumentation during right upper lobectomy.

using a suture, which was also used for retraction during resection. Then wedge resections were performed using curved endostaplers with margins ≥2 cm. Frozen-section examination confirmed an adenocarcinoma in the upper lobe and a carcinoma *in situ* in the lower lobe. One chest tube was placed at the posterior part of the incision. After the left-side operation, the patient was rotated to the opposite side for right upper lobectomy. Cushions were used to lift the patient to avoid kicking or compression to the contralateral chest tube during positioning. On the right, a 4.5 cm incision was made in the fifth intercostal space at the anterior axillary line (*Figure 1G*). Right upper lobectomy (*Figure 2*) was performed with the right upper pulmonary vein, arterial branches, bronchus and pulmonary fissures dissected and divided sequentially. Then frozen-section examination confirmed two adenocarcinomas and systematic lymph node (LN) dissection was performed (a total of 7 stations and 15 LNs were harvested). One chest tube was placed at the posterior part of the incision. Patient 2 was also firstly placed in a right lateral decubitus position to undergo left lower lobe superior segmentectomy (*Figure 3*) via a 4.5 cm incision made in the fifth intercostal space at the anterior axillary line. The superior segmental artery, bronchus, drainage vein, and the intersegmental plane were dissected and divided sequentially. Frozen-section examination confirmed an adenocarcinoma followed by

Figure 2 Right upper lobectomy (6). Single port was made in the 5th intercostal space about 4 cm. Wedge resection was first performed, which confirmed the malignant lesion; the right upper lobe was gripped and tucked dorsally; the front of the right hilus was exposed, and the pleura were peeled with the electrocoagulation hook; the right superior pulmonary vein was dissected and transected by a stapler; the apico-anterior arterial trunk was dissected and transected by a stapler; after that, the posterior ascending artery was ligated with silk thread and transected by harmonic scalpel; the next step was to dissect and transect the right upper bronchus; at last, the pulmonary fissures were completed by stapler; the specimen was then retrieved via a self-made protective bag using a rubber gloves; systemic mediastinal lymph node dissection was following. We stuck to the non-grasping and en bloc strategies. Firstly, stations 2 and 4 LNs were dissected; station 3 LNs were dissected; the inferior pulmonary ligament was transected and the station 9 LNs were simultaneously harvested if there was any; the last step was to dissect the subcarinal station 7 LNs; bronchial arteries across the subcarinal area were clipped by hem-o-lock and cut by the harmonic scalpel. Available online: http://www.asvide.com/articles/277

Figure 3 Superior segmentectomy of left lower lobe (7). The target nodule in superior segment of left lower lobe was firstly located by digital palpation and marked via a stitch; the posterior part of the major pulmonary fissure was incompletely developed, and was opened with electric hook and harmonic scalpel to facilitate the exposure of the interlobar artery; the superior segmental artery had two branches, which were dissected and transected by stapler one by one; subsequently, the underlying superior segmental bronchus was dissected and transected by a gold color stapler; the posteroinferior drainage vein was isolated, and clipped by a hem-o-lock, cut by harmonic scalpel; the last step was to identify the intersegmental plane and cut it; the intersegmental plane was identified by inflation of left lung and cut along the remnant basilar artery and bronchus; the specimen was then retrieved via a self-made protective bag using a rubber gloves. Available online: http://www.asvide.com/articles/278

systemic LN dissection (a total of four stations and seven LNs were harvested). After the left-side procedure, she was rotated to the opposite side for right upper lobectomy followed by systemic LN dissection (a total of five stations and seven LNs were harvested) after confirmation of adenocarcinoma by frozen-section examination. Chest tube strategy was the same as did for patient 1. The operation time for patient 1 and 2 were 260 and 285 min, respectively. The intraoperative blood loss of patient 1 and 2 were 30 and 60 mL, respectively. The postoperative courses were both uneventful. Pathological examination documented four primary lung cancers of patient 1 (right upper lobe, two minimally invasive adenocarcinomas, T2aN0M0 and T1aN0M0, respectively; left upper lobe, minimally invasive adenocarcinoma, T1aN0M0; left lower lobe, adenocarcinoma *in situ*, TisN0M0) and two primary lung cancers of patient 2 (right upper lobe, acinar predominant adenocarcinoma, T1bN0M0; left lower lobe, lepidic predominant adenocarcinoma, T1aN0M0).

Discussion

The common criteria used for differentiating between SMPLC and intrapulmonary metastases depend on the results of pathologic examination and even molecular and genomic analysis (8). However, preoperative diagnosis is often difficult due to difficulty in obtaining sufficient specimens for histological examination whether through bronchoscopy or percutaneous puncture, especially for those small peripheral lesions. Single-staged procedures executed via traditional multiportal VATS have been demonstrated to be feasible and safe for selected patients with bilateral SMPLC (3). Although it may be also reasonable to perform delayed resections for some small GGO lesions with no negative effect on outcomes (9), we

prefer to perform single-staged surgery when the lesions are highly suspected of malignancy. Since introduced by Rocco *et al.* in 2004 (10), sporadic reports on uniportal VATS for lung cancer have been published (5,11,12). Uniportal VATS causes less postoperative pain and fewer paresthesia owing to less intercostal space involved (13). For our patients, it's hard to procure thorough diagnoses for all lesions through neither bronchoscopy nor percutaneous puncture due to their disperse locations, small sizes, and manifestations of GGO. To simplify the diagnosis and treatment course, we transferred the less invasive technique of uniportal VATS into the management of SMPLC to achieve mini-invasive diagnosis and synchronous treatment. Systemic LN dissection is routinely performed when anatomic pulmonary resection (lobectomy or segmentectomy) is planned in our daily work. But for pure GGO lesions, especially those ≤1 cm, wide wedge resection with adequate free margin seems to be oncologically enough because there is seldom invasiveness or LN involvement (14). Therefore, we didn't perform LN dissection for the left side of patient 1 while station seven would be dissected from the right side.

This successful attempt first demonstrates the feasibility of simplified mini-invasive diagnosis and synchronous treatment using bilateral uniportal VATS major pulmonary resection for the management of SMPLC with multiple bilateral lesions.

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Review Article

Cardiovascular, diabetes, and cancer strips: evidences, mechanisms, and classifications

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Objectives: To report and name firstly that there are cardiovascular disease (CVD), diabetes mellitus (DM) and cancers (CDC) strips; and disclose their mechanisms, classifications, and clinical significances.

Study design: Narrative and systematic review study and interpretive analysis.

Methods: Data sources and study selection: to collect and present related evidences on CDC strips from evidence-based, open-access, both Chinese- and English-language literatures in recent 10 years on clinical trials from PubMed according to keywords "CVD, DM and cancers" as well as authors' extensive clinical experience with the treatment of more than fifty thousands of patients with CVD, diabetes and cancers over the past decades, and analyze their related mechanisms and categories which based on authors' previous works. Data extraction: data were mainly extracted from 48 articles which are listed in the reference section of this review. Qualitative, quantitative and mixed data were included, narratively and systematically reviewed.

Results: With several conceptual and technical breakthrough, authors present related evidences on CDC strips, these are, CVD and DM, DM and cancers, cancers and CVD linked, respectively; And "Bad SEED" +/– "bad soil" theory or doctrine may explain this phenomenon due to "internal environmental injure, abnormal or unbalance" in human body resulting from the role of risk factors (RFs) related multi-pathways and multi-targets, which including organ & tissue (e.g., vascular-specific), cell and gene-based mechanisms. Their classifications include main strips/type B, and Branches/type A as showed by tables and figures in this article.

Conclusions: There are CDC strips and related mechanisms and classifications. CDC strips may help us to understand, prevent, and control related common non-communicable diseases (NCDs) as well as these high risk strips.

Keywords: Cardiovascular disease (CVD); diabetes; cancer; evidence; mechanisms

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As we all known, chronic non-communicable diseases (NCDs) are now totally over 1.0 billion in the globe and may account for 85% of deaths nowadays. It's a big problem and challenge due to leading to 70% burden of public health. And we find that there is a common phenomenon of co-morbid diseases in NCD, especially three most commonly occurring, namely, cardiovascular diseases (CVDs), diabetes mellitus (DM), and cancers, which are responsible for more than 25 million deaths in the world each year, and millions more live with one or more of these diseases. They undermine health, shorten life expectancy, and cause enormous suffering, disability, and economic costs due to lifestyle changes, urbanization and longevity according to the USA agenda and the Report on Cardiovascular Diseases in China [2010] (1-4). Here, the authors found and firstly named it "CVD-DM-cancers

strips" (CDC strips) because they are linked with each other. NCD, especially CDC strips author discovered, are the major causes of morbidity and mortality, high direct cost of care, high indirect cost in loss of production. However, these strips could be prevented by controlling the modifiable risk factors (RFs).

In this article, with several conceptual and technical breakthroughs, we will present related evidences on CDC strips from open-access literatures on clinical trials as well as the great clinical experiences, and analyze its related categories and mechanisms which based on our previous works (5-9).

CDC strips: evidences

These evidences on CDC strips from open-access literatures are based on the linkages between CVD and DM, DM and cancers, cancers and CVD, respectively and each other. And we think these evidences are enough to support our views on CDC strips.

CVD and DM linked

CVD has a raised and potentially modifiable risk of type 2 diabetes (T2DM). Patients with coronary heart disease (CHD) and impaired fasting glucose (IFG) have a very high rate of conversion to T2DM (4).Those patients with more RFs, such as higher body-mass index (BMI), fasting glucose, C-reactive protein (CRP), triglycerides, homeostatic assessment of insulin resistance (HOMA-IR) and diastolic blood pressure at baseline, 44% developed diabetes. 26.7% overweight women with one or more cardio-metabolic high-risk factors developed gestational DM in a subsequent pregnancy (10). Thus, metabolic screening could be included in routine health assessments. In the Valsartan Antihypertensive Long-Term Use Evaluation trial, at baseline, more than 1/3 were diabetic, and during follow-up, new-onset diabetes was about 13% (3). There is a high prevalence and incidence of diabetes in patients with CHD and chronic heart failure (CHF) (11,12), and new onset diabetes is more likely to occur during treatment with ß-blockage.

Also, T2DM has a raised and potentially modifiable risk of CVD. Among screen-detected diabetes, 10-year risk of CHD was 11% in women and 21% in men. Among them, 73% had high blood pressure (HBP) and high cholesterol levels were in 70%. Definitely, T2DM was linked with CVD; especially those were not being treated. There were often micro-vascular or macro-vascular complications, peripheral vascular disease (PVD) in T2DM, but those patients who received intensive glucose therapy had a lower risk or a reduction in vascular events (13,14). Survival of coronary artery bypass grafting (CABG) surgery patients with diabetes is greatly affected by associated co-morbidities of PVD and renal failure (15). Suppression of atherosclerosis (AS) in T2DM with pioglitazone therapy is linked to its ability to raise HDL cholesterol for reducing carotid intima-media thickness (CIMT) progression (16). Besides, DM is highly associated with cardiomyopathy (17). Common RFs, such as BMI and waist circumference, were both strongly linked to CVD and especially to DM. The risk for T2DM was increased by 78% in the overweight group (18).

CVD is a major contributor to morbidity and mortality in T2DM. Patients with diabetes at baseline had the highest cardiac morbidity defined as myocardial infarction (MI) and HF with a hazard ratio of 2.20. Those with new-onset diabetes had significantly higher cardiac morbidity, especially more congestive HF (CHF), than those without diabetes, with a hazard ratio of 1.43 (3). The coincident linkage suggests that identification of the underlying genes may help clarify the relationship between diabetes, metabolic syndrome (MetS), and CVD (19). For example, there is often coronary artery calcification (CAC)—a marker of subclinical atherosclerosis in subjects with type 1 diabetes mellitus (T1DM) (20).

DM and cancers linked

DM has a raised and potentially modifiable risk of cancers. By examined the association of DM history with total and common site-specific cancers, scientists found that DM significantly increased the risk of liver cancer for both men and women. Significant increased and reduced risk due to DM for men were also found for non-Hodgkin lymphoma (NHL) and stomach cancer, respectively. For females, a reduced risk of stomach cancer due to DM was also revealed.

A history of T2DM is one of few consistent RFs for pancreatic cancer. Potentially modifiable RFs related to fasting insulin and glucose concentrations may influence its risk. Therefore, dietary fat associated with higher fasting insulin concentrations may increase its risk in smokers. Pancreatic cancer is a powerful diabetogenic state and appears to be associated with conventional RFs for DM. This DM is often new-onset; it is likely induced by the tumor.

Weight is associated with greater prostate cancer

mortality in men, which is mediated by mechanism(s) other than the characteristic metabolic alterations of diabetes. As the same, MetS was a RF for incident colorectal cancer in men but not women (21). It may be a marker encouraging tumor initiation, promotion, and/or progression.

DM is associated with breast cancer. Hyperinsulinemia and the MetS are both RFs for breast cancer. After the diagnosis, women with a BRCA1 or BRCA2 mutation face a 2-fold increase in the risk of diabetes (22). However, gestational DM was inversely associated with breast cancer in Hispanic women, a population with a high prevalence of diabetes and non-Hispanic Whites (23).

There was a significant positive correlation between acute lymphoblastic leukaemia (ALL) and T1DM, and the incidence of chemotherapy-induced transient hyperglycemia in childhood ALL is common.

DM and cancers incidence and mortality linked focused mainly upon T2DM. As incidence of T1DM increases, by around 3% annually among children, as well as the inconsistency within available results, it's necessary to study further its impact upon other cancers incidence and mortality increases.

Cancers and CVD linked

Cancers have a raised and potentially modifiable risk of CVD. CVD is the leading cause of late morbidity and death among cancer survivors. With the high rates of kidney cancer in European countries, there was an increased risk for self-reported hypertension (24). And polycystic ovary syndrome (PCOS) is also associated with increased risk of cardiovascular morbidity.

High-dose chemotherapy may develop late cardiotoxicity in cancer patients although it is very effective in children all (25). Angiotensin-converting enzyme inhibitors (ACEI), e.g., Enalapril or Perindopril seem to prevent elevations in troponin I or troponin T (26,27). Clinical and animal studies showed that increased TnI or TnT is an indicator of cardiotoxicity and poor cardiologic outcome (28,29). The LVEF significantly declined and a trend for LVEF to decline was observed in advanced non-small cell lung cancer (NSCLC) patients receiving cisplatin-gemcitabine (CG) or epirubicin-gemcitabine (EG) as first-line treatment resulting from cardiotoxicity due to irreversible cardiomyopathy (30). Onset of HBP during treatment for advanced NSCLC may be associated with improved outcomes. CVD or CVEs frequently occur after lymphoma therapy. Patients are at long-term high risk of CHF after doxorubicin-based chemotherapy for NHL and need therefore life-long monitoring (31), for example, genetic variation of human cytochrome p450 reductase as a potential biomarker (32). Gonadotropin-releasing hormone (GnRH) agonists are associated with greater risk of CHD and MI in men with prostate cancer (33), but it do not seem to increase cardiovascular mortality (CVM) in those. As literature reported, a history of chemotherapy-induced cardiomyopathy was present in 21%, and 5.7% had known AS disease. One fourth had hypertension; 32.1%, dyslipidemia and 13%, DM.

Atrial arrhythmias are common after thoracic surgery, and the incidence of no sustained ventricular tachycardia after major thoracic surgery is 15%. Postoperative cardiovascular events are often seen in patients with cancers. For example, postoperative supraventricular arrhythmias are a common complication in elderly patients undergoing lung resection surgery for lung cancer.

Among adult survivors, exposure to total body irradiation or abdominal plus chest radiation, and a sedentary life-style are associated with cardiovascular RF cluster (CVRFC). Radiation exposure (e.g., X-ray) during the diagnosis and treatment may lead to or increase risk of both CVD or CVEs and cancers. On the one hand, long-term survivors of cancers treated with radiation therapy have an increased incidence of irradiation-related CHD. Radiotherapy for breast cancer as delivered in the 1970s has been associated with increased risk of CVD (34), and to refrain from smoking may reduce this risk. On the other hand, interventional diagnosis and treatment of CVD increase obviously exposure of radiation dose and cancer risk. Therefore, we should try to find novel methods which resulted in significant reductions in patient radiation dose and cancer risk, for example, dual-source CT coronary angiography.

CVD has a raised and potentially modifiable or non-modifiable risk of cancers. Hypertension is a known risk factor for renal cell carcinoma (RCC), the role and biological mechanisms of hypertension in RCC related to common genetic variants of angiotensinogen (AGT), particularly those in the promoter, which increased RCC risk among subjects who are hypertensive or overweight (35). Apolipoprotein E (ApoE) genotypes associated with increased risk of CHD, may influence development of colon cancer among those who are older at diagnosis (36).

Besides, the MetS is not only associated with increased risk of T2DM and CHD, but also with breast cancer, due primarily to the same RFs. Androgen deprivation therapy in patients with prostate cancer is commonly associated

Table 1 Mechanisms of CDC strips involved single or multiple risk factors (RFs)

E(e)SEED-BasED	Lifestyles	Main RFs
E(e)	Environment	WAS pollutions, irradiation, lower income and social status, self-diseases: such as acute or chronic infection, etc.
S	Sleeping	Insomnia, stay up later; OSA, etc.
E	Emotion	Stress, depression, etc.
E	Exercise	Physical inactivity, setting for a long time, overweight, obese, etc.
D	Diet	Unhealthy diet, active or passive smoking, dead drunk, poor nutrition, reuse of cooking oil, salt intake (>6 g/day), etc.
B	Behavior	Drug addiction, gambling, overflow sexual life, etc.
/a	Age (38,39)	Age, aged, no healthcare, etc.
/s	Safety	Unexpected events: traffic crash, drown, electric shock, fall, etc.
	Sex (39)	Male or female, divorced, bereft of one's spouse, lonely, etc.
	Study	Not study, not thinking, lack of medical knowledge, etc.
E	Education (40)	Lower education, lack of knowledge, etc.
	Employment	Unemployed, high risk occupation (e.g., IT, account), etc.
	Ethnic	The Black, epidemic region, etc.
D	Disease	A positive family history, such as AS; hypertension; CHD; DM, etc.
		Abnormal index, such as GFR (41); ABI (42); CIMT (43,44), etc.
		Precancerous pathogenesis (45), etc.
	Drug	Adverse drug effects, no herbs, no Traditional Chinese medicine, etc.

All of these RFs, standard, common, classic, single or multiple modifiable (lifestyle related) or non-modifiable (genetic), confer significant risk for developing CVD, DM, cancer, even CDC strips. General or specific RFs screening recommendations for CDC strips are outlined. In addition, E(e)SEED-BasED, healthy lifestyles were named for Hu's healthy lifestyles (HHL). WAS, water-air-sound; OSA, obstructive sleep apnea; AS, ankylosing spondylitis; CHD, coronary heart disease; DM, diabetes mellitus; GFR, glomerular filtration rate; ABI, ankle brachial index; CIMT, carotid intima media thickness; CVD, cardiovascular disorder.

with CVD, obesity, MetS and DM (37). An increased risk of RCC has been reported in subjects with hypertension and a history of DM.

From all above, due to CVD, DM and cancers linked, each other, and as co-morbid diseases, the authors think that there are actually CDC strips and named them firstly. And, the authors think that OOH syndrome is a high risk status and easy to develop CDC strips.

CDC strips: mechanisms and classifications

Here, the authors explore related mechanisms on CDC strips with several novel conceptual breakthrough, classifications (total strips, Branches/type A and main strips/type B) and clinical significance.

Mechanisms

As acquired diseases, minorities of CDC strips are related to genetic factors. The development of most of CDC strips was related mainly to lifestyles, which involved mechanisms of multi-pathways and multi-targets. On the one hand, the shared common main RFs including unhealthy lifestyles (here we mean them "Bad SEED") may link for the development of CDC strips (*Table 1*). These RFs, which related to "E(e)SEED-BasED" healthy lifestyles developed in our previous works (5-7), and named for Hu's healthy lifestyles (HHL), include environmental factors: water-air-sound (WAS) pollutions, irradiation, stress, lower social status and economic income, etc; sleep factors: insomnia, OSA; emotion factors: depression, nervous, psychological disorders; exercise factors: physical inactivity, sitting too much; dietary factors: tobacco use, harmful use of alcohol, and unhealthy diet (water, vegetable and fruits intake not enough, but red meat intakes over), etc, as well as other factors, such as age, sex, education, disease and drug. On the other hand, the shared common RFs including a positive history of family related genetic factors (here we mean them

Table 2 Mechanisms of CDC strips involved multi-pathways and multi-targets

Mechanisms of CDC strips	Pathways and targets
Organ & tissue-based (e.g., vascular-specific)	Lifestyles risk factors (*Table 1*):
	→ Immunity function (–)
	→ Acute or chronic inflammation
	→ Vascular endothelial cells (VEC) injure
	→ Vascular injure
	→ AS or stiff or rupture
	→ Ischemia or oxygen not enough
	→ Microcirculation dysfunction
	→ Organ or tissue injure
	→ NCDs (CVD, DM, cancer, even CDC strips)
	→ Others
Cell-based	Internal or external stimuli → inflammation
	Cells including: TAM, mast cells, dendritic cells, NK cells, neutrophils, eosinophils and lymphocytes
	Cytokines, chemokines, transcription factors, etc: (+)
	Including: ROS & RNS, MMP, TNF, IL-1, I-L6, IL-8, IFNs, NF-κB, etc.
	Enzymes, such as COX-2, LOX-5, PLA2, etc.
	Biomarkers, such as vitamin D, Vit E and Vit C levels, hs-CRP, MAU, Hcy, Homocysteine, CA125, CA19-9, and CA153, etc.
	Signals, such as SMAD, STAT3, AMPK, etc.
	Apoptosis
	Telomerase
	(+) CSC and (–) adults SC (46)
	Others, such as eicosanoid, kinins, etc.
Gene-based	A positive family history
	Genetic variants
	Gene mutation
	DNA repair
	DNA methylation
	Micro-RNA
	Others: P53, Bcl-2, etc.

Lifestyles risk factors (showed in *Table 1*) mean "Bad SEED"; genetic risk factors mean "bad soil". The shared "Bad SEED"+/– "bad soil" leading to "internal environment injure, abnormal, or unbalance" [e.g., (+) CSC and/or (–) adults SC?] may explain the mechanisms of CDC strips involved multi-pathways and multi-targets. Here, - means decrease or inactivate; + means increase or activate. TAM, tumor-associated macrophages; NK, natural killer; ROS, reactive oxygen; RNS, nitrogen species; MMP, matrix metalloproteinase; TNFα, tumor necrosis factor α; CVD, cardiovascular disorder; DM, diabetes mellitus; CRP, C-reactive protein; NcDs, non-communicable diseases; interleukins (IL-1, IL-6, IL-8), interferon (IFNs), cyclooxygenase-2 (COX-2), lipooxygenase-5 (LOX-5), phospholipase A2 (PLA2), transcription factors nuclear factor κB (NF-κB); STAT3, signal transducers and activators of transcription-3; CSC, cancer stem cell.

"bad soil"). Therefore, we think that "Bad SEED" +/– "bad soil" Theory or Doctrine on CDC strips may explain this phenomenon of co-morbid diseases. Actually, it's due to "internal environment injure, abnormal or unbalance" in human body resulting from the role of RFs related multi-pathways and multi-targets, which including organ & tissue (e.g., vascular-specific), cell and gene-based mechanisms (*Tables 1*,*2*, *Figure 1*), for example, it may activate cancer stem cells (CSCs), according to the update verified CSC hypothesis (46), and/or inactivate adults stem cells (SCs).

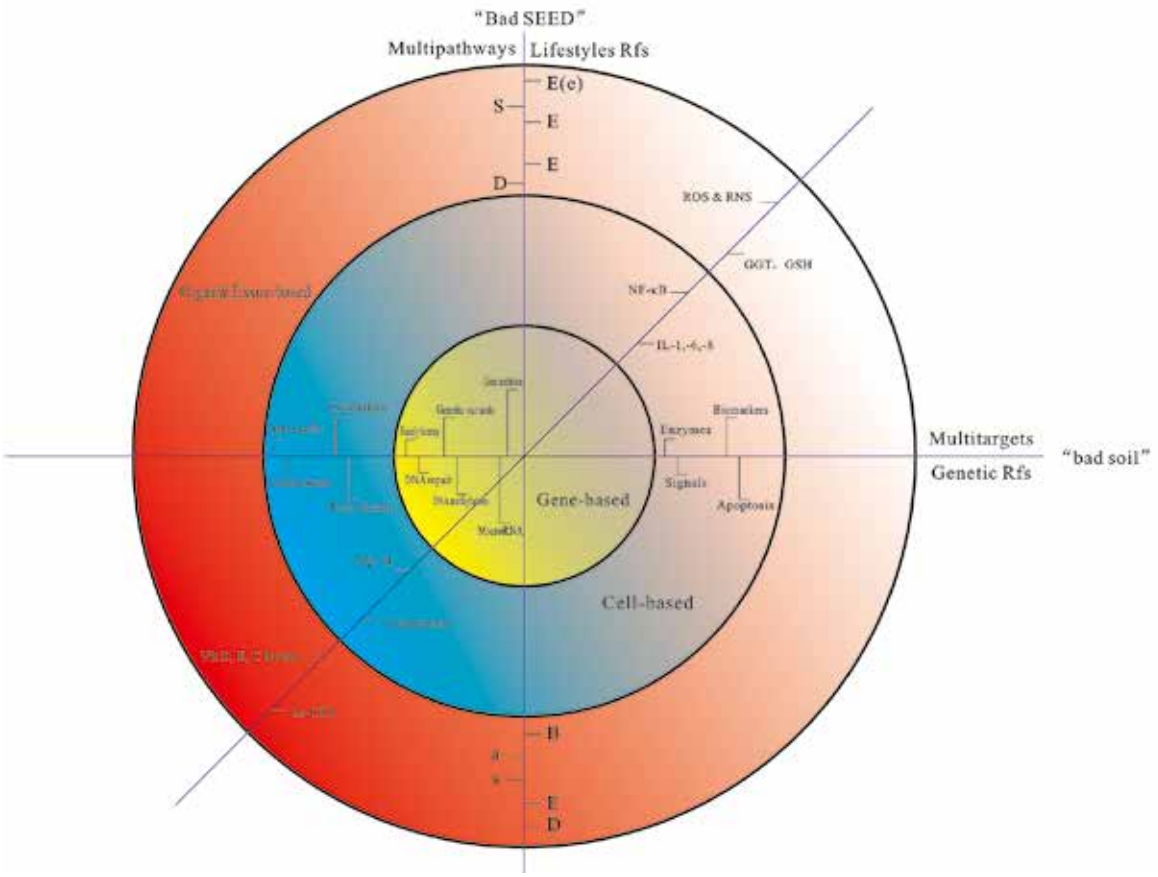

Figure 1 Mechanisms on CDC strips: "Bad SEED" +/- "bad soil" Theory or Doctrine, which involved organ & tissue (e.g., vascular-specific), cell and gene-based multi-pathways and multi-targets. Here, "Bad SEED" means abnormal E(e)SEED-BasED lifestyles which including related RFs; "bad soil" means related genetic RFs, such as family history, gene mutation, etc. These lead to "internal environment injure, abnormal or unbalance", and finally to CDC strips. RFs, risk factors.

Table 3 Classifications of CDC strips: their mains (type B) and branches (type A)

Total CDC strips	Cv(a)-DM-Ca(v) strips
Main strips (type B)	1 Cv-DM-Ca
	2 Ca-DM-Cv
	3 DM-Cv-Ca
	4 DM-Ca-Cv
	5 Cv-Ca-DM
	6 Ca-Cv-DM
Branch (type A)	1 Cv-DM or DM-Cv
	2 Ca-Cv or Cv-Ca
	3 Ca-DM or DM-Ca

Ca, cancer; Cv, cardiovascular; CVD, cardiovascular disease; DM, diabetes. Total CDC strips mean Cv(a)-DM-Ca(v) strips; CDC strips consist of linked CVD, DM and Ca, each other.

Classifications

Among CDC strips, there are three different but linked diseases, CVD, T2 or T1 DM, and cancers. Each patient may be diagnosed firstly one kind of diseases, e.g., CVD, DM or cancer. Sometimes, two or three diseases are diagnosed at the same time due to the shared RFs and not physical examination in time. Therefore, there are 3 pairs of branches (type A, *Table 3*, *Figure 2A*), which including Cv-DM or DM-Cv, Ca-Cv or Cv-Ca, and Ca-DM or DM-Ca, and 6 main strips (type B, *Table 3*, *Figure 2B*), which including Cv-DM-Ca, Ca-DM-Cv, DM-Cv-Ca, DM-Ca-Cv, Cv-Ca-DM, Ca-Cv-DM, according to the onset time of each disease. But in fact, there is often first vascular injure or pathogenesis (e.g., Chronic inflammation or AS is a common and basic factor) in most of patients, then

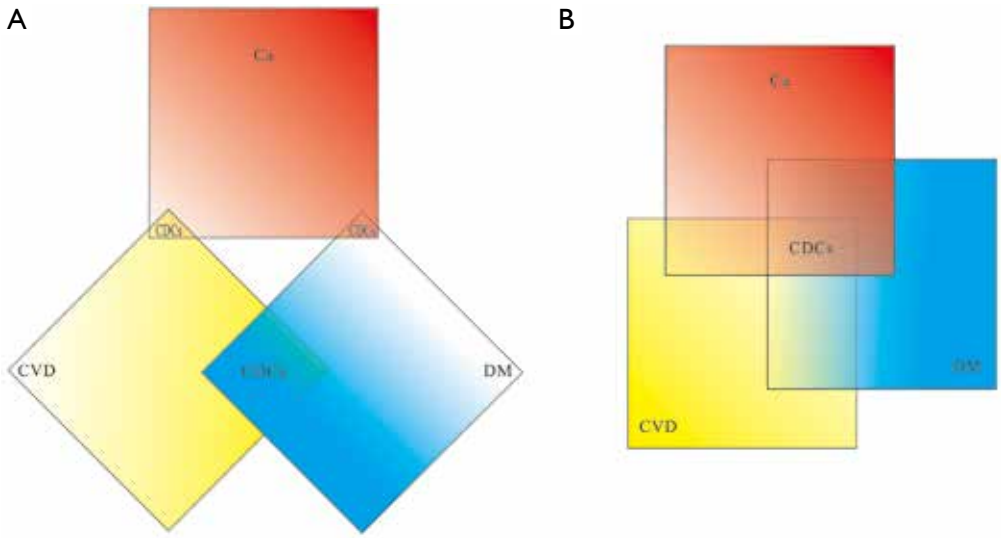

Figure 2 (A) There are three pairs of branches (type A) in CDC strips, which including Cv-DM or DM-Cv, Ca-Cv or Cv-Ca, and Ca-DM or DM-Ca, according to the onset time of each disease; (B) there are six main strips (type B), which including Cv-DM-Ca, Ca-DM-Cv, DM-Cv-Ca, DM-Ca-Cv, Cv-Ca-DM, Ca-Cv-DM, according to the onset time of each disease.

other pathogenesis. That is to say, the initial and progress of CDC strips are often from vascular tissues and involved three kinds of diseases, which including CVD, DM and cancer. So, we think Cv(a)-DM-Ca(v) strips are total strips (*Table 3*, *Figure 2A,B*). Obviously, branches of CDC strips just involved two diseases.

CDC strips: significances and prospects

As the novel conceptual breakthrough, clinical significance of CDC strips is obvious and very helpful. First, to develop new warnings, CDC strips we discovered and named may remind us of paying more attention to early detection, early prevention and early intervention of these diseases, halting the development of CDC strips; CDC strips help us understand that early prevention is the best treatment and the most important thing, and the role of primary and secondary prevention; To treat positively and to control RFs before main or branch strips are formed. Second, to create novel theories or doctrine on CDC strips—"bad SEED" +/– "bad soil" leading to "internal environment change, abnormal or unbalance"; To give new concepts on CDC strips, such as, main or branch strips, and total strips; To explore organ & tissue-based (e.g., vascular-specific pathology), cell and gene-based mechanisms on CDC strips resulting from multi-pathways and multi-targets. Third, to conduct and verify interventional effects of novel strategies we developed, such as RT-ABCDEF strategy, intervention with SEED, E(e)SEED, or E(e)SEED-BasED, that is to say, SEEDi, E(e)SEEDi, or HHLi.

All in all, the concepts, mechanisms, and classifications of CDC strips may help us to understand these NCD, prevent and control these common and high risk strips. As Chinese famous cardiologist Academician Run-Lin Gao said, "By the best and perfect prevention, CHD will disappear in the future". Of course, we think CDC strips are also included. And just as the famous professor and editor-in-chief of New England Journal of Medicine, Dr. Jeffrey M. Drazen said, "Smoking leads to cancer, heart disease and chronic obstructive lung disease. Once a smoker quits, there are substantial health benefits. It is never too late to stop smoking". Indeed, because smoking is also related with T2DM (47), we can say that smoking is the very common RFs leading to CDC strips. The earlier one stops smoking, the better it benefits one's health. It's better to stop smoking before the development of main or branch of CDC strips. In addition, chronic respiratory diseases, often caused by tobacco consumption, are considered as major NCDs that cause great mortality worldwide. In many cases, respiratory diseases, CVD, DM, and cancer are listed as "big four" NCDs. Hence, we think that "CDC strips" are the first strips among NCDs, we may promote the concept of "Re-CDC strips" in the next step as the second strips, which include Respiratory diseases. We also think it's time for us to take acts for preventing or halting CDC strips in the globe. On the one hand, we need to find

new targets for CDC strips; On the other hand, we need to develop novel targeted drugs or therapies to prevent or halt CDC strips which have the role of "a stone for three birds". At the same time, we definitely should pay more attention to their safety, efficacy and stability (48), which just like that in gene therapy. In fact, according to up-to-date global status report on NCDs released by WHO on 15 May 2014, many countries are experiencing a rapid rise in obesity among infants and children under 5 years of age. More than 40 million children under the age of 5 were overweight or obese in 2012, and 70 million children under 5 will be overweight or obese by 2025 if current trends continue. Thus, tackling childhood obesity now represents an important opportunity to reduce the development and impact of CDC strips in future—while immediately improving the health of children.

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Review Article

The latest progress in research on triple negative breast cancer (TNBC): risk factors, possible therapeutic targets and prognostic markers

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Abstract: Triple negative breast cancer (TNBC) is one type of breast cancer (BC), which is defined as negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (Her2). Its origins and development seem to be elusive. And for now, drugs like tamoxifen or trastuzumab which specifically apply to ER, PR or Her2 positive BC seem unforeseeable in TNBC clinical treatment. Due to its extreme malignancy, high recurrence rate and poor prognosis, a lot of work on the research of TNBC is needed. This review aims to summarize the latest findings in TNBC in risk factors, possible therapeutic targets and possible prognostic makers.

Keywords: Triple negative breast cancer (TNBC); risk factor; therapeutic target; prognostic marker

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Introduction (What is TNBC?)

Triple negative breast cancer (TNBC) is characterized by the absence of estrogen receptor (ER) and progesterone receptor (PR), as well as human epidermal growth factor receptor-2 (Her2) (1). Recently when referring to TNBC, the terms basal-like breast cancer (BC) and claudin-low BC should be mentioned. Gene expression profiling and molecular pathology have revealed that BC naturally divides into luminal A and B, HER2-enriched, basal-like and claudin-low subtypes (2). The basal-like BC is tumor that possesses characteristics of breast basal epithelial cells at the gene level (3). The claudin-low BC is characterized by loss of tight junction markers (notably claudins) and high expression of markers of epithelial-to-mesenchymal transition (EMT), in addition to being enriched for markers of mammary stem cells (4). And they are also associated with low expression of hormone receptor (HR) and HER-2, a trait shared by TNBC. However, since micro-array gene expression assays are only used in the research, it's not practical for clinicians to make such pathologic diagnosis. What's more, Falck, *et al*. advice against using the markers to define the basal-like and claudin-low subtypes, considering them insufficiently reproducible (5). For these reasons, BC in the clinical setting is more typically categorized by routine immunohistochemistry as TNBC as a proxy for the basal-like and claudin-low subtypes.

TNBC is characterized by a typically ductal histology, high grade, and high proliferation and mitotic rates. It is associated with poor prognosis, a high risk of the local recurrence rate (LRR), and poor disease-free survival (DFS) and cancer-specific survival (CSS) (6). A study of 906 women with early-stage invasive BC demonstrated that, instead of margin status, TNBC subtype and increasing number of positive lymph nodes were associated with local recurrence (7). And the risk of recurrence in patients with TNBC is higher in the first 3 to 5 years after diagnosis than

those with ER positive BC (8-10).

For the time being, there are only few therapeutic options, and the conventional chemotherapy is probably the only treatment which may be effective for patients after surgery (11). And several studies showed that TNBC was more sensitive to adjuvant or neoadjuvant chemotherapy than other subtypes of BC (1,12). It had been shown that pathologic complete response (pCR) correlated with better prognosis in all the neoadjuvant trials. Within the TNBC group, those who reached pCR had an overall survival similar to that of the non-TNBC group who also reached pCR. In one of these studies (12), the authors analyzed a total of 1,118 patients who had undergone neoadjuvant chemotherapy (mainly anthracyclines alone or in combination with taxanes). Of these, 255 patients (23%) had TNBC. This particular subgroup of BC correlated with significantly higher pCR rates when compared to non-TNBC patients (22% *vs.* 11%, respectively) (1). However, when comparing the patients that did not reach pCR in both groups, those with TNBC had a worse outcome (13,14). The risk of recurrence was higher for the TNBC group only in the first three years but not thereafter (15-17); and the median survival time from recurrence to death was significantly shorter in the TNBC subtype when compared with the non-TNBC group (12). It is a pity that only a minority of TNBC patients is extremely sensitive to chemotherapy and may have an excellent outcome. And who are sensitive to it remains unknown. So there are two assumptions: TNBC is chemo- sensitive, more than those types with positive ER and/or PR; but when, by yet unknown mechanisms, it escapes control by conventional treatment, the relapse is more aggressive and confers worse overall survival (1).

Risk factors

Although the specific pathogenesis of TNBC has not been found, studies suggest that there are many risk factors may lead to its occurrence.

Research indicated that BC subtypes were related with race and age. Premenopausal women and African American women were far more likely to develop basal-like BC and far less likely to develop luminal A BC than their postmenopausal and white counterparts (8,18-22). TNBC prevalence in the study population was higher than that reported in white patients with BC (6). The prevalence is 10-13% in white patients (6), 23-30% in African-American patients (23), 82% in Ghana (24), 39% in Saudi Arabia (25), 19.3% in Chinese Mainland (26), and 15.9% in Taiwan (10,27), 10-19.2% in Hispanic (6,10) which much similar to the Japanese series (8-14%) (26,28).

Lara-Medina, *et al*. suggested that younger age, premenopausal status, increased parity, hormonal contraceptive use, high histological grade, and advanced disease were associated independently with TNBC (6). They did not observe a correlation between over-weight or obesity and a diagnosis of TNBC when all patients considered. In premenopausal women, body mass index (BMI) was associated inversely with HR expression. However, in postmenopausal women, BMI had a positive association with HR and HER2 levels (6). In contradistinction to luminal BC, higher parity and young age at first birth may be risk factors for basal-like BC, whereas lack of breast feeding and early age of menarche may be stronger risk factors for luminal BC (8,21,29,30).

Genome-wide association study identified 25 known BC susceptibility loci (LGR6, MDM4, CASP8, 2q35, 2p24.1, TERT-rs10069690, ESR1, TOX3, 19p13.1, RALY, PEX14, 2q24.1, 2q31.1, ADAM29, EBF1, TCF7L2, 11q13.1, 11q24.3, 12p13.1, PTHLH, NTN4, 12q24, BRCA2, RAD51L1-rs2588809, MKL1) as risk factors for TNBC. And two SNPs independent of previously reported signals in ESR1 and 19p13.1 were associated with TNBC. A polygenic risk score (PRS) for TNBC based on known BC risk variants showed a 4-fold difference in risk between the highest and lowest PRS quintiles. It suggested that genetic variation may be used for TNBC risk prediction (31).

In addition, several studies had investigated the associations between height, weight, BMI (32-34), PA (35), cigarette smoking (36) and BC risk. However, only a few or even no patients in those studies were TNBC patients. Future research needs to be focused on TNBC patients.

Possible therapeutic targets

Targeted therapies for TNBC patients remain under study. Many researchers have been studying on this thorny problem from different focus as BRCA1, endothelial growth factor receptor (EGFR), Notch receptors, etc. There are lots of new researches from different aspects as follows.

Gene level

MicroRNAs (miRNAs or miRs) are a family of small (19 to 25 nucleotides in length) non-coding RNAs that regulate gene expression by the sequence-selective targeting of

mRNAs (37). Radojicic, *et al*. used RT-PCR to study the 49 primary TNBC cases and found that among the investigated 9 miRNAs, miR-21, miR-210 and miR-221 were significantly overexpressed, whereas miR-10b, miR-145, miR-205 and miR-122a were significantly under-expressed in the TNBC. The molecular data supported the hypothesis that miR-221/222 contribute to the aggressive clinical behavior of basal-like BC (38). Furthermore, Zhao, *et al*. demonstrated that plasma miR-221 can be considered as a predictive biomarker for chemo-resistance in BC patients who have previously received neoadjuvant chemotherapy. The expression level of miR-221 was significantly associated with the HR status. Patients with higher plasma miR-221 levels tended to be HR-negative (39). So, in miRNA therapeutics, miRNA silencing therapies may be a valuable approach in conjunction with anticancer drugs and chemotherapy treatments. Peptide nucleic acid (PNA) is a DNA analogue in which the sugar-phosphate backbone is replaced by N-(2-aminoethyl) glycine units (37). Although this is a hypothesis that miRNA-targeted molecules based on PNA can be successfully applied to treat human diseases, it is still to be hoped that this can be applied to relevant patients based on the data of clinical trial.

Maire, *et al*. showed that TTK/hMPS1 was an attractive therapeutic target for TNBC (40). High levels of TTK mRNA had been found in BC, particularly in TNBC where it has been shown to protect cancer cells from aneuploidy (41). With immunohistochemistry and reverse phase protein array, Maire, *et al*. confirmed that TNBC expressed higher levels of TTK protein compared to the other BC subgroups. They determined the biological effects of TTK depletion by RNA interference, through analyses of tumorigenic capacity and cell viability in different human TNBC cell lines. TTK siRNA-treated TNBC cells exhibited a remarkable decrease in their ability to form colonies in semi-solid medium. The depletion of TTK in TNBC cells leads to a strong reduction in cell viability as a result of an induction of apoptosis. These results indicated TTK as a protein kinase over-expressed in TNBC, which may represent an attractive therapeutic target specifically for this poor prognosis associated subgroup of BC (40).

Recently, it is founded that RB1 expression is lost in -20% of TNBC, which is identified by recent genomic sequencing, transcriptome analysis, epigenetic and proteomic analysis (42). Robinson, *et al*. demonstrated that RB-negative TNBC cell lines were highly sensitive to gamma-irradiation and moderately more sensitive to doxorubicin and methotrexate compared to RB-positive TNBC cell lines. In contrast, RB1 status did not affect sensitivity of TNBC cells to multiple other drugs including cisplatin (CDDP), 5-fluorouracil, idarubicin, epirubicin, PRIMA-1 met, fludarabine and PD-0332991, some of which are used to treat TNBC patients. The results suggested that patients carrying RB-deficient TNBC would benefit from gamma-irradiation as well as doxorubicin and methotrexate therapy, but not necessarily from many other anti-neoplastic drugs (43).

What's more, studies had shown aldehyde dehydrog enase 1 (ALDH1) and cyclooxygense 2 (Cox-2) gene products were involved in a variety of tumor processes including tumor cell proliferation, tumor invasion, and metastasis of TNBC. Therefore, ALDH1 and Cox-2 may be ideal targets for developing agents for TNBC treatment (15).

Receptors

MUC1 is a binding partner for EGFR, and more specifically, MUC1 and EGFR interact in the nucleus of BC cells to facilitate the association of EGFR with transcriptionally active promoter regions (44). In addition, MUC1 inhibited the degradation of ligand-activated EGFR, and this association might promote cell transformation through the inhibition of EGFR degradation (45). This finding suggested that most TNBC expressed MUC1 to a degree that might render these tumors sensitive to MUC1-based peptide vaccines. One study of MUC1 vaccination had demonstrated the activation of cellular immunity in patients with advanced cancers (46). Siroy, *et al*. demonstrated that MUC1 was expressed in 94% of early-stage high-grade TNBC according to 52 cases patients and the expression of MUC1 in most TNBC provided a rationale to treat patients who had completed standard therapy for early-stage TNBC with a vaccine that generates immunity against MUC1 (47).

Exploratory biomarker assessment suggested that patients with high pretreatment plasma VEGFR-2 might benefit from the addition of bevacizumab (48). A neoadjuvant trial showed a weaker bevacizumab effect in TNBC than in HR-positive disease (49). A multinational open-label randomized phase 3 trial showed that the addition of bevacizumab to chemotherapy during adjuvant therapy did not improve invasive disease-free survival (IDFS) in patients with TNBC. Bevacizumab cannot be recommended as adjuvant treatment in unselected patients with TNBC. HR-negative tumours were associated with high concentrations of VEGF (50). Plasma VEGFR-2 concentrations showed no prognostic value but potential

predictive value for bevacizumab efficacy (48).

Androgen receptor (AR) expression had been observed in about 50% of patients with TNBC (51). Clinical studies had shown that the response of BC to high-dose Medroxyprogesterone-Acetate (MPA) therapy was dependent on the expression of AR, but not ER or PR (52). And the data from Xiangying, *et al*. provided clinical evidence that MPA/megestrol acetate (MA) therapy mightbe an alternative treatment for patients with recurrent TNBC, especially for multi-treated patients with poor physical conditions (53). However, the study was observational and the sample (51 patients) was small. Further studies with larger datasets and prospective research are needed to provide confirmatory evidence for or against the feasibility of MPA/MA treatment for recurrent TNBC.

Immunomodulatory

Engel, *et al*. showed that NK-cell induced lysis was significantly increased in four TNBC cell lines [MDA-MB231, MDA-MB468, HCC-1937 (BRCA 1 mutated) and HCC-1806 TNBC cells] compared to ER + MCF 7 cells (54). The largest study to investigate tumor samples of more than 1,400 patients and found that Treg infiltration was associated with TNBC (55). TNBC cells provided more significant stimulation to the NK-cell immune response than ER positive BC cells which could explain why infiltration with immunosuppressive Tregs is increased in human specimens of TNBC with and without mutated BRCA 1 (54). Accordingly, immunomodulatory treatment strategies should be further explored in TNBC.

Signaling pathway

Serin/threonin kinase AKT is emerging as a key target in oncology. Except for its immunosuppressive properties, the signaling pathway is involved in resistance to apoptosis and chemotherapy, as well as in cell proliferation and metabolism (56). López-Knowles, *et al*. found alterations of the AKT pathway in basal-like BC significantly increased, accounting for more than 70 % of the TNBC population (57). However, Engel, *et al*. only found increased expression of AKT in TNBC with BRCA 1 mutation, while this might be due to the small sample size, which became the major limitation of the study (54).

The extracellularly regulated kinase/mitogen activated protein kinase (ERK/MAPK) signaling pathway is a critical regulator of cellular processes in adult and developing tissues. Depending on the cellular context, MAPK cascade can act as a rheostat, a switch, or an oscillator (58). We know that EGFR is expressed in 13% to 70% of TNBC (1,47). And it is a member of the HER family. Ono, M. and M. Kuwano demonstrated that the ligand binding to HER family leads to activation of various signal cascades including MAPK (59). What's more, Park, *et al*. found that the activation of ERK/MAPK pathway is required for TGF-α and EGF-induced upregulation of Matrix metalloproteinase 1 (60).

Others

Recently, a Phase 2 trial of everolimus and carboplatin combination in patients with triple negative metastatic BC had a conclusion that Everolimus-carboplatin was efficacious in metastatic TNBC. Dose limiting hematological toxicity was observed when AUC5/6 of carboplatin was combined with everolimus. However, carboplatin AUC 4 was well tolerated in combination with everolimus with continuing responses (61).

Possible prognostic markers

In addition to the known ones, such as, EGFR and ALDH1, there are new possible prognostic makers for TNBC including Lysyl Oxidase-Like 2 protein (LOXL2), Synuclein gamma (SNCG), LDHB (Lactate Dehydrogenase B).

Ahn, *et al*. demonstrated that LOXL2 was an independent prognostic factor in BC patients (62). In univariate analysis for OS, higher expression of LOXL2 was associated with poor outcome after a median follow-up time of 9.3 years. The clinical and preclinical data confirmed that the rate of positive LOXL2 was higher in TNBC than non-TNBC tumors. LOXL2 expression promoted epithelial-mesenchymal transition (EMT) and invasiveness of basal-like BC cell lines, a finding that was compatible with previous *in vitro* study results (63). Silencing of LOXL2 resulted in a marked decrease in migratory ability and invasion capacity. It potentially suggested that the interruption of the LOXL2-dependent activity contributing to metastasis could bring survival benefit to BC patients, as well as in a preclinical condition.

SNCG, identified as BC-specific gene 1, was an independent predictive marker for recurrence and metastasis in BC. 34.3% TNBC showed moderate to strong positive SNCG expression. Wu, *et al*. found that tumor size was significantly associated with SNCG expression. Patients

whose tumors expressed SNCG had significantly shorter DFS and a higher probability of death when compared with those whose tumors did not express SNCG (64).

McCleland, *et al*. identified that LDHB was an essential gene for triple-negative BC by an integrated genomic screen (65). And Dennison, *et al*. suggested that LDHB was able to predict the prognosis of the basal-like subtype within the HR-positive/HER2-negative and TNBC groups with a high degree of power (66). BC with high LDHB was most responsive to neoadjuvant chemotherapy independently of established prognostic factors (grade, tumor size) and molecular markers (HR status and PAM50 subtyping) (66).

Conclusions

As one special type of BC, the pathogenesis of TNBC is at present yet to know. Clinical data demonstrated that risk factors like race, age, premenopausal status, increased parity, hormonal contraceptive use, high histologic grade, and advanced disease were independently associated with TNBC. As there are no first-line therapies specific for these patients at the moment, lots of researchers are working on this from different aspects, such as Gene level, Receptors, Immunomodulatory, Signaling pathway and others. Researchers also found some possible prognostic markers like EGFR, ALDH1 LOXL2, SNCG and LDHB. However, most of these studies on TNBC were at the cellular level and subject to its limitation. Due to the low incidence of the disease, there are only a few clinical trials for TNBC patients so far. Therefore, we are expecting more large scale clinical trials to be conducted in the future.

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Review Article

The challenging management of hepatopulmonary fistulas

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Abstract: Hepatopulmonary fistula although benign in nature carries an unacceptable mortality risk up to 10.3 % in some case series mainly due to surgical complications. From the first description by Ferguson and Burford in 1967 till present different approaches have been applied and with the introduction of less invasive techniques the results have significantly improved. Interestingly the prevalence of the different etiological factors has changed over the years especially with the advance of liver ablating techniques and surgery. A step by step approach to this entity, from diagnosis to treatment has to be reestablished in order to identify the role of interventional modalities and to develop a management algorithm.

Keywords: Hepatopulmonary fistulas; hydatic liver disease; hybrid approach

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Introduction

Hepatopulmonary fistula represents a rare benign clinical entity related with a significant mortality risk. Interestingly the prevalence of the different etiological factors has changed over the years especially with the advance of liver ablating techniques and surgery. Although surgery remains the gold standard definite option, recent and less invasive techniques have given a new perspective in their management. A step by step approach to this entity, from diagnosis to treatment has to be reestablished in order to identify the role of interventional modalities and to develop a management algorithm.

Aetiopathogenesis

Hepatic hydatidosis although the most common predisposing factor for years, has been reported in only few case series in last three decades (1). Instead of it, other etiological factors have arisen related with the widespread use of conventional liver surgery and modern ablating techniques for liver diseases (2). All potential causes of hepatopulmonary fistulas can be summarised in the following five categories.

(I) Congenital;
(II) Hepatic hydatid disease or liver abscess (echinococcic, amoebic, pyogenic);
(III) Biliary tract obstruction secondary to tumors (more frequently biliary tree tumors);
(IV) Blunt or penetrating injury (with or without an expanding hematoma causing obstruction);
(V) Iatrogenic fistulas (following liver resection, RFA ablation, radiation, thoracic drainage).

There are two major ways of fistula formation (3-5). The first follows the expanding mechanism of an infected biloma that resides underneath the diaphragm in a jaundiced patient. It is presumed that the existence of bile underneath diaphragm can erode tissues reaching the pleural space, bronchus or both (6,7). In addition, biliary stasis predisposes to abscess formation and further tissue damage. Factors contributing to biloma formation are diaphragmatic injuries with a concomitant liver trauma, tumors (most common cause according to literature), postoperative or post ablating biliary stenosis and lithiasis (3,8).

The other mechanism involves spreading of a hydatid liver cyst or other invasive liver process (e.g., amoebic abscess) to the adjacent lung or pleural space. In the same manner as infected biloma, the erosion of diaphragm gradually predispose to fistula formation (9). This inflammatory

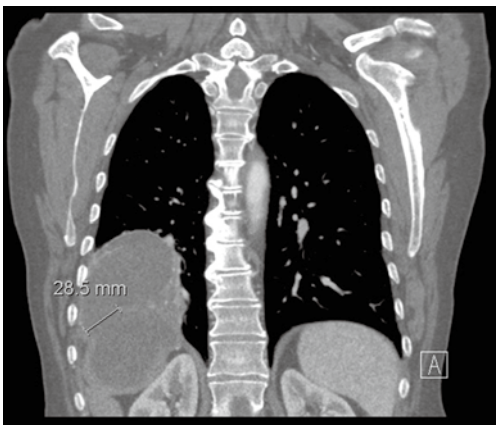

Figure 1 CT scan demonstrating the hepatopulmonary fistula.

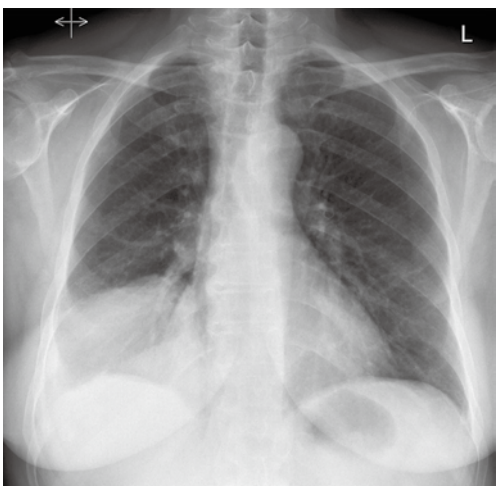

Figure 2 Chest X-ray showing haziness in the right lower lobe of the lung.

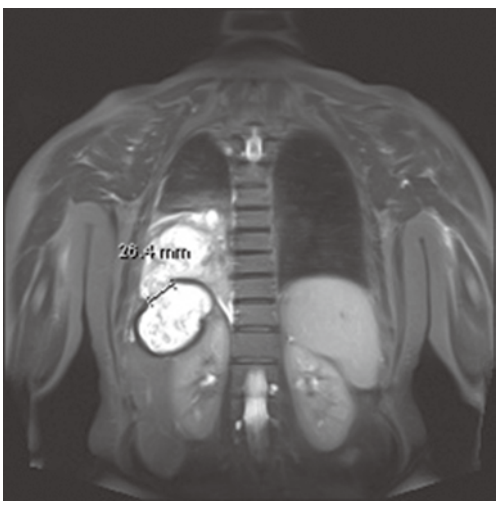

Figure 3 MRI scan demonstrating the fistula in the background of hydatic liver disease.

process usually is not associated with biliary obstruction in these patients, distinguishing them from the former group.

A fistula between right hemidiaphragm and nuda hepatis is the most frequently reported while a bronchobiliary fistula to the left lung has only been reported once in the literature (1).

Clinical features

Clinical features preceding the development of a hepatopulmonary fistula can be indicative of the underlying disease in the abdomen. Normally it is an evolving clinical situation with signs and symptoms of the abdominal infection, biliary obstruction and finally respiratory distress. Most frequent symptoms include fever, productive cough, chest pain, right upper abdominal pain, jaundice and bile stained sputum (2,10).

Biliptysis (bile stained sputum) and presence of bile in the pleural effusions, are both pathognomonic of the existence of a bronchobiliary fistula (1,11).

Sepsis or preliminary signs of the inflammatory process with tachypnea, tachycardia and low grade fever, or no specific symptoms (due to a chronic process) constitute the ongoing illness. The fulminant disease presents in the form of acute respiratory distress syndrome (ARDS) (12).

Another form of communication between abdomen and chest, the so called pleuro biliary fistula causes dry and irritating cough, chest pain and findings from the right chest, according to fluid accumulation in the right pleura and development of right basilar atelectasis. Pleuro biliary fistula is more difficult to be diagnosed unless high degree of suspicion exists, in a patient with predisposing factors.

Investigations

CT scan (*Figure 1*) remains a useful tool in delineating the pathology, especially when subtle symptoms exist. It can easily distinguish air into the biliary tree, an underlying hepatic abscess, effusion in the pleural space or basilar atelectasis and lung abscess (8). However in most of cases fails to demonstrate the fistulous tract.

Some of these findings can also be suspected on plain chest (*Figure 2*), abdominal radiographs or demonstrated by ultrasonography.

Bile stained sputum, bile presence in the pleural effusions or even jaundice should raise concerns for more precise depiction of the biliary tree. From the less invasive techniques, MRI (*Figure 3*) and MR cholangiography, can

establish the diagnosis, although there are reports that it can also fail to demonstrate the fistulous tract (13). Hepatobiliary imino-diacetic acid (HIDA) scan can be considered, as a non-interventional alternative with increased diagnostic value, in patients with good performance status (14).

If further investigation is necessary, interventional depiction has to be considered. Cholangio-pancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) provide direct evidence of the fistula, possible distal biliary obstruction and offer therapeutic options (15,16). There are reports of spontaneously fistula closure after therapeutic PTC or ERCP (2).

Percutaneous tubography remains an immediate and absolute tool to delineate a hepatopulmonary fistula after evacuation of the abscess cavity in the chest or abdomen (2). It offers symptomatic relief to the patient and offers a surgical plan with minimal adverse effects, even under local anaesthesia.

Unstable septic patients in admission require circulatory and respiratory support followed by immediate surgical exploration.

Management

Regardless the interventional option applied, antibiotic therapy is primarily instituted to cover from gram negative microbes that usually are present into the sputum of these patients (17,18).

Of paramount importance is to maintain low pressures in the openings of fistula. This can be achieved with thoracostomy tube placement and biliary decompression with ERCP (endoscopic sphincterotomy and stend placement or nasobiliary drainage) or PTC (15,19). In presence of liver or lung abscesses it has to be drained under CT guidance in order to gain control of sepsis.

Literature review reveals cases of spontaneously closure of the fistula (up to 60% in posttraumatic fistulas) after endoscopic or subcutaneous biliary drainage (1). Other studies depict that the more conservative methods need a long standing drainage period that sometimes exceeds 5 weeks in duration. Reinsertion of tubes or drainage of new inflammatory foci gives a complete non-surgical approach in management of these patients. Nevertheless, the success of these methods depends on the degree of the inflammatory process.

In more chronic fistulas associated with clinical deterioration with respiratory compromise and uncontrolled abdominal and thoracic sepsis, aggressive therapy with surgery has considered traditionally the gold standard.

Surgical approach via thoracotomy can became in many cases the treatment option. Except drainage of pleural empyema, segmental excision of devitalized lung tissue or decortication, one can obtain immediate access to abdominal cavity through a severe diseased diaphragm, or take control over a penetrating injury with a phrenotomy. In addition, the hepatic area of involvement can be inspected for bilomas, abscesses and any other pathology that may require a formal access to abdomen. If there is no need for that, completion of therapy with biliary decompression can be managed postoperatively endoscopically. The principles according to Ferguson and Burford (20) for a successful management of the fistula involve:

- Early aggressive treatment by thoracotomy;
- Adequate subcostal drainage of the hepatic bed under direct vision;
- Secure closure of the diaphragmatic perforation by non-absorbable sutures;
- Decortication for the lung;
- Lobectomy for broncho biliary fistula and the awareness of the need for prophylactic decompression of the biliary tree.

These principles are applied to the most modern hybrid approaches (surgical plus endoscopic or interventional radiologic) that alleviate the risk of a major thoraco-abdominal operation.

The most challenging step of the operation is to restore the natural barrier between chest and abdomen. Diaphragm as part of the inflamed continuity among these compartments seems severely damaged as dissection proceeds. Huge defects can be managed with mobilisation of nearby tissue such as intercostal muscle or pericardial fat in a thoracic approach and with omentum majus in an abdominal approach (12,17). Synthetic mesh and AlloDerm® (17,21-23) have also been used in the past although the more desirable scenario is a primary closure with non-absorbable suture.

Reports of bronchoscopic attempts to seal the bronchobiliary communication and somatostatin analogues administration can all be considered, but evidence based data are limited.

Conclusions

Hepatopulmonary fistula although benign in nature carrying an unacceptable mortality risks up to 10.3% in some case series mainly due to surgical complications. From the first description by Ferguson and Burford in

1967 till present different approaches have been applied and with the introduction of less invasive techniques the results have significantly improved. Current data suggest a hybrid approach (surgical plus endoscopic or interventional radiologic) to this rare clinical entity individualised to each patient according to aetiology and severity of illness.

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Review Article

Magnetic resonance imaging for lung cancer screen

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Abstract: Lung cancer is the leading cause of cancer related death throughout the world. Lung cancer is an example of a disease for which a large percentage of the high-risk population can be easily identified via a smoking history. This has led to the investigation of lung cancer screening with low-dose helical/multi-detector CT. Evidences suggest that early detection of lung cancer allow more timely therapeutic intervention and thus a more favorable prognosis for the patient. The positive relationship of lesion size to likelihood of malignancy has been demonstrated previously, at least 99% of all nodules 4 mm or smaller are benign, while noncalcified nodules larger than 8 mm diameter bear a substantial risk of malignancy. In the recent years, the availability of high-performance gradient systems, in conjunction with phased-array receiver coils and optimized imaging sequences, has made MR imaging of the lung feasible. It can now be assumed a threshold size of 3-4 mm for detection of lung nodules with MRI under the optimal conditions of successful breath-holds with reliable gating or triggering. In these conditions, 90% of all 3-mm nodules can be correctly diagnosed and that nodules 5 mm and larger are detected with 100% sensitivity. Parallel imaging can significantly shorten the imaging acquisition time by utilizing the diversity of sensitivity profile of individual coil elements in multi-channel radiofrequency receive coil arrays or transmit/receive coil arrays to reduce the number of phase encoding steps required in imaging procedure. Compressed sensing technique accelerates imaging acquisition from dramatically undersampled data set by exploiting the sparsity of the images in an appropriate transform domain. With the combined imaging algorithm of parallel imaging and compressed sensing and advanced 32-channel or 64-channel RF hardware, overall imaging acceleration of 20 folds or higher can then be expected, ultimately achieve free-breathing and no ECG gating acquisitions in lung cancer MRI screening. Further development of protocols, more clinical trials and the use of advanced analysis tools will further evaluate the real significance of lung MRI.

Keywords: Lung; cancer; screening; MR; CT

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Background of lung cancer screening

Lung cancer is the leading cause of cancer related death throughout the world (1). Lung cancer is also an example of a disease for which a large percentage of the high-risk population can be easily identified via a smoking history. This, coupled with the high success of other screening programs for prostate, breast, and cervical cancers has led to the investigation of lung cancer screening with low-dose multi-detector CT. Evidences suggest that early detection of lung cancer allow more timely therapeutic intervention and thus a more favorable prognosis for the patient (2-4).

The majority of smokers who undergo thin-section CT have been found to have small lung nodules, most of which

are smaller than 7 mm in diameter (5,6). However, nodule features such as shape, edge characteristics, cavitation, and location have not yet been found to be accurate for distinguishing benign from malignant nodules (7,8). The positive relationship of lesion size to likelihood of malignancy has been clearly demonstrated (9-12). In a meta-analysis of eight large screening trials, the prevalence of malignancy depended on the size of the nodules, ranging from 0% to 1% for nodules 5 mm or smaller, 6% to 28% for those between 5 and 10 mm, and 64% to 82% for nodules 20 mm or larger (9). Even in smokers, the percentage of all nodules smaller than 4 mm that will eventually turn into lethal cancers is very low (<1%), whereas for those in the 8-mm range the percentage is approximately 10-20%. The 2005 Fleischner Society guideline stated that at least 99% of all nodules 4 mm or smaller are benign and because such small opacities are common on thin-section CT scans, follow-up CT in every such case is not recommended; in selected cases with suspicious morphology or in high-risk subjects, a single follow-up scan in 12 months should be considered (13).

When the nodule is 5-9 mm in diameter, approximately 6% of cases showed interval nodule growth detectable on 4-8 months follow-up scans (10). For these nodules the best strategy is regular follow-up. The timing of these control examinations varies according to the nodule size (4-6, or 6-8 mm) and type of patients, specifically at low or high risk of malignancy concerned. Frequent follow-up increases radiation burden for the affected population (14-16). The radiation dosage for a chest varies between 1-10 mSv, while that of whole body FDG-PET/CT is 10-30 mSv. More details on medical X-ray radiation risk can be found at (http://www.xrayrisk.com/).

Noncalcified nodules larger than 8 mm diameter can bear a substantial risk of malignancy (9,12,13). In the case of nodules larger than 8 mm, additional options such as contrast material-enhanced CT, positron emission tomography (PET), percutaneous needle biopsy, and thoracoscopic resection or video-assisted thoracoscopic can be considered (9,17).

Current status of MR imaging for the lung

Use of MRI in the evaluation of pulmonary nodules has thus far been limited. The reasons include limited spatial resolution, high susceptibility differences between air spaces and pulmonary interstitium, and the presence of respiratory and cardiac motion artifacts. However, in the recent years, the availability of high-performance gradient systems, in conjunction with phased-array receiver coils and optimized imaging sequences, has made new approaches possible to MR-based pulmonary imaging (*Figures 1,2*). Electrocardiogram (ECG) and respiratory triggering or breath-holding techniques is used to eliminate the motion artifacts.

Turbo spine echo sequence shows many pulmonary nodules, including lung cancers, pulmonary metastases, and low-grade malignancies such as carcinoids and lymphomas, with low- or intermediate-signal intensity on T1-weighted imaging and slightly high intensity on T2-weighted imaging (18). For various pulmonary metastasizing malignancies, with a 1.5 T scanner and breath-hold 2D Half-Fourier Acquisition Single-Shot Turbo Spin-Echo (HASTE) sequence Schroeder *et al.* (19) reported an axial spatial resolution of 2.4×1.3 mm^2. To compensate for the poor resolution in the z-axis of slice thickness of 5 mm, image sets in both the axial and coronal planes were collected (19). The sensitivity values for the HASTE MR sequence were 73% for lesions smaller than 3 mm, 86.3% for lesions between 3 and 5 mm, 95.7% for lesions between 6 and 10 mm, and 100% for lesions bigger than 10 mm. Although the spatial resolution of the HASTE MR sequence is lower than that of multi-detector CT, both imaging techniques correlated well regarding the determination of size, number, and location of the pulmonary lesions. Pulmonary arteries and veins are depicted as flow voids without any apparent signal black blood inversion sequence. This represents an advantage over CT, on which small pulmonary masses often have attenuation levels similar to those of blood vessels and thus are often indistinguishable from vessels of similar size. Recently, Koyama *et al.* (20) directly compared capabilities of pulmonary nodule detection and differentiation of malignant from benign nodules between noncontrast-enhanced multi-detector CT and MRI using a 1.5 T system in 161 patients with 200 pulmonary nodules. Although the overall detection rate of thin-section multi-detector CT was superior to that of respiratory-triggered short tau inversion recovery (STIR) turbo SE imaging, there were no significant differences in malignant nodule detection rate between the methods (20). In that study the malignant nodule detection rate including bronchioalveolar carcinoma had no significant difference between thin-section multi-detector CT and noncontrast-enhanced MRI, but significantly more benign nodules were missed on noncontrast-enhanced MRI. Koyama *et al.* suggested that it would be preferable to accept a decrease in the detection

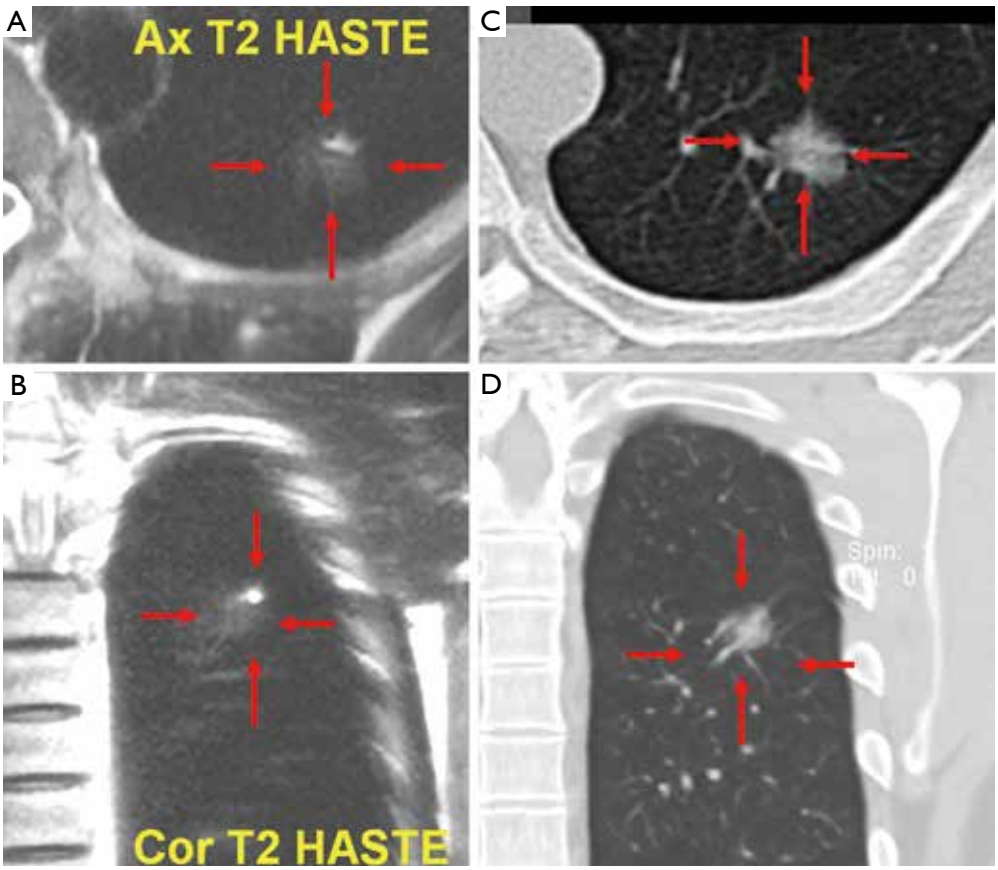

Figure 1 A 42-year-old male. T2 weighted HASTE MR axial (A) and coronal (B) imaging of the chest shows a nodule (arrows). It was also shown by CT (C, axial; D, coronal) and confirmed to be a bronchioalveolar carcinoma by surgery. HASTE, Half-Fourier Acquisition Single-Shot Turbo Spin-Echo.

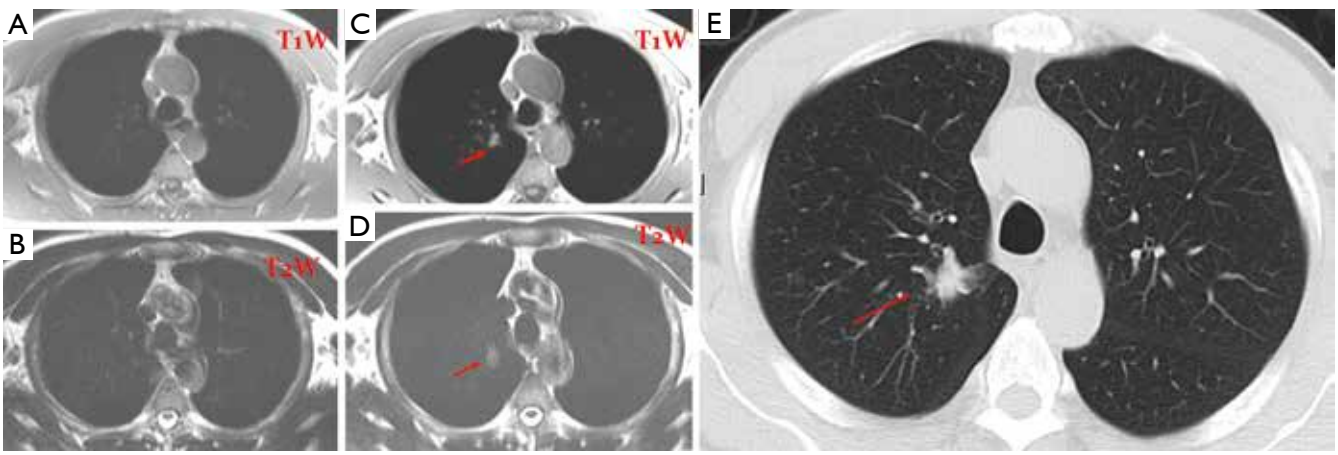

Figure 2 A 72-year-old male. (A,B) T1 & T2 weighted MR screening of the chest; no abnormality was detected in 2005; (C,D) T1 & T2 weighted MR screening of the chest shows a nodule (arrow) in 2008. It was also shown by CT (E) and confirmed to be a bronchioalveolar carcinoma (stage I) by surgery.

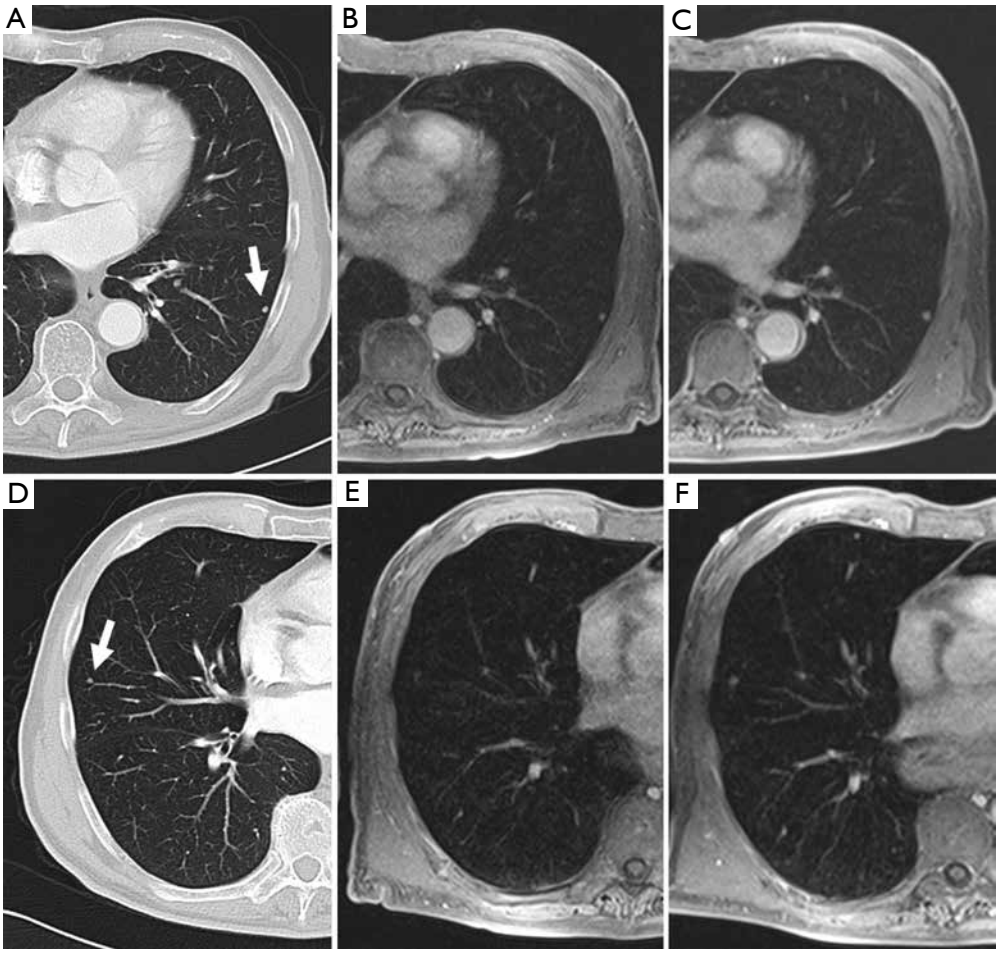

Figure 3 An example demonstrates MRI for the detection of small lung nodules: (A,D) small pulmonary metastases of a malignant melanoma in a 62-year-old patient (5 mm slices of a standard helical CT scan); (B,E) MRI of the corresponding positions at the same time; (C,E) the follow-up MRI after 3 months [the contrast enhanced transverse 3D-GRE (VIBE) images; TR/TE 3.15/1.38 ms, flip angle 8°, FOV 350 mm × 400 mm, slice thickness 4 mm]. The clearly visible 3 mm nodule in the left lower lobe [(A) and (B); marked with an arrow on (A)] grew to a diameter of 5 mm within 3 months (C). Another 3 mm nodule in the lateral right middle lobe [marked with an arrow on (D)] is hardly visible on the corresponding MRI due to cardiac pulsation, but becomes clearer in the follow up study after growing to 4-5 mm (F) [Reproduced with permission from reference (23)].

rate of benign nodules without significantly missing malignant nodules (20).

Studies have shown that 3-T systems afford higher lesion contrast, higher spatial resolution, and less image blurring with shorter echo trains at high acceleration factors than do 1.5-T systems (21). 3D or 2D gradient recalled echo (GRE) and T2-weighted fast spin-echo or T2-weighted HASTE sequences are practical for detection of pulmonary nodules. Puderbach *et al.* (22) suggested detailed standard protocols for lung MRI, including a transverse T1-weighted breath-hold 3D-GRE sequence and a breath-hold coronal T2-weighted HASTE sequence. It can now be assumed a threshold size of 3-4 mm for detection of lung nodules with MRI under the optimal conditions of successful breath-holds with reliable gating or triggering. Biederer *et al.* (23) suggested that 90% of all 3-mm nodules are correctly diagnosed and that nodules 5 mm and larger are detected with 100% sensitivity (*Figure 3*).

While in view of the limited spatial resolution of MR imaging, MRI's differentiation on morphologic criteria is not likely to be better than CT, however, the analysis of signal properties or enhancement profiles may aid in this regard. For example, because MRI affords better tissue contrast, MRI with thin-slice collimation of a pulmonary

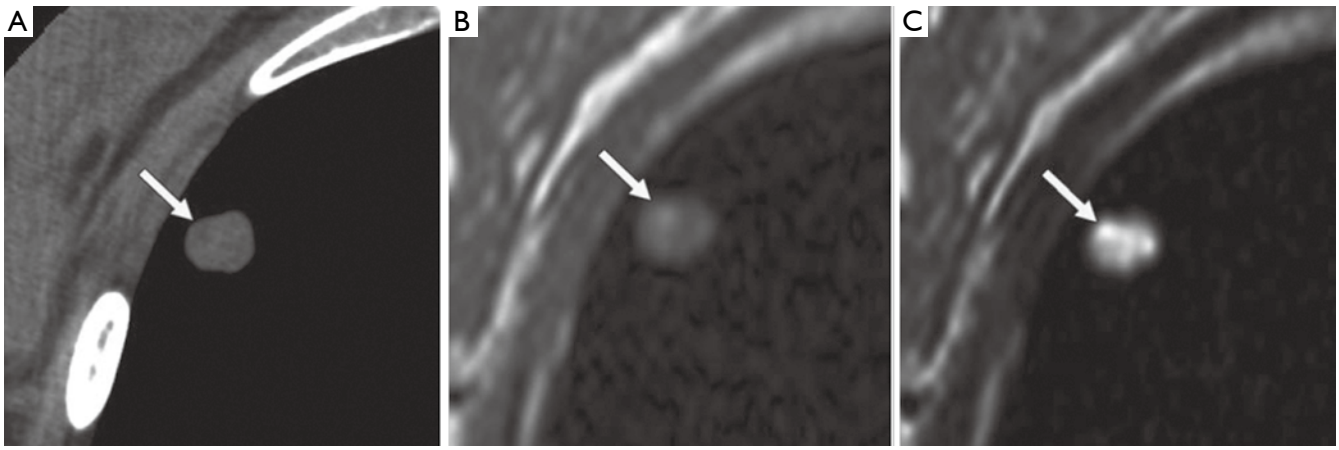

Figure 4 A 40-year-old woman with pulmonary hamartoma. (A) CT image shows low-attenuation spot (arrow) within nodule, suggesting lipoid tissue; (B,C) axial T1-weighted (B) and T2-weighted (C) MR images show hyperintense spots (arrows) within nodule. T2-weighted image (C) also shows hyper-intense matrix consistent with cartilaginous tissue [Reproduced with permission from reference (21)].

hamartoma shows the fat and calcification foci and can be interpreted in a manner similar to that for CT (*Figure 4*). Fat suppression techniques are also preferable when macroscopic fat is suspected. Chemical-shift MRI with in- and opposed-phase acquisition may be an important tool for detecting fat in pulmonary hamartomas (24). In the absence of markedly calcified cartilaginous tissue, myxoid matrices of the cartilaginous tissue produce very high signal intensity on T2-weighted images (25). Although MRI detection of pulmonary nodules is inferior to CT detection, MRI yields supplementary morphologic information that is valuable for differential diagnosis, including for sclerosing hemangioma, bronchial carcinoid tumor, tuberculoma, aspergillosis, progressive massive fibrosis (21).

Enhancement patterns or blood supply evaluated with dynamic contrast-enhanced (CE) MRI is helpful for diagnosis of pulmonary nodules (26,27). It has been suggested that dynamic CE MRI is effective for assessment of tumor angiogenesis (27). The lack of ionizing radiation makes MRI a safe tool for repeated dynamic evaluations of tumor perfusion. Dynamic MRI with the 3D GRE sequence requires less than 30 second breath-holding for acquisition of all data (26). There are various dynamic MR techniques for distinguishing malignant nodules from benign nodules, with reported sensitivities range from 94-100%, specificities from 70-96%, and accuracies of more than 94% (28-30). These specificities and accuracies for dynamic MRI are equal to those for FDG-PET or PET/CT (27). A recent meta-analysis reported that there were no significant differences in diagnostic performance among dynamic CE-CT, dynamic CE-MRI, FDG-PET and single photon emission tomography (SPECT) (31).

Recently, diffusion-weighted imaging (DWI) has been suggested as new method for nodule detection and/or evaluation including subtype classification of pulmonary adenocarcinoma (28,29,32). Theoretically, DWI, as does the apparent diffusion coefficient (ADC), assesses the diffusivity of water molecules within tissue in terms of cellularity, perfusion, tissue disorganization, extracellular space, and other variables (28). Quantitative and/or qualitative sensitivities and specificities of the ADC for differentiation of malignant from benign SPNs were 70.0% to 88.9% for sensitivity and 61.1% to 97.0% for specificity (28,30,32). One report stated specificity of DWI (97.0%) was higher than that of FDG-PET/CT (79.0%) (28).

The direct multiplanar capability of MRI is also one of the advantages for the detection of lymph nodes in areas that are suboptimally imaged in the axial plane, such as in the aortopulmonary window and subcarinal regions. Nowadays whole-body MRI has become clinically feasible with the installation of fast imaging and moving table equipment. Whole body DWI has been recommended as a promising new tool for whole-body MR examination of oncologic patients (33-39). When comparing whole-body MRI with FDG-PET for the M-classification capability of head and neck metastases, including brain metastases, the accuracy (80.0%) of whole-body MRI was significantly better than that of FDG-PET (73.3%). When this technique adapted for M-stage assessment including brain metastasis in non-small-cell lung carcinoma, diagnostic accuracy of

whole-body MRI with DW imaging (87.7%) showed no significant difference with that of integrated FDG-PET/CT (88.2%) on a per patient basis (40). Early ADC changes observed after the initial chemotherapy course reportedly correlated with the final tumor size reduction (41).

Computer assisted detection and diagnosis (CAD) systems are becoming increasingly important in the clinical setting, serving as a second reader in image interpretation, effectively improving the detection accuracy and consistency of pulmonary nodules in chest X-ray and CT (42). Awai *et al.* (43) compared the nodule detecting performance of five radiologists and five radiology residents in 50 chest CT scans. Statistically significant improvements in lung nodule detection were achieved for all radiologists using the CAD system ($P<0.1$), with a true positive rate of 94%. The CAD for MRI has not yet been developed. The development of CAD for MRI can be greatly assisted by the techniques already established for CT.

In the meantime, it is important to note that the clinical importance of detecting a 3 mm nodule in a patient with malignant disease and the decisions for treatment depending on the absence of lung metastases differs from detecting a similar lesion in a healthy patient who takes part in a screening program. In a patient with known primary malignancy lung nodules would be deemed suspicious for metastases (9). MRI cannot replace CT for the diagnosis of pulmonary metastases (21). Although 6-mm or greater-diameter pulmonary metastatic nodules may be readily identified with MRI, smaller nodules in lung (<6 mm) are detected with less sensitivity (34,44).

Future directions of MR technology development for lung cancer screening

Current MRI techniques are capable of detecting 4 mm or larger nodules with reasonable spatial resolution and provide clinically valuable information for prognosis and management of possible lung cancers. Till now the imaging acquisition is usually performed with breath-holding and/or some gating methods to reduce motion artifacts caused by respiratory motion, heart beating and cerebrospinal fluid pulsation. The current imaging protocols for lung cancer imaging have a total acquisition time of ~20 seconds for a single scan. Twenty-second breath-holding is often challenging for patients, and long breath-holding increases the possibility of inducing involuntary motions during the imaging acquisition. It is desired to have a much faster imaging method to image the lung so that respiratory and ECG gating can be eliminated in the lung cancer imaging protocols.

The use of high field MR scanner improves the sensitivity and provides more signals for expediting image acquisition. Recent advance in fast MR imaging using parallel imaging and compressed sensing technology have made a great impact in MR imaging community and demonstrated excellent capability in accelerating MR imaging acquisition (45-48). Parallel imaging can significantly shorten the imaging acquisition time by utilizing the diversity of sensitivity profile of individual coil elements in multi-channel radiofrequency receive coil arrays or transmit/receive coil arrays to reduce the number of phase encoding steps required in imaging procedure (49-52). The performance of multi-channel radiofrequency coil arrays is critical to parallel imaging and its imaging acceleration capability (53-56). Unlike parallel imaging techniques, recently introduced compressed sensing technique accelerates imaging acquisition from dramatically undersampled data set by exploiting the sparsity of the images in an appropriate transform domain (4,57-59). Compressed sensing technique can be implemented by using not only multi-channel radiofrequency coil arrays but also conventional non-array radiofrequency coils. Given large field-of-view requirement in lung imaging and currently radiofrequency coil array technology, it is technically challenging to accelerate the imaging by 20-fold or more and make lung imaging acquisition time down to 5 second or less by using parallel imaging technique or compressed sensing technique alone. To achieve this goal, a technique that combines parallel imaging and compressed sensing with optimized imaging parameters and acceleration performance has to be developed. In addition, an advanced multi-channel (e.g., 32-channel, or 64-channel) radiofrequency coil array for lung imaging with sufficient imaging coverage, MR sensitivity and parallel imaging performance is also needed. A major challenge in the design of radiofrequency coil arrays with large channel counts is the electromagnetic coupling among the channels or array elements. This most likely can be addressed by using recently introduced magnetic wall or induced current compensation or elimination (ICE) decoupling technique which has demonstrated a unique capability in decoupling densely-placed resonant elements in massive arrays (60). For a 32-channel or 64-channel RF coil array, it is possible to accelerate imaging by 5-6 folds based on parallel imaging technique with no noticeable image artifacts or distortion. On the top of this, further acceleration of 4 folds can be

obtained by using compressed sensing technique or its derivatives, given the good sparsity behavior of lung images. Therefore, with the combined imaging algorithm of parallel imaging and compressed sensing and advanced 32-channel or 64-channel RF hardware, overall imaging acceleration of 20 folds or higher can then be expected. This could reduce the acquisition time of lung imaging protocols down to 5 second or less, ultimately achieving free-breathing and no ECG gating acquisitions in lung cancer MRI screening.

Another promising technique for imaging pulmonary nodules is ultrashort echo time (UTE) MR image. This technique uses specialized radiofrequency excitation pulses with center-out k-space trajectories to minimize the echo time (61). This ultimately allows for direct imaging of the lung parenchyma, which has a T2 of ~80 ms T2* of ~0.5-3 ms due to the high susceptibility. UTE MR imaging is also advantageous for lung imaging because it is relatively robust to motion artifacts and therefore high quality clinical images can be acquired with free-breathing in the limited field-of-view setting despite the regular non-accelerated acquisitions (62). Recent preclinical studies have shown excellent results depicting lung cancer nodules in a mouse model even without cardiac or respiratory gating (63).

Conclusions

The current development in MR technology data are encouraging for considering follow-up studies of proven pulmonary cancer and for pulmonary screening of populations at risk for pulmonary cancer. Whole body MR screening has also become a reality. Further development of protocols, more clinical trials and advanced analysis tools will further evaluate the real significance of lung MRI.

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Editor's note:
Biostatistics is a growing topic with a continuous development of new techniques. With a computer and the aid of many websites, even the most sophisticated statistical analyses can be done. These technical revolutions mean that the boundary between the essential statistics and the more advanced statistical methods has been blurred.

The understanding of biostatistics is important to all thoracic surgeons, as most of them received some statistics lessons in their training. Nevertheless, I think that few surgeons sit down to read statistics books. What thoracic surgeons need is to take very small doses of biostatistics, absorbed in a few minutes.

Therefore, the Statistic Corner in the *Journal of Thoracic Disease* (*JTD*) should keep the emphasis on enabling the reader to confront which method applies and when. Thus, in the corner, we could write about the analyses of different types of outcomes variable, the linking analyses of study design, the measures of association and impact, and the general strategies for the statistical analysis.

Statistic Corner

The chicken-and-egg debate about statistics and research

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Statistics as a science began in the second half of the XVII century with the aim to collect data in order to lay down laws as a rational foundation of decision-making. The word statistics derives from the Latin word, *Status*. In Hamlet, William Shakespeare first used the word *statist* with a political meaning (*Devised a new commission, wrote it fair: I once did hold it, as our statists do, a baseness to write fair and labour'd much/how to forget that learning, but, sir, now, it did me yeoman's service: wilt thou know. The effect of what I wrote?*). Nevertheless, it is only in the last century that a few statisticians were active in developing new methods of analysis, theories, and applications of statistics. Nowadays, many branches of surgeries are completely penetrated by statistics and decision-making is often based on statistical analyses and accompanies the life of thoracic surgeons.

The goal of statistical analysis is to gain a better understanding of measurements; however, the inappropriate use of statistics can be confusing. In the 1860, Benjamin Disraeli, British Prime Minister, said that *there are three types of lies: lies, damned lies, and statistics.* Personal and subjective "good" judgment are not fact, and do not constitute substantive evidence (1). Statistical analyses make possible the elaboration of complex data and provide a mathematical basis with which to draw conclusions.

Despite the wide use of statistics, thoracic surgeons should carefully guard against pitfalls that can produce misleading conclusion. As a matter of facts, Sir Douglas G. Altman affirmed that general standard of statistics in medical journals is poor (2). Truthfully, properly used statistical methods can reject a hypothesis, but the statistics alone can never establish that a hypothesis is certainly true. Among the statistical methods, tests of significance have a prominent position. A test of significance is a statistical procedure by which one determines whether collected data are consistent with a specific hypothesis under investigation. The correct interpretation of P values, ubiquitous in surgical literature, is of paramount importance. An understanding of the meanings of the null and alternative hypotheses is fundamental. The null hypothesis of a study states that no difference exists between the study groups; in a two-armed

randomized controlled trial, the null hypothesis is that there is no difference between arms for the endpoint under investigation. On the contrary, the alternative hypothesis is that a difference exists between arms. The P value represents the probability that the difference observed between studies arms could occurs only by chance. The magnitude of the P value depends, among other factors, on sample size. If the sample size is sufficiently large, even tiny differences between study groups will become statistically significant. The question is whether small differences are of clinical relevance or not. A significant P value not necessarily reflects a clinical relevant difference and a not significant P value might mask clinically important results (for instance a serum level of potassium of 4.2 mEq/L can be significantly lower that a 4.4 mEq/L level if a large sample size is used but its relevance in clinical practice is of no meaning). Therefore, the distinction between statistical significance and clinical relevance will become even more important (3). Thus, a procedure may be found to be not statistically significant because of inadequate sample size (3,4).

According to Doug Altman, the unperceived misuse of statistics could interest the patients, the resources, and the consequences of publishing misleading results (5).

The development in computing technologies and the great availability of statistical software packages joined to the lack of a control system to validate the competence of people who perform statistical analysis can explain this prevalent misuse of statistics (6). Basic knowledge about medical statistics is invaluable for critical assessment of scientific findings. The learning curve for appropriate interpretation of biostatistics is sharp and the process highly interactive (7). Although the errors in research methods are mainly authors' responsibility, a clear attitude taken by the editorial boards of medical journals is also required to minimize this problem in forthcoming years (4).

Unappropriated or wrong statistical analysis, words of great concern when we read them in reviewers' comments. Hence, the *Statistic Corner in the Journal of Thoracic Disease (JTD)* intends to launch a series of invited reviews about statistics in thoracic surgery research. Obviously, these articles will only scratch the surface of medical statistics. Nonetheless, we hope that will provide a stimulus to enhance the skills to interpret statistical analyses. We welcome ideas and suggestions, from readers as well as potential authors, regarding other topics within the field of medical statistics. I will coordinate these reviews and, therefore, please feel free to contact me (preferably by e-mail).

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Video-assisted thoracoscopic sleeve lobectomy

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Abstract: Although minimally invasive video-assisted thoracic surgery (VATS) lobectomy has proved to be equal and in some aspects superior to open lobectomy in T1 and T2 lung cancers, video-assisted thoracic sleeve lobectomy is not widely practiced. Reconstruction is one of the most problematic techniques in thoracic surgery. We present a case of a patient who underwent VATS right-sided sleeve lobectomy due to right lung cancer. Based on the preoperative examinations, our VATS technique consisted of four incisions: three ports and a 3-4 cm long utility incision without any kind of rib spreading. Total surgery time was 180 min and blood loss was 100 mL. The chest tube was removed on the 5th post-operative day and the patient was discharged home on the 10th postoperative day. The final histopathological examination confirmed squamous cell lung cancer (T2aN0M0 stage IB). In the authors' opinion VATS right-sided sleeve lobectomy should be performed by a surgeon with adequate experience with this approach. Despite limited indications for VATS right-sided sleeve lobectomy, if the patients fulfill the sleeve lobectomy inclusion criteria in general, they may gain from all the advantages of minimally invasive techniques.

Keywords: Video-assisted thoracic surgery (VATS); sleeve lobectomy

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Introduction

Video-assisted thoracic surgery (VATS) lobectomy is an acceptable alternative and seems equivalent to open lobectomy in terms of complications and oncological value. Its advantages compared to thoracotomy are less surgical injury, decreased postoperative pain, fewer postoperative pulmonary complications, shorter hospital stay, improved quality of life, and improved delivery of adjuvant chemotherapy, with a comparable long-term survival rate. Endobronchial tumours requiring sleeve resection have been usually considered a contraindication for VATS. However, with new technical advances and the experience gained in VATS, sleeve lobectomy has been performed by thoracoscopy in experienced VATS centres (1).

We present a case of a patient who underwent VATS right-sided sleeve lobectomy due to lung cancer at the Thoracic Surgery Department of Zhengzhou University with special consideration of technical aspects of the procedure (*Figure 1*).

Case report

The 78-year-old patient with right upper lung cancer was admitted to the Thoracic Surgery Department. On admission the patient gave a 20-day history of dry cough, hemoptysis. The main comorbidities were chronic obstructive lung disease. Computed tomography (CT) scan of the chest revealed a 2.4 cm × 3.4 cm mass located in the right upper lobar bronchus without infiltration of the pulmonary vessels in the hilum and mediastinum. Bronchoscopy confirmed exophytic tumor obliterating the distal part of the right main bronchus and infiltrating orifices of both the upper and the intermedius bronchus. A biopsy was carried out and the histopathological diagnosis of squamous cell carcinoma was made. The patient was clinically staged as IB (T2aN0M0) and was qualified for VATS sleeve lobectomy.

Surgical technique

Surgery was performed under general anesthesia. The

Figure 1 Video-assisted thoracoscopic upper right bronchial sleeve lobectomy (2). Available online: http://www.asvide.com/articles/281

patient was intubated with a left double-lumen endotracheal tube which allowed one lung ventilation during surgery. The patient was placed in the lateral decubitus position. Ports were placed in for VATS lobectomy: the first in the 7th inter-costal space in the anterior axillary line for camera pole; the second in the 8th intercostal space in the infrascapular line; and the third in the 6th inter-costal space in posterior axillary line. A 3 cm long utility incision was made at the level of the 4th intercostal space in the anterior axillary. An incision protection retractor was attached to each port. No rib spreader was used and the whole procedure was controlled on the monitor. The doctor and the camera holder stand in the ventral side of the patient during the process of operation.

Typically, single-direction lobectomy could be considered for the procedure. So we divided the superior pulmonary vein and segmental PA branches and then N2 lymph nodes were dissected (3). At first the anterior mediastinal pleura of the hilum was dissected by ultrasonically activated scalpel (UAS). After the dissection of the adhesions the superior pulmonary vein was stapled and cut off with a vascular (white cartridge) 60 mm long endostapler (EC60, JJMC, USA). Next the first branch pulmonary artery, horizontal fissure were treated with a linear stapler in this order. Taking into account the second bronch of pulmonary artery is less than 4 mm and its angle are not suitable for application of linear stapler, it was knotted and dissected by UAS. The facts prove that it is feasible and safe for PA segmental vessels less than 4 mm (4).

The inferior pulmonary ligament was divided to expose the mediastinal pleura. The surrounding connective tissue of the right main bronchus and the intermedius bronchi of the right lung was removed. Stations 2, 3, 4, 7, 8, 9, 10 and 11 lymph nodes were dissected before dissection of bronchus. It is beneficial for the anastomosis without tension.

The right main stem bronchus was divided first, and then the bronchus intermedius was divided using scissors and a scalpel. Frozen sections of the cut ends of the right main bronchus and the bronchus intermedius were negative of tumor infiltration as confirmed pathologically during surgery.

Right bronchial sleeve lobectomy was then performed. We place no stay sutures in the bronchus to facilitate the anastomosis. Bidirectional and uninterrupted sutures were used for the bronchial anastomosis with 2-0 prolene suture to first anastomose the less exposed tracheal wall (3). A total of two ligation position, the first in suture starting position, second in the suture end position. The entire operation was performed with conventional long instruments. Freed lobes were placed in an endocatch bag. Leak testing was conducted following the anastomosis, in which no leakage was detected up to an airway pressure of 30 cm H_2O (2.94 kPa). Two 26F chest tubes were placed, and the incisions were closed.

Total surgery time was 180 min and blood loss was 100 mL. The chest tube was removed on the 5th post-operative day. Postoperative bronchoscopy and CT scan were performed to observe the healing of the anastomotic stoma. The final histopathological examination confirmed squamous cell lung cancer (T2aN0M0 stage IB). The patient was discharged home on the 10th postoperative day.

Patient was followed up for 2 months after surgery without occurrence of death, tumor recurrence or other adverse events.

Discussion

Despite advances in VATS lobectomy, sleeve lobectomy and bronchoplastic procedures in general have traditionally been performed through a posterolateral thoracotomy. Until recently sleeve resection has been viewed as an absolute contraindication to VATS lobectomy, despite numerous advantages associated with minimally invasive procedures (1). The first documented VATS sleeve lobectomy was reported by Santambrogio and colleagues in 2002 for a 15-year-old female with low-grade mucoepidermoid carcinoma of the left lower lobe bronchus (5). VATS sleeve lobectomy should be performed in comparatively experienced centers.

A interrupted suture was used in bronchial anastomoses in the published studies (3,6), while Liu *et al.* reported the use of a continuous suture with 3-0 or 4-0 prolene sutures (7,8). In the case we also use 3-0 prolene sutures at the beginning, but

suture is broken when knotted. This is a fatal for beginners, so we modified the method in this case. We used 2-0 prolene sutures in bronchial anastomosis with the first suture made in the less exposed tracheal wall about the six o'clock position of the bronchial wall and knotted outside the bronchus, followed by further bidirectional and continuous sutures to cover the entire circumference, with a final knot at the outer side of the wall to complete the anastomosis. The outcome of the anastomosis was considered satisfying.

Xu *et al.* have reported the sleeve reconstruction of the left upper lobe. The deep location of the operative field partly hidden under the left pulmonary artery trunk during bronchial anastomosis in this region has made it even more difficult to operate thoracoscopically. To improve exposure of the operative field, they managed to raise the left main bronchus by passing two 1-0 silk sutures. In this way, a widely open, exposed field was achieved (9). Compared to the sleeve reconstruction of the left upper lobe, the right is relative easy, we place any stay sutures in the bronchus to facilitate the anastomosis.

Our techniques have some advantages. Firstly, four ports were placed in for VATS sleeve lobectomy, which greatly reduced the entanglement of sutures as reported by Liu *et al.* (7). Secondly, the whole-course of application of UAS reduces operation time and bleeding. Thirdly, the anastomosis in an uninterrupted and bidirectional fashion with 2-0 prolene suture makes surgery satisfying and more safety.

Very limited indications for VATS sleeve lobectomy are the reason why the frequency of this type of procedure remains low. However, if the patients fulfill the sleeve lobectomy inclusion criteria in general, they may gain from all the advantages of minimally invasive techniques.

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Laparoscopic and thoracoscopic esophagectomy with intrathoracic anastomosis for middle or lower esophageal carcinoma

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Abstract: Thoracoscopic mobilization of esophagus and laparoscopic mobilization of stomach with cervical anastomosis is employed widely in minimally invasive esophagectomy (MIE) for esophageal carcinoma. However, it is associated with high incidence of complications, including recurrent laryngeal nerve injury and anastomotic leak. This paper summarizes the key techniques in total laparoscopic and thoracoscopic esophagectomy with intrathoracic anastomosis for MIE in 62 patients of middle or lower esophageal cancer between March 2012 and August 2013. Total laparoscopic and thoracoscopic esophagectomy with intrathoracic anastomosis was performed to treat the middle or lower esophageal cancer. Laparoscopic and thoracoscopic Ivor-Lewis esophagectomy was performed using a circular stapler (Johnson and Johnson) intrathoracically to staple esophagogastric anastomosis and reconstruct the digestive tract. In addition, we performed tension-relieving anastomotic suture and embedded with pedicled omental flap. Compared with the trans-orally inserted anvil (OrVil) approach, the technique reported here is safe, feasible and user-friendly. Total thoracoscopic intrathoracic anastomosis can be performed with a circular stapler (Johnson and Johnson).

Keywords: Thoracoscope; laparoscope; intrathoracic anastomosis; esophageal cancer; minimally invasive esophagectomy (MIE)

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Introduction

Currently, minimally invasive esophagectomy (MIE) for esophageal cancer entails laparoscopic and thoracoscopic esophagectomy with cervical anastomosis. Esophagogastric anastomosis is mainly performed by thoracoscopic mobilization of esophagus and laparoscopic mobilization of stomach with cervical anastomosis. Total laparoscopic and thoracoscopic esophagectomy with intrathoracic anastomosis is a major challenge in MIE (1-3), resulting in failure of minimally invasive endoscopic surgery for esophageal cancer (4-6). Cervical anastomosis is still an invasive approach and high incidence of recurrent laryngeal nerve injury and anastomotic leak.

Intrathoracic esophagogastric anastomosis is used for most radical resections of middle or lower esophageal cancer. However, total laparoscopic and thoracoscopic esophagectomy with intrathoracic anastomosis is associated with technical difficulty and complexity. A total of 62 patients with middle or lower esophageal cancer were treated with this approach between March 2012 and August 2013. This paper describes the total laparoscopic and thoracoscopic Ivor-Lewis esophagectomy, focusing on the surgical procedures and the key technical details of thoracoscopic intrathoracic anastomosis using a circular stapler (Johnson and Johnson).

Subjects and methods

Subjects totally 62 patients were enrolled, including 46 males

and 16 females, with a mean age of 61±12 years (range, 42-72 years). Progressive dysphagia was the major symptom for 0.5-6 months, with a mean duration of 2.5±2 months. The preoperative barium swallow study was followed by contrast-enhanced computed tomography of the chest, and upper endoscopy and biopsy. The findings revealed a middle or lower esophageal carcinoma occurring as a single tumor in all subjects. The lesions were 2-5 cm in length, with a mean length of 3±1.2 cm. No obvious outward invasion was detected (stage T3 or lower). No significantly enlarged lymph node was detected. CT scan of the head, bone scan and abdominal ultrasonography revealed no distal metastases. Cardiopulmonary evaluation showed no apparent surgical contraindications. Postoperative pathology included squamous carcinoma in 57 cases and adenocarcinoma in 5 cases. Tumors were staged as T1N0M0 in 27 cases, T2N0M0 in 29 cases, T3N0M0 in 5 cases and T3N1M0 in 1 case (UICC esophageal carcinoma pathological stage, 2009).

Anesthesia

All cases underwent intravenous anesthesia and inhalation anesthesia through a double-lumen endotracheal tube. Two-lung ventilation was administered during the abdominal stage, while single left-lung ventilation was performed during the thoracic stage. However, artificial pneumothorax was not employed during the surgery.

Position and incision

Patients were placed in a supine position, and underwent laparoscopy-assisted abdominal surgery with five abdominal ports. The 11-mm incision besides the umbilicus was used as the observation port, and the other four ports were positioned at the incisions in the subcostal region of the left (5-mm port) and right midclavicular lines (5-mm port), and the incisions 3 cm superior to the umbilicus in the left (5-mm port) and right parasternal lines (11-mm port). The surgeon stood on the right side of the patient (*Figure 1*).

The patient was repositioned to the left lateral decubitus position during the thoracic stage, and was moderately anteverted (4). Thoracoscopy was performed with four thoracic ports. The camera port was located at the 8th intercostal space on the posterior axillary line, the major operation port between the 4th and 6th intercostal space on the anterior axillary line, and the operation port for the assistant at the 7th intercostal space on the scapular line.

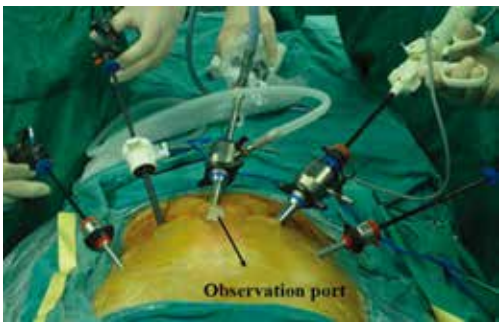

Figure 1 Abdominal incision with five abdominal ports, the surgeon stood on the right side of the patient.

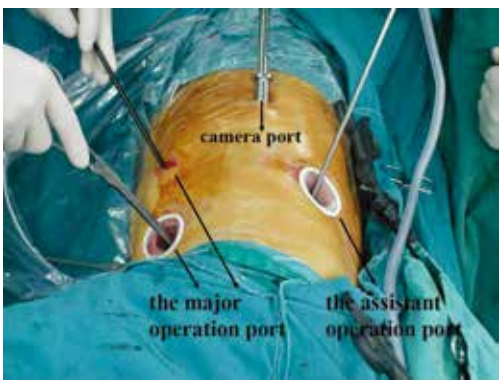

Figure 2 Thoracic incision with four thoracic ports, the surgeon stood on the abdominal side of the patient.

The incision at the 4th intercostal space on the anterior axillary line was approximately 2.5 cm long, while the other incisions were about 1.5-2 cm in length. The surgeon stood on the abdominal side of the patient (*Figure 2*).

Surgical procedures (*Figure S1*)

Laparoscopic mobilization of the stomach

The stomach was routinely mobilized, the abdominal lymph node dissected, and the pedicled omental flap was reserved at the site close to the fundus of the stomach. The greater omentum was mobilized towards the margin of the colon to the splenogastric ligament, and then mobilized towards the margin of the stomach. A pedicled omental flap about 10 cm long and 5 cm wide was reserved to embed the anastomosis. A median abdominal incision of about 5 cm in length was cut below xiphoid, and a gastric conduit of about 3.5 cm in diameter was created using a

linear stapler (Johnson and Johnson) outside the abdominal cavity. The tip of the gastric conduit was temporarily attached to the surgical specimen with interrupted sutures. A jejunostomy was created about 30 cm distal to the ligament of Treitz.

Thoracoscopic mobilization of thoracic segment of esophagus and tumor

The esophagus was mobilized at the site 4 cm superior to the azygos vein with a cautery hook and ultrasonic scalpel in a bottom-up approach. The azygos vein was ligated using Hem-o-lok clip and divided by ultrasonic scalpel. The pleura surrounding the esophagus at the anastomotic stoma were reserved for subsequent use. Thoracic lymph nodes were systematically dissected, including the left and right recurrent laryngeal nerve chain lymph nodes.

Purse-string suture and insertion of the stapler anvil

Esophageal purse-string suture is the most difficult procedure during the total thoracoscopic intrathoracic anastomosis. The 3-0 Surgipro suture was used for esophageal purse-string suture. The purse-string was hand sewn through the muscular layer of the esophagus about 3 cm superior to the azygos vein, encircling it (five needles). The esophagus was pulled straight downwards during the suturing, altering the position to facilitate the suture. A horizontal incision was then made in the wall of the esophagus, 3 cm distal to the purse-string. First, the oval clamp was inserted through the incision to appropriately expand the purse-string, so as to facilitate the insertion of the stapler anvil, and then, the anvil was inserted into the esophagus through the incision and pushed upward above the purse-string via the working port at the 4th intercostal space on the anterior axillary line. The purse-string was tied using a knot pusher, and the distal esophagus between the purse-string and the incision was then transected. Esophageal mucosal layer was reserved 5 mm longer than the muscular layer to prevent slipping.

Intrathoracic anastomosis

The attached gastric conduit was pulled into the right thoracic cavity via the diaphragmatic hiatus, and the circular stapler was placed through the working port at the 4th intercostal space on the anterior axillary line. The circular stapler was inserted into the gastric conduit in the thoracic cavity, and the side of the gastric conduit was anastomosed to the end of the esophagus by joining the anvil to the stapler. The joining space between the anvil and the stapler was thoroughly checked before the excitation to ensure no involvement of the surrounding tissues. After the anastomosis, the thoracoscope served as an endoscope, which was inserted into the gastric conduit to check the anastomotic stoma, to ensure the integrity of the anastomotic stoma and prevent bleeding. After the examination, a linear stapler (Endo-GIA60-4.1; Johnson and Johnson) was used via the port at the 6th intercostal space on the anterior axillary line to close the stump of the gastric conduit, and the cutting edge was embedded with the seromuscular layer. The position of the cutting margin was over 2 cm from the anastomotic stoma to prevent the occurrence of anastomotic stricture after embedding with the seromuscular layer.

Tension-relieving suture of the anastomotic stoma, embedded with pedicled omental flap

Based on our previous clinical experience, we interrupted suture of the gastric wall below the anastomosis and the pleura surrounding the anastomosis to relieve the tension of the anastomotic stoma. A circular embedding of the anastomosis with pedicled omental flap was performed to effectively prevent the occurrence of anastomotic leak, which was consistent with previous reports (7,8). Interrupted suture was performed at 4, 8 and 12 o'clock position (via the thoracoscopic direction) surrounding the anastomosis. The gastric wall below the anastomosis closely adhered to the reserved pouch-like mediastinal pleura surrounding the esophagus to reduce the tension of the anastomosis. The anastomosis was circularly embedded with the reserved pedicled omental flap, and interrupted suture was performed at the same position to achieve intact and tight embedding of the anastomosis. In the present study, one case (1/62, 1.6%) showed the postoperative anastomotic leak, which was an esophageal leak above the anastomosis. It was probably associated with an accidental injury during the mobilization of the esophagus.

Results

The endoscopic surgeries were successfully performed without conversion to laparotomy or thoracotomy. The mean overall operation time was 260±35 min (range, 250-320 min), the mean thoracoscopic operation time was 155±20 min (range, 110-170 min), and the mean laparoscopic operation

time was 115±21 min (range, 90-140 min). The mean estimated blood loss was 210±32 mL (range, 180-270 mL). The mean number of nodes harvested from every patient was 23±5 (range, 11-29). No operative mortality or severe complications occurred, including anastomotic stricture, respiratory failure, trachyphonia or chylothorax. Anastomotic leak was observed in one case (1/62, 1.6%), which was cured with conservative treatment. The patients commenced ambulation 2 days post-operation, with a mild sensation of chest pain. The mean length of hospital stay was 11±2 days (range, 10-14 days; except one case with anastomotic leak). The cases were followed up for 1-17 months, with normal diet. No death or recurrence was observed.

Conclusions

Minimally invasive surgery offers valuable alternatives to enhance traditional open surgery. Total laparoscopic and thoracoscopic esophagectomy with intrathoracic anastomosis overcomes the bottlenecks associated with endoscopic surgery of esophageal cancer, which facilitates the real MIE. It is reported that trans-orally inserted anvil (OrVil) can be used for intrathoracic gastroesophageal anastomosis (9-11). However, OrVil was too expensive to be popular. The transoral insertion of the anvil increases the probability of thoracic infection. Compared with the OrVil approach, the technique reported here is safe, feasible and user-friendly. Total thoracoscopic intrathoracic anastomosis can be performed with a circular stapler (Johnson and Johnson).

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Supplementary material

Figure S1 Laparoscopic and thoracoscopic esophagectomy with intrathoracic anastomosis (12): (I) laparoscopic mobilization of the stomach; (II) thoracoscopic mobilization of thoracic segment of esophagus and tumor; (III) purse-string suture and insertion of the stapler anvil; (IV) intrathoracic anastomosis; (V) tension-relieving suture of the anastomotic stoma, embedded with pedicled omental flap. Available online: http://www.asvide.com/articles/282

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Unidirectionally thoracoscopic resection of lingual segment of the left upper pulmonary lobe

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Abstract: A patient with adenocarcinoma in situ was reported to undergo unidirectionally thoracoscopic resection of lingual segment of the left upper pulmonary lobe and lymphadenectomy in the order of the lingual segmental vein, the lingual segmental bronchus, the lingual segmental artery, and the pulmonary tissues of the lingual segment in turn. As the concepts of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) are defined in the latest international classification of lung adenocarcinoma, pulmonary segmentectomy has been initially used in some multi-center clinical studies to treat these early lung cancer lesions. Pulmonary segmentectomy is currently one of the most minimally invasive lung surgeries, with its unique technical essentials different from those of pulmonary lobectomy. Some studies have shown that pulmonary segmentectomy for early lung cancer, especially for tumors with a diameter of less than 2 cm can achieve a similar long-term survival rate as pulmonary lobectomy, yet its effectiveness and safety should be confirmed in further large-scale prospective studies.

Keywords: Thoracoscope; lung adenocarcinoma; lung segment resection

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, more than 85% of which is non-small cell lung cancer (NSCLC) (1). Lung adenocarcinoma is not only one of the common types of non-small cell lung cancer, but also a pathological type with the highest incidence rate in non-smoking patients (2,3). Various histological subtypes of lung adenocarcinoma greatly differ in clinics, imaging, pathology, genetics, treatment and prognosis. In 2011, the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS) jointly released the latest classification of lung adenocarcinoma (4), removed the concept of bronchioloalveolar carcinoma (BAC) that had been used for a long time, added the concepts of both adenocarcinoma in situ (AIS): a solitary pulmonary adenocarcinoma with tumor of ≤3 cm in diameter and tumor cell growth along the alveolar wall, but no stromal, vascular, or pleural invasion, and minimally invasive adenocarcinoma (MIA): a small adenocarcinoma with tumor of ≤3 cm in diameter, tumor cell growth along the alveolar wall and local infiltration lesion of ≤5 cm. Present studies have shown that the disease-free survival (DFS) in patients with AIS or MIA can achieve 100% if the tumor is completely removed (5). A patient with AIS undergoing unidirectionally thoracoscopic resection of lingual segment of the left upper pulmonary lobe and lymphadenectomy was reported in this video (*Figure 1*).

Case report

The 54-year-old male patient was admitted into the hospital due to repeated coughing for more than a month as well as chest tightness for more than 10 days. He had no history of smoking. At a local hospital before admission, he underwent

Figure 1 Unidirectionally thoracoscopic resection of lingual segment of the left upper pulmonary lobe (6). Available online: http://www.asvide.com/articles/283

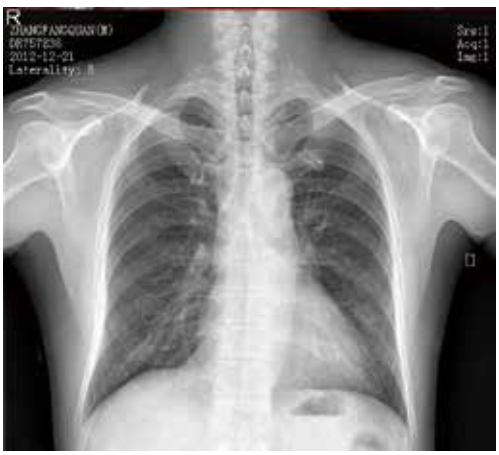

Figure 2 Preoperative chest radiographs.

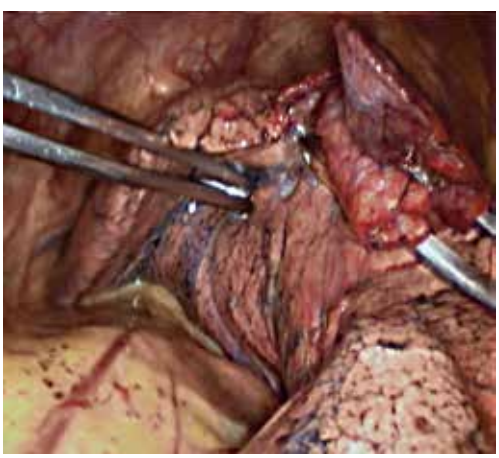

Figure 3 Lesions were seen by exploration in the lingual segment of the left upper pulmonary lobe, which was consistent with preoperative imaging findings.

enhanced chest CT scan, which showed a nodule of 18 mm × 15 mm in size on the lower lingual segment of the left upper pulmonary lobe, possibly considered as peripheral lung cancer. After admission, the patient underwent head MRI, bone scan, ultrasound examination of abdominal organs and other associated auxiliary examinations, and no distant metastases were found. *Figure 2* shows the preoperative chest radiographs. *Figure 3* shows the lesions in the lingual segment of the left upper pulmonary lobe. Considering preoperative auxiliary examinations, unidirectionally thoracoscopic resection of lingual segment of the left upper pulmonary lobe and lymphadenectomy was finally performed in the order of the lingual segmental vein, the lingual segmental bronchus, the lingual segmental artery, and the pulmonary tissues of the lingual segment in turn. The intraoperative frozen section pathological diagnosis was AIS.

Video description

Under combined intravenous general anesthesia, double-lumen endotracheal intubation and contralateral one-lung ventilation were performed. Double-lumen endotracheal intubation is essential for smooth thoracoscopic surgery. The lung tissue at the operating side should be fully collapsed so that the surgery can be successfully performed.

The patient is placed in a 90-degree position lying on the contralateral side.

The incision was designed appropriately for unidirectionally thoracoscopic resection of the left pulmonary lobe. An incision of about 1.5 cm was made as the thoracoscopic observation hole in the 7th intercostal space between the anterior axillary line and the median axillary line; then an incision of about 4 cm was made as the main operation hole in the 4th intercostal space between the anterior axillary line and the median clavicular line; and finally an incision of about 1.5 cm was made as the auxiliary operation role in the 9th intercostal space between the posterior axillary line and the inferior subscapular line. The surgeon stood at the ventral side of the patient and performed the surgery with a thoracoscopy device under the monitor.

The surgery was performed unidirectionally, that is, the resection was performed right under the operation hole by first dissecting tissues to be resected from the most superficial structure, then exposing it, and finally cutting it off only in an unidirectionally gradual deepening way, and by disposing the pulmonary fissure without overturning the pulmonary lobe back and forth, up and down (7,8).

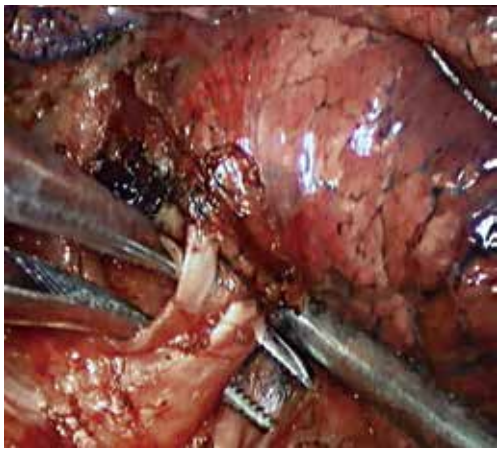

Figure 4 Free the lingual segmental vein.

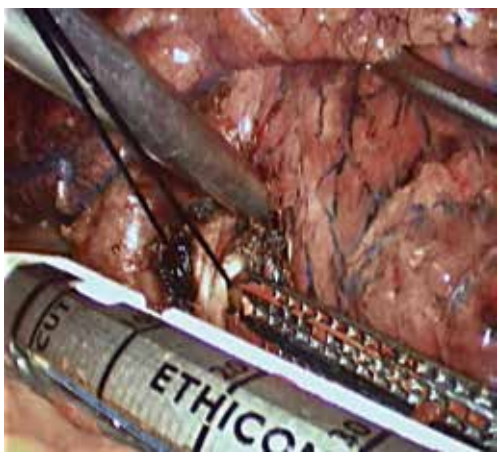

Figure 5 Free the lingual segmental vein, then pull it with a silk suture, and cut it off with an endoscopic linear stapler.

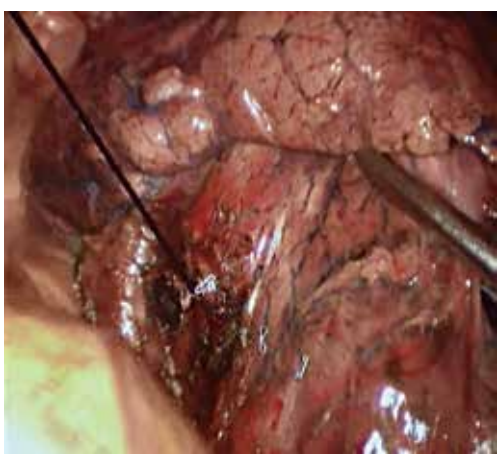

Figure 6 The lingual segmental vein stump after resection.

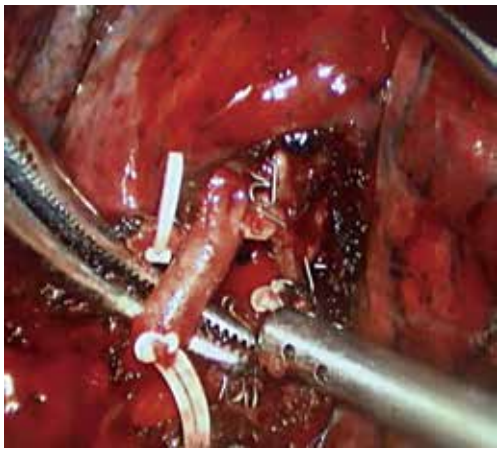

Figure 7 Free the lingual segmental bronchus, then pull it with a silk suture, close with a linear stapler, ventilate for bilateral lungs, and cut off the trachea after confirming no ventilation of the lingual segment.

In terms of the technical essentials, unidirectionally thoracoscopic resection of lingual segment of the left upper pulmonary lobe was basically the same as the right middle pulmonary lobectomy, with a resection direction of the lingual segmental vein, the lingual segmental bronchus, the lingual segmental artery, and the pulmonary tissues of the lingual segment in turn (9). The tissues were freed mainly with a coagulation hook and supportively with an aspirator. Vascular, bronchial and pulmonary parenchymas were handled with the endoscopic linear stapler or hem-o-lok clip applicator.

Step 1: Amputate the vein (*Figures 4-6*). Lingual segmental vein is the most subordinate branch of the left superior pulmonary vein. Pull back the pulmonary lobes, expose the lingual segmental vein, free it, and cut it off.

Step 2: Amputate the bronchus (*Figures 7,8*). Lingual segmental bronchus starts from the bronchial bifurcation of the upper pulmonary lobe. Free it, and cut it off.

Step 3: Amputate the artery (*Figures 9,10*). Lingual segmental truncus arteriosus mainly supplies the blood for the lingual segment, which is the most anterior branches of the posterior lingual segmental artery. Lingual segmental artery starts from the front side of the pulmonary artery in the pulmonary fissure, and divides into two pulmonary segmental branches. During the surgery, the frontal segment of the oblique fissure was first opened, the start of the lingual segmental artery was found, then the oblique fissure was fully opened to the hilum of the lung, the trunk

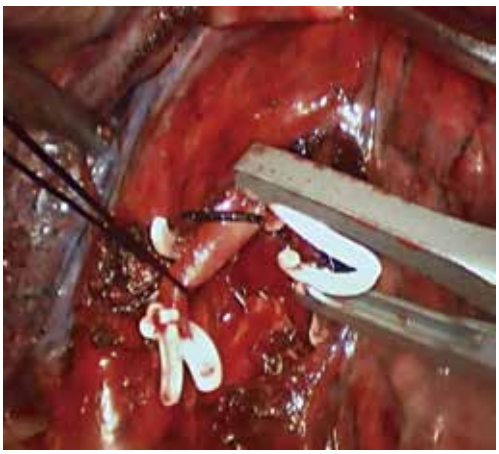

Figure 8 The lingual segmental bronchial stump after cutting.

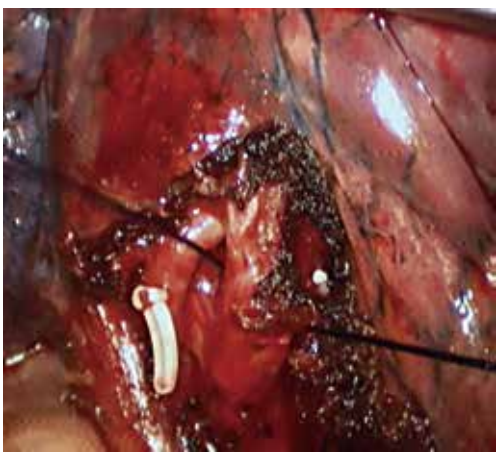

Figure 9 Free the lingual segmental artery, then pull it with a silk suture.

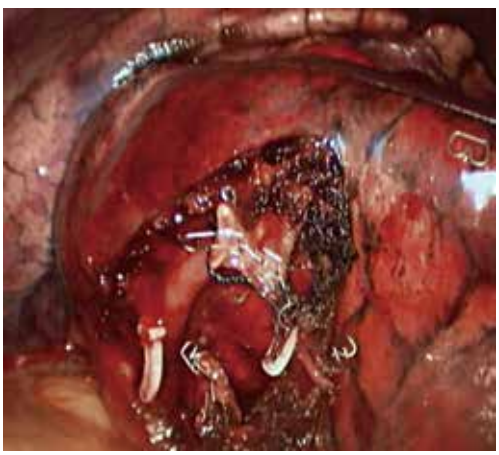

Figure 10 Clamp the lingual segmental artery with a hem-o-lok clip applicator.

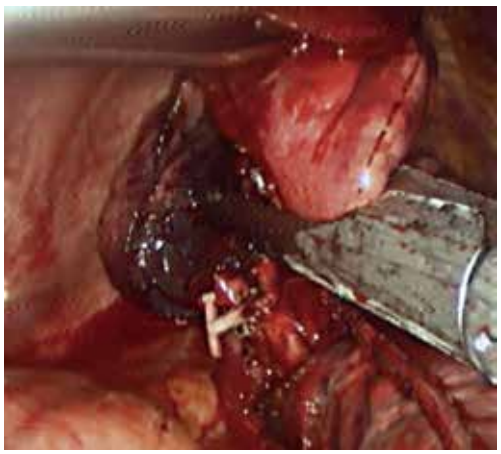

Figure 11 Resect the pulmonary tissues of the lingual segment after confirming the boundary of the lingual segment.

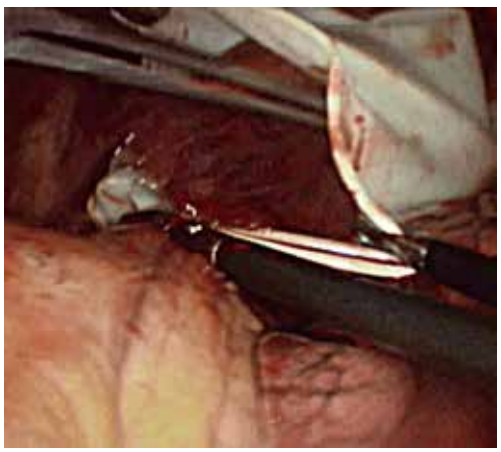

Figure 12 Remove the specimen with a size 8 glove.

of the pulmonary artery between the lobes was exposed, the vascular sheath was opened and the lingual segmental artery was cut off (10).

Step 4: Resect the pulmonary tissues of the lingual segment (*Figure 11*). Ventilate at the operational side to confirm the boundary of the lingual segment, and resect the pulmonary tissues of the lingual segment with the endoscopic linear stapler. Remove the specimen with a size 8 glove (*Figure 12*).

Comments

Thoracoscopy, also known as video-assisted thoracic surgery (VATS), is one of most attractive new technologies

in the field of thoracic surgery in recent 30 years. By full thoracoscopic resection of lung cancer, the incision is small, only 3-5 cm in size, which avoids applying the rib spreader and cutting the chest muscles in large areas, thus better protecting the neuromuscular system, and significantly reducing postoperative pain, intraoperative hemorrhage and incidence rate of postoperative complications for patients. All these advantages are greatly appealing to both doctors and patients.

In the past, lobectomy with systematic lymphadenectomy was considered as the standard surgical procedure for treatment of early lung cancer (11). With the increasing popularity of lung cancer screening and gradual development of imaging technology, especially the emergence of multi-slice spiral CT scan technique, some small lung lesions can be found at an earlier stage; and clinical application of PET-CT allows more accurate early diagnosis and clinical staging of lung cancer than ever before; all of which have greatly improved the resection rate of early lung cancer. The establishment of a new classification of lung adenocarcinoma, especially the introduction of the concepts of AIS and MIA, has presented a new problem in the treatment of thoracic surgery: since the complete tumor removal can achieve complete healing of AIS and MIA, can pulmonary segmentectomy substitute pulmonary lobectomy in the treatment of AIS and MIA?

Video-assisted thoracoscopic segmentectomy is currently one of the most minimally invasive lung surgeries. In terms of pulmonary functions and anatomy, the lingual segmentectomy (S^4 + S^5) is equivalent to the right middle pulmonary lobectomy resection. From the technical perspective, the complexity of pulmonary segmental dissection and the individual variability of human anatomical structure are the greatest difficulties of pulmonary segmentectomy. First, surgeons should familiarize with the three-dimensional relationships among bronchus, artery and vein, and pay particular attention to the arterial anatomic variations that may occur. The anatomical structure of hilum of pulmonary segment has some certain regularities. In pulmonary segments, the arterial branch runs with the bronchi branch, while the pulmonary venous branch runs in the pulmonary segment receiving the venous blood from two adjacent pulmonary segments. The pulmonary segment artery may present with anatomical variations, of which the most common variation is that two corresponding arteries supply blood to the same pulmonary segment. Therefore, we should pay attention to whether there is another variant arterial branch when pulmonary segmental arteries are dissected. The most reliable way of determining pulmonary segmental variation is to determine the bronchus of appropriate pulmonary segment because pulmonary segmental bronchus seldom has variation. Second, we should determine the gap between pulmonary segments. It may be determined in accordance with inflatable pulmonary segments, by closing the pulmonary segmental bronchus in the collapsed pulmonary lobes and make it ventilated, the pulmonary segment to be resected is no longer inflated (12).

The literature has shown that pulmonary segmentectomy for early lung cancer, especially for tumors with a diameter of less than 2 cm can achieve a similar long-term survival rate as pulmonary lobectomy (13,14). However, the effectiveness and safety of pulmonary segmentectomy in treatment of AIS or MIA should be confirmed in further large-scale prospective studies.

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Prof. De-Min Li: what we expect from da Vinci robotic surgery

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The Department of Cardiothoracic Surgery of Nanjing General Hospital of Nanjing Military Command has a distinguished reputation among Chinese patients for decades. In recent years, the introduction of the "da Vinci" robot in the hospital has allowed the Department of Cardiothoracic Surgery to carry out newer and more sophisticated surgeries and research projects. Under the leadership of its director Prof. De-Min Li and the tireless efforts of all the staff members, the Department of Cardiothoracic Surgery has gained many academic achievements, benefiting many patients and their families.

Recently, the JTD interviewed Prof. De-Min Li and invited him to share his insights on the application of the "da Vinci" robot in cardiothoracic surgeries and some other related issues (Figure 1).

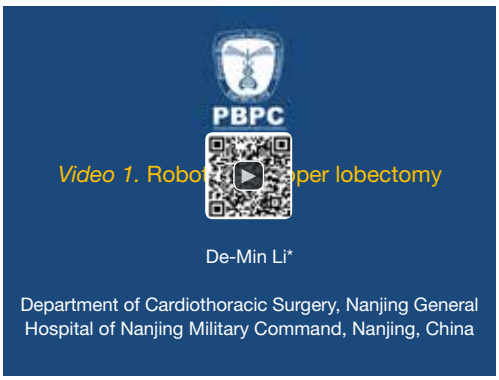

Figure 1 Robotic left upper lobectomy (1). Available online: http://www.asvide.com/articles/279

Introduction

Prof. De-Min Li (*Figure 2*), Chief Physician, Professor, and director of the Department of Cardiothoracic Surgery, deputy Director of the lung cancer center of Nanjing General Hospital. In 2002, Prof. Li was trained on cardiovascular surgery at the heart unit at Monash Medical Centre in Melbourne, Australia for one year. Currently he is the director of the Department of Cardiothoracic Surgery of Nanjing General Hospital of Nanjing Military Command and professor and master's/doctoral supervisor of the School of Medicine of the Second Military Medical University, Nanjing University and Southern Medical University. He is also the Deputy Director of Lung Cancer Center of Nanjing General Hospital of Nanjing Military Command (*Figure 3A*,*B*). He performs various coronary artery bypass surgeries, major vascular surgeries and interventional treatment, and has rich experiences in the peri-operative management of elderly patients with severe coronary artery disease. He is skillful in the surgical treatment of severe valvular diseases and complex congenital heart diseases. He also performs surgeries including tracheal surgery, surgeries for esophageal cancer invading the descending aorta and/or left main bronchus, bronchial sleeve resection/reconstruction, bronchial and pulmonary arterial sleeve resection, and resection and reconstruction of carina. He has accumulated rich experiences in the intensive care and treatment after cardiothoracic surgery.

JTD: As we know, you were trained in coronary surgery at Monash Medical Centre in Melbourne, Victoria, Australia from 2002 to 2003. What was the domestic level of cardiac surgery at that time? What's your feeling about staying abroad then?

Prof. Li: Generally speaking, the performance of cardiovascular surgery was quite good at that time in China. While the cardiovascular surgeries were well performed in some large general hospitals (e.g., third-grade class-A hospitals), they were not so successful in many other hospitals. In 2002, I began to receive training in the Monash Medical Centre in Melbourne, where they had academic capacity parallel to those in Europe and North America. The Australian centers had excellent concepts and modes in medical sciences; meanwhile, they paid particular attention to training, especially trainees from other countries. As I know, many well-known Chinese cardiovascular surgeons had been trained or did their internships in Australia. During the training period, the trainees not only could observe but also be involved in the clinical practice. The study in Australia was a fruitful trip for me. After I returned to China, I was able to perform coronary surgeries independently.

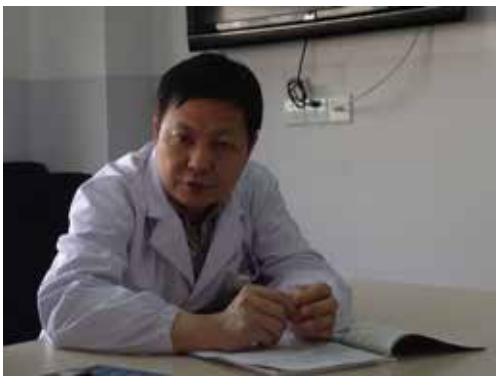

Figure 2 Prof. De-Min Li introducing the da Vinci surgery in his department.

JTD: As we know, your team has performed well in both clinical practice and scientific research. Would you please briefly introduce your department and your team to us?

Prof. Li: The Department of Cardiothoracic Surgery of Nanjing General Hospital currently is divided in two sections: the Cardiovascular Surgery and the General Thoracic Surgery. The latter is focused on pulmonary and esophageal diseases as well as some general chest diseases and mediastinal tumors. The minimally invasive surgery in the General Thoracic Surgery is currently one of our priorities. Thoracoscopic lung resection is the preferred surgical procedure for lung cancer, and video-assisted thoracoscopic surgery (VATS) is also the mainstream treatment for mediastinal tumors. In recent years, the rapid development of completely endoscopic radical resection of esophageal cancer has achieved good results. The Cardiovascular Surgery is mainly focused on heart valve diseases, coronary heart disease, and macrovascular disease, with the minimally invasive treatment of heart valve disease and coronary heart disease and the hybrid cardiac surgery for macrovascular disease as the priorities.

JTD: Coronary artery bypass grafting (CABG) has become a relatively mature procedure. Would you like to introduce the use of CABG in China?

Prof. Li: Coronary surgery has been widely performed in China, and its levels in the majority of Chinese third-grade class-A hospitals are comparable to their international counterparts. Now our goal is to do it better, though CABG is the gold-standard treatment for multiple-vessel lesions, most eligible patients prefer coronary intervention, which is less invasive. Only patients with poor vascular conditions

Figure 3 (A,B) Nanjing General Hospital of Nanjing Military Command.

and therefore not feasible for intervention undergo surgical treatment, which make the surgery more difficult and risky. Therefore, cardiac surgeons must try their best to maintain good quality control and expected long-term outcomes. The long-term role of internal mammary artery in anterior descending coronary artery reconstruction is irreplaceable and therefore the internal mammary artery should be routinely used. CABG should be actively applied in young patients with coronary heart disease to achieve good long-term patency rate and maintain good quality of life. The concept of "minimally invasive" should be rationally applied in the surgical treatment of coronary heart disease. Off-pump CABG can lower the impact of extracorporeal circulation on human body and thus reduce the peri-operative risks. By cooperating with the Department of Cardiology, we are using the Hybrid Operation Room and da Vinci robot for hybrid coronary surgery. More specifically, the left internal mammary artery (LIMA) reconstruction or the anterior descending artery reconstruction is performed under the assistance of the robot or completed by the robot, whereas the international intervention except for the anterior descending artery is performed by the Department of Cardiology. The joint efforts of these two departments enable us to apply the most

advanced treatment concepts to our patients, thus reducing the trauma and achieving the optimal efficacies.

JTD: How about the treatment of aortic dissection in your department?

Prof. Li: More patients with aortic dissection have been identified along with the advances in diagnostic technology and the increased awareness of this condition, particularly when the climate changes. The routine use of ECG and CT for patients with acute chest pain has increased the detection rate of acute aortic dissection. Aortic dissection is a very dangerous disease, and therefore must be appropriately managed according to patients' conditions. The type A aortic dissection is easy to become ruptured at its early stage and is associated with high mortality; thus, active surgical treatment is warranted. The improvements in the surgical procedures, anesthesia, and other techniques for the type A aortic dissection have made the surgical treatment more effective. In addition to the routine techniques including deep hypothermic circulatory arrest for aorta/aortic arch replacement and the "elephant trunk" technique, we also apply hybrid procedures without deep hypothermic circulatory arrest in carefully selected cases, which avoids the impact of deep hypothermic circulatory arrest on human body and reduces the post-operative complications. For type B aortic dissection, minimally invasive interventions are preferred, which are featured by good effectiveness, small trauma, and quick recovery.

Enter the era of minimally invasive surgery with the help of the da Vinci robot

JTD: The Nanjing General Hospital was one of the hospitals that introduced the da Vinci Surgical System at an early stage. In 2012, the first case of robotic assisted heart repair surgery in Jiangsu Province was completed in the hospital. What are the indications for the robotic surgeries?

Prof. Li: The da Vinci robotic surgery is a specific example of the application of modern high technology in surgery and also represents one of the future directions of minimally invasive cardiothoracic surgery. However, a wider application of da Vinci robot in the cardiothoracic surgery still has a long way to go, since it may involve many issues such as the costs of the system, the cost of treatment, the training of medical staff, and the acceptance of the relevant concepts. Generally, the applications of robotics in cardiothoracic surgery have many advantages. For instance, the robotic hand, when replacing the human hand, can reduce surgical trauma; also, the 3-dimensional vision of the robot is more accurate when compared with the 2-dimensional vision of the conventional endoscope and therefore allows the operator to directly transfer his/her ideas to the robot hand. The robot can perform reconstruction accurately, which is also superior to the endoscope. Currently, the applications of the robot in the cardiothoracic surgery include CABG assisted by or fully by the robot, mitral valve repair or replacement, repair of atrial septal defect, and resection of cardiac tumors. In the General Thoracic Surgery section, it is mainly applied in the treatment of thymic tumor, lung tumor, and esophageal surgeries. In 2014, the application of robot to cardiothoracic surgery has been listed as a key academic project in our department. It is planned that about 150 robotic operations will be performed this year. Before the robotic surgery, the doctors must carefully evaluate patients' conditions. Only those who are expected to achieve therapeutic effectiveness comparable to the routine surgeries and meanwhile will benefit from the "minimally invasive" and "aesthetic" features will be considered appropriate for the robotic surgery.

JTD: After the use of robotic assisted treatment, will the priority of a specific surgical procedure be changed?

Prof. Li: The role of doctors remains critical during the robotic cardiothoracic surgeries. The operators must have rich experiences in the conventional surgeries. In other words, only surgeons who are good at the conventional surgeries are possible to carry out the robotic operations. Robot is just a tool used by doctors. With the robot, the surgeons just operate in the console instead of the operative field. Therefore, the use of robot does not cause changes in the key surgical procedures.

JTD: As the deputy director of Lung Cancer Center of Nanjing General Hospital, what's your opinion on the role of surgery in the multidisciplinary treatment of lung cancer?

Prof. Li: The treatment for lung cancer differs based on the disease stage. Multidisciplinary management currently is the main treatment for lung cancer. Surgery plays an important role in the treatment of lung cancer, particularly those at an early stage (stages I and II). For resectable tumors (stage III), tailored multidisciplinary management is needed. In our department, the treatment for lung cancer focuses on

surgical treatment (e.g., bronchial sleeve resection and reconstruction, bronchial/pulmonary arterial double-sleeve resection and reconstruction, and carina resection and reconstruction) for complicated lung cancer; and, minimally invasive radical resection of lung cancer (totally thoracoscopic lung resection and robotic lung resection). The Hybrid Operation Room in our hospital allows us to carry out accurate thoracoscopic resection of the small lung lesions under digital subtraction angiography (DSA).

JTD: In fact, in addition to surgery itself, post-operative care is also very important for the recovery and treatment of a patient. What kind of work is expected in post-operative care? Is there any experience you would like to share with our readers?

Prof. Li: Post-operative care is important to ensure the effectiveness of surgical treatment. An increasing number of our patients are elderly people, and they often have concomitant conditions such as diabetes, hypertension, chronic obstructive pulmonary disease, and organ dysfunction. For these patients, in addition to minimally invasive surgery, post-operative care including peri-operative airway management, fluid management, maintenance of water and electrolyte balance, blood sugar regulation, anti-infection treatment, nutritional support, and supportive therapy of vital organs are also very important. Treatment and care should be conducted in a more proactive manner. We must carefully observe and analyze the disease conditions and take effective preventive measures before the occurrence of any complication. All in all, modern surgery has placed higher demand on surgeons.

JTD: Thank you very much!

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Prof. Shijiang Zhang: the development of hybrid surgery in China

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The People's Hospital of Jiangsu Province is the largest tertiary general hospital in the province and has been shouldering the pivotal tasks of providing medical services to province-wide patients, mentoring medical practitioners, and advancing medical research. As the hospital's new clinic building is going to be put into use, a batch of advanced medical instruments will be introduced to provide better care and treatment to the patients.

Prof. Shijiang Zhang, Director of the hospital's cardiothoracic surgery department, is a well-known expert of cardiothoracic surgery and has carried out many ingenious surgeries and some complicated heart and lung transplantations over the past 30 years. He is well versed in complicated surgery for congenital cardiac disease like Tetralogy of Fallot (TOF), Modified Fontan operation, operation for Ebstein' s anomaly on adult (Figure 1) etc.

He is also a member of several charity foundations, and frequently flies to Xinjiang Province, more than 2,000 kilometers away, to perform free operations for local kids with heart problems, establishing him as a role model for his extraordinary professional skills and occupational ethics.

Recently JTD has invited Prof. Zhang for an interview to talk about several topics related to transcatheter aortic valve implantation (TAVI) surgery, hybrid surgery, and postoperative care.

JTD: You have made extraordinary achievements in cardiothoracic diseases and devoted almost half of your life into the healthcare service. How did you decide to be a cardiothoracic surgeon from the very beginning?

Prof. Zhang: Actually, I had not even thought about being a doctor in my early years, as my favorite subject at that time was literature. After graduation from middle school, I was about 15 years old and went to Lianshui county and work as a farmer in the countryside. I joined the army in 1970, first as a medical soldier, and later pursued study of clinical medicine at the Nanjing Medical University. I was assigned to work at the radiology department after graduation from the university in 1975, and was transferred to the cardiothoracic surgery department the next year because my health conditions did not allow me to work at the radiology department. Since then I gradually develop a love for cardiothoracic surgery and finally became who I am today.

JTD: We understand that you had once studied at the School of Medicine, University of Massachusetts, and Harvard Medical School's Brigham and Women's Hospital to learn how to perform cardiovascular surgeries and lung transplantation. Would you like to share with us your experiences during these trips?

Prof. Zhang: The oversee study period started in 1999. Originally, I was offered an opportunity to study abroad back in 1990, but I had to give up because of family reasons. I went to Boston in 1999 and first worked as a visiting doctor at the affiliated hospital of the School of Medicine, University of Massachusetts, and later was trained on cardiovascular surgery at BWH (*Figure 2*). Doctors at these hospitals were highly qualified, but the most impressive thing to me during my stay at the Harvard Medical School was its underground operation room. An underground operation room is cleaner and more concentrated with less distraction and disruption during the surgery. No underground operation room has been built in China. The Harvard Medical School holds a regular breakfast meeting at 6:00 AM every Friday to discuss complicated cases and share the latest development in medical technology, and all faculty members will attend the meeting.

Note: BWH stands for Brigham and Women's Hospital and is affiliated to the Harvard Medical School. BWH library is shared with the school, and its sixth floor houses the editorial department of *the New England Journal of Medicine*.

JTD: You have been working at the cardiothoracic surgery department for almost 30 years and have successfully performed several cases of extremely complicated lung transplantation. What is the biggest challenge for lung transplantation? In which direction you think this area is going?

Prof. Zhang: Lung transplantation is much more difficult

Figure 1 Operative treatment of Ebstein's anomaly on adult (1). Available online: http://www.asvide.com/articles/280

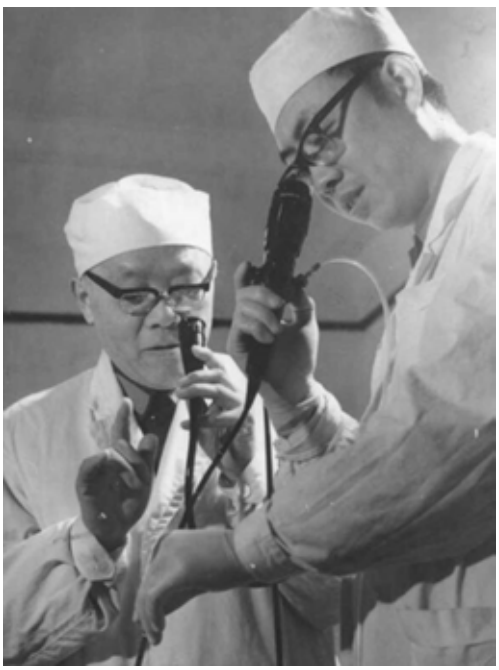

Figure 2 Prof. Gongliang Wu (left), Prof. Shijiang Zhang (right). Prof. Zhang was learning bronchoscope under the guidance of Prof. Wu.

than transplantation of other organs such as the kidney, because the lung is a hollow organ that is connected to the outside world. That means once transplantation is completed, the new lung must be working immediately at its full capacity. Generally speaking, patients with chronic obstructive pulmonary disease (COPD) and people with middle and terminal pulmonary diseases can undergo lung transplantation, but there is still no consensus whether lung cancer patients should get such an operation. We generally believe that lung transplantation is viable as long as the patient does not have any lung infection. Patients with lung infection cannot have lung transplantation because immunosuppressive agent must be used during the surgery. A prominent developmental trend in lung transplantation is towards donation after cardiac death (DCD). The survival rate of grafts from DCD has been close to those from heart-beating donors. DCD is expected to be of growing significance in the future because it can address, to some extent, the shortage of grafts.

JTD: We understand that a team under your leadership has also made enormous progress in hybrid operation, and the hybrid operation room is under construction. What is the status quo of hybrid operation in China? What are its advantages and disadvantages?

Prof. Zhang: We will have our own hybrid operation room when the hospital's new clinic building is completed. The People's Hospital of Guangdong Province has already built digital subtraction angiography (DSA) hybrid operation room. The hybrid operation room is a product of multi-disciplinary integration, and it can mitigate risks during the operation and reduce peri-operative mortality. The introduction of hybrid operation room places higher demand on doctors because they must be knowledgeable about some technologies used in other medical departments. That seems like a versatile drama performer who can play different roles in a show. Hybrid operation room brings obvious advantages of one-stop service. Take the coronary artery bypass grafting (CABG) as an example: before the operation, coronary arteriography must be carried out in the related department to determine the location and characteristic of the artery stenosis, after which a surgical plan can be finalized, and the surgery is then performed back at the surgical department. Within the hybrid operation room, coronary arteriography and CABG surgery can be done in the same room if the doctor deems surgery is needed based on the result of arteriography. All the procedures are completed in the same room without having to transfer the patient. It is not a medical model where doctors from different departments work together, but one where a single or several doctors perform the surgery based on their extensive knowledge base. This revolutionary model can help many patients. Another example is a dissecting aneurysm, which normally has very high mortality rate. For DeBakey I type dissecting aneurysm, the mortality rate will increase one percentage point each hour within the first 72 hours. That is to say, a patient

would have 50% chance to die if he or she does not receive surgery within the first 48 hours. Based on the conventional surgical methods, the patient is likely to have died before the surgery can begin, particularly due to the time delay in ascertaining imaging results. In a hybrid operation room, however, the patient is much more likely to survive. Hybrid operation is an apparent trend for the future development of cardiothoracic surgery, and more and more hospitals in China will have their own hybrid operation rooms.

JTD: In TAVI, the impaired cardiac valves should be replaced by the artificial ones. We understand you are launching the project of potential artificial valves in China. Would you like to introduce the progress of the project?

Prof. Zhang: TAVI is a procedure where an artificial cardiac valve attached to a wire frame is guided by catheter to the heart via femoral artery; once in the proper position in the heart, the wire frame expands, allowing the new valve to open and begin to pump blood. The procedure involves only minor trauma and patients can make a quick recovery. At present, the domestically-made artificial cardiac valves are developed by a team led by Prof. Runlin Gao (who later became the Academician of the Chinese Academy of Engineering in 1999) from the Fuwai Hospital CAMS&PUMC. We began animal tests of the products since 2005, and we can only spare the time to do the tests on weekends because we are already occupied on the weekdays. I remember that in a period we had almost no holidays for a couple of months. So far we have done 48 clinical tests and China Food and Drug Administration told us that we can apply for approval of the product's clinic application if we complete 80 tests. All of the 48 cases are retrograde surgeries and anterograde surgeries are still under research and development. At present, a TAVI procedure costs roughly 50,000 Euros, and about 50,000 such procedures have been carried out worldwide. We hope to reduce treatment cost for patients though our effort.

JTD: What are the pros and cons of full aortic root reconstruction and aortic valve sparing operation?

Prof. Zhang: There are two procedures for aortic root reconstruction: Bentall procedure and David procedure. Bentall procedure refers to the total aortic root replacement with a composite valve-graft; in the David procedure however, the patient's own aortic valve is preserved. The David procedure requires higher technical skills and carries greater risk. The two procedures also apply to different indications. David procedure applies to patients whose aortic valve functions well while aortic root aneurysm is damaged. If the patient's aortic valve is diseased, the Bentall procedure is more appropriate.

JTD: As we know, in addition to a successful operation, postoperative monitoring and care is also very important for the patient's recovery and further treatment. Would you please share your experience in this regard?

Prof. Zhang: Postoperative care is indeed very important, because after the cardiac surgery the heart must be able to work immediately and at full capacity. This is crucial to the success of the surgery. We have seen some patients who have had their damaged valves replaced and then quickly deteriorated to critical conditions. These emergency cases remind us the importance of doctors keeping a close eye on the patients' vital signs. Therefore, I always ask our fellow colleagues to spend some time in the ICU to learn how to monitor the vital signs of critical patients, because the experience is very helpful for them to monitor their patients' physical conditions after cardiac surgeries.

JTD: Thank you very much!

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Disclosure: The author declares no conflicts of interest.

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Mei-Shin Shih: a surgeon, master, and mentor

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Studying medicine

Dr. Mei-Shin Shih (*Figure 1*) was born on January 5, 1918 to a literary family in Fuzhou City, Fujian Province. In his early years China was being plagued by years of fighting among factional warlords, and people were living in misery. He studied very hard and was determined to get enrolled into the Shanghai Medical College, now an affiliate to Fudan University. His name appeared on the school's admission list published by Shun Pao newspaper on August 18, 1936.

After the Anti-Japanese War broke out, the school had to be relocated again and again across the country and he finally graduated in 1943 and worked at the department of surgery as an assistant resident and teaching assistant. In 1946, he returned to Shanghai, and served as senior assistant resident at the Red Cross Hospital (now the Huashan Hospital), and later he went on to work at Zhongshan Hospital.

In 1947, Prof. Chia-ssu Huang established the department of cardiothoracic surgery in the Zhongshan Hospital and Shi soon became his right arm. Under Prof. Huang's instructions, Shi embarked on an extraordinary journey of medical explorations. It's worth mentioning that Prof. Huang personally performed two surgeries (appendectomy and phrenic nerve blockage) for Mei-Xin Shi. The inheritance of Prof. Huang's medical legacy to Shi was marked by the opening of the 7th annual conference of the Chinese Medical Association in 1947, when the two masters jointly published an important article—*Experience on Surgical Treatment for Pulmonary Tuberculosis: A Preliminary Report*. This article was published on the *Chinese Medical Journal* and later became normative guidelines for Chinese thoracic surgeons to treat tuberculosis. The inheritance of their medical legacies later became a much told tale.

Figure 1 Dr. Mei-Shin Shih.

Dr. Shi helped Prof. Huang in the establishment of the department of cardiothoracic surgery in Zhongshan Hospital, and later he became director of the department and head of Shanghai Institute of Cardiovascular Diseases. Under his leadership, Zhongshan Hospital has developed into one of China's largest and most advanced diagnosis & treatment centers of thoracic and cardiac diseases.

Innovations

Prof. Shi has been treating cardiothoracic diseases for decades and has dedicated his whole life to the development

of cardiothoracic surgery in China.

In 1945, a US surgeon Leo Eloesser, 19th President of the American Association for Thoracic Surgery [1936-1937], was invited to China and make a speech about the latest advances in the surgical treatment of cardiothoracic diseases. When talking about the surgery for tetralogy of Fallot, he joked to the audience that he would cut off his head if anyone else in the room could perform this sophisticated surgery.

In the newly founded China, the most sophisticated surgical instruments were not available from the Western due to disembargoes. That made it extremely difficult to carry out this complicated surgery. In the first place, a very tiny and specially curved needle must be in place before the surgery can begin. Even such a needle could not be produced in China at that time.

Dr. Shih was determined to make this kind of needle by himself. He bought tiny crewel needles and heated them on the alcohol lamp so that the needles could bend. It's easy saying than doing, because quenched metals are prone to break up. After numerous failed attempts in more than 10 days, he finally made a batch of needles that could be used in the surgery. He then used the needles to perform surgeries on animals and gained confidence after several successful practices. Early in 1953, a patient with tetralogy of Fallot was admitted in Zhongshan Hospital. After making full preparations for the surgery, Dr. Shi adopted new procedures and used the self-made needles to perform the first Blalock-Taussig shunt in China.

After successful completion of the surgery on March 2, 1953, Dr. Shih did neither make it public nor make aggressive efforts to spread news about his successful practice, because what he did was not for personal gains. The surgery was not known by the outside world as the first Blalock-Taussig shunt for tetralogy of Fallot in China until the patient died 41 years later. When asked about this landmark operation, Shi said there was no special feeling after the surgery, but he indeed felt a sense of relief for he did what was once considered a mission impossible.

In addition to the first Blalock-Taussig shunt for tetralogy of Fallot in China, he also performed the many "firsts" in China's history of cardiothoracic surgery: resection of pulmonary metastases (January 1948); primary resection of lungs for the management of empyema, thoracoplasty after lung resection, ligation & division of the aberrant right subclavian artery, and substernal jejunal interposition [1953]; suturing and division of the patent ductus arteriosus [1954]; primary radical treatment for the congenital esophageal atresia and esophago-tracheal fistula; and mitral commissurotomy via interatrial groove through right thoracotomy [1957]; direct closure of atrial septal defects under hypothermia (April 1958); homograft repair of aortic arch aneurysm [1959]; direct repair of ruptured sinus of Valsalva under cardiopulmonary bypass [1960]; resection of left ventricular aneurysm under deep hypothermic cardiopulmonary bypass, and mitral valve repair under direct vision [1962]; resection of manubrium chondroma and allograft transplantation for the cryopreserved manubrium and bilateral sternoclavicular joints (in cooperation with the Department of Orthopedics) [1970].

With his unique innovations, Dr. Shi completed many "impossible" missions for China.

Another extraordinary contribution by him was the development of artificial heart-lung machine. Due to political reasons, Western countries barred export of such machines into China at that time. Prof. Shi came up with a bold idea of independently developing the machine. He drew schematics of the machine and brought the drawings to machinery plants in Shanghai to consult experts. After more than 1 year of relentless efforts and 191 animal tests, China's first static vertical screen artificial heart-lung machine finally rolled off the production line. With this machine, Zhongshan Hospital had carried out a series of open heart surgeries since September 1959 and the safety of these surgeries was substantially improved. These domestically-made machines were later used in many medical institutions across the country and saved numerous lives.

Given Prof. Shi's remarkable contributions, the Chinese Medical Association's Society of Surgery decided in 1975 to dispatch him to attend the 26th conference of the International Society of Surgery at Edinburgh, UK. Only three Chinese attended this conference.

Role model

In the 1950s, Mei-Xin Shi was the first to open training courses for thoracic surgeons in China and a large number of thoracic surgeons acquired skills and expertise from these training programs.

Prof. Shi was president of Shanghai First Medical College from 1978 to 1984. As a man of dedication, candor, integrity and simplicity, he had been making every effort to restore order at the college disrupted during the "Cultural Revolution". As a mentor of postgraduates, he had been tireless in teaching and trained roughly 300 thoracic surgeons from China as well as Indonesia, Mongolia and Vietnam.

Prof. Shi has been a rigorous scholar with many works to his credit. He has published nearly 100 scientific articles. He was chief editor of medical publications like *Practical Surgery*, *Illustrated Cardiothoracic Surgery*, *Atlas of Vascular Surgery*, and *Manual for Grassroot Doctors*.

He also participated in the compilation of professional medical textbooks including *Surgery*, *James Shen's Textbook of Surgery*, *Chia-ssu Huang's Textbook of Surgery*, *Vascular Surgery*, and *Cardiothoracic Surgery*. He was nearly 90 years old when editing *Practical Surgery*, a textbook that had been revised 7 times. He reviewed scripts of millions of characters and carefully read every sentence before making any revision. He would not miss any mistake, even a punctuation mark or a typo. He said even the slightest error was not acceptable for a reference book that every young doctor would have to use.

Prof. Shi was also deputy chief editor of major dictionaries like *Cihai*, *Da Cihai*, and *Chinese Medical Encyclopedia*, and he was in charge of reviewing the definition of medical terms.

What impressed us most is Dr. Shih's care and support to younger doctors. In January 2013 the Ministry of Health planned to publish Color Illustrations for *Cardiothoracic Surgery*, an important book under the key national publishing project [2011-2015]. The publishing house had already decided to name Dr. Shih as chief editor, but he insisted this honor should be granted to his student, Prof. Chun-sheng Wang. He wrote an ebullient preface for the book, saying "the book, with exquisite pictures, accurate descriptions and prominent practicality, will definitely play a positive role in conducive to deeper study on cardiothoracic diseases". In the preface he expressed a sincere hope that the younger generation can really excel their masters in terms of academic achievements.

Life in the late years

Dr. Shih has also spent a colorful life in his late years. He set and repeatedly renewed his own record of being the oldest doctor joining in expert consultations. He and his beloved wife, Prof. Zhong-Nian Chen, who is also a medical professor, accompanied each other and led a peaceful life in their final years. Their residence was just a few meters away from Zhongshan Hospital, and students of the medical school had always met them on the way between the hospital and their house.

Compared with doctors "in the modern times", Prof. Shi looked more like a doctor of the past. He cares much more about creation and giving than receiving or self-consummation. Once there was a proposal that he should apply to be an academician of either the Chinese Academy of Sciences or Chinese Academy of Engineering, and his application, if submitted, stands a good chance of being approved given his reputation and contribution. However, he flatly rejected the proposal. His rejection is apparently unimaginable in today's world. This might be what is supposed to be for a master of thoracic surgery.

Several months after his wife passed away, Prof. Shi also left the world he had loved so deeply, with his wisdom and his hands. Definitely, the legend of the master continues, as the Memorial Chia-ssu Huang Lecture will be held to pass down the story between the two giants in thoracic surgery in China, which was a deep wish from Prof. Shi. A Chinese's journal on thoracic disease would be honored to have their legend continue, and world widely spread.

The life of Dr. Mei-Shin Shih

- January 5, 1918, born in Fuzhou, Fujian
- 1933-1936, studied in Gezhi High School, Fuzhou
- 1936-1943, studied at Shanghai School of Medicine
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- 1978-1984, president of Shanghai First Medical College
- January 10, 2014, passed away

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Case Report

Gastrointestinal bleeding in lung leiomyosarcoma history: report of a case

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Abstract: The paper presents an unusual case of single small bowel metastasis from primary lung leiomyosarcoma (PLL) presenting with abdominal pain and gastrointestinal (GI) bleeding successfully treated by surgery with radical aim.

Keywords: Lung sarcoma; gastrointestinal bleeding; bowel metastasis; laparoscopic surgery

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Introduction

Primary pulmonary sarcoma is a very rare entity, accounting for less than 0.5% of all malignant lung cancers, originating from the smooth muscle of the pulmonary parenchyma, bronchi, or pulmonary arteries, in order of decreasing frequency (1). Because of their rarity, the biologic behaviour of these tumours is not well known. Metastases to the small bowel from primary tumours in extra abdominal sites are uncommon and the most common primary tumours that metastasise to the bowel are malignant melanoma, carcinoma of the breast and lung (2). Clinical features of gastrointestinal (GI) metastases are abdominal pain, bleeding, obstruction, and perforation: GI haemorrhage is the most common symptom of GI metastasis (3). Abdominal metastasis is considered an uncommon event in the natural history of sarcoma and limited information are available regarding the natural history of primary lung sarcoma, the influence of abdominal metastasis and the significance of surgical resection. To our knowledge, small bowel metastasis from primary lung leiomyosarcoma (PLL) has never previously been reported.

We present an unusual case of single small bowel metastasis from PLL presenting with abdominal pain and GI bleeding successfully treated by salvage surgery.

Material and method

A 67-year-old woman presented to our Hospital with intermittent upper-abdominal ache for common bile duct calculosis; a routine radiographic image of the chest exposed an abnormal lung shadow in the upper lobe of his right lung. Computed tomography (CT) scan of the chest noted a mass in the right upper lung base with no evidence of mediastinal lymphadenopathy (*Figure 1*) and positron-emission tomography (PET) ruled out extrathoracic locations of the disease. Evaluation of transbronchial needle aspiration (TBNA) specimens showed undifferentiated non small cell lung carcinoma.

The patient presented to the thoracic surgeon and underwent right thoracotomy with upper pulmonary lobectomy and mediastinal lymphadenectomy; grossly the lesion was round and white, measuring 31 mm × 22 mm, infiltrating the visceral pleura. Surgical pathology report revealed that the lesion was composed of bundles of spindle-shaped cells, with areas of necrosis, sclerosis and hyalinosis. Immunohistochemical study revealed that tumor was positive for smooth muscle actin, CD68 but negative for CD34, CK(PAN), desmin, TTF, S100, ACS, AML, CD117, MIB-1 >20%. The lesion was diagnosed as leiomyosarcoma. Mediastinal lymphadenectomy was negative for metastatic

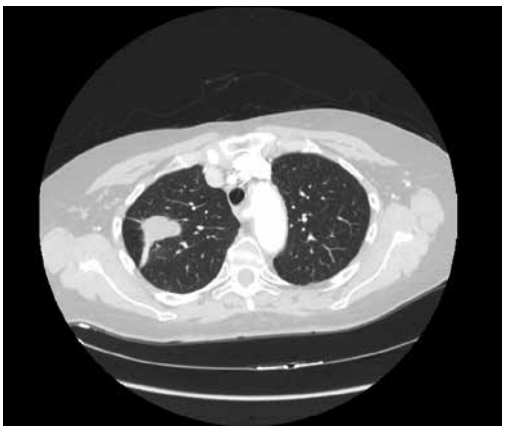

Figure 1 Contrast-enhanced CT scan of the chest showing a mass measuring 3.0 cm × 2.0 cm in the right upper lobe. CT, computed tomography.

disease.

Because the patient had no history of a resected leiomyosarcoma and no tumor was detected by clinical and diagnostic imaging studies, a diagnosis of PLL was made.

The patient did no underwent radiotherapy or chemotherapy and was on regular follow-up: whole-body PET/CT or CT scan of chest and abdomen were performed every 3 months.

Two years after surgery the patient presented abdominal pain. Upper GI endoscopy showed hiatal hernia. Fecal occult blood test was positive and colonoscopy did no detect lesions or bleeding. Following the onset of melena and worsening anemia she was admitted to hospital. Video capsule endoscopy (VCE) showed a stenosing and ulcerative ileal lesion. Double-balloon enteroscopy with biopsies of the lesion resulted positive for spindle-cell carcinoma, suggestive of leiomyosarcoma metastasis.

We performed an oncological correct laparoscopic segmental ileal resection. Pathology evaluation of the specimen verified a white, stenosing lesion, measuring 60 mm × 24 mm retracting and infiltrating serous membrane and involving the adjacent mesentery. Surgical pathology revealed high degree leiomyosarcoma, with markedly increased areas of mitotic activity, with full-thickness bowel infiltration with mucosal ulceration; lymph nodes and surgical margins of resection were negative for neoplastic disease. Immunohistochemical study revealed that tumor was positive for smooth muscle actin, desmin but negative for CD34, CK(PAN), DOG1, S100, AML, CD117, MIB-1 >20%. The lesion was diagnosed as lung leiomyosarcoma metastasis.

Results

The postoperative course was uneventful. The patient received adjuvant chemotherapy and is still alive without recurrence for >3 years.

Discussion

Leiomyosarcoma represent a heterogeneous group of tumors and usually arises in the uterus, GI tract, retroperitoneum or soft tissue accounting for 1% of all malignancies. Pulmonary leiomyosarcoma is a rare disease representing 9% of all sarcomas (4), originating from the neoplastic transformation of the peribronchial smooth muscle fibers, most frequently the larger bronchi of the left lower lobe (5). Risk factors include radiation therapy, chemotherapy and environmental and occupational exposures. Most primary sarcomas of the lung occur in middle age with a slight predominance of male and show no specific presenting symptoms and characteristic roentgenologic manifestations (6). CT scan of the thorax is crucial in defining contiguous thoracic structures invasion (pleura, pericardium, vessels, chest wall), and it allows the determination of local extension. But diagnosis of primary lung sarcoma should be considered only when there is no evidence of a former treated soft tissue sarcoma, and if no sarcoma is detected by extensive clinical and diagnostic imaging studies. Most series reported a median survival near to 24 months, and a 3-year survival between 17% and 50% (7). Surgical treatment without lymph node resection is the therapy of choice in all patients and tumor size to be one of the most important prognostic factors (8). Radiotherapy con be used in case of incompletely resected tumors whereas adjuvant chemotherapy may be indicated, depending on the size and grade differentiation of the tumor (9). Leiomyosarcomas can be primary or secondary in the intestine. Secondary neoplastic involvement of the small bowel is more frequent than primary small bowel malignant neoplasms and it can occur by direct invasion, lymphatic, haematogenous or intraperitoneal metastasis (10). Tumour invasion of all or parts of the bowel wall leads to the most common symptoms like gastro-intestinal bleeding, abdominal pain, obstruction, perforation, malabsorption and peritonitis. Secondary small bowel involvement by leiomyosarcoma is extremely rare. Recent Behranwala's report (11) evaluated abdominal metastasis from primary soft tissue sarcoma (STS) and described 19 patients, with an incidence 0.9%, 4 of whom (21.1%) affected by STS

leiomyosarcoma with dismal survival after surgery. Other authors described small bowel metastasis from primary bone leiomyosarcoma (12) successfully treated with surgery and still alive after short-term follow up. There is a large agreement that small bowel metastases usually represent a poor prognostic indicator of lung carcinoma (13). Surgical treatment of GI metastasis is considered as a palliative treatment to prevent bowel obstruction or peritonitis (3).

To our knowledge this is the first report of small bowel metastases from a pulmonary leiomyosarcoma with good results in terms of disease-free survival after surgical resection.

In the management of lung sarcomas it is very important to differentiate primary pulmonary sarcoma by metastatic spread from an extra pulmonary sarcoma. It is therefore necessary to reconstruct carefully the clinical history, and to use appropriate investigations to address this possibility. In conclusion a prompt operative management is essential not only in distinguishing the lesion such as metastasis from a primary tumor or preventing potentially lethal abdominal complications but also in improving survival.

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Case Report

Primary pleural liposarcoma, pleomorphic variant

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Abstract: Primary pleural liposarcoma (PPL) is a rare tumor derived from primitive mesenchymal tissue. We report a case of a 49-year-old female patient complaining of thoracic pain and dyspnea for 3 months. The chest X-ray showed a left basal opacity of lobulated contours and the thoracic computer tomography (CT) scan revealed a left pleural collection/mass, of 18 HU density and passive pulmonary atelectasis. The patient was taken to surgery and the cytologic examination of the gelatinous mass found in the procedure confirmed the diagnosis of a pleomorphic variant of pleural liposarcoma. We emphasise in the importance of careful inspection of the origin of the tumor in the diagnostic images to allow accurate diagnosis.

Keywords: Primary pleural liposarcoma (PPL); pleomorphic variant; thoracic computer tomography; pleural neoplasms

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Introduction

Primary pleural liposarcoma (PPL) is an uncommon tumor. The pleomorphic variant of PPL is difficult to diagnose due to a nonspecific clinical presentation and radiologic manifestations simulating a pleural collection of different etiology.

The first case of PPL was reported by Ackerman and Wheeler in 1942. Less than 20 cases of PPL have been described in the literature.

We are presenting the case of a female patient with the pleomorphic variant of a PPL.

Case

A 49-year-old female patient with thoracic pain and dyspnea for 3 months. The chest X-ray showed a left basal opacity of lobulated contours, compatible with an extrapulmonary mass. The thoracic computer tomography (CT) scan showed a left pleural collection/mass, of 18 HU density and passive pulmonary atelectasis (*Figure 1*). At surgery a pleural mass (19×10 cm) of gelatinous consistency was found. Histopathological findings confirmed the diagnosis of a pleomorphic variant of pleural liposarcoma (*Figure 2*). The patient showed evidence of tumor recurrence 6 months after surgery.

Discussion

Pleural neoplasms are generally secondary to primary breast, lung and gastrointestinal tract tumors.

Malignant primary pleural neoplasms represent 10% of the pleural tumors. Mesothelioma is the most frequent tumor in this group (90%) (1). Primary pleural sarcomas and lymphomas are also described. Sarcomas originating in the pleura are rare and include: liposarcoma, synovial sarcoma, malignant fibrous histiocytoma, primary neuroectodermal tumor/Ewing's sarcoma, angiosarcoma, chondrosarcoma, osteosarcoma and leiomyosarcoma (2).

There are less than 20 cases of PPL described in the literature. In 16 documented cases of PPL it was more frequent in men (11 men and 5 women), between the ages of 19 and 80 years (average of 50 years).

Liposarcomas, including the one originated from the

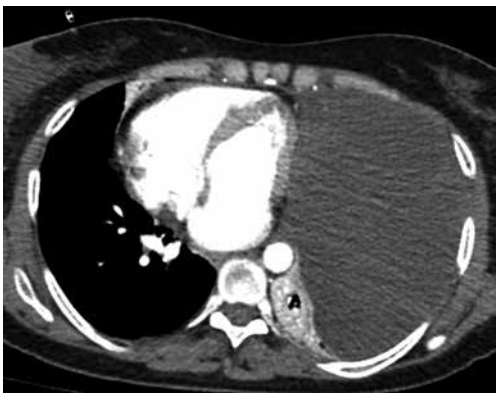

Figure 1 Contrast-enhanced chest CT scan demonstrates mass in the left pleural cavity with attenuation measurements of 18 HU. CT, computed tomography.

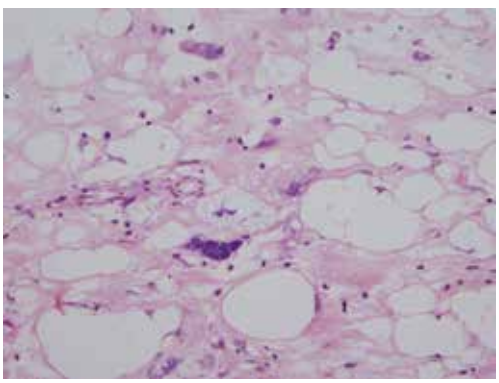

Figure 2 Lipoblasts with cytoplasmic vacuolization (Hematoxylin-eosin ×40).

pleura, are thought to derive from residual primitive mesenchymal tissue. Malignant transformation of a preexisting lipoma, parietal pleural adipose tissue or subpleural fat, are considered alternative hypotheses for the pathogenesis of PPL (2,3).

The histologic variants described for PPL include: myxoid, well differentiated, round and pleomorphic cells. The most common and with the best prognosis are the myxoid (40-50%) and the well differentiated types (3). Undifferentiated types have poor prognosis and are associated to metastatic disease (mainly lung and bone) (2,3).

Macroscopically, PPL is nodular, lobular and has a gelatinous appearance. A series of four patients by Okby and Travis, describes tumors with largest diameters of 16 to 20 cm and weighing up to 1,868 g (3). The pleomorphic variant of PPL is characterized by the presence of a background of pleomorphic spindled and rounded cells and a variable number of pleomorphic lipoblasts (often multivacuolated lipoblasts with bizarre scalloped nuclei), positive to immunohistochemical markers (S100) (2,4). Mesothelioma must be considered as a differential diagnosis.

PPL grows slowly inside the pleural cavity and patients remain asymptomatic for prolonged periods of time. Clinical manifestations are delayed and nonspecific (cough, dyspnea and chest pain) and are related to displacement and compression of adjacent structures. PPL can be an incidental finding on imaging studies.

There are no series reported on the literature reviewing imaging manifestations of PPL. Due to the size these tumors can reach, the imaging approach is difficult (particularly chest X-rays). In early stages, chest X-rays can show an extra-pulmonary opacity. In CTs it is described as a mass of heterogenous density, with soft tissue and fat attenuation coefficients (2). Macroscopic features of the pleomorphic PPL variant can make the diagnosis difficult, due its appearance of pleural collection on CT, without fat attenuation coefficients.

The treatment of choice for PPL is radical surgery and radiotherapy. Surgical therapy alone results in local recurrence in about 70% to 90% of the cases. The series by Wong *et al*. showed 5-year survival of 71% for the myxoid and well differentiated PPL, compared to 12.5% for the other subtypes (3,5).

This case shows evidence of the importance of considering the pleomorphic variant of PPL among the differential diagnoses of a large, homogeneous pleural collection/mass, with attenuation coefficients above water, in the context of patients with nonspecific respiratory clinical signs or symptoms and without an important clinical record.

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Case Report

Pulmonary arteriovenous malformations presenting as refractory heart failure

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Abstract: A 22-year-old young man with a history of idiopathic dilated cardiomyopathy (IDC) was admitted to our hospital due to difficult-to-control heart failure. A thoracic X-ray showed multiple nodules at the both pulmonary hilus and upper lobe of the right lung. Computed tomography (CT) angiography of the thorax confirmed arteriovenous malformation (AVM). However, effective treatment was impossible due to the poor physical condition; he died a few days later. Here we reported on the case of pulmonary arteriovenous malformations (PAVMs) being misdiagnosed as refractory heart failure.

Keywords: Pulmonary arteriovenous malformations (PAVMs); heart failure; idiopathic dilated cardiomyopathy (IDC)

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Introduction

Pulmonary arteriovenous malformations (PAVMs) are abnormal direct communications between the pulmonary arteries and veins without interposition of a capillary bed (1,2). PAVMs are lack of specificity and relatively rare, which are sometimes misdiagnosed as other common cardiopulmonary problems (3,4).

Case presentation

A 22-year-old young man with a history of idiopathic dilated cardiomyopathy (IDC) was admitted to our hospital during the past 7 months. He presented with progressive dyspnea on exertion, palpitation, cough and cyanosis. He had a history of viral encephalitis, which presented with epilepsy 7 years ago. There was no personal of family history of hereditary haemorrhagic telangiectasia (HHT). At first admission, he was admitted to Department of Neurology due to epilepsy and syncope. While in hospital, he developed third-degree atrioventricular (AV) block and sudden cardiac arrest. Receiving cardiopulmonary resuscitation (CPR) and endotracheal intubation, he was transferred to the intensive care unit (ICU) for further treatment. Subsequently, he experienced cerebral infarction. After neurological recovery, he was transferred to the Department of Cardiology owing to intermittent third-degree AV block. Hemoglobin (HGB), pro-B-type natriuretic peptide (pro-BNP), and arterial blood gas analysis were almost normal. Echocardiography (UCG) revealed that moderate dilation of the left ventricle (LV) and severely decreased LV function with ejection fraction (EF) of 31% (*Table 1*). Thoracic X-ray did not show nodules (*Figure 1A*). Computed tomography (CT) of the thorax revealed right upper lobe pneumonia (*Figure 1B*). CT of the head revealed a right cerebral infarction. Coronary angiography showed normal coronary arteries. Excluding other common reasons resulting in heart failure, the patient was diagnosed with IDC, congestive heart failure, NYHA Class III-IV, intermittent third-degree AV block and acute cerebral infarction. He received permanent pacemaker implantation and his medications included aspirin, simvastatin, metoprolol, losartan, digoxin, and diuretic. Then, he was hospitalized due to recurrent dyspnea for four times which can be relieved by anti-heart failure therapy temporarily. With implanted pacemaker, his symptoms of

Table 1 The parameters of echocardiography

Time of admission	Date of admission	Left ventricle (mm)	Left atrium (mm)	Right ventricle (mm)	Right atrium (mm^2)	Ejection fraction (EF) (%)	Predicted pulmonary arterial pressure (mmHg)
1	08 Aug 2012	55	46	19	Normal	45	Normal
1	22 Aug 2012	57.2	28	12	Normal	45	Normal
1	05 Sep 2012	68	40	12	Normal	31	47
2	02 Nov 2012	64	39	12	Normal	48	38
3	05 Jan 2013	64	41	13	35×48	31	56
4	07 Feb 2013	68	42	20	63×55	23	45
5	19 Feb 2013	65	55	20	57×55	38	58

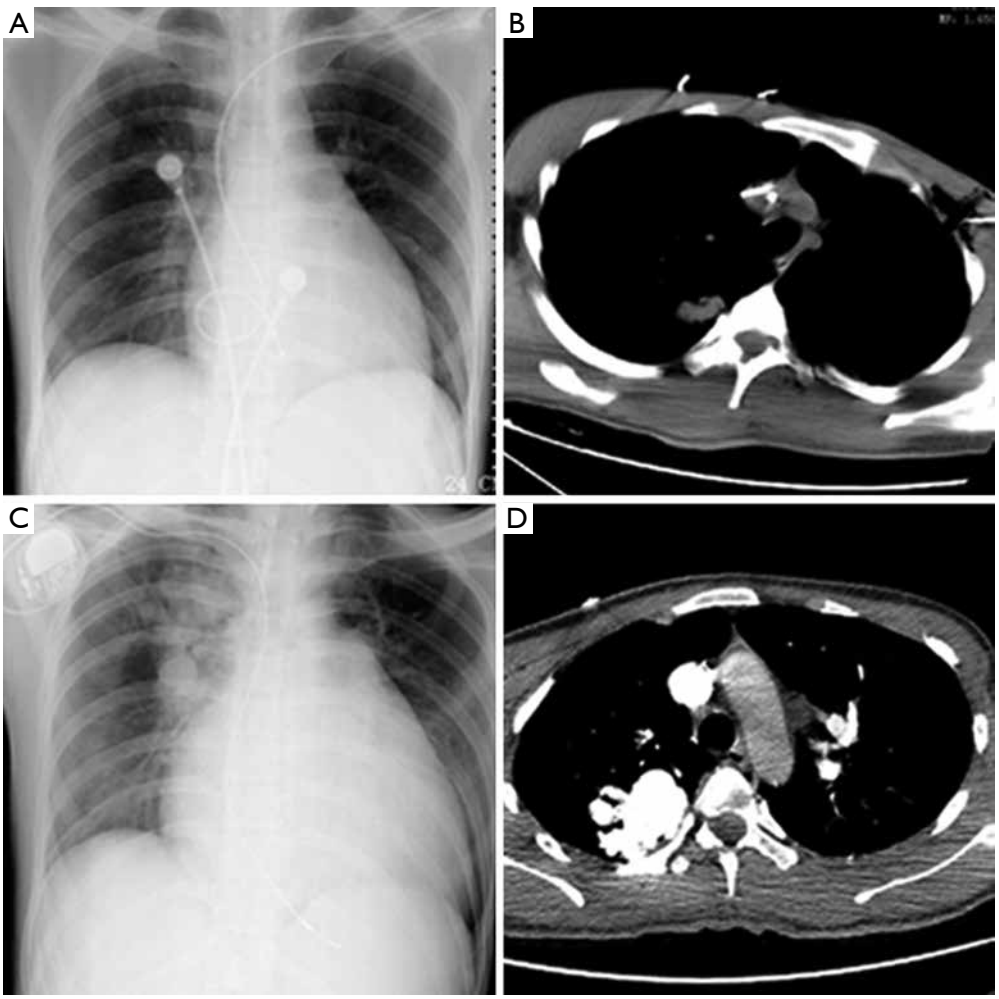

Figure 1 Imaging findings of a 22-year-old young man with pulmonary arteriovenous malformations. (A) Thoracic X-ray revealing no nodule for the first admission; (B) thoracic CT revealing right upper lobe pneumonia; (C) thoracic X-ray revealing nodules at the both pulmonary hilus and upper lobe of the right lung for the last admission; (D) contrast-enhanced CT revealing a large nodular lesion suggestive of pulmonary arteriovenous malformations at right upper lobe. CT, computed tomography.

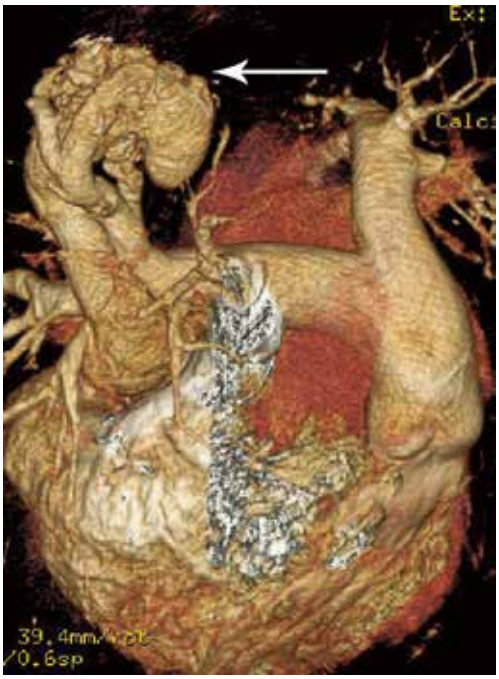

Figure 2 CT angiography showed a 33×35 mm^2 arteriovenous malformation at right upper lobe. CT, computed tomography.

epilepsy did not happen again.

At the last admission, he had cyanosis and dyspnea at rest without improvement to oxygen supplemental and anti-heart failure therapy. The patient's HGB was 170 g/L, pro-BNP was 7,851 pg/mL. Arterial blood gas analysis revealed pO_2 30.9 mmHg, pCO_2 28.9 mmHg, SaO_2 62.8%. Electrocardiogram (ECG) and Holter ECG screenings revealed sinus tachycardia, abnormal Q waves in lead V1-V4. UCG revealed a severely dilated, poor functioning heart (LV 65 mm, EF 38%); predicted pulmonary arterial pressure was 58 mmHg (*Table 1*). Thoracic X-ray showed multiple nodules at the both pulmonary hilus and upper lobe of the right lung (*Figure 1C*). We believed that "IDC, congestive heart failure" cannot explain the patient's cyanosis, so CT angiography was obtained to detect other pulmonary diseases. CT angiography showed a 33×35 mm^2 arteriovenous malformation (AVM) at right upper lobe (*Figures 1D,2*). However, effective treatment was impossible due to the poor physical condition; he died a few days later.

Discussion

PAVMs are usually congenital in origin, but may be acquired in various conditions, such as hepatic cirrhosis, mitral stenosis, trauma, actinomycosis, schistosomiasis and other cancers (1,5,6). In congenital PAVMs, 70% of patients have a history of HHT. PAVMs are usually asymptomatic, but can cause dyspnea, chest pain, cough, and haemoptysis. Various neurological complications such as stroke, brain abscess and paradoxical embolism may occur. It is a remarkable fact that HHT is characterized by the development of multiple AVMS in the skin, mucous membranes, and/or visceral organs, e.g., epitaxis, telangiectasia, PAVMs, and liver AVMs. Sometimes, the two diseases may coexist (5). Contrast-enhanced UCG is useful in the assessment of PAVMs since it helps to distinguish between intracardiac and extracardiac shunts. Intracardiac shunts are characterized by the visualization of bubbles in the left heart chambers within 1-2 cardiac cycles after appearing in the right atrium. In patients with intrapulmonary shunts, this event occurs after a delay of 3-8 cardiac cycles (3). Indeed, CT angiography is a valuable tool in diagnosing and defining the vascular anatomy of PAVMs (5). Symptomatic PAVMs were treated surgically before, such as surgical ligation, segmentectomy, lobectomy and pneumonectomy (7-9). Nowadays transcatheter embolization is recognized to be more efficacious and safe, such as embolic agents, stainless steel embolization coils, mini-balloons, or Amplatzer vascular Plug II (10,11).

There are some points to be considered. Firstly, this patient with a history of IDC was admitted to hospital with recurrent dyspnea. UCG showed dilated LV with decreased function. He can be temporarily relieved by anti-heart failure therapy, but was repeatedly hospitalized due to recurrent attacks of dyspnea. The diagnosis of IDC must be reviewed once symptoms cannot be improved. Secondly, at first hospitalization, HGB, BNP and arterial blood gas analysis did not reveal any abnormality. X-ray did not show nodules. CT revealed right upper lobe pneumonia, which should relate to endotracheal intubation at that time. During treatment, HGB and BNP gradually increased with blood oxygen declining. At the fourth time, X-ray revealed nodules, but we did not pay attention yet. Seven months later, the pneumonia was confirmed as PAVMs by CT angiography. We believed that clinical symptoms and signs of PAVMs were absent initial. The PAVMs have a natural tendency to increase in size over time owing intrinsic and extrinsic factor, which caused recurrent dyspnea ultimately. Various factors including stress, hypoxemia, and also pulmonary arterial hypertension (PAH) may explain this phenomenon (5,6). Thirdly, the patient suffered from cerebral infarction, which was believed to

relate to thromboembolia after CPR initial. Combining with the history, stroke may be responsible for a right-to-left shunt leading to paradoxical embolism. Fourthly, it is difficult to explain why the patient presented with third-degree AV block. We speculated that the patient might present with myocarditis, AV block and Adams attack 7 years ago. Unfortunately, he was misdiagnosed as epilepsy and viral encephalitis, because the symptoms of "epilepsy" disappeared after the pacemaker implantation.

The last, heart failure secondary to the hyperdynamic circulatory situation caused by AVMs is a well-known clinical entity. Cho *et al*. (12) described unusual cases in which HHT patients presented with high-output heart failure, which usually caused by shunting of blood through AVMs in the liver. In order to supply blood to vital organs, cardiac output is increased with elevated stroke volume and heart rate, leading to high out-put heart failure (12,13). Besides the influence of PAVM, We supposed high-output failure may be another explanation for dyspnea. But it was a pity that the CT angiography of the liver did not obtain.

Even though PAVMs are rare anomalies, they should be considered in the differential diagnosis of cardiopulmonary disorders. The diagnosis of IDC requires excluding other diseases carefully, especially in cases not responding to anti-heart failure therapy.

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Case Report

Mediastino-hepato-renal cystic lymphangiomas—diagnostic and surgical considerations

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Abstract: Cystic lymphangiomas or hygromas are rare benign vascular tumours, caused by congenital malformation of the lymphatic vessels. It appears as a progressive swelling in the head or neck of children during 2-5 years of life, yet rarely seen in the mediastinum or abdomen. Symptomatic mediastinal cystic lymphangiomas provide symptoms such as chest pain, breathlessness, cough, and dysphagia, making it difficult to differentiate from other mediastinal tumours. The tumour can become larger due to infections, inflammations, obstructions and bleedings. Chest X-ray, ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) provide helpful information but the diagnosis appears merely after surgical resection and histological examination. Only a few cases have been reported. Hence, we report the first case of a mediastinal and asymptomatic renal and multiple hepatic cystic lymphangiomas in a 71-year-old male with respiratory symptoms and sever reduction in lung capacity. The symptoms regressed fully after surgical excision and lung diffusions capacity increased significantly.

Keywords: Mediastinum; lymphangioma; congenital; malformation

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Introduction

Lymphangioma is a rare benign tumour due to congenital lymphatic vessels abnormalities. Almost 90% of cases are diagnosed at birth or within the first 2 years of life (1-4). They appear as fluctuant, freely mobile, compressible, painless and slow growing asymptomatic masses mostly in the head and neck but occasionally in the axilla, or groin. The cysts can occur anywhere in the lymphatic channels of the body.

Case report

A 71-year-old man was referred for surgical resection of a mediastinal mass (*Figure 1*). He was diagnosed with an asymptomatic 5 cm mediastinal cyst in 2007 and the decision was follow-up. In 2013, a computed tomography (CT) scan disclosed growth of the mass to 9-10 cm. Lung function test (LFT) was significantly reduced with a diffusion capacity of 48%. The mass was resected with an uneventful operation and postoperative period. Pathology disclosed a cystic lymphangioma. Seven weeks after surgery, the patient was asymptomatic and with an improved LFT with diffusion capacity 67%, FEV1 95% and FVC 99% of expected, respectively.

Discussion

Embryonic lymphatic vessels fail to communicate to venous channels. Abnormal lymphangiogenesis thus ends as single or multiple cysts in one or multiple organs, growing as unilocular or multilocular masses that contain serous or milky fluid. Khobta *et al.* (2) classified lymphangiomas into: capillary, cavernous and cystic, whose full pathogenesis is not fully established yet (5). Cystic lymphangiomas were first described in 1843 by Wernher, while the first thoracic case of lymphangiomas was reported in 1973 (2). There have been previous

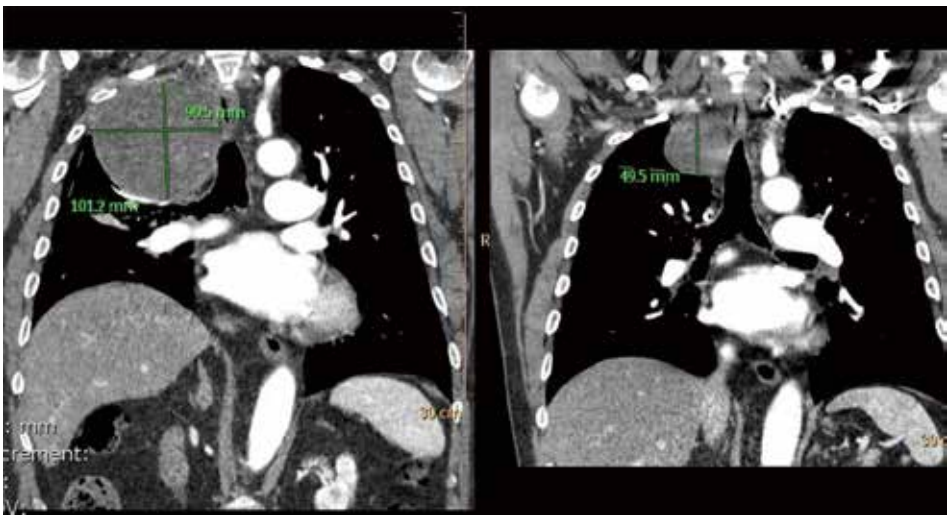

Figure 1 Computed tomography (CT) shows enlargement of cystic lymphangioma during a periode of 5 years (cystic value 10-20 on Hounsfield scale).

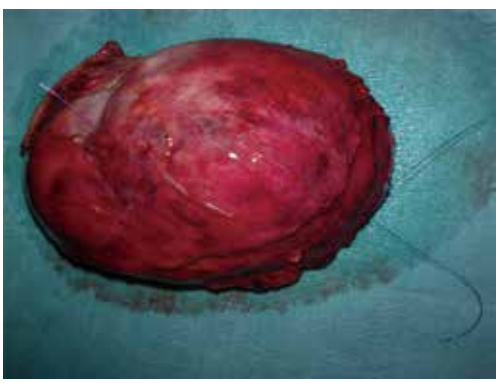

Figure 2 Cystic lymphangioma also called hygroma are soft tumours filled with milky fluid within a thin walled sac, vascularised by small tiny vessels from parietal pleurae.

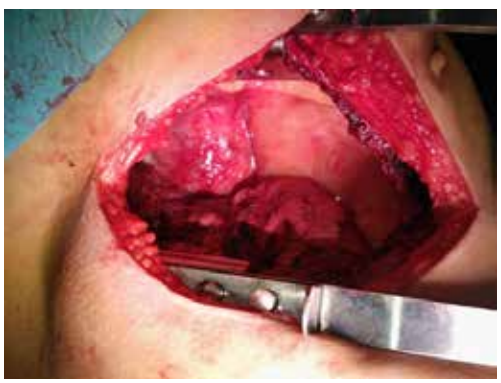

Figure 3 Perioperative picture showing mediastinal cystic lymphangioma.

reported cases of asymptomatic lymphangioma involving the spleen and mediastinum (5). Our case is extraordinary since the patient had a combination of a single cystic lymphangioma in mediastinum causing symptoms and multiple asymptomatic cysts in lever and both kidneys. Differential diagnose include bronchogenic cysts, thymic cysts, thymomas, hydatid cysts, neurofibroma and malignant bronchogenic tumours. Mediastinal cysts form 12-18% of all primary mediastinal tumours (6). Diagnosis is almost always established after surgery despite extensive diagnostic procedures. Complete surgical resection with an intact cyst capsule is recommended in order to minimize risk of recurrences (2,7) (*Figures 2,3*). Other therapies (2,7) such as aspiration, incision and drainage, irradiation, and sclerotherapy seem to be short time treatment with a high risk for complications like infection, haemorrhage, damage to muscle/nerve, rupture and recurrences.

Conclusions

We report a cystic lymphangioma diagnosed in an elderly patient's mediastinum, lever and both kidneys. The symptoms regressed fully and lung function normalised after surgical intervention. Although cystic lymphangiomas are rare, they must be considered in differential diagnoses of the mediastinal tumours.

Acknowledgements

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Case Report

A case of heart failure due to alcoholic cardiomyopathy combined with acute pulmonary embolism

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Abstract: It has not been reported that cases of alcoholic cardiomyopathy (ACM) combined with acute pulmonary embolism (PE). We hereby present a case of a 48-year-old male with ACM with significant enlargement of the heart and heart failure is described. Then, the patient was seized with acute PE which was confirmed by specific examination and his symptoms.

Keywords: Alcoholic cardiomyopathy (ACM); pulmonary embolism (PE); heart failure

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Introduction

Acute pulmonary embolism (PE) is a cardiovascular emergency associated with significant morbidity and a 5-35% mortality for untreated PE (1,2). The classic risk factors for PE are those identified as Virchow's triad (hypercoagulable state, stasis and injury) (3,4), which include deep vein thrombosis (DVT), major surgery, major trauma, high age, myocardial infarction and chronic heart failure (5). A 48-year-old man presented to Emergency Department with a PE and a history of taking inferior liquor for more than 30 years, 500-750 g per day. The patient was confirmed with alcoholic cardiomyopathy (ACM) by further examinations. We had excluded common risk factors for PE, and here we discuss the relationship between ACM and PE. The following is a detailed report of the case accompanied by a review of previous studies.

Case report

Case one

A 48-year-old male patient presented with chest discomfort for more than one month, accompanied by hemoptysis for ten days. He felt persistent chest discomfort under no obvious predisposing causes at the beginning of March in 2013, mild with no influence on daily life at first but gradually aggravated with abdominal distention, poor appetite and without cough, expectoration and fever. He was diagnosed with 'coronary heart disease, DM type II, pneumonia and pleural effusion' by a local hospital on 15th of March, treated for more than 10 days in the hospital with unclear exact details and the symptom alleviated after the treatment. The hemoptysis began with no obvious causes from the middle of April with plentiful sputum, about 50 mL per day, dark red bloody at first and then turning bright and with mucus, accompanied with chest discomfort continually, shortness of breath and dull chest pain mainly located in the bilateral hypochondriac regions and together with poor appetite, upper abdominal distending pain and without fever. The patient was hospitalized in the local Department of Gastroenterology on 25th of April. The results of gastroscopic examination showed chronic superficial gastritis with antral mucosal atrophy, and the examination of cardiac ultrasonography showed

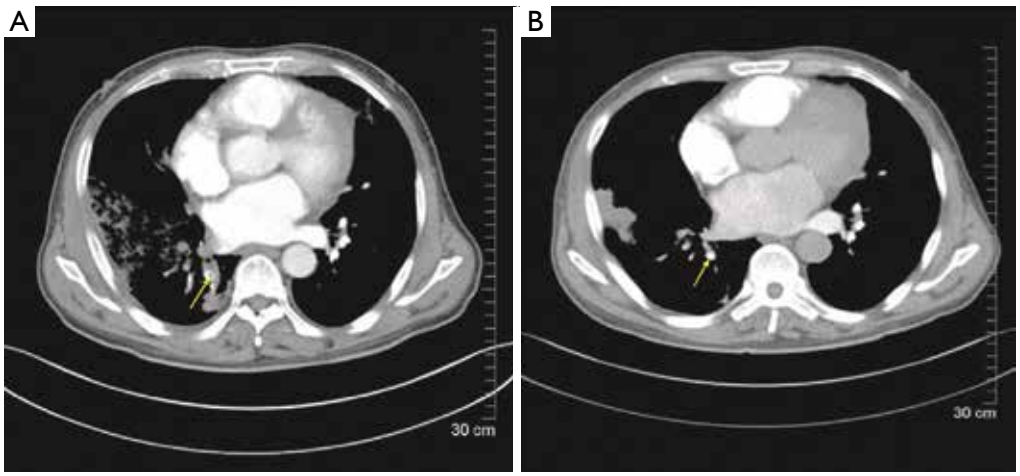

Figure 1 CTA revealed an embolus located in the right inferior pulmonary artery, which was disappeared after the treatment (yellow arrow). CTA, computer tomography angiography.

left cardiac insufficiency, enlargement of the whole heart, moderate mitral regurgitation, mild to moderate aortic regurgitation, mild tricuspid and pulmonary regurgitation and a severe reduction in ejection fraction (24%). Chest computer tomography (CT) showed the inflammation on bilateral lobes. In the next four days, the patient was given corresponding treatments but with no significant therapeutic efficacy and transferred to our hospital on 30th of April in 2013. In the emergency room, the results of CT angiography (CTA) revealed thrombosis in the branches of bilateral pulmonary arteries, bilateral pneumonia and right pleural thickening (*Figure 1*). While deep venous ultrasound of lower limbs revealed bilateral femoral venous valve insufficiency and bilateral calf muscular venous thrombosis. Then, the patient was hospitalized in our department as 'PE and pulmonary infection'.

Past illness: the patient has a history of taking inferior liquor for more than 30 years, 500-750 g per day and smoking for more than 20 years, 10^{+} cigarettes per day.

Physical examination: the whole skin mucous membrane dyed mild yellow and had no rash or petechia. Right thorax had stronger tactile fremitus and slightly flat percussion sound. Respiratory sound was bilateral rough and moist rales were heard in bilateral lower lung. Systolic cardiac murmurs could be heard on mitral valve area, III/6 and conducted to left axilla.

Laboratory examination: blood routine test: WBC: 15.64×10^{9}/L, N: 80.20%; liver function: AST: 172.9 U/L, ALT: 272 U/L, ALP: 166.4 U/L, TBIL: 70.4 μmol/L, DBIL: 45.9 μmol/L, IBIL: 24.5 μmol/L. Coagulation indicators: PT: 14.2 t, FIT: 5.0 g/L, INR: 1.06, APTT: 1.22 t, TT: 17.20 t, D-dimers: 9.55 mg/L, BNP: 2,205 pg/mL, CRP: 148 mg/L. ECG: (I) sinus tachycardia; (II) left atrial and ventricular enlargement; (III) left axis deviation. Blood gas analysis: PO_2: 111 mmHg, PCO_2: 39 mmHg. Tumor markers: CEA, NSE, CY21-1, CA-199, CA-125(-), HCY(-), sputum cultivation(-), ESR, HLA-B27, RF(-), IgA, IgM, IgG, C3, C4(-).

Heart magnetic resonance imaging (MRI) at 3 T (GE Signa Excite HD scanner) enhancement scanning: cardiac insufficiency (*Figure 2*, panel A-D). 2D-heart ultrasound: cardiac enlargement, mainly appearing on left atrium and ventricle, mitral, aortic, tricuspid and pulmonary valves incompetence, and the ejection fraction was 40.2% (*Figure 3*, panel A,B).

Treatment: the patient received cefoperazone and tazobactam as an anti-infection therapy, tanreqing and ambroxol to reduce phlegm, enoxaparin as an anti-coagulation therapy, alprostadil to drop the pressure of pulmonary artery down, hydrochlorothiazide and spirolactone to improve cardiac function and then treated with warfarin as an anti-coagulation therapy. During the whole process, the patient gave up drinking totally. He wanted to take some alcohol sometime, especially when his condition improved, but the abstinence symptoms did not experience. Gradually, chest discomfort, chest pain and hemoptysis were alleviated and pulmonary rales reduced obviously.

On May 11th, chest CTA showed most thrombosis were absorbed, a little shadow of embolism in the right lower branch of pulmonary artery, multiple patching shadow in bilateral lungs which were considered as the infection and

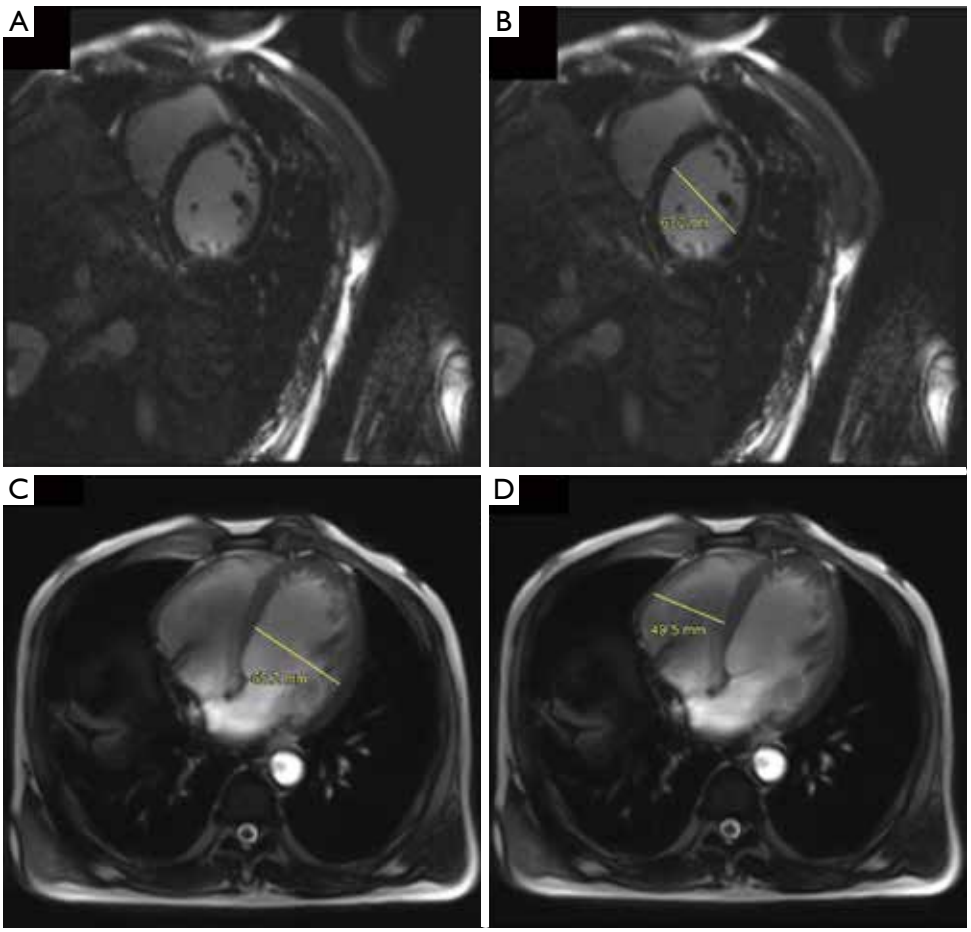

Figure 2 Heart MR3T showed enlargement of the whole heart. (A,B) On the short axis, the left ventricle's diameter was 63.2 mm at the end of diastole; (C,D) the diameter of left and right ventricle was 65.2 and 49.5 mm, respectively (through the axial view). MR3T, magnetic resonance imaging at 3 T (GE Signa Excite HD scanner) enhancement scanning.

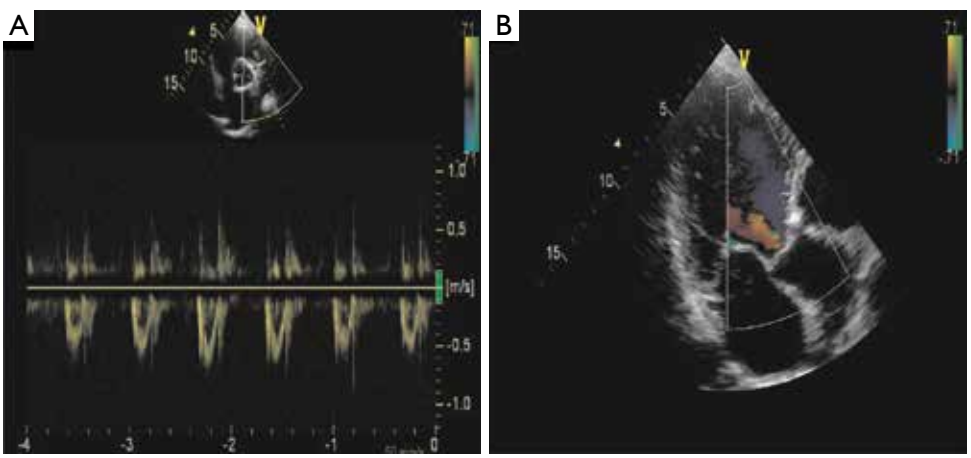

Figure 3 2D-heart ultrasound showed a diffuse hypokinesia of the left ventricle with a mild mitral regurgitation and a moderate reduction fraction (40.2%).

right pleural thickening (*Figure 1B*).

Liver function: ALT: 149.12 U/L, AST: 66.22 U/L, TBIL: 29.2 μmol/L, DBIL: 17.00 μmol/L, IBIL: 12.2 μmol/L. Obviously, these figures were all reduced, and confirmed that the patient's liver function was recovered after the treatment and abstinence from alcohol.

Coagulation indicators: PT: 38.6 t, APTT: 20.5 t, FIT: 4.20, INR: 3.38, TT: 15.80, D-diners: 5.42 mg/L, BNP: 2,205 pg/mL, CRP: 74 mg/L. Blood routine test: WBC: 6.50×10^9/L, N: 54%.

On May 14th, the patient had a favorable turn and discharged with doctor's advice of giving up smoking and drinking, continuing the oral treatment of warfarin, monitoring blood pressure, INR, 2D-heart ultrasound and chest CTA and follow-up by telephone. On May 21st, the feedback of 2D-heart ultrasound showed left ventricular diastolic insufficiency and EF was 62%.

Discussion

PE is a general term of a series of diseases and clinical syndromes which are cause by various emboli (endogenous and exogenous) blocking the pulmonary arterial system, whose clinical symptoms are various and lack of specificity (6). Limited by the condition of examination and the experience of clinical doctors, many mistaken and missed diagnoses exist. Main reason is DVT and dangerous factors contain trauma, long-term bed rest, varicose veins, venous cannula, pelvic and hip surgery, obesity, DM and contraceptive. In addition, various heart diseases are also the main reasons, especially cardiomyopathy, heart valve diseases and infectious endocarditis (5). The hypercoagulable state caused by malignant tumors can also lead to PE. In this case, we highly suspected that primary heart diseases lead to the embolism because of no dangerous factors related to DVT and negative results of rheumatic, immunological or tumor markers.

ACM is a kind of disease that has typical hemodynamic change, symptoms, signs and imaging findings of dilated cardiomyopathy (DCM) and its symptoms can be released or cured after 4-8 weeks of giving up drinking (7). The incidence of this disease is higher in males than in females, also higher in Europe, the US and Russia than in other regions of the world (7,8). In China, there are sporadic case reports. It mostly occurs on male of 30 to 55 years old with over-drinking history for more than ten years. It has various clinical manifestations, including the main features of cardiac enlargement, cardiac insufficiency and arrhythmia (9). The diagnosis criterion contain long history of excessive drinking, the manifestation of cardiac enlargement, CHF and getting better apparently after giving up drinking for 4-8 weeks. In this case, the patient had a long history of drinking massive liquor and stopped drinking from the onset of this disease. His main initial symptom was whole heart enlargement, which similar with manifestations of the DCM. As a matter of fact, heart MRI-3T and 2D-heart ultrasound help us exclude other non-ischemic cardiomyopathy, such as hypertrophic cardiomyopathy and restrictive cardiomyopathy. His younger brother, 46-year-old, has a similar habit of drinking as well. During this hospitalization, we also performed the examination of 2D-heart ultrasound for him, which showed the existence of cardiac diastolic insufficiency and proved the basis of ACM from another point of view.

We hold the opinion that analyzing the case and making a diagnosis can be based on several points below.

(I) Routine thoughts: bilateral calf muscular venous thrombosis→PE→cardiac insufficiency. It seems well-reasoned. But here is a question. PE caused by thrombosis from lower extremities mostly leads to the increase of pulmonary arterial pressure and then increases afterload of right heart, which induces the enlargement of right atrium, right ventricle, pulmonary and the insufficiency of tricuspid. But in this case, the results of 2D-heart ultrasound and heart 3TMRI both shows the enlargement of whole heart, manifested mostly by the hypertrophy of left atrium and ventricle, multiple valves incompetence and whole cardiac insufficiency, which cannot be explained by emboli from systemic circulation;

(II) Monistic thoughts: long-term over-drinking→ACM→cardiac insufficiency→cardiac hemodynamic disorder→primary thrombosis attached to vessel wall falling off→PE. This analysis seems more reasonable;

(III) During the whole treatment, heavy hemoptysis is one contraindication of thrombolytic therapy. The thrombus dissolved quickly only with anticoagulant therapy and without thrombolytic therapy, which was considered as the result of thrombus autolysis. The cardiac function recovered quickly. So, the reason of this case may be the ACM.

Acknowledgements

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Case Report

Primary myelolipoma in posterior mediastinum

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Abstract: Myelolipoma in posterior mediastinum is indeed rare. As a benign tumor, it consists of mature fat with scattered foci of haematopoietic elements resembling bone marrow. The computed tomography (CT) and magnetic resonance imaging (MRI) are effective methods to detect them, while the definite diagnosis still depends on pathological diagnosis. Up to now, there is no standard treatment for this disease. Surgery is thought to be the best choice in some literatures reports. In this paper, two patients with primary posterior mediastinal tumor are reported, both of whom were underwent Video-assisted thoracoscopic surgery (VATS). Postoperative pathological diagnosis was myelolipoma.

Keywords: Mediastinum; myelolipoma; extra-adrenal; video-assisted thoracic surgery (VATS)

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Introduction

Myelolipoma was first described in 1905, and named 'myelolipoma' in 1929 (1). It is an unusual benign neoplasm composed of mature adipocytes and hematopoietic tissue (2). It is commonly found in adrenal gland. Myelolipomas can also occur in extra-adrenal location. The occurrence in extra-adrenal site is quite rare with an incidence of 0.08-0.2% at autopsy (3). Atypical sites of origin include the presacral region, retroperitoneum, liver, spleen, stomach, greater omentum, leptomeninges, and mediastinum, where myelolipoma is discovered accidentally (4-10). Until now only 28 cases of mediastinal myelolipoma (1-3) including our cases have been reported (11-32). Some of the patients were asymptomatic, while others suffered from a wide variety of symptoms, such as endocrine disorder, anemia, hypertension, splenomegaly, etc. (20-32). Here we represent two cases of posterior mediastinal myelolipoma, whose clinical features and treatments after using minimally invasive thoracic surgery are discussed.

Case report

Case one

A 60-year-old woman presented to our department with a right lower posterior mediastinal mass which was incidentally revealed by chest computed tomography (CT) scan. Repeated coughing and expectoration for one month made her seek medical assistance. Her past medical history was significant for thalassemia and splenomegaly for 10 years. Enhanced CT scan revealed a partial enhanced mass located in the right lower posterior mediastinum. It was 3.7 cm in diameter beside the vertebral column (*Figure 1*). There was no evidence of bony erosion in nearby rib or vertebra, pleural effusion or surrounding tissue infiltration. Magnetic resonance imaging (MRI) demonstrated that the mass extended from the paravertebral region and moderately intensified signal showed in T1-weighted images (*Figure 1*). Complete blood cell count revealed her red blood cells of 3.65×10^{12}/L, hemoglobin of 65 g/L, white blood cells of 3.54×10^{9}/L and platelets of 75×10^{9}/L. It was considered as a neurogenic tumor initially and video-assisted thoracic surgery (VATS) was performed for tumor resection. Grossly, the surgical specimen was approximately 3.7 cm × 3.5 cm × 3 cm as a round-shaped, well-encapsuled, soft and purple mass (*Figure 2*). A microscopic examination revealed a predominant mature adipose and hematopoietic tissue with intermingled. Immunohistochemical stains showed positivity for CD3, CD15, CD20, CD68, CD138 and MPO antibodies

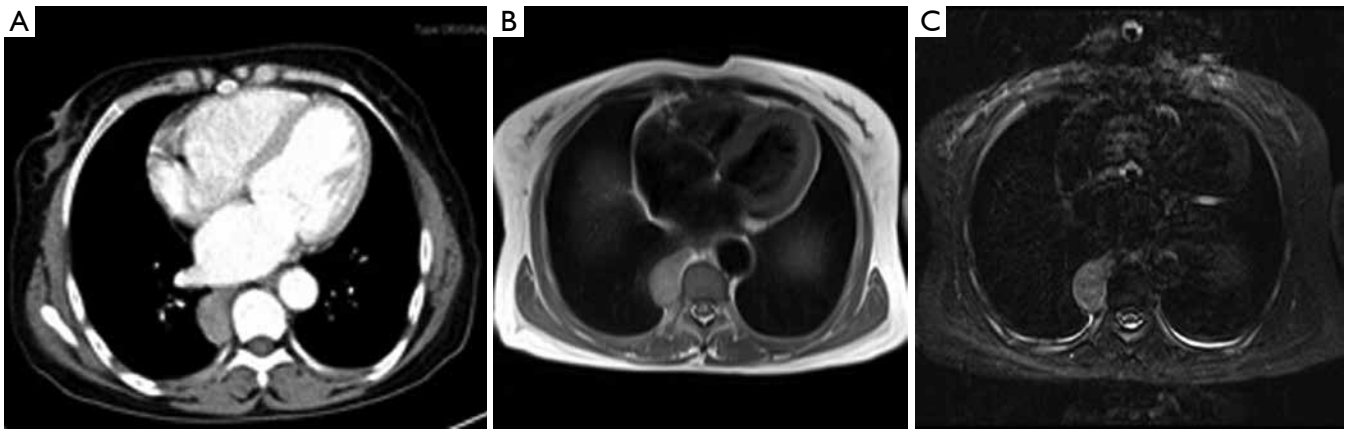

Figure 1 (A) An enhanced chest CT scan revealed a posterior mediastinal mass, which could be partially enhanced; (B,C) MRI demonstrated that the mass extended from the paravertebral region and was moderately intensified in T1-weighted image. CT, computed tomography; MRI, magnetic resonance imaging.

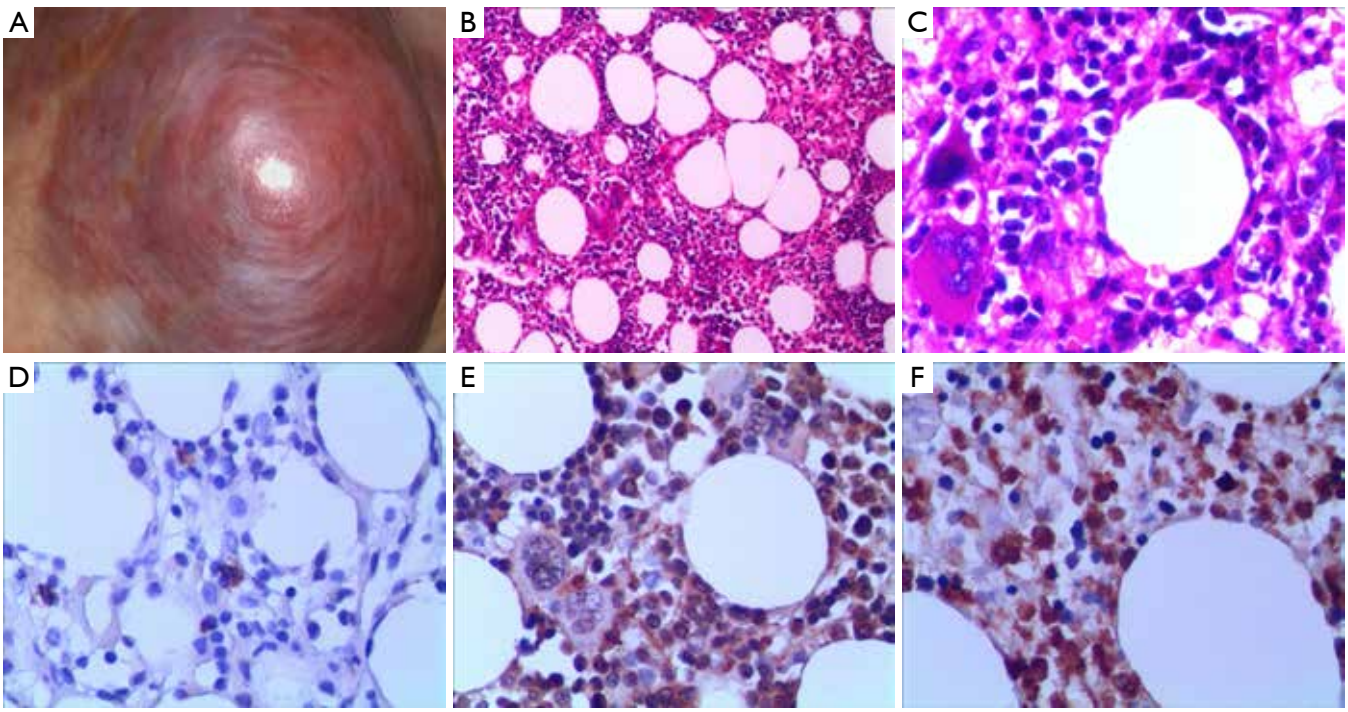

Figure 2 Macro and microscopical findings of this myelolipoma: (A) a round-shaped, well-encapsued, soft and purple mass was identified in the posterior mediastinum; (B,C) a microscopic examination revealed predominant mature adipose tissue with hematopoietic tissue. There was a variable blend of adipocytes, myeloid, erythroid precursors and mature cells and even megakaryocytes and lymphoid cells resembling all together bone marrow. (Hematoxylin and eosin, B: ×200, C: ×400); (D-F) immunohistochemical stains showed positivity for CD20, CD68 and MPO antibodies (×400).

(*Figure 2*). Cytokeratin, neuron specific enolase (NSE) and S100 antibodies were negative. Based on these findings, the myelolipoma was confirmed. The patient discharged in the third postoperative day and has remained disease free at 6-month follow-up.

Case two

A 68-year-old man was admitted to our hospital and underwent chest CT scan because of palpitation, chest tightness, and shortness of breath. He was diagnosed with

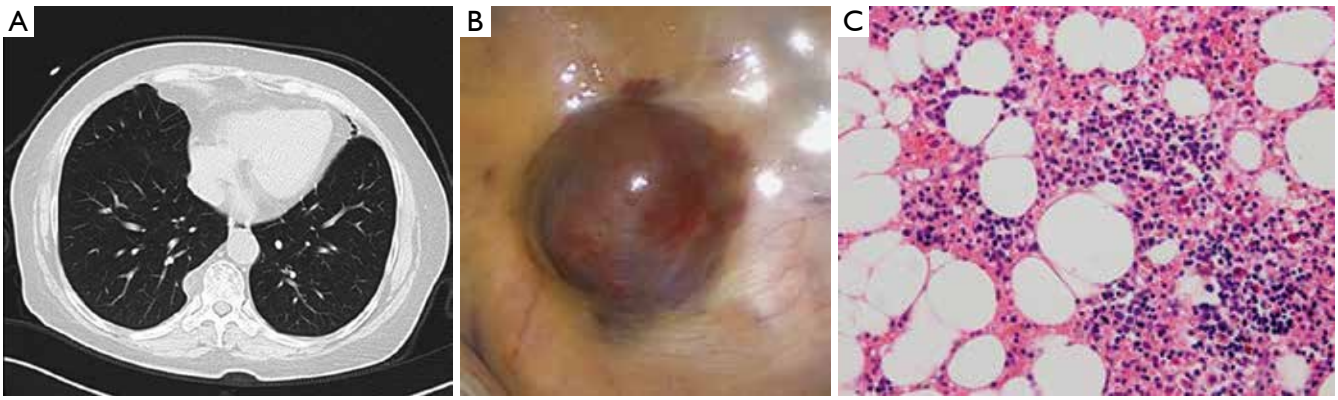

Figure 3 (A) Chest CT scan revealed one posterior mediastinal mass; (B) grossly, a round-shaped, well-encapsued purple mass was identified in the posterior mediastinum; (C) the pathology demonstrated predominant adipose tissue interspersed with mature bone marrow elements (Hematoxylin and eosin, ×200). CT, computed tomography.

a right lower posterior mediastinal tumor. He had been through paroxysmal hypertension (the highest value was 200/100 mmHg) for 1 year and it hard to be controlled by medicine. The patient also had a history of type 2 diabetes for 15 years. Noradrenaline and epinephrine of blood and urine were relatively normal. We suspected that it was pheochromocytoma initially. CT revealed there was a mass shadow, which was 2.1 cm in diameter and located in the right lower posterior mediastinum. Its boundary was clear. Enhanced chest CT revealed the mass was partially enhanced (*Figure 3*). We considered it as a pheochromocytoma and VATS was performed for tumor resection. During the operation, a round-shaped, well-encapsued purple mass was identified in posterior mediastinum in diameter of 1.5 cm. A pathological examination was the same as above-mentioned in the case one postoperatively (*Figure 3*). Thus mediastinal myelolipoma was confirmed, and no signs of malignancy were observed. Paroxysmal increased blood pressure was disappeared and the blood pressure was easy to control by medicine after surgery. After more than 6-month follow-up, he remained clinically well and a CT scan showed no residual tumor.

Discussion

Myelolipoma is a familiar adrenal tumor with an incidence of 3-5%. However, extra-adrenal myelolipoma is rare with the morbidity of 0.08-0.2% (3). Since the first mediastinum myelolipoma reported in 1925, only 28 cases including our cases have been reported so far in English literatures (*Table 1*). Based on the literature reviews (*Table 2*), most of them arose from the posterior mediastinum (93%). There were 12 females and 16 males, at a mean age of 64 years. The mass diameter ranged from 1.5 to 25 cm with mean diameter of 5.9 cm. About 25% patients were asymptomatic, while 75% of them were symptomatic. Mainly complaints were cough, chest pain and dyspnea. Almost all the tumors were benign and non-invasive, so did our cases. The prognosis was well after tumor resection.

The etiology of myelolipoma is unclear at present. About four hypotheses were proposed to explain the pathogenesis: (I) most theories indicated that the development and differentiation of either ectopic adrenal or hematopoietic stem cell received triggering stimulus by obesity, hypertension, chronic inflammation, carcinoma, previous trauma or endocrinic disorders, which had been studied in some reported cases. Maybe our second case supports this opinion (23,29,30); (II) some studies suggested that myelolipoma evolved from metaplastic change of embryonic primitive mesenchymal cells or embolism of bone marrow cells via the blood stream (14,17,29); (III) Chang *et al*. reported chromosomal translocations (3,21) (q25;P11) in one case of adrenal myelolipoma without other adrenal lesions (33). This clonal chromosome abnormality was commonly reported to be found in acute myelogenous leukemia and myelodysplastic syndrome. Therefore, this finding suggested that the myelolipoma might be a neoplastic phenomenon as the result of a particular chromosomal mutation. Some cases which were related to anemic condition such as hereditary spherocytosis and thalassemia, might support this hypothesis, so did our first case; (IV) another theory raised the hypothesis that majority of tumors were attached to vertebral bodies, haematopoietic

Table 1 Reported cases of mediastinal myelolipoma*

Main author	Age/sex	Tumor location	Size (cm)	Clinical feature	Treatment or management	Outcome
Saleeby, 1925 (1)	81/F	Posterior mediastinum	2.5	/	Autopsy	Death
Foster, 1958 (11)	80/M	Posterior mediastinum	4.0	/	Autopsy	Death
Litwer, 1960 (12)	63/M	Posterior mediastinum	9.0	Chronic anemia	Autopsy	Death
	62/M	Posterior mediastinum	7.0	Chronic anemia	Thoracotomy	Not stated
Krag, 1972 (13)	71/F	Anterior mediastinum	5.0	/	Autopsy	Death
Schön, 1984 (14)	50/M	Posterior mediastinum	Not stated	Anemia	Not stated	Not stated
Kim, 1984 (2)	55/M	Posterior mediastinum	7.0	Coronary heart disease, hypertension	Thoracotomy	Not stated
Bastion, 1990 (15)	72/F	Posterior mediastinum.	10.0	Hereditary spherocytosis	Thoracotomy	Not stated
Pulsoni, 1992 (16)	60/M	Bilateral paravertebral area	Right: 4.0; left: 4.4	Hereditary spherocytosis	Thoracotomy	Not stated
De Montpréville, 1993 (17)	65/M	Posterior mediastinum	8.0	Anemia	Thoracotomy	Not stated
Strimlan, 1993 (18)	65/F	Posterior mediastinum	5.0	Chronic obstructive lung disease, chronic respiratory failure	Thoracotomy	No recurrence
Wyttenbach, 1994 (19)	53/M	Anterior mediastinum	8.0	/	Thoracotomy	Not stated
Minamiya, 1997 (20)	59/M	Posterior mediastinum	6.5	/	Thoracotomy	No recurrence
Koizumi, 1999 (21)	55/M	Posterior mediastinum	4.0	Chest pain	VATS	No recurrence at 8 months
Fonte, 1999 (3)	74/F	Posterior mediastinum	2.0	Back pain	Not stated	Not stated
Kawanami, 2000 (22)	72/M	Bilateral paravertebral area	Not stated	Diabetes mellitus	CT-guided needle biopsy	Not stated
Gao, 2002 (23)	59/ M	Posterior mediastinum	2.5	Hypertension, bronchitis	Thoracotomy	Not stated
Franiel, 2004 (24)	65/ F	Bilateral posterior mediastinum	Left: 4.5; right: 6.5	Hypertension, chronic obstructive bronchitis	Thoracotomy	No recurrence at 12 months
Mohan, 2006 (25)	46/M	Paratracheal mediastinum	4.5	Chest pain	Not stated	Not stated
Rossi, 2007 (26)	73/F	Posterior mediastinum	7.0	/	Fine–needle aspiration, thoracotomy	Not stated
Vaziri, 2008 (27)	56/M	Posterior mediastinum	25.0	Cough, dyspnea	Thoracotomy	No recurrence
Geng, 2013 (28)	68/F	Bilateral posterior mediastinum	Right: 10.0; left: 9.0	Back pain, cough, anemia, type 2 diabetes	Thoracotomy	No recurrence at 3 years

Table 1 (*continued*)

Table 1 (*continued*)

Main author	Age/sex	Tumor location	Size (cm)	Clinical feature	Treatment or management	Outcome
Ema, 2013 (29)	68/M	Posterior mediastinum	3.0	/	VATS	No recurrence at 10 months
Fonda, 2013 (30)	64/F	Posterior mediastinum	3.0	Type 2 diabetes, leukocytosis	VATS	No recurrence
Migliore, 2014 (31)	56/F	Posterior mediastinum	3.5	Obese, chest pain	VATS	No recurrence at 11 months
Nakagawa, 2014 (32)	79/M	Bilateral paravertebral area	Th-8:1.9; Th-10:4; Th-9~10:7.5	Hypertension, nephrosclerosis, alcoholic liver hepatitis	VATS	No recurrence at 4 years
Our case	60/F	Posterior mediastinum	3.7	Cough, thalassemia, splenomegaly	VATS	No recurrence
	68/F	Posterior mediastinum	2.1	palpitation, chest tightness, Hypertension, type 2 diabetes	VATS	No recurrence

F, female; M, male; VATS, video-assisted thoracoscopic surgery; /, the clinical feather has nothing to do with the tumor; *, the report cases from references (1-3) and (11-32).

Table 2 The summary characteristics of reported patients with mediastinal myelolipoma*

Characteristics	Number
Age [mean] (year)	46-81 [64]
Male:female	16:12
Symptoms [%]†	
Endocrine disorder	6.0 [21]
Hematopoietic systemic abnormality	9.0 [32]
CVD	5.0 [18]
Symptoms of respiratory system	10.0 [36]
Another	6.0
Tumor size [mean] (cm)	1.5-25 [5.9]
Tumor location [%]	
Posterior mediastinum	26.0 [93]
Anterior mediastinum	2.0 [7]
Treatment	
VATS	7.0
Thoracotomy	13.0
Another	8.0

*, values are number of patients unless specified otherwise; †, some patients had multiple symptoms; symptoms (%), number of patients with this symptom/total number of patients (%); tumor location (%), number of patients in this location/total number of patients (%); VATS, video-assisted thoracoscopic surgery; CVD, cardiovascular disease. Data from references (1-3) and (11-32).

tissue might project from vertebral microfractures to paravertebral space. Ectopic haematopoietic tissue may include stem cells that would be the origin of myelolipoma formation (30).

The mediastinum myelolipoma does not have any pathognomonic signs or symptoms. Thus it is difficult to definitively diagnose without histopathologic evaluations. Ultrasonography, CT scan and MRI have become more common as useful diagnostic tools and given some clues to the correct diagnosis (19,22,26). Although CT and MRI were effective in diagnosing myelolipoma, a confident conclusion was made difficultly before surgery. Some authors reported that Fine-needle aspiration under the guidance of CT scan or ultrasonography—combined with pathological examination—could be used to confirm the diagnosis (22,23,26). However, due to myelolipoma mostly occurring in posterior mediastinum (93%), especially for small mass, it is too difficult to biopsy accurately by Fine-needle aspiration from anterior chest wall, which can be associated with a risk simultaneously, such as hemorrhage, pneumothorax etc. The spine blocks the Fine-needle aspiration if entering from posterior chest wall. Therefore, Fine-needle aspiration with posterior mediastinum is not be advocated in our opinion.

At present, there is no standard treatment for mediastinal myelolipoma. According to treatment with mediastinal tumor (34), once a neoplasm is discovered in the mediastinum, especially unconfirmed behavior of the tumor, surgical resection may be an optimal treatment for patient. Particularly, VATS is a satisfactory choice (30-32). As we can see in *Table 1*, the tumor size ranges from 1.5 to 25 cm, which reveals that the myelolipoma has potential of continuous growth. With the tumor growing constantly, the patients have to receive thoracotomy eventually, which would cause more trauma and risks, particularly to seniors. Therefore, once the mediastinal myelolipoma is found, surgery is a preferred treatment for patient in our opinion, especially with VATS.

Conclusions

Myelolipoma in posterior mediastinum is a rare tumor, without exact etiology. It primarily occurs in seniors with concealed onset. The patients usually resort to medical attention for symptoms by chest discomfort, anemia, hypertension, endocrinic disorders. In our reports, they might be closely related to ectopic hematopoiesis and endocrine disorder. Maybe we should spend more time and energy on investigating the cause of myelolipoma. Radiological investigations are the diagnostic modality of choice. Surgery is an optimal treatment for patient, especially VATS. The long-term prognosis is very good.

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Case Report

Undifferentiated pleiomorphic sarcoma simultaneously occuring with thymoma

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Abstract: We report here a case of thymoma simultaneously associated with neuroendocrine tumor. A 65-year-old male, presented with cough. Radiographic studies showed a mediastinal mass. On fine needle aspiration cytology and histopathological examination, a diagnosis of thymoma with coexisting undifferentiated pleomorphic sarcoma was made. Although thymoma is associated with many extrathymic malignancies, its association with neuroendocrine tumor is rare. This case is being reported on to reinforce that clinicians should bear in mind the possibility of extrathymic malignancies in patients with thymoma.

Keywords: Thymoma; cancer; neoplasm; diagnosis

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Introduction

Thymoma is a tumor of anterior mediastinum, however, thymomas may develop at various other sites like neck, trachea, thyroid, lung, and heart (1). It is the most common neoplasm of thymus, more common in men and in eighth decade of life (2). Thymoma is an uncommon neoplasm which arises from thymic epithelium. Thymomas are associated with paraneoplastic syndromes such as myasthenia gravis, hypogammaglobulinemia (3), pure red cell aplasia (4), and many kinds of immune mediated systemic disorders; however, few cases of extrathymic malignancies have been reported. Reported incidence of extrathymic malignancies is 2.6-27% (5-8). We report here a case of mediastinal thymoma with coexisting neuroendocrine tumor.

Case report

A 65-year-old male, presented with easy fatigability and a lump in the left side of his axilla for four months. On general examination mild pallor was noticed. Local examination of left axilla showed a lump of 8 cm × 8 cm, firm in consistency, fixed to underlying structures, and overlying skin was normal. Investigations showed Hemoglobin is 7 g/dL and Erythrocyte sedimentation rate 25 mm in first hour. X-ray chest posteroanterior view revealed a mediastinal mass. CECT obtained at the level of arch of aorta and main pulmonary artery showed a well-defined enhancing mass of soft tissue attenuation in the left anterior mediastinum abutting arch of aorta, main and left pulmonary artery with maintained fat planes.

Adjacent mediastinal fat plane was partially obliterated. CT guided FNAC was done which showed moderately cellular smears consisting of a dual population of epithelial cells and mature appearing lymphocytes. The epithelial cells comprised of oval to elongated nuclei with dispersed chromatin and inconspicuous nucleoli.

Mitosis was not seen. Histopathology of mass revealed loose aggregates of lymphocytes admixed with neoplastic epithelial cells. A diagnosis of thymoma was rendered. Excisional biopsy of axillary mass was done which was composed of cells having pleomorphic, hyperchromatic spindle-shaped nuclei with clumped chromatin. Mitotic rate was high. Occasional multinucleated cell was also seen. Immunohistochemical analysis showed positivity for vimentin and focal positivity for CD 68 along with negative

smooth muscle actin, desman, epithelial membrane antigen, CD 45, CD 3 and CD 30. On the basis of the above findings a diagnosis of thymoma with co-existent undifferentiated pleomorphic sarcoma was made. Postoperatively patient was discharged on 6th post-operative day. Follow up in our patient with invasive thymoma (surgical resection), treatment is based on induction chemotherapy and post-surgical radiation. 5-year survival for invasive thymoma is between 12-54% regardless of any myasthenia gravis symptoms.

Discussion

The coexisting thymomas with other malignancies is relatively rare, and the most common site for these extrathymic malignancies is colorectal (6,8) followed by lung, thyroid, prostate, female reproductive organs, breasts, kidney and skin melanoma. Only few cases of co-existent thymoma with coexisting undifferentiated pleomorphic sarcoma not otherwise specified (9,10) are reported in the literature. The pathogenesis of these associations is still unclear. In most of the cases associated tumors were diagnosed either before or at the same time of thymoma as in our case, which suggests that these patients may be genetically predisposed to develop tumors (11). Several different theories about the pathological basis have been proposed. According to Friedman (12), the onset of thymoma indicates defect within the thymus epithelium which is responsible for immune defect and increased incidence of neoplasia. Another theory suggests the potential ability of thymoma epithelial cells to stimulate T cells which predisposes to the onset of tumors (13,14). Undifferentiated pleomorphic sarcoma is the most common soft tissue sarcoma in adults, usually arising in extremities with a peak in seventh decade although cases in children have been reported (15,16). It can also develop at the site of previous radiation therapy (17). Enzinger and Weiss classified it histologically into storiform-pleomorphic, myxoid, giant cell, and inflammatory types (18). Storiform pleomorphic is the most common histologic type which consists of highly pleomorphic tumor cells arranged in storiform pattern. Immunohistochemistry is required for confirmation of diagnosis. Vimentin positivity and smooth muscle actin, desmin, epithelial membrane antigen, CD 45, CD 30, and CD 3 negativity as in our case made the final diagnosis. Local recurrence and metastasis to distant sites especially lungs and regional lymph nodes are common (19). Treatment is surgical resection and with or without adjuvant radiation and/or chemotherapy.

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Letter to the Editor

The burden of *Lophomonas blattarum* under the light microscope

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To the editor,

We read with interest the article published in your journal by Zeng *et al.* (1), reporting a case of infection by the multi-flagellated protozoon *Lophomonas blattarum* (LB) in an acute exacerbation of chronic obstructive pulmonary disease (COPD) (*Figure 1*).

On carefully examination of the two of the images provided in the article (*Figure 1F*,*G*), we think that on balance this article may have misidentified respiratory ciliated cells for multiflagellated protozoon. Our concerns are based on a set of morphological features that we have developed to differentiate ciliated epithelial cells from flagellated protozoa under the light microscopy (2,3).

We believe that *Figure 1F* shows a small group of ciliated bronchial cells (similar to a Creola body) with two large nuclei occupying almost the half of the cytoplasm and numerous short, regular and well oriented cilia (rather than true flagella). Similarly, we would argue that *Figure 1G* probably represents three ciliated bronchial cells, as the cells are columnar in shape, with large reed nuclei located at the basal end and tufts of cilia located at the apical ends of the cells.

Leaving the morphologic considerations aside, it is true that a positive response to the therapy with albendazole is an important point to consider. However, albendazole and other similar drugs such as nitroimidazoles are highly active against gram-negative anaerobic bacteria (4), which can be the causative agent in acute exacerbations of COPD.

The majority of articles reporting clinical cases of LB have been written by Chinese authors but in a lot of them, as it has been pointed out by Mu *et al.* (5), ciliated bronchial cells may have been erroneously misidentified as multiflagellated protozoa. We are similarly conscious that the

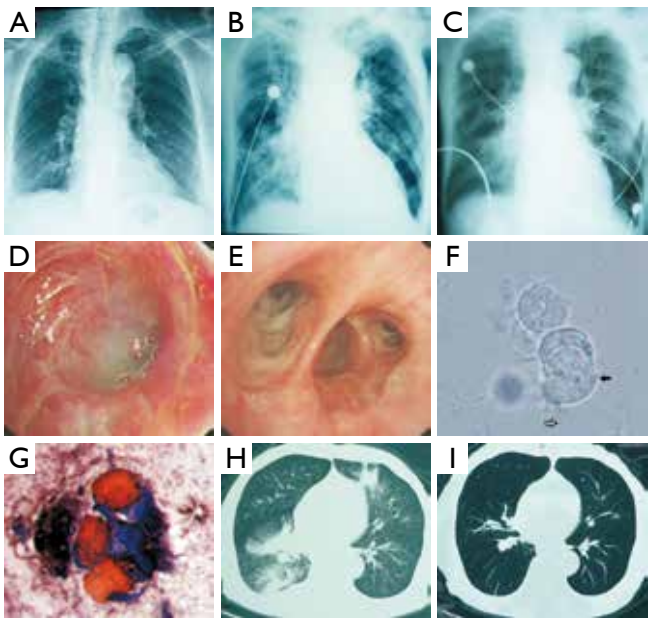

Figure 1 Image, bronchoscopy and smear finding in this case. (A) Chest X-ray showed no signs of any infiltration, masses and lymphadenopathy, at the fifth day from onset; (B) chest X-ray showed bilateral effusion, infiltrated and linear opacities, at the nineth day from onset; (C) chest X-ray showed improvement after tinidazole injection, at the fifteenth day from onset; (D) bronchoscopy showed a lot of purulent sputum, and diffusely swelling and friable mucus on the left lingual bronchus; (E) bronchoscopy showed a lot of purulent sputum, and diffusely swelling and congestion mucus on the right middle bronchus; (F) (×400); (G) (Leifson, ×400): Lophomonas blattarum clustered in direct suction specimen. ➡, body of Lophomonas blattarum; ⇨ , wave flagellates; (H) pulmonary CT scan presented bilateral effusion, infiltrated, at the twenty fifth day from onset; (I) pulmonary CT scan presented improvement and resolved of lesion, 3 months later after discharge.

misidentification of epithelial ciliated cells as multiflagellated protozoa needs to be considered when respiratory samples are examined under light microscopy (6,7).

In the absence of culture or molecular techniques, strict morphologic criteria need applied during light microscopy.

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Letter to the Editor

The importance of definition of active pulmonary tuberculosis and non-tuberculous pulmonary diseases in studies of diagnostic accuracy in high incidence areas

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To the editor,

In a recent study evaluating diagnostic accuracy of the interferon gamma release assay (IGRA) T-SPOT.TB for the diagnosis of tuberculosis in Southern China the authors found a low specificity of this assay in a group of patients with active pulmonary tuberculosis and non-tuberculous pulmonary diseases (NTBPD) (1). The authors may not be right in attributing this entirely to the presence of latent mycobacterium tuberculosis infection in the group of patients with NTBPD.

This group of patients contained 40.6% patients with pneumonia and 30.2% patients with bronchitis. It is not clear how active tuberculosis was ruled out in those patients if they had a positive IGRA. In studies of diagnostic accuracy it is essential that tuberculosis is ruled out thoroughly by adequate mycobacterial culture of at least three adequate sputum specimens and if necessary bronchoscopy in all chronic bronchitis cases with mycobacterial culture of lavage samples. The isolation of a pathogenic bacterium other than mycobacteria from sputum would not be adequate for ruling out tuberculosis as this may merely reflect nasopharyngeal carriage. NTBPD diagnosis requires rigorous ruling out of tuberculosis for the purpose of assessing an assay to avoid underestimation of specificity particularly in a high incidence area.

On the other hand there is need for a more stringent definition of active tuberculosis in diagnostic studies particularly in high incidence areas. A bacterial (e.g., staphylococcal) pneumonia may present with X-ray images characteristic of tuberculosis (cavity like lesions) (2), tuberculosis symptoms (night sweats, acute weight loss and fatigue) and respond to antituberculous treatment (e.g., rifampicin as an effective anti-staphylococcal treatment). Diagnosis of active tuberculosis during an investigation of the diagnostic accuracy of a laboratory test has to be a rigorous process and rely solely on positive smear, characteristically abnormal histology, positive culture or nucleic acid amplification to avoid underestimation of sensitivities and enable comparability of diagnostic studies and pooling in a meta-analysis.

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Letter to the Editor

Red cell distribution width: a novel predictor of mortality in critically ill patients

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To the editor,

We have read with great interest the recently published article titled "Red cell distribution width is associated with hospital mortality in unselected critically ill patients" by Zhang *et al*. (1). In that very well-presented article, the authors aimed to investigate the role of red cell distribution width (RDW) in prediction hospital mortality in critically ill patients. They concluded that RDW measured on ICU entry is an independent predictor of in-hospital mortality in critically ill patients and higher RDW was associated with longer length of ICU stay, and the change of RDW in a short interval provided no additional prognostic value in critically patients. We would like to thank Zhang *et al*. (1) for their comprehensive contribution.

RDW is a quantitative measure of anisocytosis, the variability in size of circulation erythrocyte and is routinely reported as a component of the complete cell count analysis. In the past, RDW is usually used for the differential diagnosis of anemia (especially iron-deficiency anemia) (2). In recent years, RDW has been demonstrated to significantly associated with mortality and other adverse outcomes in various clinical conditions, including chronic and acute diseases such as chronic and acute heart failure, acute dyspnea, acute pancreatitis, severe sepsis and septic shock, trauma, acute pulmonary embolism, and even community-dwelling older adults (3-8). In addition, the change of RDW is affected by many factors such as anemia, renal dysfunction or hepatic dysfunction, thyroid disease, transfusion, acute or chronic inflammation, neurohumoral activation, malnutrition (i.e., iron, vitamin B12 and folic acid), ethnicity, bone marrow depression, and use of some medications (i.e., erythropoietin use and antibiotic use) (2,5). However, in the present study, the authors did not describe these conditions in detail and also did not exclude relevant diseases in their exclusion criteria. Therefore, it would be better if the authors described the above mentioned RDW affecting factors in more detail. In addition, it is better to determine the time elapsed between blood sampling and RDW measuring, because the length of this interval may significantly alter RDW levels (2). In addition, RDW discussed in this study was measured on entry to ICU; however, we believe that RDW may be significantly different between patient admitted to the ICU from emergency department directly and patient admitted to the ICU who is transferred from other hospitals or departments.

In conclusion the study by Zhang *et al*. (1) will lead to further studies regarding the association between RDW and mortality or other adverse outcomes. However, one should keep in mind that RDW should be evaluated together with other prognostic or inflammatory markers. Only in this way, can we obtain exact information from these predictors.

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Letter to the Editor

Too much covariates in a multivariable model may cause the problem of overfitting

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To the editor,

Many thanks for the thoughtful insights into our work by Prof. Zhang and coworkers. We strongly agree with the reader that red blood cell distribution width (RDW) can be influenced by varieties of medical conditions including but not limited to anemia, renal dysfunction, hepatic dysfunction, thyroid disease, transfusion, acute or chronic inflammation, neurohumoral activation, malnutrition (i.e., iron, vitamin B12 and folic acid), ethnicity, bone marrow depression, and use of some medications (1-4). From the perspective of controlling for confounders, incorporation of a large number of covariates into a regression model will make the independent association more reliable. As a result, some investigators suggest incorporate as much covariate as possible when the study is aiming to explore the association between a variable of interest and clinical outcome. However, the benefit of including too many covariates should be balanced with the problem of overfitting (5,6). Overfitting occurs when too many variables are included in the model and the model appears to fit well to the current data. Because some of variables retained in the model are actually noise variables, the model cannot be validated in future dataset. In essence, overfitting is caused by multiple testing in which some noise variables are entered into the model simply by chance.

Another reason that we did not incorporate so many confounding factors had something to do with technical issues. The study was a retrospective study and involved strenuous work on data extraction from electronic medical record (EMR) system. The EMR was not designed for research purpose but instead it was used for clinical practice. Some information may not be very reliable in such circumstance. For instance, the use of medications in past history may not be complete that some drugs may be omitted because it was thought to be unrelated to current disease. Furthermore, the information related to previous drug use was recorded as text, which imposed great challenge on data mining.

Finally, we acknowledge that confounding factors have not been thoroughly explored in our study and it is one of the limitations (7). As I have pointed out previously, confounding is the Achilles' heel in observational studies (8). The ultimate solution to the problem may be the randomization which, when performed in an infinitely large sample size, can balance both known and unknown confounders and make the association between the variable of interest and outcome reliable. With respect to the time interval between blood sampling and laboratory analysis, I feel sorry I cannot provide enough information for analysis (the time was not recorded in EMR). The time was actually determined by the availability of transport workers. When they are busy, the blood sample may be delayed for half an hour. However, the blood sample can be delivered to the department of laboratory within 10 minutes in most circumstances. Prof. Zhang has mentioned the impact of admission source (emergency department *vs.* floor ward) on the level of RDW. However, there is no empirical evidence to support this notion and I feel that it is trival. Additionally, many patients from emergency department are transferred from other hospitals, making them equivalent to those transferred from floor wards of our hospital.

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Letter to the Editor

Pulse rate trends in obstructive sleep apnea: a reliable tool to predict long term response to CPAP?

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To the editor,

A predictive model of long term response to CPAP could be a useful tool for the clinician. In this regard, previous studies considered that changes in heart rate variability (HRV) are a key variable to assess continuous positive airway pressure (CPAP) response (1,2). We read with interest the recent article by Pengo MF *et al*. (3) were authors hypothesized that baseline nocturnal pulse rate (PR) trends help predict long term response to CPAP. In this study, main findings were improvement in daytime sleepiness among obstructive sleep apnea (OSA) patients with baseline negative change in PR contrary to OSA patients with positive change in PR. Nonetheless, we consider that a few aspects of this study deserve reviewing.

First, the diagnostic modality was unattended pulse oximetry. So far, the published data on this method is difficult to compare because of differences in the parameters measured and differences in the reference standard. Some studies reported high specificity while others reported a high sensitivity. For screening purposes, both high sensitivity and high pretest likelihood of OSA are needed. Additionally, age, pulmonary function, and degree of obesity impact on nocturnal desaturation and also influence sensitivity and specificity. Therefore, for research purposes, diagnosis should be confirmed by polygraphy or polysomnography (4-6).

In Pengo MF *et al*. patients in the OSA group had lower mean saturation of hemoglobin (SpO_2) than controls (92.7% *vs*. 95.4%). This difference makes the OSA group more likely to desaturate during sleep just by virtue of the oxyhemoglobin dissociation curve dynamics (5). Furthermore, some of the OSA patients may have suffered from other comorbidities such as obesity hypoventilation syndrome. This was more likely in the OSA group with positive change PR, where patients were more obese (122+/–26 kg) and had lower mean SpO_2 (90.9%) compared to those with negative change PR (107+/–26 kg, and 93.2%, respectively).

Secondly, inclusion criteria required a ≥4% oxygen desaturation index (ODI) ≥15 or ODI ≥5 plus Epworth sleepiness score (ESS) >10. In the developed world, prevalence of daytime hypersomnolence is significantly higher than OSA (7), so subjects with mild OSA were probably overtreated with CPAP.

Third, pulse rate index (PRI) > or < than 20 was used as criteria to select patients from controls. However, low HRV or respiratory events with <4% hemoglobin desaturation could make OSA patients be included as controls.

In a previous study, Zamarrón C *et al*. found no significant nightly changes in PR trends among 111 OSA patients (8). In the article by Pengo MF *et al*., it is not clear how PR trend is defined and why it is considered a determinant variable. One wonders how such a trend makes a patient more or less prone to respond to CPAP. Moreover, different CPAP compliance among OSA groups makes both this hypothesis and ESS outcomes unreliable.

In a nutshell, HRV reflects the relationship between parasympathetic and sympathetic nervous system, and, when abnormal, it raises the risk to future cardiovascular

problems. In regard to the work by Pengo MF *et al*., we think careful subject characterization and confirmed diagnosis is required, and we agree with the authors that more studies about PR and HRV analysis on assessing CPAP response are needed. Concomitantly, a more reliable pulse oximetry analysis might be used for doubtful OSA wherever access to polygraphy or polysomnography is limited (8-10).

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Letter to the Editor

Response from the authors to the letter "Pulse rate trends in obstructive sleep apnoea: a reliable tool to predict long term response to CPAP?"

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To the editor,

We appreciate the interest of Dr. Navarro-Esteva in our study (1). We are well aware of the contributions of previous studies within the field by Kufoy *et al.* (2) and Kawano *et al.* (3), which described the changes in physiological parameters but no symptomatic response to continuous positive airway pressure (CPAP) in patients with obstructive sleep apnoea (OSA).

We believe we have explicitly acknowledged the methodological limitations of pulse oximetries pointed out by Dr. Navarro-Esteva in our paper. However, nocturnal pulse oximetries are easily available, often used in clinical settings and comply with evidence-based guidance to diagnose OSA (4). In addition, in a randomised controlled trial they were found to be non-inferior when compared to inpatient polysomnography (5).

Obese patients with lower oxygen saturations are more likely to suffer not only from OSA but also from obesity hypoventilation syndrome (6). This can only be confirmed by nocturnal carbon dioxide measurements, a measurement that is not included in a standard polysomnography setup. Hence, we argue that the contention by Dr. Navarro-Esteva that "for research purposes, diagnosis should be confirmed by polygraphy or polysomnography" is hardly feasible in practice, as the best approach to diagnose OSA remains a controversial issue. The decision over which overnight investigation to employ is influenced by the available resources in the respective health care system. Moreover, in our study any decision to offer treatment was derived from evidence-based guidelines (4) and only 6 out of 58 (10%) patients with mild OSA were offered CPAP following physicians' review.

Dr. Navarro-Esteva is correct in stating that the symptom of hypersomnolence is of multi-factorial aetiological origin (7). Although OSA has got a high prevalence in the general population (8), hypersomnolence affects a larger group of people than those who suffer with sleep-disordered breathing.

The main inclusion criteria in our study was a 4% oxygen desaturation index (ODI) greater than 5/h. We added the pulse rise index (PRI) as additional inclusion criteria for the control group to exclude patients with additional conditions which could lead to autonomic arousals from sleep and affect pulse rate variability.

Zamarrón *et al.* studied the approximate entropy (ApEn) analysis of heart rate data derived from nocturnal pulse oximetries in OSA. They concluded that '(…) the results presented prove that this method is very well suited to recognize the sleep-apnoea-specific cyclic variability of heart rate'. They also postulated that studying the heart rate signal was an effective tool to understand how brain, sleep and autonomic nervous system interact (9).

As regards the definition of PR trend that left Dr. Navarro-Esteva uncertain, in the method section of our paper we have defined '*PR trend*' as the difference between the average pulse rate of the first and the last hour of sleep. We hypothesised that an increase in 'PR trend' reflected an increased sympathetic activation throughout the night and that 'PR trend' could be a predictor of treatment success in

a group of OSA patients treated with CPAP.

In our study, there was no significant difference in CPAP compliance between groups. The observed trend towards a longer use in the group with a negative 'PR trend' is consistent with the clinical observation that patients who respond better to CPAP treatment are more likely to use it longer.

Heart rate variability, pulse rate and the change in nocturnal pulse rate are important markers of autonomic nervous activity in OSA. Combined with the Epworth Sleepiness Scale (ESS), a patient-based symptoms score, and the response to CPAP therapy they are crucial markers to identify patients who are at an increased risk of cardiovascular events.

In conclusion, our data support the usefulness of nocturnal pulse oximetry recordings in a clinical setting of a sleep centre. Although polysomnography remains the Gold-standard for the diagnosis of sleep disorders, nocturnal pulse oximetry has been shown to provide reliable results (10). Indeed, pulse oximetry data convey not only data on ventilation and oxygen saturation, but they also provide an insight into autonomic nervous activity at-a-glance with the potential to identify elevated cardiovascular risks. This finding is not negated by the aforementioned methodological limitations.

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ICC policy statement concerning ICC sponsorship funds

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As the accompanying article concerning the medical-industrial complex explains (1), in many countries the government, health care businesses, and physician groups act to maximize their profits at the expense of patients' well-being. International COPD Coalition (ICC), whose mandate is to improve patient well-being, must expose and oppose such organizations that overcharge, over treat, and under deliver patient benefits. ICC works to convince the worldwide medical-industrial complex not to focus their efforts on profits, but to make improved patient outcomes their first priority.

ICC has historically accepted industry grants from companies that we believe to be sincere in their commitments to patients in order to help fund our global programs; however, in view of the global actions of some Pharma companies to harm and exploit patients (1), ICC decided last year to stop accepting industry funding where it represents a conflict of interest with our purpose of preventing COPD and benefiting respiratory patients.

While Pharma support has often benefited patient advocacy, companies such as Glaxo Smithkline and Boehringer Ingelheim now insert stipulations in their funding of patient organization activities that compromise their integrity and ability to advocate for patients. These contracts demand that the company's funding must be repaid in full at any time the company says that the patient organization has acted in a way that might adversely affect the company. This can occur even at the end of a fiscal year when all the operating funds have been spent on patient programs and no budgetary funds remain. This requirement mandates that patient organizations put Pharma welfare above patient welfare. This makes it impossible for a patient organization to effectively advocate for patients. It requires them to praise a sponsoring company even if they act to harm patients! Patient organizations that accept this gag rule lose their ability to be honest and fulfill the trust that patients have in them.

ICC rejects such limitations on patient advocacy, and we have made our position concerning Pharma funding clear on our website (www.internationalcopd.org). We urge all patient organizations to do the same. Many patient organizations receive Pharma funding but conceal this revenue and their contractual obligation not to criticize these companies. In effect, these organizations are money laundering for Pharma. If patient organizations do not publicly provide information about such conflicts of interest, one must assume that they have allowed financial bribes to take precedence over their commitment to patient welfare and their policies and pronouncements should not be believed.

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ICC COLUMN: The Voice of the Patient

Cost-effective medicine *vs*. the medical-industrial complex

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Moneyball medicine

In the fascinating non-fiction book Moneyball (and the movie produced therefrom) the story is told of a major league baseball general manager whose team (the Oakland Athletics) did not have the revenue to compete with other major league teams in hiring the expensive superstar players whose celebrity and superior abilities were thought to be necessary for a winning baseball team.

To combat this business model, he analyzed the ability of lesser known (and less expensive) players to get on base and score runs, which is the goal in winning baseball games. He found that a team of carefully selected ordinary players who had the ability to deliver hits and runs (and victories) for the team could be organized for a small fraction of the cost of hiring superstar players. By focusing on selecting the most cost-effective players in achieving victories, his team beat the teams that paid many times more for players. His strategy is working again this year!

Western medicine is increasingly suffering from an analogous malady of an overly expensive health care business model (1) whose goal is maximizing profit by overusing high-priced procedures and diagnostic tests and forcing patients to take expensive, unnecessary medications through-out the rest of their lives. With this strategy the losers are the patients and the health care systems. In most cases physicians can choose a much less expensive medicine that is as effective as the highly promoted brand name medicine that costs much more. I believe that health care would be benefited by changing its business model to cost-effective medicine with the goal of maximizing favorable patient outcomes at the lowest cost. Many US academic groups agree with the value of cost-effective medicine (2).

Wallowing in unnecessary expense, Western medicine embraces new, high-price diagnostic and therapeutic approaches whether or not they benefit the patient and public health. Published articles about new therapies seldom even mention cost, as if it were irrelevant to health care. In reality, high cost, even of a good therapy, greatly limits its availability and greatly increases the damage done to patients who are forced to bankrupt themselves in seeking the expensive care or to go without any care. The problem has become so pervasive that experts have advocated that high cost of medicines be listed as a side effect of their use (3).

As US President Eisenhower warned in 1961, the people of the world face serious danger from the global power of what he called the "military-industrial complex", which is the influence of the powerful multi-national corporations that are driven only by the quest for profit and power. The danger persists today, and it is represented globally in the medical arena by what Dr. Arnold Relman, the former editor of the New England Journal of Medicine, referred to as the "medical-industrial complex" of medical companies. These medical companies focus on profit and power without regard for patient and public health outcomes (4,5). The purpose of this article is to discuss whether or not medicine that focuses on cost-effective management would provide better patient outcomes than the current expensive medical overtreatment that is forced on many national health care systems by the medical-industrial complex.

Pharma business plans

Pharmaceutical companies have been one of the most profitable global industries for many decades. Their business plan depends on marketing new "blockbuster" drugs and maximizing their profits from these drugs to drive their profitability. They sell these proprietary "branded" drugs at huge mark-ups during the period of their patent

protection. For example, for the new anti-coagulants like Xarelto, a daily dose in the US (assuming twice daily dosing) may cost $20 USD, while the generic warfarin 5 mg tablet costs about $0.10.

In many cases Pharma target patients with chronic diseases that are not curable, and their medicines are designed to reduce or delay the severe effects of the diseases or often just to reduce the symptoms of the diseases. In the case of COPD, the medicines often force patients to suffer with an unhealthy life for a longer time. The companies' goal is to have patients take their expensive medicines through-out their lives with diseases such as hypertension, diabetes, elevated lipids, COPD, and asthma. The problem with this business plan is that new drugs that actually benefit clinically-relevant patient outcomes more than established inexpensive therapies are rare. In order to force broad usage of "me too drugs" and other drugs of questionable efficacy, the companies are forced to falsify clinical trial data, conceal serious drug side effects, fail to release patient-level clinical trial data, bribe physicians to prescribe the drugs, pay to have false and misleading information released in medical communications, pay to prevent cheaper generic drugs from being available, market the drugs heavily during their early release to maximize profit before side effects and other problems are discovered following longer use, and provide payoffs to politicians to pass legislation that will increase company profits without benefiting patients (4-7). While some categories of new medications, such as anti-neoplastic drugs, often can provide life-saving results (at a great cost), treatments in most other clinical areas have not been so successful.

In a recent interview of former US Vice President Al Gore by Dr. Eric Topol on Medscape, the Vice President described how the vast majority of US senators and representatives are dependent on money they receive from corporate interests. These politicians spend half of their time meeting with lobbyists, and when they receive their payoffs from the corporations they are committed to vote for laws that benefit their donors and harm their constituents. That is what American democracy looks like today (8).

Cost-effective versus cost-ineffective COPD therapy

Cost-effective care could be implemented in medical treatments for COPD. One example in the US is the availability of generic formoterol inhalers, which provide a therapeutic dose at about $0.37 each, while newly-introduced branded indacaterol inhalers provide a therapeutic dose at about $7.00 each (9). Yet there is no convincing evidence that the branded drug provides improved survival or better exacerbation reduction or quality of life than the generic drug, and the use of the less expensive drug could save COPD patients and the health care system millions of dollars each year. However, because companies heavily promote their new drugs as major advances and physicians are insensitive to their patients' costs, they are used in preference to generic drugs by US physicians.

In the US, the FDA's criterion for approval of a new drug is not improved patient benefit, but non-inferiority to other available medicines. Many other countries' regulatory authorities have more cost-effective approaches to drug approvals by insisting on cost limits and improved patient benefits over existing drugs for approval of a new drug to be given. This is a proper exercise of the use of cost-effectiveness in selecting medical therapy, but because it reduces corporate profits it is seldom done in the US and other countries where the medical-industrial complex controls medical practice and bribes the political system for their own profit and to the detriment of patients.

Another example of cost-effectiveness in COPD management is the use of products such as acetylcysteine and long-acting theophylline oral medications. N-acetylcysteine is difficult to obtain in the US, probably because it is so inexpensive that drug companies do not want to waste their time making and selling it, and they do not want it to compete with their expensive brand-name drugs that are no more effective. As a result, few physicians prescribe N-acetylcysteine for COPD because it is not marketed to them, but studies have established that it reduces COPD exacerbations for a daily dose of $0.12 while other therapies that are said to delay next exacerbations, such as roflumilast, cost about $8.00 for a dose. In Asia, however, N-acetylcysteine is regularly used, and this represents cost-effective COPD management.

Similarly, inexpensive oral long-acting theophylline preparations are seldom used for COPD in the US even though they are effective and much less expensive than other broncho-dilators. Although methylxanthines can have serious side effects at high blood levels, use of long-acting theophylline products in clinically relevant dosages has been shown to be safe and effective (10). However, the profit from an inexpensive, non-branded product such as long-acting theophylline is miniscule compared to the profit from the array of new branded long-acting beta

agonists (LABAs) and long-acting anti-muscarinic agents (LAMAs) whose use has been heavily promoted by Pharma and endorsed by clinical practice guidelines developed by physicians who have received large payments from the many companies who market and sell these agents. Few, if any, of these guideline experts receive payments from generic long-acting theophylline marketers. New perspectives on the benefits of theophylline use in COPD and new clinical trials with long-acting theophylline have been undertaken and may provide even stronger evidence for its cost-effective usage (11).

US government promotes cost-ineffective care

COPD prevention and early diagnosis of COPD offer the best hope of cost-effective management of the development and early treatment of COPD. However, since these approaches are contrary to the high profit business plan of the medical-industrial complex, they are seldom implemented. In the US, tobacco companies pay large fees to state governments to allow them to promote COPD development among their populations by marketing and selling their tobacco products. In providing this deadly permission for tobacco companies, US states promised to use the large fees they received for tobacco use prevention and programs for smoking cessation to protect their citizens; however, almost none of this promised preventive medicine funding has ever occurred. Instead, US politicians direct the money to projects that benefit them and their donors. This is a perfect example of cost-ineffectiveness in managing COPD (12).

In the US, multi-national corporations pay generic drug companies to prevent them from producing inexpensive versions of their drugs that come off patent protection. By maintaining their monopoly on the drugs they can force patients to continue to pay artificially high prices. The US Supreme Court, in considering the legality of this anti-patient policy, ruled that in many circumstances it is legal for corporations to pay to keep their monopolies (13). This ruling is another example of institutionalized cost-ineffectiveness for medical care. There are many examples of collusion by drug companies to increase profits and take actions that injure and lead to patients' deaths, particularly in the US (14).

Steps to oppose the medical-industrial complex

It is apparent that the policies of the global medical-industrial complex are not only cost-ineffective in managing COPD (and other diseases) but they harm patients. Theirs are the economic policies that kill, as Pope Francis explained (15). Those who wish to improve global public health and help COPD patients must look elsewhere to find cost-effective approaches for COPD to implement. We must oppose the policies of the medical-industrial complex worldwide and its corruption of physicians, governments, and health care systems that lead to patients' suffering and death.

Developing countries should steer away from health care systems like the US that harm patients. To help patients they should do as is currently being done in China by acting to foster lower cost generic drugs. For COPD it is hard to think of a circumstance in which the expensive new drugs provide any substantial medical advantage over older, less expensive drugs, but generic drugs save the patient and the health care system an enormous amount. In some developing countries, hospitals and physicians make excessive profits from selling drugs. This is not a proper approach. For physicians, the problem is that their salaries are much less than they should be, and physician charges should increase. For hospitals, they should charge more for the valuable services they provide; they should not encourage the sale of expensive drugs that are a bad buy for patients.

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Erratum

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Erratum to: J Thorac Dis 2014;6:888-95

VATS biopsy for undetermined interstitial lung disease under non-general anesthesia: comparison between uniportal approach under intercostal block vs three-ports in epidural anesthesia

In the article entitled "VATS biopsy for undetermined interstitial lung disease under non-general anesthesia: comparison between uniportal approach under intercostal block vs three-ports in epidural anesthesia" that appears on Pages 888-895 (1) of the July 2014 Issue of *Journal of Thoracic Disease* (*JTD*), there were two errors. The corrections are as follows.

(I) In the page 891, "Postoperative care" Paragraph, Line 212, the sentence "Each item is linked to a 5-point Likert scale [1-5] with a minimum cumulative score of 5 (maximal impairment) and maximum of 200 (no impairment)." should be corrected into "Each item is linked to a 5-point Likert scale [1-5] with a minimum cumulative score of 40 (maximal impairment) and maximum of 200 (no impairment).";

(II) In *Table 3* at page 893, the "24-hour postop QoR40 [5-200]" should be "24-hour postop QoR40 [40-200]".

Erratum to: J Thorac Dis 2014;6:1143-9

Preservation solutions for cardiac and pulmonary donor grafts: a review of the current literature

In the article entitled "Preservation solutions for cardiac and pulmonary donor grafts: a review of the current literature" that appears on Pages 1143-1149 (2) of the August 2014 Issue of *Journal of Thoracic Disease* (*JTD*), there were two errors. The corrections are as follows.

(I) In the Paragraph 7, Line 5, the two sentences "The development of newer solutions containing alternate impermeants/colloids led to superior protection against cellular swelling. UW contains lactobionate and the trisaccharide impermeant raffinose as well as the synthetic colloid HES (Roskott *et al*.). HTK, CEL, and Papworth rely on mannitol to combat tissue edema (9)." should be corrected into "The development of newer solutions containing alternate impermeants/colloids led to superior protection against cellular swelling. UW contains lactobionate and the trisaccharide impermeant raffinose as well as the synthetic colloid HES (Roskott *et al*.) (9). HTK, CEL, and Papworth rely on mannitol to combat tissue edema.";

(II) In *Table 3* "Struber (34) study", the number of cases should be "106 (EC 55, LPD 51)" instead of "106 (EC 63, LPD 57)".

Erratum to: J Thorac Dis 2014;6:988-94

Relation of late gadolinium enhancement in cardiac magnetic resonance on the diastolic volume recovery of left ventricle with hypertrophic cardiomyopathy

In the article entitled "Relation of late gadolinium enhancement in cardiac magnetic resonance on the diastolic volume recovery of left ventricle with hypertrophic cardiomyopathy" that appears on Pages 988-994 (3) of the July 2014 Issue of the *Journal of Thoracic Disease* (*JTD*), there was one minor error. The correction is as follows.

(I) In the page 988, title page, the authors information "Xiaorong Chen[1,2], Hongjie Hu[2], Yue Qian[2], Jiner Shu[1]" should be corrected into "Xiaorong Chen[1,2], Hongjie Hu[1],Yue Qian[1], Jiner Shu[2]".

The publisher regrets these errors.

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