

The surgeon thunderbolts in 2016 lung cancer literature

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Introduction

Lung cancer is the primary cause of cancer deaths. Surgery is the preferred treatment for early-stage non-small cell lung cancer (NSCLC), and over the last 20 years, video-assisted thoracic surgery (VATS) lobectomy has developed into a safe and efficient treatment (1).

In this issue of the *Annals of Translational Medicine*, leading authors have introduced another valued educational source with the newest advances in NSCLC to keep busy practitioners, scientists, and others interested in lung cancer up-to-date. In this context, our article is meant not to be an all-encompassing review, but to cover the 2016 surgeons highlights along with the necessary references for further reading.

Lung cancer screening

Low-dose computed tomography (CT) screening increased identification of small lesions warrants further assessment and referral to thoracic specialists for decision-making plans. Thoracic surgeons play a critical role in the care and management of these patients, engaging in a management role within a multidisciplinary group. For the evaluation of the CT detected does not currently exist guidelines, and screening detected lung nodules incidence continues to rise. VATS approaches are suggested; sublobar resection can be performed in peripheral tumours <2 cm in larger dimension and <50% non-solid component. Otherwise, lobar resection is preferred. The radiographic surveillance is suitable in subcentimeter nodules with predominant nonsolid component which typically follow a slow growth pattern. On the other hand, mediastinal lymph node assessment should be performed in all patients with the predominantly

solid component. Omitting mediastinal lymph node assessment in subcentimeter mostly non-solid lesions can be considered, particularly with low suspicion index on CT scan or PET (2). Several studies discuss the characteristics of the high-risk screening population, the values of early detection, assessment and management of the relatively high number of positive results, and benefits and harm of screening. However, many questions remain regarding the broad application of testing. A major question is whether distinct low-dose CT screening trials will demonstrate comparable results to National Lung Screening Trial findings. Another unanswered question is whether future screening results will be equal to the ongoing projects results. There is some uncertainty regarding the accessibility of lung cancer screening with low-dose CT is implemented on a broader population. Lastly, there remains a lack of analysis into the cost-effectiveness of screening that could affect his use because of potential implications for healthcare budgets (directly related to government institutions, taxpayers and society members in general) (3).

Other questions are whether other low dose CT screening trials will demonstrate comparable results to National Lung Screening Trial and if future screening results will be equal to the ongoing 3-year results (3).

Minimally invasive surgical treatment

Over the past 20 years, surgical treatment of lung cancer was shifted to minimally invasive surgical techniques. When compared to thoracotomy, VATS was associated with larger perioperative outcomes, and numerous meta-analyses demonstrated reduced complication rates, shorter hospital stay and improved long-term survival. In recent

years, the uniportal VATS technique has emerged as an alternative to the conventional multiport approach. Since its adoption, there have been numerous reports on the feasibility and advantages of the uniportal VATS approach. These comprised a significant reduction in postoperative pain, paraesthesia and improved patient satisfaction. In the systematic review and meta-analysis from Harris *et al.*, (comparison of uniportal VATS and multiport VATS lobectomy for lung cancer), uniportal VATS was related to a statistically significant reduction in the number of the chest tube, the length of hospital stay, and the overall morbidity (4). Regarding the VATS lymph nodes dissection efficacy, Zhang *et al.* performed a systemic review and meta-analysis. Thoracotomy and VATS harvested a similar number of total lymph nodes, mediastinal lymph nodes, and N1 lymph nodes stations. However, the possible existing bias in the original studies, the inter-study heterogeneity, and the inherent limitations of meta-analytic approach require that the findings should be validated in high-quality, large-scale randomised controlled trials (5). Nevertheless, a meta-analysis from Meng *et al.* indicated that lymph node sampling was associated with inferior survival rates in patients with early-stage NSCLC. Lobe-specific nodal dissection provided equal survival benefits compared with systematic nodal dissection in early-stage NSCLC patients, and the indications need to be identified by further prospective studies (6).

VATS segmentectomy in early stage lung cancer

Although lobectomy has considered the standard procedure in stage I NSCLC, the role of sublobar resection for stage I NSCLC remains controversial. Amidst growing enthusiasm for this approach, the clinical outcomes after thoracoscopic sublobar resection versus VATS lobectomy may be uncomparable. A study by Liu *et al.*, analysing the overall and disease-free survival outcomes of patients who underwent VATS segmentectomy, found survival rates comparable to VATS lobectomy (7). In another meta-analysis, Hou *et al.* compared the results of overall, cancer-specific, and disease-free survival for patients with stage I NSCLC who underwent VATS segmentectomy. Authors found that overall and cancer-specific survival rates for stage I NSCLC after segmentectomy are superior to those obtained after wedge resection. On the other hand, wedge resection and segmentectomy produce similar cancer-specific and overall survival rates for patients with NSCLC in stage IA with a tumour size of 2 cm or less. Fortunately,

the role of segmentectomy may be clarified by the two ongoing randomised controlled clinical trials: the phase III trial WJOG4607L/JCOG0802 (from the West Japan Oncology Group and Japan Clinical Oncology Group), and the CALGB 140503 trial (from the National Cancer Institute). In CALGB 140503, more than 1,200 patients in a multicentre design will be recruited for a randomised study comparing lobectomy and sublobar resection (segmentectomy and wedge resection) for stage IA NSCLC with peripheral tumours <2 cm (8).

Enhanced recovery after surgery (ERAS)

The fast-track surgery concept, also known as ERAS was introduced in patient care in 1990 by Kehlet and Wilmore. Primarily developed to prevent factors of delayed postoperative recovery in patients undergoing colic surgery, protocols were established to achieve faster mobilisation and resumption of regular activities without an increase in complications. In thoracic surgery patients, the goals of ERAS protocols are the prevention of respiratory complications that lead to increased morbidity and mortality. Systematic reviews and meta-analyses recommend significant benefits from ERAS pathways or interventions. Nevertheless, there are still major hitches when introducing these evidence-based guidelines into routine practice. The anesthesiologist plays a key role in preoperative assessment and postoperative care. Also, thoracic anaesthesia will affect the outcome of optimal fluid therapy, protective lung ventilation, and adequate analgesia (9). The influence of ERAS on postoperative outcomes after lung resection has not been extensively studied in comparative studies involving a control group receiving traditional care. Studies suggest that this intervention may reduce the length of stay and hospital costs, but they should be interpreted considering several methodologic limitations. A review from Fiore *et al.* highlights the need for well-designed trials to provide conclusive evidence about the role of enhanced recovery pathways in thoracic surgery (10). However, controversy and confusion remain regarding the appropriate number of chest tubes (balancement of drainage effectiveness and lessen postoperative pain), the suitable size, the active suction or the use of a digital classification system. Chest tube drainage could be omitted in selected VATS sublobar resections. One 28-Fr chest tube could be placed with a digital monitoring system in VATS lobar resections. The chest tube could be removed within 48 h postoperatively

when the air leakage is resolved, and the fluid drainage is <400 mL/day (11).

Complications of lobectomies after induction chemotherapy

Since 1990, thoracic surgeons have increasingly paid attention to neoadjuvant therapy for improving the resectability. Systematic reviews have concluded that induction therapy can significantly benefit the survival outcomes of operable patients. However, the impact of neoadjuvant therapy on intraoperative and postoperative complications remains a debate. Li *et al.* conducted a systematic meta-analysis to determine the association between neoadjuvant therapy and the risk of bronchopleural fistula in patients undergoing lobectomy. They concluded that neoadjuvant therapy is significantly associated with the risk of bronchopleural fistula after lung cancer surgery (12). In another meta-analysis from same authors, the residual disease at the bronchial stump is positively associated with the increased risk of bronchopleural fistula formation (13).

Lymph node ratio as prognostic indicator

Multiple investigators have demonstrated the heterogeneity in the survival of patients with N0 resections, suggesting the possibility that a considerable proportion of these patients are understated, probably because lymph node metastasis is missed. On the other hand, the survival of patients with pathologic N1 is also heterogeneous. These results advocate a need to identify patterns of lymph nodes involvement that more accurately predict survival, particularly in patients with the N1 disease. Since the thoroughness of nodal examination interacts with the likelihood of detecting nodal metastasis, the number of positive lymph nodes may depend on by the number of lymph nodes examined from the resection specimen. Therefore, the prognostic accuracy of the number of positive lymph nodes is potentially restricted. The lymph node ratio, the number of positive lymph nodes divided by the number of lymph nodes examined, has been suggested to be a more accurate prognostic indicator than the number of lymph nodes with metastasis in thyroid, gastric, and colorectal cancer. The prognostic value of the lymph node ratio in N1 NSCLC remains controversial. Li *et al.* conducted a meta-analysis to evaluate the lymph node ratio as a predictor of survival and recurrence. Their results support the use of the lymph node ratio as an independent means of risk-stratifying N1 patients and potentially

recognise patients who might benefit from postoperative adjuvant therapy or require closer surveillance or targeted for enrollment into clinical trials for novel induction treatments (14).

Management of stage IIIA/N2 NSCLC

Approximately 15% of patients with NSCLC will present in stage IIIA/N2 disease. The optimal management of stage IIIA/N2 NSCLC disease remains widely debated among surgeons, pulmonologists, and oncologists. Many trials have set out to determine the optimal combination and timing of multimodality treatment. Such tests have historically been challenged by accrual issues and relevance to modern practice by the time of publication. Unfortunately, this leaves many aspects unclear. Mediastinal sterilisation with neoadjuvant chemoradiation confers a superior 5-year survival with surgical resection, emphasising the importance of preoperative treatment while maintaining acceptable levels of toxicity. A lobectomy is safer than a pneumonectomy following neoadjuvant chemoradiation and surgery can be performed safely. Although currently enrolling studies on N2 disease exist, much of issues will remain unresolved for the foreseeable future and lay in the subjective hands of expert opinion and consensus guidelines. Then, up to now, there is no consensus in the management of IIIA/N2 NSCLC (15).

Oligometastatic lung cancer

Five-year survival in stage IV NSCLC remains as low as 1% with a median survival of 8 to 11 months. Nevertheless, a subclass of patients with stage IV NSCLC with primary lung cancer and a single site of extrapulmonary oligometastatic benefits from complete resection or local control. In the absence of randomised data to guide appropriate management of oligometastatic NSCLC, patient selection for curative intent is primarily based on retrospective data derived from single centre experiences. The evidence thus far supports aggressive treatments for fit patients with a single organ site of synchronous (or metachronous) extrathoracic M1 disease without signs of intrathoracic lymph node (N0) involvement. Local control of both the primary and oligometastatic site can be achieved by either complete surgical resection or ablative radiotherapy modality. A therapeutic strategy for oligometastatic patients should be carefully considered on a case-by-case basis. Systemic chemotherapy is often used

somewhere in this policy, but the timing and efficacy remain unclear. Targeted chemotherapy (in addition to a dynamic local control) should be strongly encouraged in patients with oligometastatic driver mutated NSCLC (16).

Stereotactic body radiotherapy (SBRT) in early stage lung cancer

SBRT, likewise known as stereotactic ablative radiotherapy (SABR), is a treatment option for medically inoperable stage I patients. SBRT has achieved local control and overall survival rates comparable with lobectomy in non-randomized studies in medically inoperable or elderly patients. SBRT can also produce high local control and low toxicity in patients with peripheral lung metastases and limited oligometastatic disease. Until now, no randomised trials comparing VATS lobectomy with SBRT have been conducted, and imbalances may hamper non-randomised comparisons in baseline characteristics between groups. In the meta-analysis of Ma *et al.*, VATS and SBRT showed inconspicuousness differences; then, the two treatments are feasible and practical (17). Deng *et al.* conducted a meta-analysis to compare the efficacy of SABR with surgery and found that lobectomy produced better survival outcomes than SABR, whereas SABR produced comparable rates when compared with sublobar resection (18). In another meta-analysis, lobectomy yielded significantly superior long-term survival outcomes compared with SABR, whereas SABR yielded a local control rate comparable to lobectomy or sublobar resection (18). Therefore, lobectomy is still the preferred method for treating early-stage NSCLC. Well-designed and multicentred randomised controlled trials with large sample sizes, however, are needed to confirm and update our conclusions (18).

Eighth edition of TNM classification

The eighth edition of TNM classification of lung cancer is now the worldwide standard. An extensive and multifaceted analysis served as the foundation for this revision. Primary tumour size subdivides the T component into 1-cm increments as well as other descriptors of invasion into adjacent structures. The N component is determined by the location of involved lymph nodes. The M part is subdivided into intrathoracic dissemination, single extrathoracic metastasis, and multiple metastases. These coalesce into stage groups. It is essential that thoracic surgeons should be familiar with the eight edition

of classification because it will provide the universal language to describe the extent of disease (19).

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Footnote

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