



Diagnosis status and pathological diagnosis derived treatment of elderly lung cancer patients over 75 years old

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Background: The number of lung cancer in the elderly is increasing. However, a disturbing number of elderly patients failed to get pathological diagnosis and therapeutic outcomes are worse than the young. This study is conducted to explore the diagnosis and treatment status of lung cancer in patients over 75 years old.

Methods: Patients diagnosed with lung cancer between September 1, 2010 and October 30, 2017 were continuously screened. The pathological diagnosis must be based on the cytology or histology diagnosis. The clinical diagnosis must be built on both typical imaging features and increased tumor markers. Clinical features and survival information were obtained and analyzed.

Results: A total of 338 primary lung cancer inpatients were finally included with an age of 78.02 ± 2.94 years. The most frequent comorbidities were hypertension, chronic obstructive pulmonary disease (COPD) and cardiovascular disease; 290 of all these patients were pathologically diagnosed while the other 48 patients only got a clinical diagnosis. Among the pathological diagnosis, adenocarcinoma, squamous carcinoma and small cell lung cancer counted for 91.72%. Epidermal growth factor receptor (EGFR) detection was performed in 126 patients and 41 of them were sensitive mutated. Among all included patients, 150 were treated by the best supportive treatment (BST). Anti-cancer treatment is significantly associated with better survival than BST ($P < 0.001$). Definite sensitive mutation is associated with improved survival than undetected patients in EGFR-tyrosine kinase inhibitors (TKIs) treatment patients ($P = 0.039$).

Conclusions: Pathological diagnosis of lung cancer in elderly patients is relatively deficient. Pathologic and molecular pathological diagnosis derived anti-cancer treatment is effective in improving survival.

Keywords: Lung cancer; elderly; diagnosis; prognosis; treatment

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Introduction

Lung cancer is usually more frequent in the elderly population and over two-thirds of new lung cancer cases in America are diagnosed in patients over 65 years old (1). With the aging tendency of population and increased lung cancer incidence, lung cancer in elderly population is becoming an increasingly important issue (2). Because of multiple chronic comorbidity and worries about

complications related to invasive examinations, a disturbing number of elderly patients failed to receive pathological diagnosis and definitive anti-cancer therapy is thus delayed or unadopted.

Despite the significant improvement in lung cancer treatment, therapeutic outcome in elderly patients is usually worse than that in younger patients and complications are more frequent and severe (3). Remarkably, therapeutic in

elderly lung cancer patients is conservative and elderly lung cancer patients are often undertreated with higher early death rates than younger patients (4). Meanwhile, elderly patients, especially those over 75 years old are more likely to be excluded by clinical trials (5). It appears that elderly patients did not benefit from the recent oncology advances as much as the young (6). All these current issues indicated the importance of evaluating the diagnosis and treatment in elderly lung cancer patients and we conducted this study to explore the diagnosis and treatment status of lung cancer in patients over 75 years old.

Methods

Patient selection

This study was performed at the department of respiratory and critical care medicine, Jinling Hospital (Nanjing, China) and was approved by Jingling Hospital's Institutional Review Committee on Human Research. This retrospective study comprises 338 hospitalized patients diagnosed with lung cancer from September 1, 2010 to October 30, 2017. The inclusion criteria are as follows: (I) all included patients must be aged over 75 years; (II) patients must be diagnosed as primary non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) by pathologic examination (histology and/or cytology examination) or clinical examination. Clinical diagnosis of lung cancer in this study must meet both of the following 2 diagnostic criteria: (I) typical imaging features of computed tomography (CT) or positron emission tomography/computed tomography (PET/CT); (II) at least one of the following increased blood tumor markers: carcinoembryonic antigen (CEA), cytokeratin 19 fragment (Cyfra21-1) or squamous cell carcinoma antigen (SCC). Any other patients who were suspicious of lung cancer and based solely on either imaging abnormalities or increased blood tumor markers were excluded to distinguish unreliable cases.

Clinical data collection

Patients' demographic data at admission, main medical test results and treatment information were obtained through the electronic medical record system (EMR). Tumor staging was based on the 7th edition of TNM lung cancer staging system. Overall survival (OS) was defined as the length from the date of diagnosis or treatment initiation to the date of death by any cause or the last follow-up (June 21, 2018).

Statistical analysis

All statistical analyses were conducted by using PASW Statistics 18.0 (IBM Corporation, Armonk, NY, USA). Data are presented as mean \pm SD or the absolute number of subjects. The test of normality and variance homogeneity was performed and Kruskal-Wallis test was applied if analysis of variance was not applicable. Survival curve was estimated by the Kaplan-Meier analysis and the log-rank test was utilized to examine the differences of survival between different groups. In all analyses, a $P \leq 0.05$ was considered to be statistically significant.

Results

Main patient characteristics

A total of 338 lung cancer inpatients were finally included in this study. The number of patients diagnosed as lung cancer in our institution added up to 2,791 during the same period. As shown in *Table 1*, 236 of the 338 patients were male and the mean age was 78.02 years old. The most frequent comorbidities were chronic obstructive pulmonary disease (COPD, $n=126$), pulmonary tuberculosis (PTB, $n=45$), diabetes mellitus (DM, $n=39$), hypertension ($n=144$), coronary heart disease (CHD, $n=45$), coronary stented ($n=18$), arrhythmia ($n=34$), chronic heart failure (CHF, $n=12$), cerebrovascular disease (CVD, $n=34$) and other malignant tumors ($n=21$); 42 of them were identified by routine medical examination or CT follow-up and all the other patients were hospitalized with symptoms including cough, sputum, hemoptysis, dyspnea, chest pain, fever, hoarseness, lymphadenectasis, weight loss and neurological symptoms.

Diagnosis and treatment results

Among all the 338 patients diagnosed with lung cancer, 290 (85.80%) got pathological diagnosis while the other 48 patients (14.20%) were clinically diagnosed (*Table 2*). As stated above, clinically diagnosis was based on both typical imagological examination and elevated blood tumor markers.

Invasive examination taken in this study included conventional transbronchial needle aspiration (TBNA)/transbronchial lung biopsy (TBLB), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), CT-guided percutaneous transthoracic needle biopsy (CT-PTNB), closed thoracic drainage, pleural biopsy and superficial lymph node biopsy. Main complications related to

Table 1 Clinical features of included patients

Clinical features	Number
Male/female	256/82
Age, years	78.02±2.94
Smoking	
Non-smokers	135
Smokers	203
Co-morbidities	
COPD	126
PTB	45
DM	39
Hypertension	144
CHD	45
Coronary stented	18
Arrhythmia	34
CHF	12
CVD	34
Other types of cancer	21
Performance status	
0–1	252
2 or more	86
Main symptoms	
Cough	96
Sputum	138
Hemoptysis	72
Dyspnea	100
Chest pain	51
Fever	24
Hoarseness	9
Lymphadenectasis	8
Weight loss	7
Neurological symptoms	6
Medical examination only	42
Initial stage of NSCLC	
I	19
II	22
III	67
IV	191
Initial stage of SCLC	
Limited disease	10
Extensive disease	29

COPD, chronic obstructive pulmonary disease; PTB, pulmonary tuberculosis; DM, diabetes mellitus; CHD, coronary heart disease; CHF, chronic heart failure; CVD, cerebrovascular disease.

Table 2 Diagnosis information of included patients

Diagnosis information	Number
Diagnostic mode	
Clinical diagnosis	48
Pathological diagnosis	290
Invasive examination	
TBNA/TBLB	147
EBUS-TBNA	8
CT-PTNB	159
Closed thoracic drainage	68
Pleural biopsy	23
Superficial lymph node biopsy	8
Complications related to invasive examination	
Hemoptysis	45
Pneumothorax	20
Dyspnea	2
Complications with treatment	37
Reasons for failure of pathological diagnosis	
Negative pathological diagnosis	11
Patients and relatives unwillingness	32
Unable to tolerate	5
Types of pathology	
AC	132
SCC	96
SCLC	38
Undifferentiated	17
Mixed	3
Other	4
EGFR status	
Wild	84
Exon 19 del	26
Exon 21 L858R	15
Exon 21 L858R & T790M	1
Unknown	212
ALK status	
Negative	122
Positive	2
Unknown	214

TBLB, transbronchial lung biopsy; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; CT-PTNB, computed tomography-guided percutaneous transthoracic needle biopsy; AC, adenocarcinoma; SCC, squamous carcinoma; SCLC, small cell lung cancer.

Table 3 Treatment options of included patients

Treatment	Number
Initial radiotherapy	
Pulmonary	34
Brain	7
Bone	5
Multiple sites	4
Radiotherapy regimen	
Cyberknife	21
Conformal radiotherapy	24
Whole brain radiotherapy	3
Multiple	2
Surgery	
Wedge resection	5
Lobectomy	19
Chemotherapy	
Single-agent	43
Double-agent	85
Target therapy	
EGFR-TKIs	59
ALK-TKI	1

EGFR-TKI, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase.

invasive examination were hemoptysis (n=45), pneumothorax (n=20) and dyspnea (n=2) and 37 of them need further treatment. None of these complications were potentially-crippling or fatal. Among the 48 clinically diagnosed patients, 11 also received invasive examination but failed to get a definite pathological diagnosis. Most of all, 32 patients did not receive invasive examination because of their own and relatives unwillingness without any contraindications.

Among the pathological diagnosis, adenocarcinoma (132/290), squamous carcinoma (96/290) and small cell lung cancer (38/290) were the most frequent pathological type. Most patients were staged III (n=67) or IV (n=191) at the time of initial diagnosis. Epidermal growth factor receptor (EGFR) detection was performed in 126 patients and 42 patients were mutated. Exon 19 deletion was detected in 26 patients and L858R was detected in 15 patients. One patient was primarily doubly mutated with L858R and T790M. AKL-EML4 fusion gene were detected in

124 patients and only 2 of them were positive. All these molecular examinations utilized tissue specimens or cell blocks.

Twenty-four early stage patients were treated by surgery. Five of them received wedge resection and the other 19 patients received lobectomy and lymph node dissection (Table 3). Radiation therapy was used in 50 patients. Cyberknife and 3D-conformal radiotherapy were mostly used. Radiotherapy regions included pulmonary and/or hilar lymph node, brain and bones. Four patients received radiotherapy of both the primary focus and the metastasis. Systemic therapeutics were conducted in 188 patients. Main treatment included chemotherapy (n=128), target treatment (n=60). None of these patients ever participate in any clinical trials.

Survival analysis

We firstly analyze the survival of clinically diagnosed patients and pathologically diagnosed patients receiving best supportive treatment (BST). As shown in Figure 1, the OS of patients in these two groups was extremely similar in both stage I–III (p=0.760) and stage IV (P=0.579) patients. On the other hand, these results indicated that the clinical diagnosis of lung cancer in this study is reliable.

As stated above, the clinical diagnosis and staging were reliable. Base on this, we conducted Kaplan-Meier survival analysis based on diagnosis method in different stages. As shown in Figure 2, no significant difference was detected in stage I–III (P=0.393) patients. In stage IV patients, OS of pathologically diagnosed patients were significantly longer than clinically diagnosed patients (median OS: 8 *vs.* 4 months, P=0.027).

Then we further analyzed the effect of different systemic therapeutics on OS in stage III and IV patients. As shown in Figure 3A, aggressive treatment showed a tendency to improve OS than BST in stage III patients with no significant difference (P=0.06). In stage IV patients (Figure 3B), more aggressive treatment of chemotherapy and target treatment got much longer than BST (EGFR-TKIs *vs.* double agent treatment *vs.* single agent treatment *vs.* BST: 23 *vs.* 10 *vs.* 8 *vs.* 4 months, EGFR-TKIs *vs.* BST: 23 month *vs.* 4, P<0.001, double agent chemotherapy *vs.* BST: P<0.001, single agent chemotherapy *vs.* BST: P=0.006). No significant difference was detected between double agent chemotherapy and single agent chemotherapy (P=0.122). Since most patients treated by EGFR-TKIs were stage IV (n=49), we analyzed the EGFR status on survival

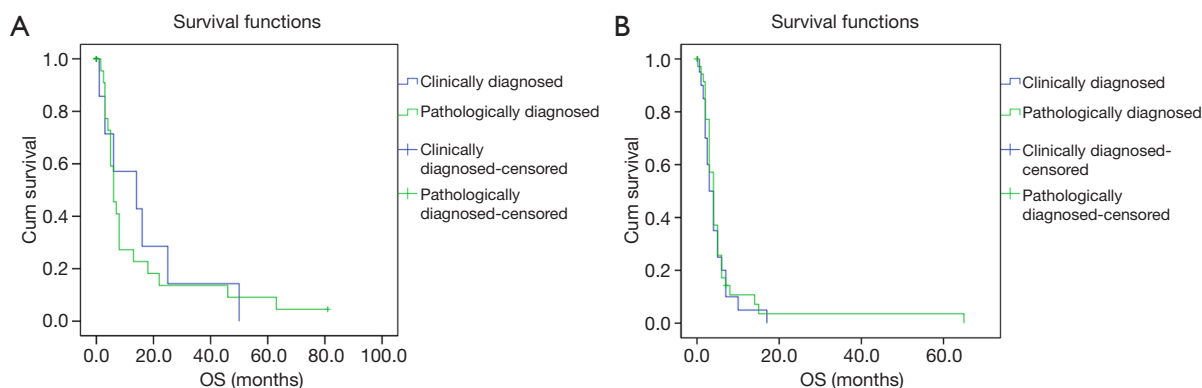


Figure 1 OS for clinically diagnosed and pathologically diagnosed patients receiving BST. (A) Stage I-III; (B) stage IV. BST, best supportive treatment; OS, overall survival.

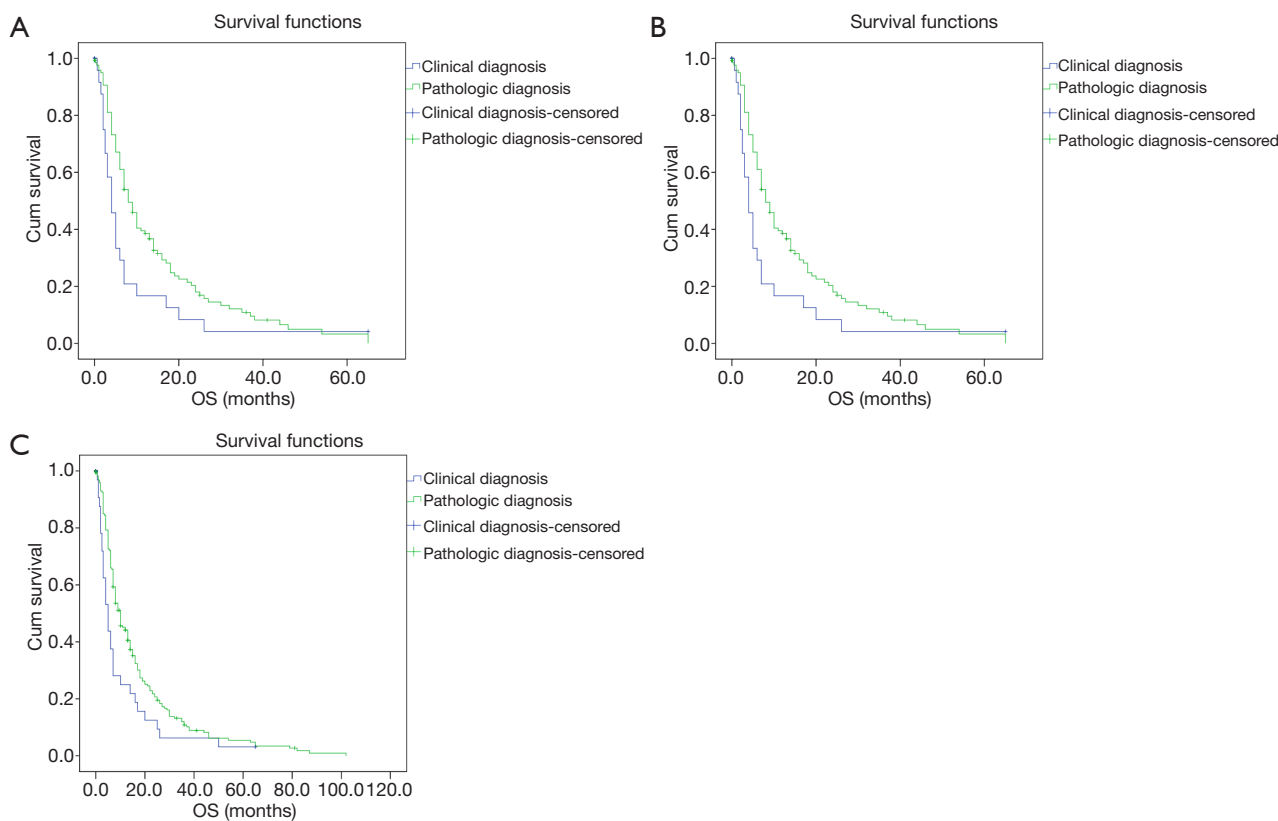


Figure 2 OS for clinically diagnosed and pathologically diagnosed patients. (A) Stage I-III; (B) stage IV; (C) all included patients. OS, overall survival.

in stage IV patients. As shown in *Figure 4*, the OS was much longer in sensitive EGFR-mutated patients (sensitive mutation *vs.* wild *vs.* unknown: 23 *vs.* 10 *vs.* 10 months, $P=0.039$) and no significant difference was detected between EGFR-wild and EGFR-unknown patients ($P=0.948$).

Discussion

In this study, it is demonstrated that about 14% of hospitalized elderly lung cancer patients aged over 75 years were not diagnosed pathologically and 9.5%

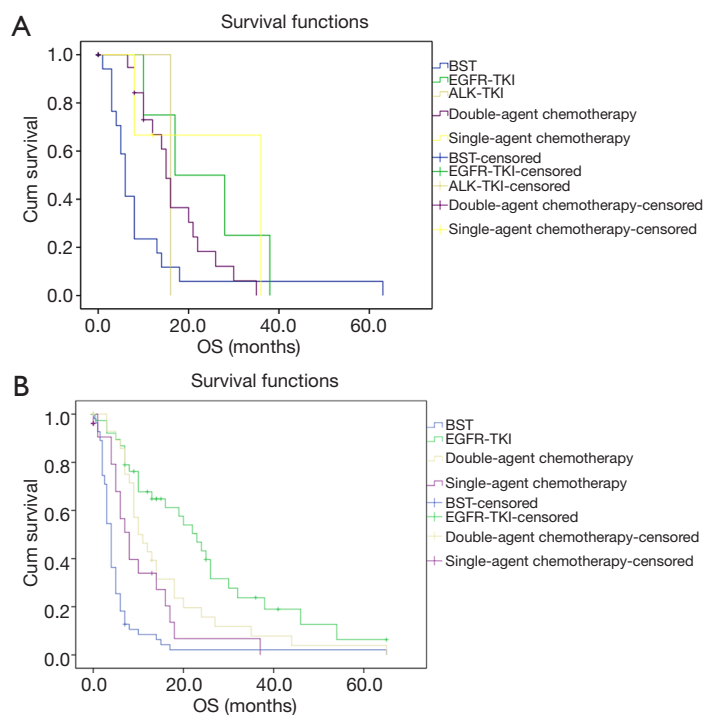


Figure 3 OS for stage III/IV NSCLC patients receiving different treatment. (A) Stage III; (B) stage IV. OS, overall survival; NSCLC, non-small cell lung cancer.

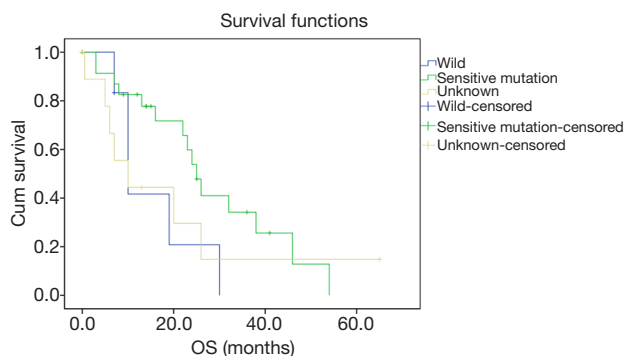


Figure 4 OS for stage IV NSCLC patients receiving EGFR-TKIs treatment stratified by different EGFR status. EGFR-TKI, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; OS, overall survival; NSCLC, non-small cell lung cancer.

of the inpatients reject invasive examination with no contraindication. Complications of invasive examination were acceptable and remediable. The survival of patients who could not get a pathological diagnosis or molecular examination was significantly worse than pathologically diagnosed patients. These results evoke the implementation of pathological diagnosis, molecular examination and anti-

cancer treatment in very elderly lung cancer patients.

Elderly patients over 70 years account about 40% of lung cancer patients (7). It is widely accepted that elderly patients are accompanied with higher incidence of chronic diseases and survival of elderly lung cancer patients is more dissatisfactory (8). Eberle *et al.* conducted a study covering around one third of the German population and included 132,612 lung cancer patients diagnosed between 2002 and 2010. It was indicated that the 5-year relative survival rate in lung cancer patients over 80 years old was less than half of that in patients below 60 years old (8.4% *vs.* 18.5% in men and 10.6% *vs.* 23.7%) (9). This might be due to worse physical condition, less willing for definite diagnosis, lower therapeutic usage and higher rate of severe adverse events (4,10,11). Our results show that survival of elderly patients with a definite pathological diagnosis is much better than clinically diagnosed patients in advanced stages. Survival analysis also indicates that the OS of clinically diagnosed patients is equal to that of pathologically diagnosed patients treated with BST only. This indicates that clinical diagnosis based on imaging examination and tumor markers is reliable and elderly patients could also benefit from a confirmed diagnosis. It is quite important to take pathological

diagnosis in these elderly patients highly suspected of lung cancer.

Previous studies have partially demonstrated the effectiveness and safety of conventional minimally invasive examinations in elderly lung cancer patients. It is revealed that conventional TBNA (12) and EBUS-TBNA (13) are valuable, safe and well tolerated procedure in patients over 70 years old. A recent study showed that the mean age of complication-present patients was slightly beyond than that of complication-absent patients with no significant statistical difference (69.4 ± 11.5 vs. 66.3 ± 11.9) (14). Despite all this, the rate of pathological diagnosis of lung cancer is relatively lower in elderly patients. Innos and his colleges reviewed the Estonian Cancer Registry data through 1995 to 2008 and founded that only 51.6% lung cancer patients aged between 75 and 84 years old were microscopically verified compared with 86.2% in patients aged below 55 years old (15). Our study indicated that even among inpatients, over 14% patients do not get the pathological diagnosis. Taken outpatients, substrate hospitals and economic conditions in consideration, the average rate of pathological diagnosis should be substantially decreased across China. Patients receiving invasive diagnosis in this present study were common and validated including conventional TBNA, TBLB, EBUS-TBNA, CT-PTNB, closed thoracic drainage, pleural biopsy and superficial lymph node biopsy. The most frequent complication is hemoptysis followed by pneumothorax and dyspnea. Notably, none fatal complications occurred. These results indicated that these minimally invasive examinations were safe in elderly patients. Recent advance in liquid biopsy technologies including circulating tumor cells, nucleic acid and exosome are potent supplementary examinations to conventional invasive examination, especially in advanced lung cancer patients (16). This current study also demonstrates the value of EGFR detection in survival improvement.

Despite the fact that a large proportion of patients with lung cancer are elderly, information remains scant on how best to treat these patients. For early stage elderly patients, SBRT (stereotactic body radiotherapy) and surgery has been regarded as primary therapeutic options. For operably recurrent patients aged over 75 years surgically resection could also achieved satisfactory long-term outcomes (17). It was demonstrated that SBRT is well tolerated and feasible in stage I patients even older than 85 years old (18). Our present study indicated that 24 of 338 patients received surgery with no severe complications. Fifty patients with different stages received radiotherapy which is feasible and

tolerant.

Multiple studies have indicated that elderly patients are less willing to adopt systemic treatment, especially chemotherapy (4,11,19). It was shown that elderly patients older than 65 years old could benefit from adjuvant chemotherapy with increment of 5-year OS varying between 4.1% and 15% (20). For patients over 70 years old with a PS scores of 0–2, platinum-based doublet chemotherapy was associated with survival benefits compared with vinorelbine/gemcitabine monotherapy by a phase III randomised trial (21). Similar results were also found in a high-quality meta-analysis (22). As for anti-angiogenic therapy, a recent secondary analysis of the ECOG 4599 and PointBreak trials demonstrated that patients between 65 and 75 years benefit from the addition of bevacizumab to paclitaxel-carboplatin chemotherapy. However, no benefit was observed in patients aged over 75 years. Target therapeutic in elderly patients were more acceptable because of relatively slighter adverse effects. Besides the first generation of EGFR-TKIs, afatinib was shown to be able to improve OS versus chemotherapy in elderly patients aged 75 years or more with sensitive mutations (23). A phase II study focusing on the treatment of second or third line erlotinib in unselected patients over 75 years old found that even though about one third patients required a dose reduction, erlotinib is still a useful therapeutic option (24). These studies revealed the survival benefit of slightly aggressive systemic treatment with tolerable adverse effects. But in consideration of the actuality that most studies are inclined to exclude patients with major comorbidities, its effect in clinical determination is restricted. This current study also revealed that systemic therapeutics were associated with survival benefit than BST and clinical diagnosis with no anti-cancer treatment. Double agent chemotherapy is tended to be superior to single agent chemotherapy with no statistical difference. EGFR-TKIs were more effective in patients with sensitive mutations with a median OS of 23 months. Unrestricted first line EGFR-TKIs in patients with none EGFR examinations benefit little. Taken the medical products donating projects of different EGFR-TKIs in consideration, neither survival nor economic benefit were obtained. These results indicated the importance of pathological and molecular examination and slightly aggressive treatment in selected elderly patients.

Worth the whistle, older patients are generally clinical trial non-participants although they constitute the majority of advanced lung cancer patients. Sacher reviewed all the 248 phase III trials of systemic therapy for advanced NSCLC between 1980 and 2010 in 2013.

It was demonstrated that 33 of the 100 most cited trials specifically excluded elderly patients in their trial design (age exclusion ranged from >65 to >75 years of age) (25). One main reason for this might be the case that most of these trials were chemotherapy involved. None of the patients included in this study ever participate in any clinical trial. Taking account of the fact that recent trials of new target therapeutic drugs and immunotherapy mostly did not specially exclude elderly patients, sponsor's attitude to elderly patients is getting favourable.

This is a retrospective single-center study and only inpatients were involved. Nevertheless, this is the first study investigating the effect of pathological diagnosis on survival in Chinese elderly patients over 75 years old. Future larger-scaled multicenter trials and prospective studies focusing on elderly patients is needed to verify this.

Taken all together, it was revealed that pathological diagnosis of elderly lung cancer patients over 75 years old is insufficient in China. Pathological diagnosis and aggressive treatment are associated with improved survival. More efforts should be made to encourage elderly patients to accept invasive examination and receive pathological diagnosis. Future well-designed, prospective studies are in need to verify this conclusion.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2018.12.35>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Jingling Hospital's Institutional Review Committee on Human Research (IRB number: 2018NZGKJ-061) and as this is a retrospective study, the informed consent of patients was waived.

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