Limited resection in clinical stage I non-small cell lung cancer patients aged 75 years old or more: a meta-analysis

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Background: This study aims to compare perioperative and oncologic efficacy of limited resection with lobectomy in clinical stage I non-small cell lung cancer (NSCLC) patients \geq 75 years old.

Methods: A systemic search of database including PubMed, OVID and Cochrane was carried out to identify the potential relevant studies published. Data extracted were analyzed with Revman 5.1.

Results: 5,304 citations were identified by the electronically search. A total of 3,461 patients were included, of whom 1,323 received limited resection and 2,139 received lobectomy. There was higher postoperative complication ratio after lobectomy (32.93% *vs.* 23.87%, RR =0.71; 95% CI, 0.54–0.93; P=0.01). There were similar total recurrent (18.56%, RR =1.15; 95% CI, 0.82–1.61; P=0.43), and distant recurrent ratio (16.17%, RR =0.67; 95% CI, 0.43–1.05; P=0.08) between groups. Lower local-regional recurrent ratio (2.40%, RR =4.31; 95% CI, 1.98–9.39; P<0.001) was observed after lobectomy. Compared with lobectomy, patients received limited resection showed poorer overall survival (HR =1.24; 95% CI, 1.07–1.44; P=0.004) and lung cancer specific survival (HR =1.37; 95% CI, 1.14–1.64; P<0.001).

Conclusions: This analysis showed superior lung cancer specific survival, and overall survival after lobectomy over limited resection for clinical stage I NSCLC patients aged \geq 75 years old. Our results confirmed that lobectomy should be considered in aged patients if tolerable.

Keywords: Non-small cell lung cancer (NSCLC); aged; limited resection; lobectomy; prognosis

Submitted Apr 05, 2018. Accepted for publication Jul 31, 2018. doi: 10.21037/atm.2018.08.35 **View this article at:** http://dx.doi.org/10.21037/atm.2018.08.35

Introduction

Lung cancer is the leading cause of cancer-related death around the world (1). With the development of medical management, the number of elderly patients with nonsmall cell lung cancer (NSCLC) is rapidly increasing. As reported, more than 40% of those diagnosed with lung cancer are over 75 years old (2). Patients over 75 years old usually represent a very heterogeneous group. They usually had shorter life expectancy and multiple comorbidities, but presented with different functional performance, nutritional status, and social resources. It is concluded that therapeutic strategy might be different from that of younger patients (3,4).

The best treatment for early stage NSCLC patients is anatomic lobectomy with mediastinal lymph node dissection (5). However, a considerable number of aged patients with early stage NSCLC might be unable to tolerate lobectomy due to their poor cardiopulmonary function and complicated comorbidities. Previous studies have shown complicated results in defining favorable surgical procedure in aged patients (6-13).

Proponents hold the opinion that limited resection should be indicated if the patient had an increased risk of complications as limited resection could provide similar survival rate compared with lobectomy (8-11). The reduction in morbidity and mortality (14) provided by limited resection might benefit the aged given their reduced pulmonary function reserve, associated comorbidities, and higher propensity for surgical complications. While opponents argued that there were poorer survival (12,13) after limited resection when compared with lobectomy.

Given that controversy remained as to whether limited resection could be a reasonable alternative to lobectomy in the treatment of early stage NSCLC for aged patients, and no randomized trials have been published, we conducted this analysis to examine the outcome of morbidity and prognosis after limited resection compared with lobectomy in clinical stage I NSCLC patients aged over 75 years old.

Methods

Search strategy and selection criteria

A systemic search of database including PubMed, OVID and Cochrane (Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, and NHS Economic Evaluation Database) was carried out to identify the potential relevant studies published, with the search terms of 'lung cancer'; 'lung neoplasm'; 'lobectomy'; 'limited resection'; 'sublobectomy'; 'sublobe resection'; 'limited resection'; 'wedge resection'; 'segmentectomy'; 'aged'; 'elderly'; and 'octogenarian'. In this study, only studies compared postoperative outcome of clinical stage I NSCLC patients aged ≥75 years between limited resection and lobectomy were included. Only articles published in English were included. Case reports, review articles, letters, editorials, and expert opinions without original data were excluded. Duplicate publications were excluded if same results were reported. AJCC lung cancer staging 7th edition was used in all studies.

Data extraction and quality control

Titles and abstracts from electronic searches and potential relevant full papers were selected by two reviewers (Z Zhang and H Fang) independently. Studies were enrolled after the full articles have been assessed by two reviewers. Disagreement between the two reviewers was settled by discussing with a third reviewer (D Liu). Newcastle-Ottawa Scale (NOS) (15) criteria was used in assessing the quality and bias of included non-randomized studies. Selection of study groups, comparability of the groups and ascertainment of either the exposure or outcomes of interest were assessed for the quality of each study.

Data including sample size, clinical stage, perioperative morbidity and mortality, total recurrence, distant recurrence, local-regional recurrence, overall survival and lung cancer specific survival in each study were extracted.

Statistical analysis

Data extracted were analyzed with Revman 5.1. Risk ratios (RRs) or hazards ratios (HRs) were used in calculating dichotomous variables. Cochrane's Q and I² statistics were used in heterogeneity analysis. Fixed-effects model was used when there was minor or no heterogeneity between studies (P>0.10, or P≤0.10 but I²≤50%). Otherwise, random-effects model was accepted when heterogeneity existed. Two-tailed P value <0.05 was deemed statistically significant. Funnel plots was used to assess the publication bias.

Results

The results of the systemic search were outlined in Figure 1. 5,304 citations were identified electronically, 3,331 by searching PubMed, 1,692 by searching the OVID, 281 by searching the Cochrane Central Register of Controlled Trials. After review of all titles and abstracts, 19 papers were selected for full text review. Eight studies were excluded as non-clinical stage I NSCLC patients were included, or the inclusion stage criteria was not clarified in the article. Five studies were excluded as younger patients (<75 years old) were included. Finally 6 retrospective studies (8-13) were included. Of included studies, perioperative complications were compared in 3 studies (9-11). Overall survival (OS), lung cancer specific survival (LCSS) and recurrence were compared in 5 (8-12), 2 (12,13), and 3 (9-11) studies respectively. 2 articles (9,12) compared outcome between segmentectomy and lobectomy. 1 article compared outcome between wedge resection and lobectomy (13). Others did not specify surgical procedure of limited resection (8,10,11). A total of 3,461 patients were included, of whom 1,323 patients received limited resection and 2,139 patients received lobectomy. Baseline characteristics of these patients are listed in Table 1.

Three studies (9-11) including 222 limited resections



Figure 1 Flowing chart of enrolled studies.

and 334 lobectomies reported their results of postoperative complications and mortalities. The pooled postoperative complication ratios are 23.87% and 32.93% in limited resection and lobectomy group respectively (risk ratio RR =0.71; 95% CI, 0.54–0.93; P=0.01; I^2 =48%, P=0.15) (*Figure 2*).

The pooled total recurrence ratio, distant recurrence ratio, and local-regional recurrence ratio were 21.17%, 10.81%, and 10.36% respectively in limited resection group (9-11). Similar total recurrence ratio (18.56%, RR =1.15; 95% CI, 0.82–1.61; P=0.43; I²=21%, P=0.28), and distant recurrence ratio (16.17%, RR =0.67; 95% CI, 0.43–1.05; P=0.08; I²=0%, P=0.58) were observed in lobectomy group. Lower local-regional recurrence ratio (2.40%, RR =4.31; 95% CI, 1.98–9.39; P<0.001; I²=32%, P=0.23) were observed in lobectomy group (*Figure 3*).

OS were reported by five studies (8-12) including 1,941 patients, of whom 1,060 received limited resection and 881 received lobectomy. Compared with lobectomy, patients received limited resection got poorer OS (hazard ratio HR =1.24; 95% CI, 1.07–1.44; P=0.004) without significant heterogeneity (P=0.35; I^2 =9%). LCSS were reported by

2 studies (12,13). Pooled results showed poorer LCSS in limited resection group compared with that in lobectomy group (HR =1.37; 95% CI, 1.14–1.64; P<0.001; I^2 =0%, P=0.60) (*Figure 4*).

Three studies (8,10,11) mixed two limited resection procedure (segmentectomy and wedge resection) in their study. Pooled total recurrent ratio, distant recurrent ratio, and local-regional recurrent ratio were 23.61%, 11.11%, and 12.50% respectively in mixed limited resection group. Similar total recurrent ratio (17.54%, RR =1.35; 95% CI, 0.90–2.03; P=0.15; I²=0%, P=0.41), and distant recurrent ratio (15.79%, RR =0.71; 95% CI, 0.41–1.23; P=0.22; I²=0%, P=0.32) were observed in lobectomy group without heterogeneity. Lower local-regional recurrent ratio (19.30%, RR =7.19; 95% CI, 2.48–20.88; P<0.001; I²=0%, P=0.82) was observed in lobectomy group. And similar OS was shown between groups (HR =1.22; 95% CI, 0.91–1.62; P =0.18; I²=0%, P=0.85) (*Figures 5,6*).

Two studies compared outcome between segmentectomy and lobectomy (9,12). One compared perioperative complications, recurrence, and survival results between groups (9), and OS and LCSS were compared in the other study (12). In Kilic and colleagues' study (9), 78 stage I NSCLC aged patients received segmentectomy, 106 received lobectomy. Compared with lobectomy, there was fewer complications (11.5% vs. 25.5%, P=0.02), similar 5-vear disease-free survival (49.8% vs. 45.5%, P=0.80) and OS (46% vs. 47%, P=0.28) in segmentectomy group. In Zhang and colleagues' study (12), patients treated with segmentectomy had significantly poorer OS (HR =1.239, 95% CI, 1.093-1.405, P=0.001) and LCSS (HR =1.308, 95% CI, 1.094-1.563, P=0.003). After pooled the OS outcome, poorer OS was shown in limited resection group when compared with that in lobectomy group (HR =1.25; 95% CI, 1.06–1.49; P=0.01; I²=75%, P=0.04) (Figure 7).

Funnel plots did not show any publication bias based on the data of morbidity, recurrence, and overall survival (*Figure 8*).

Discussion

In this article, we focused on perioperative and longterm efficacy of limited resection in aged patients over 75 years old. As the outcome demonstrated, though less perioperative complications occurred after limited resection, inferior local-regional recurrence, OS and LCSS were shown after limited resection.

Lung cancer is the leading cause of cancer-related death

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Table 1 Enrolled studies in this meta-analysis

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Study	Enrolled year	Inclusion criteria	Sample size		Surgical procedure	Populto
			Lobectomy	Limited resection group	Surgical procedure	nesuits
Okami [2009] (15), JPN	1999	cl NSCLC >80 y	245	122	Wedge resection + segmentectomy; lobectomy	Overall survival
Kilic [2009] (16), USA	2002–2007	cl NSCLC >75 y	106	78	Segmentectomy; lobectomy	Complications; recurrence; overall survival
Okami [2010] (17), JPN	2001–2007	cIA NSCLC >75 y	79	54	Wedge resection + segmentectomy; lobectomy	Complications; recurrence; overall survival
Fiorelli [2016] (18), ITA	2006–2012	cl NSCLC >75 y	149	90	Wedge resection + segmentectomy; lobectomy	Complications; recurrence; overall survival
Zhang [2016] (19), USA	1988–2012	cIA NSCLC ≥75 y	509	509	Segmentectomy; lobectomy	Overall survival; lung cancer specific survival
Razi [2016] (20), USA	1998–2007	cIA NSCLC ≥75 y	1,051	470	Wedge resection; lobectomy	Lung cancer specific survival

NSCLC, non-small cell lung cancer.



Figure 2 Postoperative complications comparison between limited resection and lobectomy in aged patients.

in aged patients. More than 40% of pathological diagnosed lung cancer are over 75 years old (2). The intrinsic feature of aged patients such as higher incidence of comorbidities, impaired cardiopulmonary function and limited life expectancy (16,17) have occluded many of them from lung surgery though pulmonary resection remained to be the best treatment for aged patients with early stage NSCLC.

Some studies (18,19) have shown that lung cancer surgery might result in poor survival outcome in aged patients. After analyzing 12,439 postsurgical lung cancer patients, Romano and colleagues (18) found that the risk of death in patients aged over 79 years old was three times higher than that of younger patients. Similar outcomes have been demonstrated by the ITACARE working group (19).

Anderson and colleagues' study has shown that

though people in their 80 s have a 50% chance of living 5 more years, an average life expectancy of 1.5-year old could be observed in patients with untreated early-stage NSCLC (20). With the development of perioperative management, minimally invasive surgery and fast recovery, significant reduction in perioperative mortality, morbidity and improved long-term survival rates have been achieved. Recently published studies have shown excellent short and long-term outcome after pulmonary resection in aged patients (9-13). Furthermore, though aged patients undergoing lung resection have higher incidence of morbidity and mortality compared (2), the inferiority might be offset by the lower recurrence ratio (21).

As demonstrated by Lung Cancer Study Group in 1995, three times higher cancer recurrence ratio was

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Study or Subaroup

Kilic 2009

Okami 2010

Fiorelli 2016

limited resection

13

13

21

Total

78

54

90

Events

lobectomy

22 106 37.7%

11 79 18.1%

29

149

44.2%



Risk Ratio

0.80 [0.43, 1.49]

1.73 [0.84, 3.57]

1.20 (0.73, 1.97)

Figure 3 Recurrence ratio comparison between limited resection and lobectomy in aged patients.



Figure 4 Survival comparison between limited resection and lobectomy in aged patients.

observed after limited resection, lobectomy with lymph node dissection was the standard surgical procedure for early stage lung cancer (5). However, the elderly subgroup patients were not further analyzed in this randomized clinical trial.

As published evidence showed an improved postoperative morbidity and mortality (22), and preservation of pulmonary function (23) after limited resection, surgical procedure (limited resection or lobectomy) should be carefully selected to balance the risk of postoperative morbidity and mortality against the risk of cancer related survival. These safety and functional benefit in postoperative morbidity, mortality and pulmonary preservation after limited resection have been verified in our study. After analyzing 222 limited resection and 334 lobectomies in aged patients, significant lower postoperative morbidity and mortality after limited resection was found when compared with lobectomy. The intrinsic features of having preexisting comorbidities, and impaired pulmonary function of aged patients should be an explanation of the lower postoperative complication in limited resection group.

Recently, Yang and colleagues published a protocol of randomized controlled multicenter non-inferiority trial which compared the long term and short-term outcome



Figure 5 Recurrence ratio comparison between mixed subgroup (segmentectomy and wedge resection) and lobectomy in aged patients.



Figure 6 Survival comparison between mixed subgroup (segmentectomy and wedge resection) and lobectomy in aged patients.







Figure 8 (A) Funnel plot of perioperative complications; (B) funnel plot of total recurrence rate; (C) funnel plot of overall survival.

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including DFS, OS, morbidity and mortality for elderly patients (\geq 70 years) with early-stage NSCLC (24). This is the first trial tried to find out which procedure (limited resection or lobectomy) should be preferred in aged patients.

The oncologic efficacy of limited resection for aged patients have been debated by decades. Proponents of limited resection hold the opinion that the recurrence and survival difference between patients who have undergone lobectomy and limited resection might vanish in aged patients. Reported evidence have shown that the survival benefit offered by lobectomy over limited resection has gradually decreased over the past 2 decades (6). Another large retrospective study (25) comparing long term outcome after limited resection and lobectomy in 1,272 stage I NSCLC showed comparable 5-year cancer specific survival between groups (92.4% vs. 85.7%, P=0.77). Several other retrospective studies with relatively small numbers also suggested similar survival outcome following limited resection compared with lobectomy (26).

Different outcomes have been reported by several other studies (12,13,27,28). After analyzing a total of 1018 patients, an OS (HR =1.343, 95% CI, 1.117–1.613, P=0.002) and LCSS (HR =1.443, 95% CI, 1.106–1.884, P=0.007) benefit of lobectomy over limited resection (segmentectomy only) were observed after propensity score matching (12). Another study (13) showed that after long term follow up (43 months in limited resection group *vs.* 60 months in lobectomy group), improved five-year LCSS was observed in lobectomy group when compared with that in limited resection group (64.5% *vs.* 42.7%, P<0.05). Several other studies (27,28) also confirmed these inferior survival outcomes after limited resection.

Our results analyzed recurrence ratio, OS and LCSS difference between limited resection and lobectomy groups and confirmed the survival benefit after lobectomy over limited resection. Though similar total and distant recurrence ratio could be observed between groups, there were higher local-regional recurrence ratio (10.36% vs. 2.40%, RR =4.31, P<0.001), poorer OS (HR =1.24, P=0.004) and LCSS (HR =1.37, P<0.001) in limited resection group. The possible explanation of this recurrence and survival difference could be that complete excision of all regional draining lymphatics is not possible during limited resection. As reported, only 36.2% of the patients during wedge resection had lymph nodes sampled, as compared with 92.8% received lymph nodes sampled during lobectomy (13). Also much more satisfied tumor free margin after lobectomy would be another explanation.

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There are several limitations that need to be acknowledged in this study. Retrospective nature which subjects it to the possible selection bias associated with surgical procedure chosen is the major limitation of this analysis. The oncologic efficacy of limited resection in this specific cohort of patients needs to be assessed in prospective, randomized study. Another limitation is that most of included studies amalgamate wedge resection and segmentectomy together, though we performed subgroup analysis between segmentectomy and lobectomy, only two studies could be analyzed. As a result, the robustness of our results could be influenced. Furthermore, data regarding radiological features such as ground glass opacity that represent minimally invasive nature of lung cancer are unavailable among all studies. It might be possible that different outcome could be shown with only pure ground glass nodules being included.

After pooled analysis of six studies, this analysis showed better LCSS, and OS after lobectomy in comparison with limited resection for patients with clinical stage I NSCLC patients aged over 75 years, though perioperative morbidity were higher in lobectomy group. These results confirm that lobectomy should be considered if tolerable in aged patients. These outcomes should be verified in randomized prospective studies.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This is a metaanalysis of retrospective study, the ethical statement was waived.

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Cite this article as: Zhang Z, Feng H, Xiao F, Liu D. Limited resection in clinical stage I non-small cell lung cancer patients aged 75 years old or more: a meta-analysis. Ann Transl Med 2018;6(18):359. doi: 10.21037/atm.2018.08.35