Appropriate Selection of Segmentectomy for Patients with Early Stage Non-small Cell Lung Cancer

* Juntang Guo¹, Xiaodong Tian¹, Chaoyang Liang¹

¹Department of thoracic surgery, Chinese PLA General Hospital, Beijing, China

ABSTRACT

Several randomized-control trials of lung cancer screening, including USA National Lung Cancer Screening Trial (NLST) and Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON), have explored the value of low-dose CT in detection of lung cancer and found an increase in the detection of early stage lung cancer. Segmentectomy with systemic lymph node dissection rather than wedge resection was preferred for patients with stage IA Non-small cell lung cancer (NSCLC) when there was a choice of sublobar resection because it is an anatomic resection and provides a lymph node profile. Previously, most studies described segmentectomy as having an equal recurrence-free survival and overall survival in less or noninvasiveness lung cancer with a predominantly ground-glass (non-solid) appearance on CT imaging. Recent evidence suggests that segmentectomy may offer survival outcomes approaching that of lobectomy for lung cancer patients with small solid predominant nodules. Nevertheless, the evidence is currently still limited. We propose that segmentectomy in a solid predominant appearance lung cancer on CT scan should be chosen with stricter indications such as a smaller solid size (≤ 1.7 cm), air bronchogram, and lower SUVmax (≤ 2.5). Large randomized trials are currently in progress to define the clinical role of segmentectomy, and results are eagerly anticipated.
INTRODUCTION

The recent development of computed tomography (CT) for the screening of lung cancer has made it possible to detect small lung nodules [1, 2]. The proportion of early stage non-small cell lung cancer (NSCLC) encountered in clinical practice has increased dramatically. Currently, most thoracic surgeons believe that a lobectomy still offers a better chance of curing lung cancer than any form of sublobar resection, including segmentectomy and wedge resection. This consensus, however, is gradually evolving.

Sublobar resection has gradually become a standard treatment for small-sized lung cancers with a wide area of ground-grass nodules (GGN) on CT scan because they are pathologically less invasive [3-5]. Some reports indicate that segmentectomy can achieve an equal oncologic outcome with lobectomy in nodules with a solid appearance on CT scan [6-8]. There is still considerable debate regarding an appropriate strategy for small size solid-dominant nodules. Several ongoing clinical trials will help in settling the debate.

The aim of this article was to examine some of the evidence for sublobar resection for early stage NSCLC. A review was done to compare segmentectomy with wedge resection. We also focused on features and strategy of choice for segmentectomy in early stage NSCLC.

1. Changes and tendency of stage composition in lung cancer

Lung cancer is a leading cause of death worldwide. Advances in surgical, radiotherapeutic, chemotherapeutic, targeted therapeutic and immunotherapeutic approaches have been made, but the long-term survival rate remains low [9]. In the past decade, high resolution CT and PET-CT have been implemented in diagnosis of lung cancer, which proceed the early detection and accurate staging of lung cancer [1, 10]. There has been a dramatic increase in solitary pulmonary nodules, including ground glass opacity, found upon medical examination. Thus, the proportion of early stage operable lung cancer has increased in thoracic clinical practice. Lung cancer CT screening and increased public awareness of lung cancer have also contributed to this favorable situation.

Several randomized controlled trials of lung cancer screening in Europe and the USA have explored the value of low-dose CT in detection of lung cancer at an early stage [11]. The first landmark study was the USA National Lung Cancer Screening Trial (NLST) [11]. NLST showed a relative reduction in lung cancer mortality of 20% with low-dose CT compared with chest radiography. In NLST, the proportion of stage I was 63%.

The largest trial in Europe is the Dutch–Belgian NELSON trial [10], which first applied semi-automated, volumetric nodule assessment of nodules and may provide important information about optimal radiology, nodule management, screen interval. The NELSON trial will report on mortality within this year.

In the NELSON trial, most lung cancers were also diagnosed at stage I. The adoption of widespread computed tomographic screening for lung cancer brought up not only stage composition changes, but also more elderly patients with comorbid illnesses, such as chronic obstructive pulmonary disease and coronary disease. Surgical intervention should be considered while balancing between surgical risk and therapeutic efficacy in an elderly population. Therefore, it is necessary to determine what factors result in an optimal surgical choice in early lung cancer.
2. Debates on sublobar resection

Open lobectomy has been the standard operation for lung cancer resection since the widespread acceptance of the 1995 Lung Cancer Study Group (LCSG) randomized study comparing open lobectomy with more limited pulmonary resection in stage I non–small-cell lung cancer (NSCLC; T1N0) [12]. This landmark trial by Ginsberg et al. demonstrated a 30% increase in mortality in the sublobar group and a statistically higher loco-regional recurrence in the limited resection group. However, this clinical trial had some limitations when viewed from current available technology and perspectives.

Firstly, the preoperative staging evaluation was based on chest roentgenogram and serum chemistry analysis. As such, some metastasis may have been underestimated. In the meantime, high-resolution CT and PET-CT have become basic tools for contemporary lung cancer staging evaluation. Secondly, outcomes were not performed with a stratified analysis by size and density of tumor. In the trial, the proportion of wedge resection was about one-third of limited resection and there was no description about the strategy for making a decision on the type of resection.

In the past decade, the number of patients presenting with very small and peripheral lung cancers has gradually increased. An increasing number of thoracic surgical leaders have reinitiated discussion about the relative merits of sublobar resection in early stage lung cancers. There are currently many vigorous debates on this topic around world.

A sublobar resection includes wedge resection and segmentectomy. A wedge resection is the removal of the part of the lung that contains lesions regardless of anatomic boundaries. However, segmentectomy implies the removal of an anatomic unit and usually includes a more extensive lymph node dissection. Segmentectomy meets the principles of surgical oncology better than wedge resection, although some studies have suggested that the two procedures have comparable oncologic outcomes for carefully staged cT1N0-NSCLC patients [13].

Smith C. et al. [5] reviewed data from the SEER registry to assess whether survival of stage IA patients treated with segmentectomy is better than for patients undergoing wedge resection. After adjusting for propensity scores, analyses showed that segmentectomy was associated with a significant improvement in overall survival (hazard ratio: 0.80, 95% confidence interval: 0.69–0.93) and lung cancer-specific survival (hazard ratio: 0.72, 95% confidence interval: 0.59–0.88) compared with wedge resection. Tamura M. et al. [14] reported that segmentectomy had a statistically better recurrence-free survival compared with wedge resection (p=0.028). Earlier reports, such as by Sienel W. [15] and El-sherif A. [16] also published similar outcomes. Therefore, most authors proposed that segmentectomy with lymphadenectomy is preferred for patients with stage IA NSCLC in cases with a choice of sublobar resection.

However, it is still up to debate whether the oncologic outcome of segmentectomy is equivalent to standard lobectomy in stage IA lung cancer. Currently, there are three multicenter, prospective, randomized studies focused on this topic (Cancer and Leukemia Group B 140503 [17], Japanese Clinical Oncology Group 0802/West Japan Oncology Group 4607L [18], The Surgical Treatment of Elderly Patients with Early Stage Non-small Cell Lung Cancer (STEPS) Study [19]). Data from these studies have not yet been published.

Among the three RCT clinical trials, JCOG0802/WJOG4607L was designed to evaluate overall survival of segmentectomy (and including wedge resection) compared with lobectomy in patients with small-sized (diameter < 2 cm) peripheral non-small cell lung cancer. These findings will help to define the role of segmentectomy in the treatment of NSCLC patients [18].
While these prospective studies are ongoing, many retrospective studies have compared the results of lobectomy and segmentectomy. Zhang L. \cite{20} conducted a meta-analysis that identified 31 comparative studies on this topic. The analysis showed that in the stage I subgroup, patients treated with segmentectomy had a risk of recurrence 1.24 times greater than those treated with lobectomy (HR, 1.24, 95% CI 1.07 to 1.44; \(p=0.005\)). However, no significant difference was found between segmentectomy and lobectomy groups in the subgroup of patients with stage IA (HR, 1.09, 95% CI 0.86 to 1.38; \(p=0.482\)).

There are also two representative studies. Tsutani Y. et al. \cite{21} reported that recurrence-free survival (RFS) and overall survival (OS) were not significantly different between patients undergoing lobectomy and segmentectomy in a multicenter study of 481 patients with clinical stage IA lung adenocarcinoma. In propensity score-matched pairs, RFS and OS were similar between patients undergoing lobectomy and segmentectomy. Landreneau R. J. et al. \cite{22} used matched segmentectomy and lobectomy cohorts (\(n=312\) patients per group) to compare outcomes after surgeries for stage I non–small-cell lung cancer. The results showed no differences in locoregional, distant, or overall recurrence rates.

Some studies had different outcomes. Okada M. \cite{23} compared the outcomes of segmentectomy (\(n=155\)) and lobectomy (\(n=479\)) in 634 consecutive patients with clinical stage IA lung adenocarcinoma and in propensity score-matched pairs. The results showed that three-year recurrence-free survival (RFS) was significantly higher after segmentectomy compared to lobectomy (92.7% vs. 86.9%, \(P=0.0394\)), whereas three-year overall survival did not significantly differ (95.7% vs. 94.1%, \(P=0.162\)). But in 100 propensity score-matched pairs with variables adjusted for age, gender, tumor size, SUVmax, tumor location, three-year RFS (90.2% vs. 91.5%) and OS (94.8% vs. 93.3%) after segmentectomy and lobectomy, respectively, were comparable. Table 1 shows the characteristics and results of the main retrospective studies in the past decade evaluating segmentectomy versus lobectomy in NSCLC patients.
Table 1. Main Characteristics and Results of Retrospective Studies in the Past Decade Evaluating Segmentectomy versus Lobectomy on Recurrence and Survival in NSCLC Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Extent of resection</th>
<th>Tumor Stage</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dai C et al(24)</td>
<td>2016</td>
<td>China(SEER)</td>
<td>4240</td>
<td>Stage IA (size ≤ 2 cm)</td>
<td>Lobectomy was superior to segmentectomy for both NSCLC ≤1 cm and &gt; 1 to 2 cm OS or cancer-specific survival</td>
</tr>
<tr>
<td>Razi s et al(25)</td>
<td>2015</td>
<td>USA (SEER)</td>
<td>119</td>
<td>Stage IA (aged 75 y)</td>
<td>No significant difference was found in 5-y cancer-specific survival for patients who underwent segmentectomy and lobectomy</td>
</tr>
<tr>
<td>Okada M et al(26)</td>
<td>2014</td>
<td>Japan</td>
<td>155</td>
<td>Stage IA</td>
<td>Recurrence-free survival (RFS) was significantly higher after segmentectomy compared to lobectomy, whereas three-year overall survival did not</td>
</tr>
<tr>
<td>Landreneau R J et al(23)</td>
<td>2014</td>
<td>USA</td>
<td>312</td>
<td>Stage I</td>
<td>There were no differences in locoregional, distant or overall recurrence rates between two groups.</td>
</tr>
<tr>
<td>Tsutani et al(27)</td>
<td>2013</td>
<td>Japan</td>
<td>98</td>
<td>Stage IA</td>
<td>RFS and OS of segmentectomy were similar with those of standard lobectomy</td>
</tr>
<tr>
<td>Yamashita et al(28)</td>
<td>2012</td>
<td>Japan</td>
<td>90</td>
<td>Stage IA</td>
<td>Morbidity and mortality were not significantly different Between groups</td>
</tr>
<tr>
<td>Schuchert et al(29)</td>
<td>2012</td>
<td>USA</td>
<td>325</td>
<td>Stage IA</td>
<td>No difference in recurrence rates or 5-year freedom from recurrence estimates</td>
</tr>
<tr>
<td>Carr et al(30)</td>
<td>2012</td>
<td>USA</td>
<td>121</td>
<td>Stage IA</td>
<td>Anatomic Segmentectomy may achieve equivalent recurrence and survival compared with lobectomy for stage 1A</td>
</tr>
<tr>
<td>Whitson et al(31)</td>
<td>2011</td>
<td>USA (SEER)</td>
<td>581</td>
<td>Stage I</td>
<td>Lobectomy conferred superior overall and cancer-specific survival compared with segmentectomy</td>
</tr>
<tr>
<td>Klic et al(32)</td>
<td>2009</td>
<td>USA</td>
<td>78</td>
<td>Stage I</td>
<td>Comparable oncologic efficacy compared with lobectomy in older patients</td>
</tr>
<tr>
<td>Yamato et al(33)</td>
<td>2008</td>
<td>Japan</td>
<td>153</td>
<td>Stage IA(T1N0M0)</td>
<td>There was no significant difference in the survival rates between two groups</td>
</tr>
</tbody>
</table>
3. Consideration of choice for segmentectomy in early stage NSCLC

Segmentectomy can be categorized as two types according to a positive or passive choice, and intentional and compromised segmentectomy. For patients who have poor pulmonary function or significant comorbidities, selecting segmentectomy for fewer perioperative complications was defined as a compromised selection. For patients that can tolerate a lobectomy procedure, intentional segmentectomy may be associated with increased lung preservation and function, and facilitate potential future resections. We considered rational intentional segmentectomy as our topic of interest.

In the Version 5, the 2017 NCCN guideline for NSCLC \[34\], sublobar resection was a recommendation to select patients, including those with peripheral nodules less than 2 cm, with at least the following: pure AIS histology, nodule has ≥ 50% ground-glass appearance on CT, and radiologic surveillance confirms a long doubling time (≥ 400 days). Nevertheless, preoperative pathology is difficult for subcentimeter nodules. To avoid tumor dissemination, fine-needle aspiration is not routine for a classic tumor on radiology.

With a new classification of adenocarcinoma, malignant nodules presenting as GGO are regarded as low-grade malignancies with three subtypes: adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) or lepidic adenocarcinoma \[35\]. Even some GGO nodules with non-lepidic growth patterns of adenocarcinoma, such as acinar and papillary, have excellent prognosis (100% 3-year RFS) \[36\].

A general consensus has not formed on the optimal method to evaluate the extent of GGO. The C/T (consolidation/tumor) ratio has usually been adopted as a clinically safe criteria to identify noninvasive cancers because of its high specificity \[37\]. Suzuki K. et al. \[38\] evaluated pathological noninvasiveness by radiological findings in peripheral clinical lung cancer from the Japan Clinical Oncology Group 0201. They found that a pathological noninvasive cancer can be predicted by a C/T ratio with a cutoff value of 0.25 and a specificity of 98.7%. In the same trial, these criteria were evaluated from the prognostic viewpoints by Asamura H. and his colleagues \[37\]. The radiologic criteria of a C/T ratio 0.25 or less in cT1a (≤ 2.0 cm) and 0.50 in cT1a-b (≤ 3.0 cm) were both able to define a homogeneous group of patients with an excellent prognosis. Okada M. et al. \[39\] examined the malignant biological behavior of clinical stage IA adenocarcinoma using high-resolution CT, and PET-CT. Analyses identified an optimal cutoff value of 2.5 for maximum standardized uptake values, and 20% for ground-glass opacity ratio to predict high-grade malignancy.

Radiologically pure-solid lung cancers exhibit more malignant behavior and are associated with a poorer prognosis than part-solid lung cancers, despite the small size of the tumor \[40-43\]. These cohorts have a dismal prognosis with pathological nodal involvement in approximately 20% of cases and even in clinical stage IA diseases. Therefore, any decision on limited surgical resection should be made cautiously for pure-solid lung cancers.

Are all pure-solid early lung cancers unfavorable for segmentectomy? In the past several years, several authors further explored this question. Koike T. et al. \[8\] retrospectively reviewed 251 patients with radiologically pure solid cT1a N0 M0 NSCLC who underwent lobectomy or segmentectomy. In the propensity score matched lobectomy and segmentectomy groups, there were no significant differences between the two groups in OS or DFS. Similar outcomes were also observed in other retrospective studies \[6-8, 27, 44, 45\]. In summary, segmentectomy has similar oncologic outcomes with lobectomy among patients with radiologically pure solid small-sized (≤ 2.0 cm) NSCLC. However, these findings should be confirmed in prospective studies.

Currently, it is important to employ strict selection in segmentectomy for solid early stage lung cancer before it becomes a standard procedure \[43\]. Some preoperative characteristics may inform the decision, such as
consolidation size, and SUVmax level. Furthermore, Hattori A. et al. [46] noticed that the presence of air bronchogram in the tumor [47], maximum tumor dimension, and SUVmax level (the optimal cutoff value was 3.2) were significant clinical factors predictive of non-invasive pure-solid lung cancer. They presented these three factors as significant favorable predictors of pathological non-invasive status, and patients with these clinical predictors could be candidates for sublobar resection for clinical stage IA pure-solid lung cancers. Moon Y. et al. [48] analyzed risk factors for recurrence after sublobar resection in solid-predominant small lung cancer (≤2.0 cm) compared to GGO-predominant cases. Their results indicated that high SUVmax and histologic types other than adenocarcinoma were significant risk factors for recurrence.

We suggest that intentional segmentectomy with systematic mediastinal lymph node dissection may become the standard treatment for clinical T1a-bN0M0 NSCLC according to the eighth edition of the TNM classification [49], especially when the C/T ≤ 0.5 or SUVmax ≤ 3.2. Segmentectomy in pure-solid appearance lung cancer on CT scan should be considered with strict indications such as a smaller solid size (≤ 1.7 cm), air bronchogram and lower SUVmax (≤ 2.5).

In conclusion, currently, there is no clear evidence from prospective, multicenter, randomized clinical trials with a larger number of patients to indicate a recommendation for minimal surgical treatment and it is necessary to wait for such results.

**DECLARATION OF CONFLICTING INTEREST**

The authors have no conflicts of interest (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript.

**FUNDING**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit organization.
REFERENCES


34. https://www.nccn.org/


