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Kwon Joong Na, MD, Young Tae Kim, MD, PhD

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Optimal resection strategies for small-size lung cancer: Is a wedge enough? Is lobectomy too much?

Kwon Joong Na, MD¹; Young Tae Kim, MD, PhD¹

¹Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

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Correspondence and Reprint requests:
Young Tae Kim, MD, PhD
Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital
101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea
Tel: +82-2-2072-3161
Fax: +82-2-764-3664
E-mail: ytkim@snu.ac.kr

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Glossary of abbreviations

- CT, Computed Tomography
- CTR, Consolidation to tumor ratio
- FEV₁, Forced Expiratory Volume in one second
- IASLC, International Association for the Study of Lung Cancer
- JCOG, Japanese Clinical Oncology Group
- NCCN, National Comprehensive Cancer Network
- STAS, Spread Through Air Spaces
Identifying ideal candidate for sublobar resection for early-stage lung cancer is critical.
Central message

The good long-term results of sublobar resection in early-stage lung cancer have led to a discussion on how to identify the right patients beyond radiologic parameters.

Perspective statement

Recent trials have shown favorable long-term outcomes of sublobar resection in early-stage lung cancer, and patient selection has become a critical issue. The size of the solid portion on CT is an important factor; however, other factors affecting locoregional recurrence are also of great concerns. Therefore, a comprehensive method for identifying candidates for sublobar resection must be developed.

Keywords

Lung cancer; Sublobar resection; locoregional recurrence
Abstract

Recently published large multi-center prospective clinical trials have demonstrated that sublobar resection is non-inferior to the traditional treatment of choice, lobectomy, for peripherally-located early stage lung cancer. Most clinical trials and several retrospective studies to date have used the consolidation to tumor ratio to define the indication for sublobar resection, as it is well known that the size of the solid portion seen on high resolution computed tomography is highly correlated with pathologic invasiveness. However, it is difficult to accurately predict pathologic features that may increase the risk of locoregional recurrence, such as specific adenocarcinoma subtypes or spread through air spaces, based on imaging characteristics alone, and the location of the nodule should also be considered as one of the important factors to obtain an adequate parenchymal resection margin. In this article, we summarized the results of the most recently published clinical trials related to sublobar resection and discuss various factors that should be considered for optimal candidate selection for sublobar resection.

Introduction

Since the Lung Cancer Screening Trial first demonstrated the clinical utility of lung cancer screening with computed tomography (CT), the increased use of low-dose CT has resulted in a higher detection rate of early-stage lung cancer.\(^1,2\) In particular, the proportion of lung nodules found in the form of pure or subsolid ground-glass nodules, which are known to have a high probability of lung cancer, has increased.\(^3\) In this context, the management of these ground-glass nodules has become a major concern for lung cancer physicians related to lung cancer. Notably, the Fleischner Society provides guidelines for a follow-up schedule for pulmonary nodules based on the risk of lung cancer, as well as the size and characteristics of
the nodule. The National Comprehensive Cancer Network (NCCN) guidelines also recommend defining the follow-up schedule and timing of intervention based on the overall nodule size and the size of the solid portion.

Surgical resection is one of the most commonly considered treatment options for small-sized pulmonary nodules that are strongly suggestive of lung cancer, or are histologically confirmed early-stage lung cancer. According to the NCCN guidelines, anatomical pulmonary resection is recommended, while sublobar resection, segmentectomy, and wedge resection may be recommended in highly selected patients meeting strict criteria. Particularly, sublobar resection is recommended for peripherally located early-stage lung cancer, when a sufficient margin-to-tumor ratio can be obtained, and the extent of resection should be determined by radiologic findings. In various clinical studies investigating the role of wedge resection or segmentectomy in early-stage lung cancer published in the last decade, have defined the extent of resection mostly based on radiologic findings, particularly the size of the entire nodule and the size of the solid portion, which is regarded as an indicator of invasiveness. Accumulating evidence supports the use of wedge resection as a more stringent criterion than segmentectomy, and indicates that this technique should be reserved for patients with a smaller overall size or solid portion size.

Several recently published randomized clinical trials have reported the long-term outcomes of sublobar resection, including wedge resection, in peripherally located early-stage lung cancer, with majority demonstrating non-inferior long-term overall survival and recurrence-free survival in comparison to lobectomy. Despite the fact that these studies have defined the indications for wedge resection based on the radiologic characteristics and nodule size, the appropriateness of performing wedge resection based on these criteria remains controversial. This is due to the fact the pathologic characteristic has a significant impact on
patient clinical outcomes, particularly in case of locoregional recurrence, whereas radiologic characteristics are not completely representative of pathologic details. This article aimed to review the current state of knowledge and considerable perioperative factors regarding resection strategies for small ground-glass nodules.

Wedge resection in peripherally located early-stage lung cancer: Is there a common indication?

The standard of care for surgical resection of early-stage lung cancer is lobectomy. A randomized controlled trial published in 1995 showed that sublobar resection in peripherally early-stage lung cancer had higher recurrence rate and a higher rate of locoregional recurrence rates than lobectomy. Subsequent retrospective studies have demonstrated similar results; therefore, anatomic lobectomy has remained the surgical treatment of choice for patients with early-stage lung cancer with adequate physiologic reserve. However, as dramatic advances in imaging technology have led to higher diagnosis rates for small-sized peripheral lung cancer, and the advantages of sublobar resection in terms of lung function preservation have been recognized, many lung cancer physicians have explored the role of sublobar resection in early-stage lung cancer. Specifically, in terms of lung function preservation, several retrospective studies have shown that wedge resection preserves lung function to a similar degree as mediastinal surgery without lung resection. In addition to wedge resection, segmentectomy has also been shown to preserve lung function compared to lobectomy, but the Japanese Clinical Oncology Group (JCOG) 0802 trial reported a smaller difference in forced expiratory volume in one second (FEV1) than was anticipated. Most recently, a randomized controlled trial by Altorki et al. comparing sublobar resection to lobectomy in peripherally located early-stage lung cancer (solid portion under 2 cm), in which 59.1% of patients had undergone wedge...
resection, showed non-inferiority in long-term survival or recurrence. The JCOG has conducted various studies to determine the role of sublobar resection by categorizing tumors based on their invasiveness, which is determined by the total tumor size and the consolidation-to-tumor ratio (CTR). Among them, the JCOG0804 study was a nonrandomized confirmatory phase III study that confirmed the efficacy and safety of sublobar resection (77.5% wedge resections). This study also demonstrated that wedge resection with adequate surgical margin ensured sufficient local control and relapse-free survival. Although many studies have reported adequate long-term outcomes of wedge resection for peripherally located small lung cancers, consistent criteria for wedge resection are still lacking. In addition, majority of studies have proposed criteria based on the location and radiologic characteristics of the pulmonary nodule, which may not accurately reflect the biology of the tumor.

Radiologic invasive ground glass nodules show a good correlation with pathologic invasiveness, but remain an imperfect parameter

As imaging technology has advances, researchers have recognized that the features of ground-glass nodules seen on high-resolution computed tomography correlate well with pathologic invasiveness. Studies have shown that persistent pure ground-glass nodules are more likely to be adenomatous hyperplasia, adenocarcinoma in situ, or invasive adenocarcinoma, while the size of the invasive component is related to the prognosis of lung adenocarcinoma. Based on these findings, the JCOG defined radiologically early peripheral lung adenocarcinoma in the JCOG0201 study as a tumor with a maximal tumor size of 20 mm or less, and a CTR of 0.25 or less, i.e., a solid component visible on CT of 5 mm or less. In addition, various studies have been conducted on sublobar resection based on the size of the invasive component using tumor size and CTR as the two axes. The importance of the solid
portion as an invasive component is also reflected in the new T descriptor for lung cancer suggested by the International Association for the Study of Lung Cancer (IASLC).\(^{17}\)

Despite the fact that the size of the solid component of a ground-glass nodule is highly correlated with its pathological invasiveness, determining the surgical extent merely based on imaging findings is fraught with pitfalls. First, there may be a size discrepancy between the radiologically measured solid portion and the pathologically invasive component. In addition, the IASLC proposal clarifies that the clinical T stage and pathologic T stage may differ, as measured by the invasive portion visible on CT.\(^{17}\) Second, on the basis of CT findings alone, it is challenging to predict all pathologic findings that are known to be related to the high risk of loco-regional recurrence or pathologic upstaging.

Can intraoperative frozen section diagnosis help determine proper surgical extent?

Intraoperative frozen section diagnosis can provide additional information about pathological characteristics that cannot be assessed using radiological findings alone. Cryosection has a few limitations due to the fact that it causes severe architectural distortion; however, recently published studies indicated various results on the utility of intraoperative pathologic feature assessment. As the size of the invasive component size is one of the most significant factors in determining the extent of surgery, a number of methods have been proposed to precisely measure its size using frozen section diagnosis. Xu et al. reported that the inflation method with diluted embedding medium injection allowed the preservation of open air spaces and normal parenchymal architectures, thereby increasing the accuracy of measuring invasive foci.\(^{18}\) In addition, frozen section diagnosis could aid in detection of pathologic findings that may affect patient outcomes. Histologic subtypes of adenocarcinoma and pathologic findings, such as spread through air spaces (STAS), can also be confirmed by
frozen section diagnosis.\textsuperscript{19,20} However, in the clinical implementation of determining surgical extent based on frozen section diagnosis, there are several factors to consider. Methods for assessing the size of the invasive component, STAS, and histologic subtype through frozen section diagnosis are inevitably time consuming, resulting in significant delays in operation time. In addition, the assessment of STAS and histologic subtypes lacks accuracy, and the inter-observer variability is high; therefore, it is challenging to apply and may not be reliable as a general assessment method.\textsuperscript{19,20}

\textit{Other factors associated with local recurrence and may affect surgical extent}

In addition to the size of the invasive component, various other factors can affect locoregional recurrence. The prognosis following wedge resection varies depending on the histological subtype of the adenocarcinoma. For example, micropapillary or solid subtypes, which are associated with a poor prognosis, are highly associated with a high rate of locoregional recurrence following wedge resection.\textsuperscript{21} Furthermore, several studies have demonstrated that STAS has a worse outcome with sublobar resection, and is a significant risk factor for recurrence.\textsuperscript{22} Certain subtypes, such as mucinous adenocarcinoma, are also strongly associated with STAS, and the appropriateness of wedge resection in these patients remains debatable. As previously described, it is challenging to ascertain the surgical extent based on preoperative testing as the size of the solid component does not reflect pathological subtype or details, both of which are known risk factors for locoregional recurrence. In addition, frozen pathologic examination is still not mature for clinical implementation. Recently, attempts have been made to predict pathological findings by analyzing CT scans using artificial intelligence.\textsuperscript{23}

Intraoperative inaccurate nodule localization and inadequate parenchymal resection margins are also contributors to locoregional recurrence. The NCCN guidelines recommend
sublobar resection only for nodules that allow sufficient parenchymal resection margins.\textsuperscript{5} Regardless of the size of the nodule, if it is not located at the periphery, sublobar resection may not provide sufficient resection margin. In addition, pure ground-glass nodules may be challenging to palpate during surgery. Therefore, precise localization is required to ensure adequate resection margins with wedge resection. Various techniques, including CT-guided and electromagnetic bronchoscopic-guided marking, have previously been utilized for localizing small nodules. Moreover, to ensure an adequate parenchymal resection margins, preoperative planning utilizing a 3D reconstruction algorithm for chest CT has been widely used, and intraoperative near-infrared imaging using indocyanine green for accurate identification of the parenchymal margin is used during surgery.\textsuperscript{24,25}

\textbf{Future perspective}

Recent studies have shown that sublobar resection in peripherally-located early-stage lung cancer has non-inferior oncologic outcomes compared to lobectomy, and the ability to preserve lung function may make it a viable option for many patients in the future. Radiologic evaluation of the invasive component remains one of the best criteria for determining sublobar resection candidacy, but it does not represent all the diverse factors that may increase the risk of locoregional recurrence in patients undergoing sublobar resection. (\textbf{Table 1}) Although frozen-section diagnosis can aid in identify important pathological findings intraoperatively, it is tedious and often inaccurate. In the future, computational models that employing artificial intelligence algorithms trained with large clinical datasets may be used to select appropriate sublobar resection candidates based on the patient’s unique clinical characteristics and preoperative examination findings.
References


Table 1. Considerable factors for deciding surgical extent of small-size lung cancer

<table>
<thead>
<tr>
<th>Factors</th>
<th>Extent of resection</th>
</tr>
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<tbody>
<tr>
<td><strong>Tumor location</strong></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>Favor lobectomy</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Favor wedge resection or segmentectomy</td>
</tr>
<tr>
<td><strong>Tumor size and CTR on preoperative CT</strong></td>
<td></td>
</tr>
<tr>
<td>Size ≤ 2.0cm &amp; CTR ≤ 0.25</td>
<td>Favor wedge resection</td>
</tr>
<tr>
<td>Size ≤ 2.0cm</td>
<td></td>
</tr>
<tr>
<td>&amp; 0.25 &lt; CTR ≤ 1.0</td>
<td>Favor segmentectomy</td>
</tr>
<tr>
<td>2.0cm &lt; Size ≤ 3.0cm &amp; CTR ≤ 0.5</td>
<td></td>
</tr>
<tr>
<td>2.0cm &lt; Size ≤ 3.0cm &amp; CTR &gt; 0.5</td>
<td>Favor lobectomy</td>
</tr>
<tr>
<td><strong>IASLC adenocarcinoma pathologic subtype</strong></td>
<td></td>
</tr>
<tr>
<td>AAH</td>
<td>Favor wedge resection</td>
</tr>
<tr>
<td>AIS</td>
<td>Favor wedge resection</td>
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<tr>
<td>MIA</td>
<td></td>
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<tr>
<td>Lepidic dominant</td>
<td>Segmentectomy or lobectomy depending on the size and CTR of the tumor</td>
</tr>
<tr>
<td>Acinar dominant</td>
<td></td>
</tr>
<tr>
<td>Papillary dominant</td>
<td></td>
</tr>
<tr>
<td>Micropapillary dominant</td>
<td>Favor lobectomy</td>
</tr>
<tr>
<td>Invasive mucinous adenocarcinoma</td>
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<tr>
<td>Solid dominant</td>
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16
<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Favor lobectomy</th>
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<tbody>
<tr>
<td>STAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPI</td>
<td>Positive</td>
<td>Favor lobectomy</td>
</tr>
</tbody>
</table>

CTR, consolidation to tumor ratio; CT, computed tomography; IASLC, International Association for the Study of Lung Cancer; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; STAS, spread through air spaces; VPI, visceral pleural invasion
Early stage lung cancer

- Pathologic subtype
- Location
- CTR
  - Size of solid portion
- Artificial Intelligence

Wedge resection

Segmentectomy

Lobectomy