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

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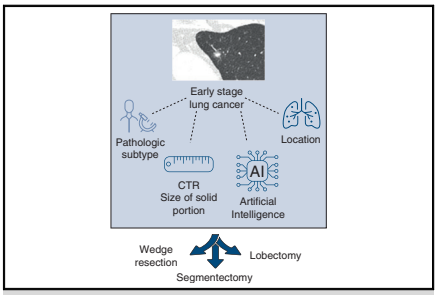
ABSTRACT

Recently published large multicenter prospective clinical trials have demonstrated that sublobar resection is noninferior to lobectomy, the traditional treatment of choice, for peripherally located early-stage lung cancer. Most clinical trials and several retrospective studies published 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 also should be considered one of the important factors in obtaining an adequate parenchymal resection margin. In this article, we summarize 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. (JTCVS Open 2023;16:17-21)



Identifying ideal candidates 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 suitable patients beyond radiologic parameters.

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.[4] 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.[5]

Surgical resection is one of the most often 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, anatomic pulmonary resection is recommended, whereas sublobar resection, segmentectomy, and wedge resection may be recommended in highly selected patients meeting strict criteria. In particular, 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. Various clinical studies investigating the

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role of wedge resection or segmentectomy in early-stage lung cancer published in the last decade have defined the extent of resection based mostly on radiologic findings, particularly the size of the entire nodule and the size of the solid portion, which is considered an indicator of invasiveness.[6-10] 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 tumor 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 noninferior long-term overall survival and recurrence-free survival compared to lobectomy.[6-10] Despite the fact that these studies defined the indications for wedge resection based on radiologic characteristics and nodule size, the appropriateness of performing wedge resection based on these criteria remains controversial. This is because the pathologic characteristics have a significant impact on patient clinical outcomes, particularly in case of locoregional recurrence, whereas radiologic characteristics are not completely representative of pathologic details. In this article, we 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 compared to lobectomy, sublobar resection in peripherally located early-stage lung cancer had a higher recurrence rate and a higher rate of locoregional recurrence. 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.[11,12] 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, numerous lung cancer physicians are exploring 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.[13]

vIn addition to wedge resection, segmentectomy also has been shown to preserve lung function compared to lobectomy; however, the Japanese Clinical Oncology Group (JCOG) 0802 trial reported a smaller difference in forced expiratory volume in 1 second than was anticipated.[7] Most recently, a randomized controlled trial by Altorki and colleagues[8] comparing sublobar resection to lobectomy in peripherally located early-stage lung cancer (solid portion <2 cm), in which 59.1% of patients had undergone wedge resection, showed noninferiority 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, as determined by the total tumor size and the consolidation-to-tumor ratio (CTR). Among these, the nonrandomized confirmatory phase III JCOG0804 study confirmed the efficacy and safety of sublobar resection (77.5% wedge resections).[9] That 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 remain lacking. In addition, the majority of studies have proposed criteria based on the location and radiologic characteristics of the pulmonary nodule, which might not accurately reflect the biology of the tumor.

RADIOLOGIC EVIDENCE OF INVASIVE GROUND-GLASS NODULES SHOWS GOOD CORRELATION WITH PATHOLOGIC INVASIVENESS BUT REMAINS AN IMPERFECT PARAMETER

As imaging technology has advanced, researchers have recognized that the features of ground-glass nodules seen on high-resolution CT scan correlate well with pathologic invasiveness.[14] Studies have shown that persistent pure ground-glass nodules are more likely to be adenomatous hyperplasia, adenocarcinoma in situ, or invasive adenocarcinoma,[15] whereas the size of the invasive component is related to the prognosis of lung adenocarcinoma.[16] Based on these findings, the JCOG defined radiologically early peripheral lung adenocarcinoma in the JCOG0201 study[10] as a tumor with a maximum size of $\leq$20 mm and a CTR of $\leq$0.25, that is, a solid component of $\leq$5 mm visible on CT scan. 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 2 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]

Although the size of the solid component of a ground-glass nodule is highly correlated with its pathologic invasiveness, determining the surgical extent based solely 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 scan.[17] Second, on the basis of CT findings alone, it is challenging to predict all pathologic findings known to be related to the high risk of locoregional recurrence or pathologic upstaging.

CAN INTRAOPERATIVE FROZEN SECTION DIAGNOSIS HELP DETERMINE PROPER SURGICAL EXTENT?

Intraoperative frozen section diagnosis can provide additional information about pathologic characteristics that cannot be assessed based on radiologic findings alone. Cryosection has limitations related to its severe architectural distortion; however, recent studies have reported variable results on the utility of intraoperative pathologic feature assessment. Given that the size of the invasive component is one of the most significant factors in determining the extent of surgery, various methods have been proposed to precisely measure it using frozen section diagnosis. Xu and colleagues[18] reported that a technique using inflation with diluted embedding medium injection allowed the preservation of open air spaces and normal parenchymal architectures, thereby increasing the accuracy of invasive foci measurement. In addition, frozen section diagnosis could aid the detection of pathologic findings that may affect patient outcomes. Histologic subtypes of adenocarcinoma and pathologic findings, such as spread through air spaces (STAS), also can be confirmed by frozen section diagnosis.[19,20] However, there are several factors to consider in the clinical implementation of determining surgical extent based on frozen section diagnosis. 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 has a high interobserver variability, and thus is challenging to apply and might not be as reliable as a general assessment method.[19,20]

OTHER FACTORS ASSOCIATED WITH LOCAL RECURRENCE 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 histologic 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.[21] Furthermore, several studies have demonstrated that STAS has a worse outcome with sublobar resection and is a significant risk factor for recurrence.[22] Certain subtypes, such as mucinous adenocarcinoma, also are strongly associated with STAS, and the appropriateness of wedge resection in these patients remains debatable. As described previously, it is challenging to ascertain the surgical extent based on preoperative testing, as the size of the solid component does not reflect pathologic 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. Recent attempts have been made to predict pathologic findings by analyzing CT scans using artificial intelligence.[23]

Intraoperative inaccurate nodule localization and inadequate parenchymal resection margins also contribute to locoregional recurrence. The NCCN guidelines recommend sublobar resection only for nodules that allow sufficient parenchymal resection margins.[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, palpation of pure ground-glass nodules may be challenging during surgery. Therefore, precise localization is required to ensure adequate resection margins with wedge resection. Various techniques, including CT-guided and electromagnetic bronchoscopy-guided marking, have been used for localized small nodules. Moreover, to ensure adequate parenchymal resection margins, preoperative planning using a 3-dimensional 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.[24,25]

FUTURE PERSPECTIVES

Recent studies have shown that sublobar resection in peripherally located early-stage lung cancer has noninferior oncologic outcomes compared to lobectomy, and its 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 (Table 1). Although frozen section diagnosis can aid in identifying important pathologic findings intraoperatively, it is tedious and often inaccurate. In the future, computational models that use 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.

Conflict of Interest Statement

The authors reported no conflicts of interest.

TABLE 1. Factors to consider when determining the surgical extent of small-size lung cancer

Factors	Extent of resection
Tumor location	
Central	Favor lobectomy
Peripheral	Favor wedge resection or segmentectomy
Tumor size and CTR on preoperative CT	
Size $\leq$2.0 cm; CTR $\leq$0.25	Favor wedge resection
Size $\leq$2.0 cm; 0.25 < CTR $\leq$1.0	Favor segmentectomy
2.0 cm < size $\leq$ 3.0 cm; CTR $\leq$ 0.5	
2.0 cm < size $\leq$ 3.0 cm; CTR > 0.5	Favor lobectomy
IASLC adenocarcinoma pathologic subtype	
AAH	Favor wedge resection
AIS	
MIA	
Lepidic dominant	Segmentectomy or lobectomy depending on the size and CTR of the tumor
Acinar dominant	
Papillary dominant	
Micropapillary dominant	Favor lobectomy
Solid dominant	
Invasive mucinous adenocarcinoma	Favor lobectomy
STAS	
Positive	Favor lobectomy
VPI	
Positive	Favor lobectomy

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.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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