Original Article

Sublobar resection for lung adenocarcinoma less than 2 cm containing solid or micropapillary components radiologically presented as consolidation-to-tumor ratio (CTR) ≤0.25 [ground-glass opacity (GGO)]

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Background: The suitability of sublobar resection as a surgical approach for early-stage non-small cell lung cancer (NSCLC) remains unclear. This study investigated the feasibility of sublobar resection in patients with pathological-stage IA adenocarcinoma less than 2 cm characterized by a high-risk pathological subtype but exhibiting radiologically noninvasive features.

Methods: We conducted a retrospective review of patients diagnosed with pathological stage IA lung adenocarcinoma who underwent surgical intervention between 2013 and 2017. The inclusion criteria included a maximum tumor diameter of 2.0 cm or less, a consolidation-to-tumor ratio (CTR) of 0.25 or less, and a histopathological confirmation of a solid or micropapillary component. Patients were categorized into sublobar resection and lobectomy groups, and propensity score matching was employed to mitigate potential confounders. The primary endpoints were lung cancer-specific survival (LCSS) and overall survival (OS).

Results: The study comprised 149 patients, with 84 in the lobectomy group and 65 in the limited resection group. In the overall cohort, the 5-year LCSS was 100% for both groups, while the 5-year OS was 97.6% (95% CI: 94.41–100.00%) in the lobectomy group and 100% in the sublobar resection group (P=0.21). After propensity score matching, the LCSS remained at 100% for both groups, and the 5-year OS was 97.14% in the lobectomy group and 100% in the sublobar resection group (P=0.32).

Conclusions: Based on our experience, for lung adenocarcinoma containing solid/micropapillary subtype, a size less than 2 cm, and a CTR ≤0.25, the oncological outcomes appeared to be comparable between sublobar resection and lobectomy, suggesting that sublobar resection might serve as an equivalent alternative to lobectomy for such lesions.

Keywords: Non-small cell lung cancer (NSCLC); lung adenocarcinoma; sublobar resection; solid pattern; micropapillary pattern

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Introduction

Lung cancer is the primary cause of cancer-related mortality worldwide (1) and is typically divided into two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for over 85% of lung cancer cases and can be further classified according to histological subtype (2). Among the NSCLC subtypes, adenocarcinoma and squamous cell carcinoma are the most common ones (3), with adenocarcinoma recently surpassing squamous cell carcinoma as the predominant subtype (2). Within invasive non-mucinous adenocarcinoma—the most frequent subtype of adenocarcinoma—the World Health Organization (WHO) identifies five histopathological patterns: lepidic, acinar, papillary, solid, and micropapillary (4). The presence of solid and micropapillary components is associated with a poorer prognosis, even when these components constitute a minor portion of the tumor (5). Evidence indicates that solid or micropapillary patterns correlate with a less favorable prognosis, regardless of their dominance in the tumor, and are linked to a higher likelihood of lymph node metastasis and recurrence rate (6-11). This suggests that adjuvant chemotherapy, even in stage I lung adenocarcinomas, may shall be included into the treatment of tumors containing these components.

Surgery is the primary treatment modality for lung cancer, particularly in the early stages. Traditionally, lobectomy has been the standard surgical approach for early-stage NSCLC. However, the rise of lung adenocarcinomas characterized by ground-glass opacity (GGO) has shifted surgical strategies. The JCOG0804/WJOG4607L clinical trial demonstrated that peripheral lung adenocarcinomas up to 2 cm in size with a consolidation-to-tumor ratio (CTR) of 0.25 or less could be effectively managed with wedge resection (12). Yet, in this study almost two-thirds of the tumors were adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA) and further investigation on high-risk pathological component was lacked. Nevertheless, solid/micropapillary components could be often found in ground-glass nodules (GGNs) (13). A previous study showed that in lung adenocarcinoma within 2 cm with a CTR ≤0.25, about 1.4% of them would contain high-risk component such as solid or micropapillary subtype (14). However, their impact on prognosis in this context was not investigated due to the sample size. To date, the influence of the presence of high-risk component on survival has not been individually studied in small GGO dominant lung cancer spectrum. Our study thus aimed to determine whether sublobar resection is adequate for treating GGNs meeting criteria set by the JCOG0804/WJOG4607L clinical trial, which contain solid/micropapillary components after pathological examination. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-231/rc).

Highlight box

Key findings

- Sublobar resection provides an equivalent treatment effect to that of lobectomy for early-stage lung adenocarcinoma containing high grade component and with a consolidation-to-tumor ratio (CTR) ≤0.25.

What is known and what is new?

- Sublobar resection is sufficient for treating noninvasive lung cancer, but the presence of a high-grade component in lung cancer indicates a worse prognosis and often warrants more radical treatment.
- For small lung adenocarcinoma with a CTR ≤0.25, sublobar resection offers equivalent oncological benefit to that of lobectomy even for high-grade invasive tumors. In the context of early-stage lung cancer, the feature of ground-glass opacity is more significant than is histological subtype for predicting prognosis.

What is the implication, and what should change now?

- The findings suggest that if a high-grade component is present after sublobar resection, the completion of lobectomy is unnecessary.

Methods

Patient selection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study received approval from the Ethics Committee of Shanghai Chest Hospital (No. IS23107). Due to its retrospective nature, the requirement for patients' consent was waived. The study reviewed patients with pT1aN0M0 peripheral lung adenocarcinoma who were treated at Shanghai Chest Hospital between September 2013 and June 2017. The inclusion criteria after primary enrollment were as follows: (I) containing solid or micropapillary components, (II) a CTR of 0.25 or less, and (III) tumor size on computed tomography (CT) not exceeding 2 cm. The CTR was calculated as the ratio of the maximum consolidation dimension to the maximum tumor dimension (15). Data collected for analysis included age at surgery, sex, smoking history, comorbidities at surgery, nodule type on CT, pathologic tumor stage [according to the seventh edition of the American Joint Committee on Cancer Staging Manual (16)], surgical procedure, predominant subtype pattern, and other relevant clinicopathological features. According to the surgical approach they received, patients were placed into a sublobar resection group or a lobectomy group. Sublobar resection is defined as lung resection that compromises less than a lobe, including wedge resection and segmentectomy. Multiple segmentectomies such as resection of two adjacent segments and basal pyramid segmentectomy were also included in our study.

Evaluation of chest imaging

Routine thin-section CT imaging with a 0.625- or 1.25-mm collimation was performed for lung nodules. Two thoracic radiologists who were blinded to the patients' clinicopathologic information independently assessed the chest CT scans. In cases of disagreement, a consensus was reached through discussion. Nodules were classified as pure GGNs (pGGNs) and part-solid GGNs according to the definitions of the Fleischner Society (17).

Surgery

All cases were discussed in a multidisciplinary setting in order to determine the optimal surgical approach to each patient. Generally, sublobar resections were more likely to be performed in smaller tumors (≤2 cm) with GGO predominance. Lobectomy was preferred for larger tumors and particularly central disease with more consolidation. The overall fitness of patients was such as pulmonary function and comorbidities is also under consideration. Surgical approach would be either wedge resection or segmentectomy for patients with compromised cardiorespiratory reservation. More precisely, wedge resection was often the first option for peripheral nodule with less consolidation. While segmentectomy was more considered for those whose location was distant to the pleura. Nodal dissection in the hilar and mediastinal regions was not mandatory during sublobar resection and the decision-making of the necessity of nodal dissection depended on the experts' choice in the multidisciplinary team. However, if there was suspicion of lymph node metastasis, such as the presence of swollen lymph nodes, lymph node sampling or dissection would become necessary. If the intraoperative frozen section of lymph nodes yield showed positive results, sublobar resection should be transited to lobectomy. The surgical margin was verified through frozen section to ensure negativity. In instances where margins might be insufficient, wedge resection would necessitate conversion to segmentectomy or lobectomy.

Evaluation of solid and micropapillary components

Lung adenocarcinoma specimens stained with hematoxylin and eosin were independently reviewed by two experienced pathologists who were unaware of the patients' clinicopathological data. The most recent WHO classification was used to define the micropapillary component (characterized by papillary tufts without fibrovascular cores) and the solid component (characterized by sheets of polygonal tumor cells devoid of lepidic, acinar, papillary, or micropapillary architecture) (4). A diagnostic consensus was reached for each case by the pathologists.

Postoperative monitoring protocol

Following surgical intervention, patients underwent semiannual evaluations. This monitoring included a comprehensive review of both inpatient and outpatient medical records to ascertain survival status and postoperative therapeutic interventions. Routine diagnostic procedures, such as biannual physical examinations, chest CT scans, and abdominal ultrasonography, were employed to monitor patient health. Overall survival (OS) was considered to be the time from the surgical procedure to either the date of mortality from any cause or the most recent follow-up. Lung cancer-specific survival (LCSS) was determined as the duration from the surgical intervention to mortality specifically attributed to lung cancer or the last patient follow-up.

Statistical analysis

To analyze the collected data, the Kruskal-Wallis test was used for continuous variables, while the chi-squared test was used for categorical variables. The Kaplan-Meier method was employed to estimate OS and LCSS, and the log-rank test was used to compare survival rates. Significance was established at a P value threshold of less than 0.05, and all P values reported were based on two-tailed statistical tests. To address potential biases due to nonrandom allocation in comparing the lobectomy group with the sublobar resection group, propensity score matching (PSM) was implemented.

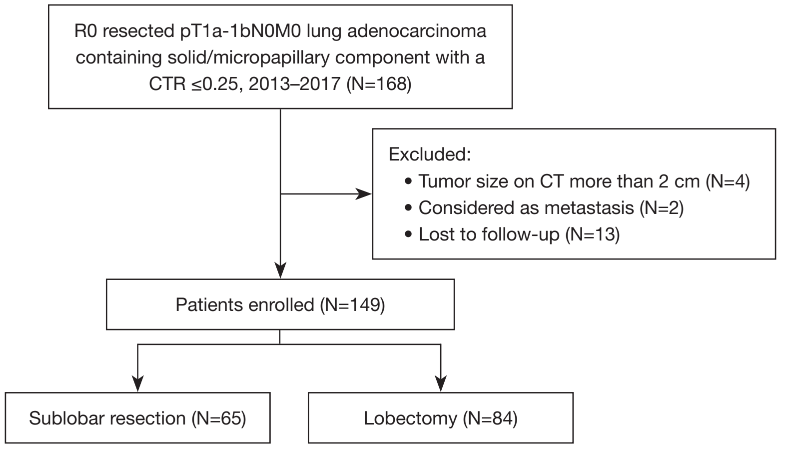

Figure 1 Flowchart of patient inclusion. CTR, consolidation-to-tumor ratio; CT, computed tomography.

This involved the use of a nearest-neighbor matching algorithm without replacement, maintaining a matching tolerance of 0.2, and deliberately excluding postoperative factors from the model. Following PSM, an evaluation of the balance of baseline characteristics was conducted. The statistical analyses were performed using R software version 4.2.1 (The R Foundation for Statistical Computing).

Results

Patient enrollment

A total of 168 patients with pT1aN0M0 peripheral lung adenocarcinoma with a solid or micropapillary component and a CTR ≤0.25 were initially selected. Of these patients, four were excluded due to a lesion size exceeding 2 cm on CT scans. Additionally, two patients were deemed ineligible due to having metastases from another tumor, and 13 were omitted from the study due to being lost to follow-up. Consequently, 149 patients were included in the final analysis, 84 of whom underwent lobectomy and 65 of whom received sublobar resection (*Figure 1*). In the sublobar resection group, 39 were wedge resections and 26 were segmentectomies.

Clinical characteristics

The analysis of demographic and clinical characteristics revealed no significant differences between the two groups in terms of age, sex, smoking history, medical history, or imaging findings (CTR), as presented in *Table 1*. The dominant pathological subtypes were acinar and papillary, representing 51.7% and 32.9% of cases, respectively. Notably, no cases predominantly featuring a micropapillary pattern were observed. There were significant differences in mean tumor size between the lobectomy group and the sublobar resection group according to both CT (lobectomy group: 1.56 cm, SD 0.391 cm; sublobar resection group: 1.38 cm, SD 0.374 cm; P=0.02) and pathological findings (lobectomy group: 1.49 cm, SD 0.346 cm; sublobar resection group: 1.26 cm, SD 0.35; P<0.001). Furthermore, a higher rate of lymph node dissection or sampling was observed in the lobectomy group compared to the sublobar resection group (100.0% *vs.* 58.5%; P<0.001). After PSM, all baseline characteristics were evenly distributed between the two groups (*Table 2*), ensuring their comparability.

Survival outcome

Data collection for follow-up concluded on April 30, 2023, with a median follow-up duration of 75 months. Among the 149 patients, there were no documented recurrence. The 5-year LCSS rate was 100% in both groups, regardless of PSM application, as illustrated in *Figure 2*. Furthermore, the 5-OS showed no significant differences between the lobectomy and sublobar resection groups, both before and after PSM application, as shown in *Figure 3*. Specifically, two patients (1.3%) in the lobectomy group died: one due to aortic dissection and one due to pancreatic cancer. As a result, the 5-year OS was 97.6% (95% CI: 94.41–100.00%) in the lobectomy group and 100% in the sublobar resection group prior to PSM (P=0.21) (*Figure 3A*); following PSM, both groups displayed similar 5-year OS rates (97.14%

Table 1 Baseline characteristics before propensity score matching

Variable	Sublobar resection (N=65)	Lobectomy (N=84)	Total (N=149)	P value
Age, years				0.48
Mean (SD)	59.6 (9.82)	56.9 (10.0)	58.1 (9.98)	
Median [Min, Max]	60.0 [37.0, 80.0]	58.0 [30.0, 73.0]	59.0 [30.0, 80.0]	
Sex, n (%)				0.98
Male	30 (46.2)	40 (47.6)	70 (47.0)	
Female	35 (53.8)	44 (52.4)	79 (53.0)	
Smoking, n (%)				0.83
Yes	9 (13.8)	16 (19.0)	25 (16.8)	
No	52 (80.0)	60 (71.4)	112 (75.2)	
Unknown	4 (6.2)	8 (9.5)	12 (8.1)	
Comorbidity, n (%)				0.82
No	49 (75.4)	70 (83.3)	119 (79.9)	
History of cardiovascular disease	8 (12.3)	4 (4.8)	12 (8.1)	
History of endocrine disease	2 (3.1)	2 (2.4)	4 (2.7)	
History of other tumors	1 (1.5)	0	1 (0.7)	
Unknown or other	5 (7.7)	8 (9.5)	13 (8.7)	
Nodule type, n (%)				0.76
pGGN	38 (58.5)	44 (52.4)	82 (55.0)	
mGGN	27 (41.5)	40 (47.6)	67 (45.0)	
CTR (%)				0.82
Mean (SD)	0.0828 (0.103)	0.0938 (0.103)	0.0890 (0.103)	
Median [Min, Max]	0 [0, 0.250]	0 [0, 0.250]	0 [0, 0.250]	
Tumor size on CT, cm				0.02
Mean (SD)	1.38 (0.374)	1.56 (0.391)	1.48 (0.393)	
Median [Min, Max]	1.40 [0.500, 2.00]	1.60 [0.700, 2.00]	1.50 [0.500, 2.00]	
Pathological tumor size, cm				<0.001
Mean (SD)	1.26 (0.350)	1.49 (0.346)	1.39 (0.365)	
Median [Min, Max]	1.20 [0.500, 2.00]	1.50 [0.700, 2.00]	1.50 [0.500, 2.00]	
Pathological T stage, n (%)				0.01
T1a	23 (35.4)	12 (14.3)	35 (23.5)	
T1b	42 (64.6)	72 (85.7)	114 (76.5)	
Main subtype, n (%)				0.95
Lepidic	11 (16.9)	9 (10.7)	20 (13.4)	
Acinar	34 (52.3)	43 (51.2)	77 (51.7)	
Papillary	19 (29.2)	30 (35.7)	49 (32.9)	
Solid	1 (1.5)	2 (2.4)	3 (2.0)	
Lymph node dissection or sampling, n (%)				<0.001
Yes	38 (58.5)	84 (100.0)	122 (81.9)	
No	27 (41.5)	0	27 (18.1)	

SD, standard deviation; Min, minimum; Max, maximum; pGGN, pure ground-glass nodule; mGGN, mixed ground-glass nodule; CTR, consolidation-to-tumor ratio; CT, computed tomography.

Table 2 Baseline characteristics after propensity score matching

Variable	Lobectomy (N=35)	Sublobar resection (N=35)	Total (N=70)	P value
Age (years)				0.99
Mean (SD)	57.7 (9.98)	58.1 (9.49)	57.9 (9.67)	
Median [Min, Max]	60.0 [33.0, 73.0]	58.0 [38.0, 78.0]	59.5 [33.0, 78.0]	
Sex, n (%)				0.77
Male	14 (40.0)	17 (48.6)	31 (44.3)	
Female	21 (60.0)	18 (51.4)	39 (55.7)	
Smoking, n (%)				>0.99
Yes	5 (14.3)	5 (14.3)	10 (14.3)	
No	27 (77.1)	26 (74.3)	53 (75.7)	
Unknown	3 (8.6)	4 (11.4)	7 (10.0)	
Comorbidity, n (%)				NA
No	28 (80.0)	26 (74.3)	54 (77.1)	
History of cardiovascular diseases	3 (8.6)	3 (8.6)	6 (8.6)	
History of endocrine diseases	1 (2.9)	2 (5.7)	3 (4.3)	
History of other tumors	0	0	0	
Unknown or other	3 (8.6)	4 (11.4)	7 (10.0)	
Nodule type, n (%)				0.63
pGGN	17 (48.6)	21 (60.0)	38 (54.3)	
mGGN	18 (51.4)	14 (40.0)	32 (45.7)	
CTR (%)				0.69
Mean (SD)	0.104 (0.106)	0.0814 (0.105)	0.0929 (0.105)	
Median [Min, Max]	0.143 [0, 0.250]	0 [0, 0.250]	0 [0, 0.250]	
Tumor size on CT, cm				0.98
Mean (SD)	1.49 (0.382)	1.47 (0.340)	1.48 (0.359)	
Median [Min, Max]	1.50 [0.800, 2.00]	1.40 [0.900, 2.00]	1.40 [0.800, 2.00]	
Pathological tumor size, cm				0.94
Mean (SD)	1.34 (0.324)	1.37 (0.330)	1.36 (0.325)	
Median [Min, Max]	1.50 [0.700, 2.00]	1.30 [0.700, 2.00]	1.40 [0.700, 2.00]	
Pathological T stage, n (%)				0.96
T1a	8 (22.9)	7 (20.0)	15 (21.4)	
T1b	27 (77.1)	28 (80.0)	55 (78.6)	
Main subtype, n (%)				0.98
Lepidic	6 (17.1)	6 (17.1)	12 (17.1)	
Acinar	21 (60.0)	19 (54.3)	40 (57.1)	
Papillary	8 (22.9)	9 (25.7)	17 (24.3)	
Solid	0	1 (2.9)	1 (1.4)	
Lymph node dissection or sampling, n (%)				NA
Yes	35 (100.0)	35 (100.0)	70 (100.0)	
No	0	0	0	

SD, standard deviation; Min, minimum; Max, maximum; pGGN, pure ground-glass nodule; mGGN, mixed ground-glass nodule; CTR, consolidation-to-tumor ratio; CT, computed tomography; NA, not applicable.

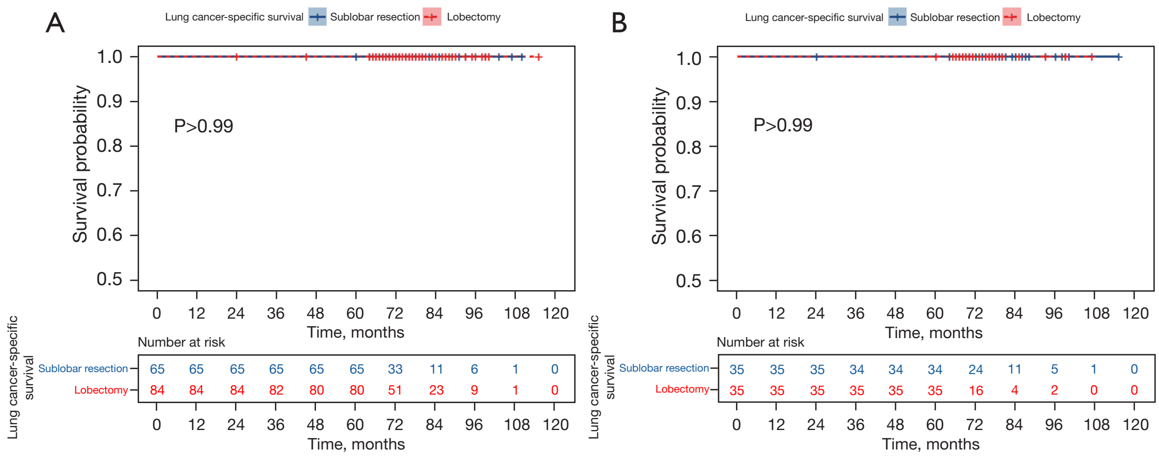

Figure 2 Kaplan-Meier survival curve for (A) lung cancer-specific survival in patients undergoing sublobar resection or lobectomy before propensity score matching and for (B) lung cancer-specific survival in patients undergoing sublobar resection or lobectomy after propensity score matching.

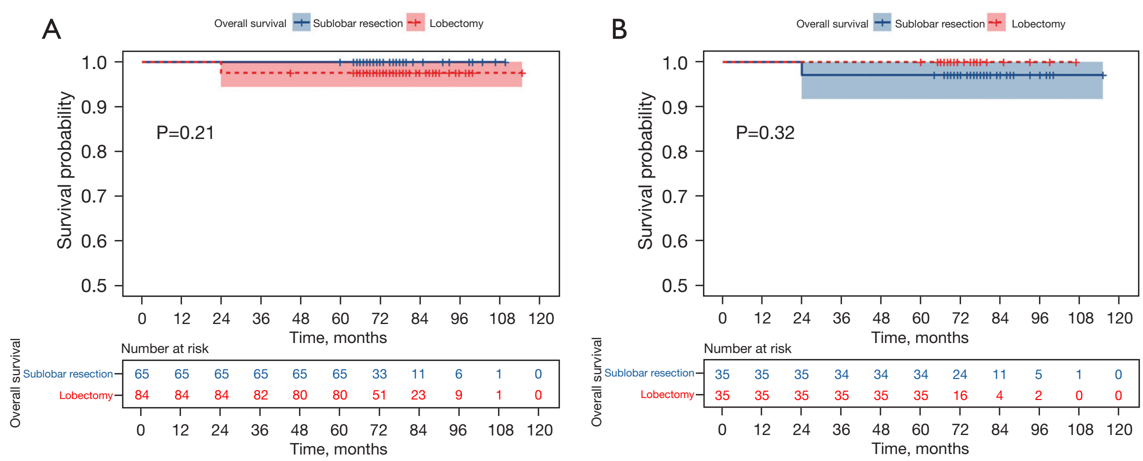

Figure 3 Kaplan-Meier survival curve for (A) overall survival in patients undergoing sublobar resection or lobectomy before propensity score matching and for (B) overall survival in patients undergoing sublobar resection or lobectomy after propensity score matching.

vs. 100%; P=0.32; *Figure 3B*). These results highlight the stability and uniformity of survival outcomes across the two surgical intervention groups, both pre- and post-PSM implementation.

Discussion

The findings of this study indicated that sublobar resection for adenocarcinoma characterized by high-risk pathological subtypes manifesting as noninvasive pulmonary nodules in CT (according to the criteria of JCOG 0804) with CTR ≤0.25 and a tumor diameter not exceeding 2 cm can achieve a notable 100% 5-year lung LCSS. Prior research suggests that micropapillary and solid patterns in lung adenocarcinoma are linked to significantly poorer OS and disease-free survival (DFS) after pulmonary resection (9,18-20). Owing to this, efforts have been made to more accurately predict the potential presence of solid or micropapillary components through imaging features before surgery in order to better guide the management (21,22). Moreover, an earlier study has suggested a survival benefit associated with completing lobectomy after sublobar resection in cases of invasive lung adenocarcinoma (23). However, this study primarily focused on lesions smaller than 3 cm and did not consider CTR. Our findings suggest that completing a lobectomy may not be necessary when a high-risk pathological subtype is identified following sublobar resection in lung adenocarcinoma cases with a CTR of 0.25 or less. Consequently, neither further evaluation nor completing a more radical procedure is necessary for patients in such circumstances. This approach could potentially enhance clinical efficiency and conserve resources in managing adenocarcinoma cases with high-risk pathological subtypes.

Our study also revealed that tumor size significantly influences the choice of surgical procedure. Surgeons tend to prefer lobectomy for larger lesions, which typically involves lymph node dissection or sampling.

The optimal criteria for selecting the extent of surgery for early-stage lung cancer remain unclear. The National Comprehensive Cancer Network guidelines suggest sublobar resection for nodules with over 50% ground-glass appearance on CT with a preference of anatomic pulmonary resection (24). This recommendation aligns with previous findings indicating that a 50% cutoff is effective (25). In contrast, the European Society for Medical Oncology reserves sublobar resection for pure GGNs (26). Currently, studies investigating sublobar resection mainly focus on early-stage lung cancer within 2 cm and the cutoff of CTR, which frequently stands at either 0.25 or 0.5. The clinical trial JCOG0804/WJOG4507L adopted the criteria of CTR ≤0.25 because according to JCOG 0201 this cutoff could well predict the non-invasiveness defined by the research and prioritized radiological findings in guiding surgery decisions regardless of histological subtype and demonstrated the feasibility of sublobar resection according to CTR assessment (12,15). Notably, by reason of its prior initiation, the invasiveness defined by JCOG is different from that of WHO classification and the latter describes the invasive component as any histological subtype other than a lepidic pattern or tumor cells infiltrating myofibroblastic stroma (4). Thus, a non-invasive tumor judged through CTR could be invasive according to the definition of WHO, compromising the most high-risk components including solid and micropapillary subtype. Furthermore, the most histological subtype in JCOG0804/WJOG4507L were AIS and MIA, which limited its exploration of impact of high-risk components in their study population. Therefore, sublobar resection has not been conclusively proven effective for invasive lesions or high-risk pathological subtypes such as solid or micropapillary patterns, as these typically imply the need for additional treatment (6,8). Research by Qi *et al.* suggests that sublobar resection might be curative for pathologically invasive but radiologically noninvasive adenocarcinoma at pathological stages IA (27). On the other hand, the lag of confirmation of histology restricts the utility of prognostic significance of solid/micropapillary subtype despite the efforts having been made to forecast the presence of high-risk components in order to better guide the decision-making of surgical approach (22,28-30). Our study indicates that the presence of a GGO component may be more predictive than pathological subtypes in determining the prognosis of early-stage lung adenocarcinoma.

Lymph node dissection is always a crucial part in the surgical treatment of lung cancer from the time of being proposed by Dr. Cahan in 1960 (31,32). Since then, the optimal strategy of lymph node exploration in the surgical treatment of lung cancer has been shifting through the years. A recent study suggests that in cases of NSCLC with a CTR less than 0.5, lymph node involvement is unlikely (33). In our study, recurrence was not observed regardless of lymph node dissection or sampling. These findings raise the possibility of performing less invasive procedures to treat lung cancer.

Limitations

Due to the retrospective nature, our study lacks the randomization and other clinicopathological risk factors such as the precise percentage of each histological subtype and the information of lymphovascular invasion. Additionally, our study contains a relatively small sample size. These factors restricted further analysis.

Conclusions

Based on our experience, for lung adenocarcinoma containing solid/micropapillary subtype, a size less than 2 cm, and a CTR ≤0.25, the oncological outcomes appeared to be comparable between sublobar resection and lobectomy, suggesting that sublobar resection might serve as an equivalent alternative to lobectomy for such lesions.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-231/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-231/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-231/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-231/coif). N.R.V. received support for registration, airfare and hotel at AATS annual meeting Los Angeles 2023 from Ziosoft. The other 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) and received approval from the Institutional Review Board of Shanghai Chest Hospital (approval number: IS23107). Due to the retrospective nature of the analysis, the need for individual consent was exempted.

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