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Sublobectomy for stage IA1-2 invasive lung adenocarcinoma with consolidation tumor ratio ≤ 0.25

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Abstract

Background: Sublobectomy for early-stage non-small cell lung cancer (NSCLC) remains a matter of debate. This study aimed to discuss the feasibility of sublobectomy in patients with pathological-stage IA1-2 confirmed as pathologically invasive but radiologically noninvasive adenocarcinoma.

Methods: From 2011 to 2019, we screened clinical stage IA1–IA2 lung cancer patients who underwent surgery at the Guangdong Provincial People's Hospital (GDPH). Inclusion criteria were maximum tumor diameter of 2.0 cm or less, consolidation tumor ratio (CTR) ≤ 0.25, and pathologically confirmed invasive adenocarcinoma. Sublobectomy (segmentectomy and wedge resection) and lobectomy groups were created, and propensity scores were computed. The primary endpoints were lung cancer-specific overall survival (LCSS) and LCS- relapse-free survival (LCS-RFS) after adjusting propensity scores.

Results: A total of 1731 patients were screened, and 100 patients were enrolled. The lobectomy group had 51 patients and the limited resection group had 49. No cases relapsed, and two patients died from nontumor causes. For the entire cohort, the 5-year LCSS and 5-year LCS-RFS were 100% in the lobectomy and limited resection groups. When propensity scores matched, there were no differences in LCSS and LCS-RFS between the two groups (LCSS:100%, LCS-RFS 100% in lobectomy and limited resection, respectively).

Discussion: Sublobectomy may be curative for pathologically invasive but radiologically noninvasive adenocarcinoma at pathological stage IA1-2.

KEYWORDS
ground-glass opacity, invasive adenocarcinoma, limited resection, lung cancer, peripheral lung lesion

INTRODUCTION

Low-dose computed tomography (LDCT) has resulted in increased detection of stage I non-small cell lung cancer (NSCLC) and a reduction in lung cancer mortality.[1,2] Surgery can cure early-stage lung cancer, while the resection range has recently troubled surgeons. The "golden standard" treatment for stage I NSCLC (tumors smaller

than 3 cm) is pulmonary lobectomy (PL).[3] Patients with poor lung function or significant comorbidities should undergo sublobar resection (SR) (wedge/segmentectomy).[4–6] However, unlike the triple local recurrence rate and 50% increase in cancer-related death rate in Ginsberg's SR group, SR recently has demonstrated compatible survival to PL in early-stage lung cancer.[7–12]

The prognosis of stage IA patients partly depends on their pathological invasiveness and imaging features.[13–18] The International Assocation for the Study of Lung Cancer (IASLC) staging project included associations between ground-glass opacity (GGO) versus solid opacities and lepidic versus invasive patterns in the eighth edition of the TNM classification of lung cancer.[15,16,19] Patients with c-stage T1aN0M0 had better outcomes with GGO and part-solid GGO than those with pure-solid GGO, so SR may be appropriate for pure GGO and part-solid GGO.[18,20–24]

Utilizing tumor diameter and consolidation tumor ratio (CTR) in thin-section CT, the Japan Clinical Oncology Group (JCOG) selected patients for SR.[12,23–26] JCOG0201 established CTR = 0.5 as the cutoff value to distinguish the radiological noninvasive and invasive adenocarcinoma in cT1a-c (≤3.0 cm).[25] A 5-year recurrence-free survival (RFS) of 99.7% and no local recurrence were subsequently shown in JCOG 0804 for patients with sublobar resected lung cancer with a tumor dimension of 2.0 cm and a CTR of 0.25.[26]

Patients meeting the JCOG0804 criteria appear to be suitable for SR (tumor ≤2.0 cm, CTR ≤ 0.25). The basis of JCOG0804 is radiological noninvasive adenocarcinoma can predict pathological noninvasive adenocarcinoma, but only seven invasive adenocarcinomas (Noguchi's categorization D/E/F) went through SR in 314 patients. We argue that JCOG0804 cannot confirm the feasibility of SR in all radiological noninvasive patients.

The aim of our study was to determine if sublobectomy is feasible for radiologically noninvasive, but pathologically invasive, NSCLC patients.

METHODS

Patients

We reviewed patients undergoing lung cancer surgery at Guangdong Provincial People's Hospital (GDPH) from 2011 to 2019. The final date of follow-up data collection for this study was July 14, 2022. Eligible patients had invasive adenocarcinoma (the International Association for the Study of Thoracic Surgeons classification) and were at pathological stage IA1–IA2 (the eighth edition of TNM classification).[16,19] We selected pulmonary nodules which had a CTR of 0.25 or less. The JCOG 0201 study defines CTR as the ratio of maximal consolidation to maximal tumor dimension on thin-section CT scan (Figure 1).[24,25] Figure 2 shows the exclusion criteria. Patients with missing baseline information were excluded. The retrospective design eliminated the need for informed consent and GDPH approved this study (no. GDREC2020175H).

Surgery

Nodal dissection was not mandatory for the hilar and mediastinal region in wedge resection. However, lymph node sampling or dissection was necessary if lymph node metastasis was suspected such as swollen lymph nodes. SR should be converted to PL if the results of the intraoperative frozen section of lymph nodes were positive. Surgical margin was confirmed by frozen section to secure the negative margin. Wedge section needed conversion to segmentectomy or PL in case of the possibility of insufficient margins.

Follow up

Thirty-day mortality was defined as death within 30 days of surgery. CT scans were performed on all patients 4 weeks post-operation, then every 4 to 6 months for the first 2 years and once a year thereafter. CT, positron emission computed tomography, magnetic resonance imaging, or bone imaging scanning optional for patients with suspected metastatic symptoms. RFS was defined as the period from surgery to relapse, death, or last day of imaging examination. OS was defined as the period from surgery to death or final contact with the alive. LCSS was the period from surgery to the death of lung cancer or last follow-up. During the follow-up period, each subsequent tumor should be assessed to see if it is a recurrence of the initial tumor or second primary lung cancer. Second primary lung cancer was characterized as (i) the subsequent tumor had a different histological type from initial cancer or (ii) a comparable histological type to original cancer but was a solitary tumor with no extra thoracic metastases and no carcinoma in the lymphatics at common to both cancers. A recurrence of the initial malignancy was deemed otherwise.[27] Local recurrence comprised tumor recurrence in the ipsilateral thorax, which includes the resection margin of the lung or bronchus, hilar lymph nodes, mediastinal lymph nodes, and malignant pleural effusion.[23,25] The rest were distant metastases.

Statistical analysis and outcomes

Categorical data are summarized as frequencies (percentages) and continuous data as mean ± SD if normally distributed, and median ± interquartile range if not normally distributed (range). Following the Shapiro–Wilk test, continuous data were evaluated with Wilcoxon and *t*-tests. Percentages were compared using χ^2 text or Fisher's exact test.

CTR was remeasured and analyzed using the two-way random model's absolute agreement to test intraclass correlation efficiency (ICC). A single measurement above 0.75 represents good repeatability.

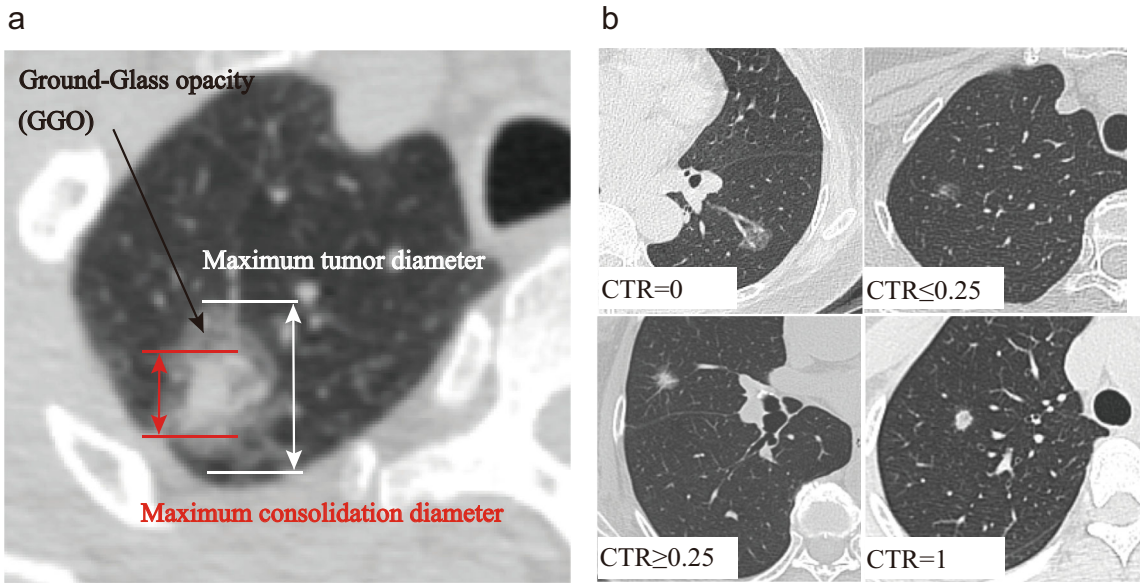

FIGURE 1 Calculation of the CTR. (a) The red line represents the maximum consolidation diameter, the white line is the maximum tumor diameter, and the black line is towards GGO. (b) Examples of the measurement of CTR. CTR, consolidation tumor ratio, GGO, ground-glass opacity

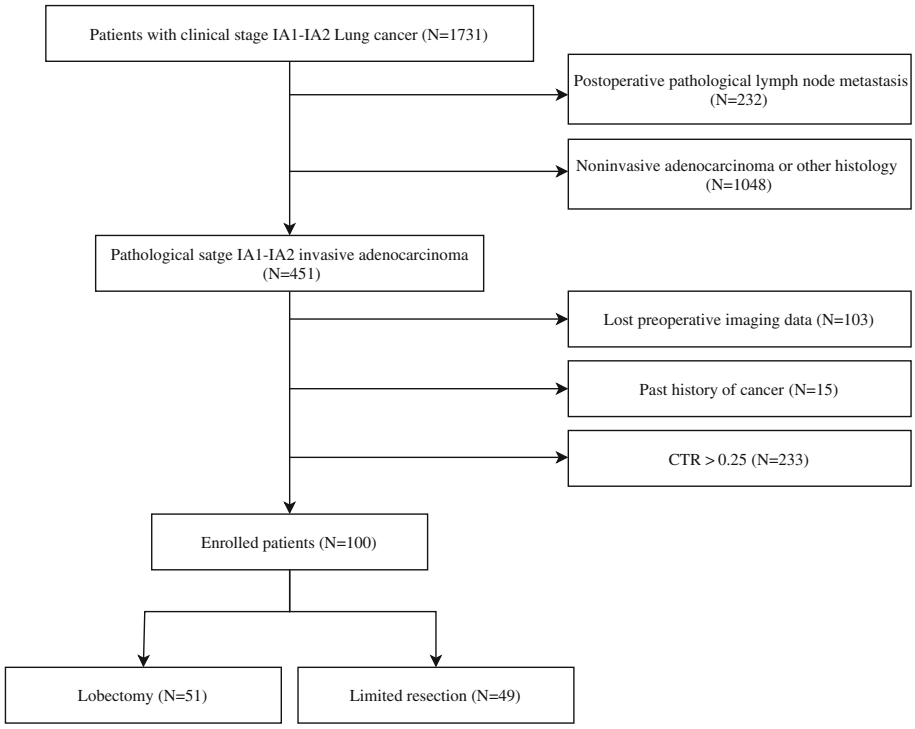

FIGURE 2 Flow chart of patients in the study. CTR, consolidation tumor ratio

Propensity scores were used to eliminate nonrandom allocation bias in PL and SR groups. Using a nearest-neighbor algorithm without replacement, propensity score matching (PSM) assessed patient features to provide scores that could be used to split patients into two groups in a 1:1 radio. Our model excluded postoperative factors. The match tolerance was 0.05. We assessed baseline attributes for balance after PSM adjustment.

The primary endpoint was lung cancer-specific survival (LCSS) and LCS-relapse-free survival (LCS-RFS) after PSM. The second endpoint was LCSS and LCS-RFS in the entire cohorts. LCSS, LCS-RFS, RFS, and OS were estimated using the Kaplan–Meier methods. We compared the PL group and the SR group's survival rates using log-rank. The median follow-up time was calculated using reverse Kaplan Meier.

TABLE 1 Baseline characteristics

Characteristics	Unmatched			Matched		
	Lobectomy $N = 51$ (51%)	Sublobectomy $N = 49$ (49%)	p-value	Lobectomy $N = 20$ (50%)	Sublobectomy $N = 20$ (50%)	p-value
Age (years, mean ± SD)	54.3 ± 10.8	54.8 ± 11.8	0.84	55.8 ± 9.98	53.55 ± 10.21	0.50
Sex (%)			0.18			0.74
Male	20 (39.2)	13 (26.5)		6(30.0)	7(35.0)	
Female	31 (60.8)	36 (73.5)		14(70.0)	13(65.0)	
Smoking history (%)			0.37			>0.99
Yes	7 (13.7)	4 (8.2)		1(5)	2(10)	
No	44 (96.3)	45 (91.8)		19(95)	18(90)	
Pathological TNM and stage (%)			0.22			0.49
IA1 (T1a)	12(23.5)	18(36.7)		5(25)	7(35)	
IA2 (T1b)	39(76.5)	31(63.3)		15(75)	13(65)	
Maximum tumor diameter on lung window (mm, mean ± SD)	13.10 ± 3.51	12.38 ± 4.15	0.36	13.19 ± 3.79	12.67 ± 3.74	0.67
Consolidation dimension on lung window (mm, median ± IQR)	1.75(0.00–2.63)	0.00(0.00–2.20)	0.05[a]	0.00(0.00–2.15)	0.47(0.00–2.15)	0.88[a]
Consolidation tumor ration (CTR) (median ± IQR)	0.15(0.00–0.20)	0.00(0.00–0.18)	0.03[a]	0.00(0.00–0.17)	0.07(0.00–0.21)	0.58[a]
Dominant pathological subtypes of invasive adenocarcinoma (%)			0.27[a]			0.31
LPA	17 (33.3)	11 (22.4)		12(60)	15(75)	
APA	34 (66.7)	37 (75.5)		8(40)	5(25)	
PPA	0 (0.0)	1 (2.0)		0	0	
Medical history	20(39.2)	15(30.6)	0.37	7(35)	6(17.1)	0.74
History of respiratory diseases	10(19.6)	6(12.2)	0.32	2(10)	3(15)	>0.99[a]
History of circulatory diseases	12(23.5)	12(24.5)	0.91	5(25)	5(25)	>0.99
History of endocrine diseases	4(7.8)	4(8.2)	>0.99[a]	2(10)	0(0)	0.49[a]

Abbreviations: APA, acinar predominant; CTR, consolidation tumor ratio; IAC, invasive adenocarcinoma; IQR, interquartile range; LPA, lepidic predominant; PPA, papillary predominant.
Categorical data are shown as numbers (%) and continuous data as mean ± SD if normally distributed, and median ± IQR range if not normally distributed.
[a]Fisher's exact test or Mann–Whitney U test.

Statistical analyses were completed using R software (version 4.0, R Foundation; Vienna, Austria) and SPSS software (version 26.0, IBM).

RESULTS

Patients

From 2011 to 2019, 1731 patients with clinical stage IA1-IA2 lung cancer at GDPH were screened. A total of 232 patients had postoperative lymph node metastasis, while 1048 had noninvasive adenocarcinoma (AIS or MIA) or other histology (73.9%, 1280 of 1731). There were 451 patients with pathological stage IA1–IA2 invasive adenocarcinoma and 333 measuring CTR. Pathological invasive adenocarcinoma was more radiologically solid than AIS or MIA, resulting in only 100 pathological invasive adenocarcinomas having CTR less than 0.25 (30%, 100 in 333) (Figures 1 and 2). ICC was 0.783 ($p < 0.001$), indicating acceptable CTR repeatability. PL had 51 patients while SR had 49 (29 segmentectomy, 20 wedge resection) (Figure 2). Twenty (39.2%) of the patients in the PL group were matched to the SR (Tables 1 and 2).

Baseline characteristics

Age, sex, tumor size, smoking history, and medical history did not differ between groups (Table 1). Most patients were pathological stage IA2 (PL: 76.5%, SR: 63.3%, $p = 0.22$). The PL group had a bigger consolidation dimension ($p = 0.05$) and CTR (0.15 [0.00–0.20] vs. 0.00 [0.00–0.18], $p = 0.03$). Pure GGO represented 37.3% in the PL group and 63.3% in the SR group (19 vs. 31 patients), respectively. The pathological subtypes showed satisfactory group balance ($p = 0.27$). After PSM, all baseline characteristics were balanced.

TABLE 2 Operative related factors

Parameters	Unmatched			Matched		
	Lobectomy N = 51 (51%)	Sublobectomy *N* = 49 (49%)	*p*-value	Lobectomy *N* = 20 (50%)	Sublobectomy *N* = 20 (50%)	*p*-value
Location of tumor (%)			0.24[c]			0.86[c]
LLL	7 (13.7)	8 (16.3)		2(10)	3(15)	
LUL	12 (23.5)	12 (24.5)		7(35)	8(40)	
RLL	3 (5.9)	9 (18.4)		1(5)	0(0)	
RML	6 (11.8)	2 (4.1)		0(0)	1(5)	
RUL	23 (45.1)	18 (36.7)		10(50)	8(40)	
Segment (%)			0.10[c]			>0.99[c]
S1	13 (25.5)	8 (16.3)		9(45)	9(45)	
S1 + 2	5 (9.8)	7 (14.3)		0(0)	0(0)	
S2	6 (11.8)	8 (16.3)		3(15)	2(10)	
S3	10 (19.6)	8 (16.3)		6(30)	5(25)	
S4	3 (5.9)	1 (2.0)		0(0)	0(0)	
S5	3 (5.9)	1 (2.0)		0(0)	1(5)	
S6	2 (3.9)	11 (22.4)		1(5)	2(10)	
S7	3 (5.9)	0 (0.0)		0(0)	0(0)	
S8	1 (2.0)	1 (2.0)		0(0)	0(0)	
S9	3 (5.9)	4 (8.2)		1(5)	1(5)	
S10	2 (3.9)	0 (0.0)		0(0)	0(0)	
Number of dissected lymph nodes[a]	12 (6–16)	2 (0–4.5)	<0.001[c]	13.30 ± 6.38	2.50 (0.25–4.00)	<0.001[c]
Operation hemorrhage (ml, median ± IQR)[a]	40.0 (20.0–55.0)	10.0(5.0–30.0)	<0.001[c]	50.0(20.0–60.0)	10.0(8.8–50.0)	0.005[c]
Perioperative complications[a]	3(5.9)	1(2.0)	0.62[c]	1	1	>0.99[c]
30-day mortality (%)[a]	1[b] (1.96)	0(0.00)	0.99[c]	1(5)	0	>0.99[c]

Abbreviations: LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.
[a]These factors were not included in the propensity-matched model.
[b]This patient died two days after lobectomy because of poor cardiac function displayed by preoperative echocardiography.
[c]Fisher's exact test or Mann–Whitney U test.

TABLE 3 Characteristics of patients with postoperative complications

No.	Sex	Age	Surgery	Blood	Clavien-Dindo Grade	Postoperative complications	OS status	OS (month)	Reason of death
1	M	72	Wedge	200	IVa	Pneumonia, Pulmonary embolism	1	42	Poor pulmonary function
2[a]	F	70	Lobectomy	200	V	Cardiac arrest	1	0	Cardiac arrest
3	F	63	Lobectomy	40	IVa	Cerebral stroke	0	106	-
4	F	34	Lobectomy	30	I	Encapsulated pleural effusion	0	29	-

Abbreviations: M, male; F, female.
[a]No. 2 patient was the only patient who died within 30 days after surgery.

Operative related factors

Table 2 summarizes the surgical parameters. All patients underwent R0 resection. The PL and SR groups had similar lobe ($p = 0.24$) and segment ($p = 0.10$) distributions of lung nodules. RUL was the most popular operation location in PL or SR (45.1% versus 36.7%). S1 (25.5%) dominated the LR group, whereas S6 (22.4%) dominated the SR group.

In the PL group more lymph nodes were dissected before and after PSM ($p < 0.001$). There was more intraoperative estimated bleeding in the PL group (40.00 [20.00–55.00] vs. 10.00 [5.00–30.00], $p < 0.001$). In addition, a patient died two days after PL because of poor cardiac function shown by preoperative echocardiography (Table 3). Therefore, 30-day mortality was 1.96% against 0.00% between cohorts ($p > 0.99$) (Table 2). Intraoperative

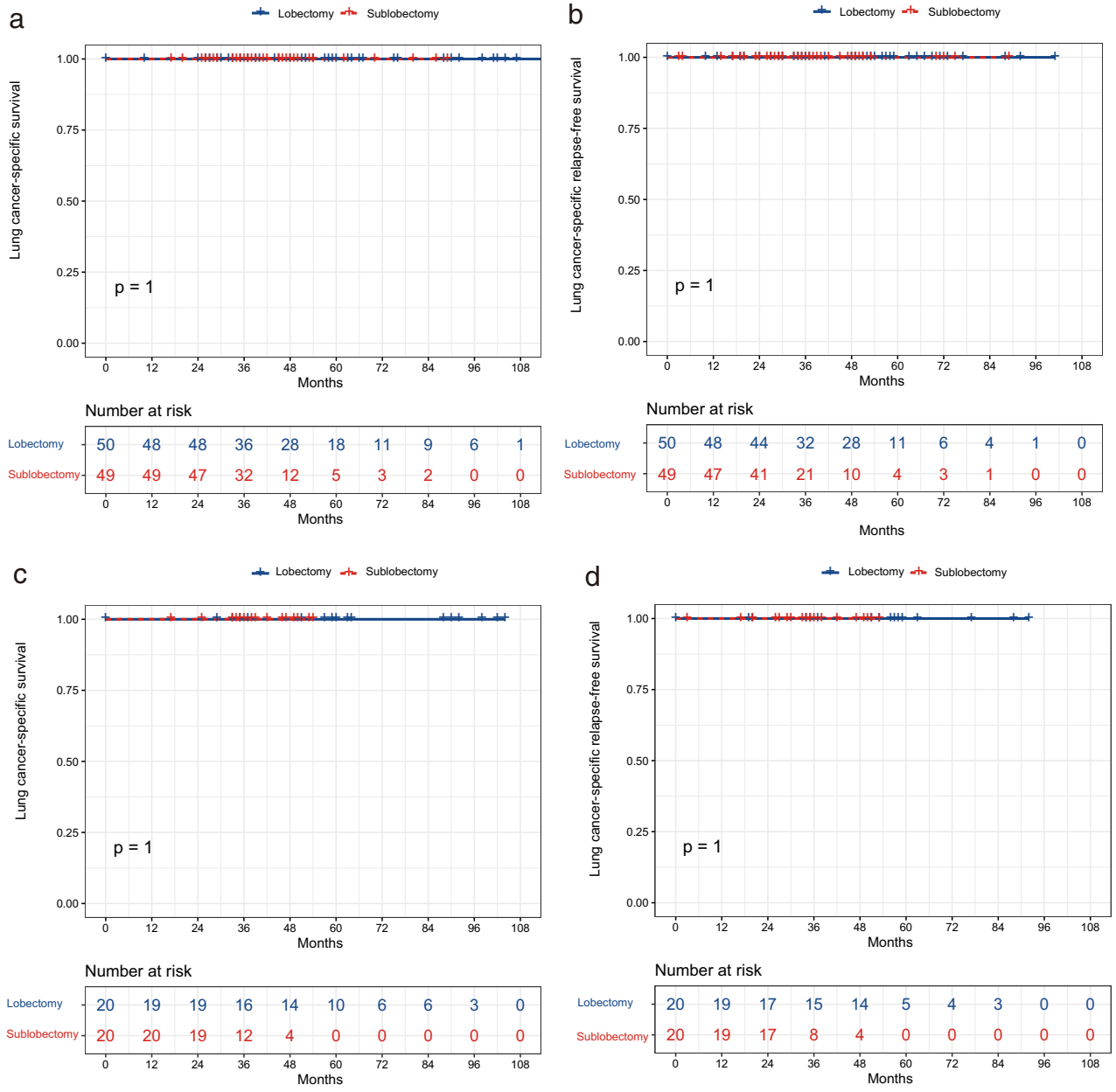

FIGURE 3 Kaplan–Meier survival curves for (a) lung cancer-specific survival and (b) lung cancer-specific relapse-free survival in the entire sets and for (c) lung cancer-specific survival and (d) lung cancer-specific relapse-free survival in the propensity score-matched patients undergoing limited resection or lobectomy

blood loss in all deceased patients was greater than, or equal to, 30 ml (Table 3).

Perioperative complications recorded in the medical record system were similar in both groups (5.9% vs. 2.0%, $p = 0.62$) (Table 3). Preoperative respiratory functions were examined in all patients and the medical history of the cardiological and respiratory functions was recorded in detail to ensure they could tolerate surgery (Table 1). The history of respiratory and circulatory diseases was balanced between the two groups (Table 1). One patient began home oxygen therapy after SR and died of pulmonary insufficiency 42 months later. Patient No. 2 died of cardiac arrest two days after PL. After PL, one patient had a cerebral stroke and one had a pleural effusion.

Matched samples showed the hemorrhage volume in the PL group was still more than in the SR group ($p = 0.005$) (Table 2). Tumor location, perioperative complications, and 30-day mortality were not different across groups.

Survival outcomes

The final date of follow-up data collection for this study was July 14, 2022. The median follow-up time was 45 months

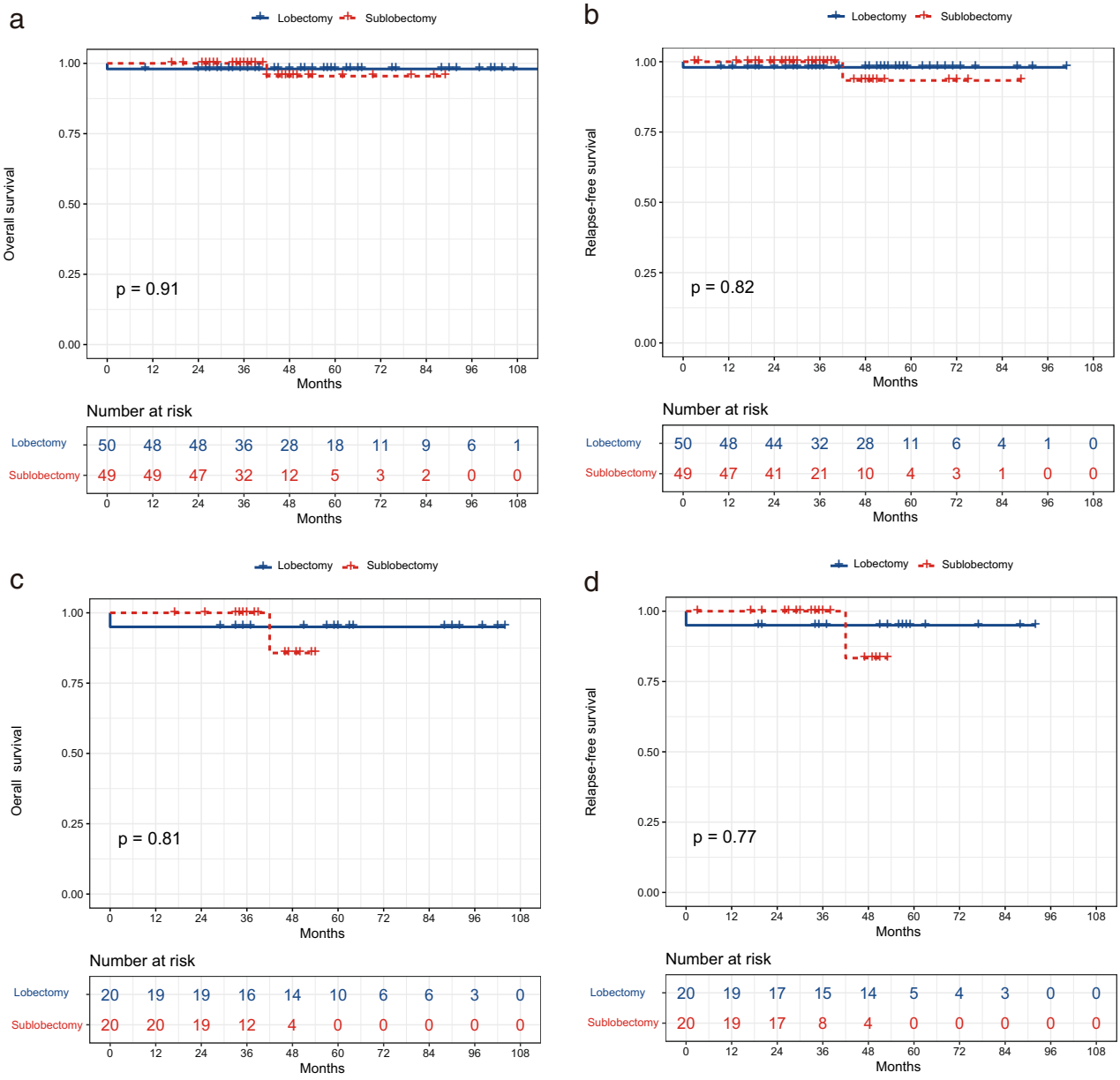

FIGURE 4 Kaplan–Meier survival curves for (a) overall survival and (b) relapse-free survival in the entire sets and for (c) overall survival and (d) relapse-free survival in the propensity score-matched patients undergoing limited resection or lobectomy

(95% CI: 38, 49). Among the 100 candidates, one (1%) patient in the PL group was lost during follow-up, no recurrences occurred, and two (2%) patients died. The 5-year LCSS and 5-year LCS-RFS were 100%, regardless of PSM (Figure 3a–d).

The 5-year OS and 5-year RFS in the PL and SR group were not significantly different before and after PSM (Figure 4). Two patients experienced nontumor-related death (Table 3). Therefore, the 5-year OS was 98% (95% CI: 94.20, 100.00) in the PL group and 95.45% (95% CI: 87.14, 100.00) in the SR group before PSM ($p = 0.91$) (Figure 4a). The 5-year RFS was similar in both groups (98% vs. 93.3%, $p = 0.82$) (Figure 4b). After PSM, the PL and SR group had similar 5-year OS (95% vs. 85.7%, $p = 0.81$) and 5-year RFS (95% vs. 83.3%, $p = 0.77$) (Figure 4c,d).

DISCUSSION

We demonstrated the pathologically invasive adenocarcinoma manifest as noninvasive pulmonary nodules on CT (CTR ≤ 0.25 and tumor diameter ≤2 cm) achieved a 100% 5-year LCS-RFS after sublobectomy. This could eliminate the need to convert an ongoing SR to PL when an unexpected frozen pathological outcome of pulmonary nodules is known. In addition, surgical time and normal lung tissue may be saved.

Our study first focused on the clinical features and prognosis of pulmonary nodules whose pathological and radiological findings were opposed (22.4% LPA, 75.5% APA, 2% PPA in the SR group). Unlike our study, JCOG 0804

emphasized a pathological noninvasive adenocarcinoma with a CTR less than 0.25. A total of 88% of patients in their study had AIS, MIA, or invasive adenocarcinoma with lepidic growth.[26] Another prospective study chose strict standards to exclude invasive cancer (GGO ratio ≥ 80% and lower 18F-fluorodeoxyglucose accumulation than the mediastinum), resulting in only six of 53 patients having invasive adenocarcinoma and undergoing SR. Similarly, no case relapsed during the study period.[21] Although previous studies showed a high recurrence of pathological stage IA invasive adenocarcinoma,[12,17,28] we demonstrated some of them could achieve a 100% LCS-RFS and LCSS after SR by carefully establishing preoperative radiological criteria (CTR ≤ 0.25, c-stage IA1–IA2) during a 45-month follow-up.

Second, some researchers have claimed that stereotactic ablative radiotherapy (SABR) achieves a good prognosis compared with PL in stage I NSCLC (5-year RFS:77% in SABR vs. 80% in lobectomy, $p = 0.57$; 5-year OS: 87% in stereotactic body radiation therapy [SBRT] vs. 84% in lobectomy, $p = 0.49$).[29] Despite the limited sample size, the findings sparked a debate on more aggressive treatment of lung cancer. The patients in the study by Chang et al. were 68.8 years old while the PL and SR groups in our study had mean ages of 54.3 and 54.8.[29] Three of four (75%) postoperative problems were in patients over 60 years old in the PL group of our study. All cases of death were in patients older than 70. Given that, we doubt that the survival outcomes of SABR versus PL are applicable for the SR with younger patients and less surgical trauma. The main flaws of our study were the lack of randomization and the small sample size. Similar clinical trials such as NCT03108560 and NCT02360761 are ongoing, but as yet none have published any results. The target patients in our study were rare and valuable, accounting for 5.8% of c-stage IA1-IA2 patients (100 of 1731) at 9 years. A total of 73.9% of patients had noninvasive adenocarcinoma (AIS or MIA) or other histology (1280 of 1731). Finally, the CTR in 100 patients with pathological invasive adenocarcinoma was less than 0.25 (Figure 2). Considering the rarity of patients, it may be difficult to produce results from large sample studies in the coming years.

In addition, the concept of moving the focus from T1N0M0 patients to a rare and understudied population is novel. Like other published studies of special populations with small sample sizes, such as 58 of 138 lung cancer patients with GGO ≥ 0.5, 46 patients diagnosed with noninvasive bronchioloalveolar carcinoma (BAC), and 53 patients (GGO ≥ 0.8, an intraoperative pathological diagnosis of BAC) proving satisfactory outcomes of SR compared with PL, our study provides another way to deal with invasive lung adenocarcinoma so that surgical time and normal lung tissue may be saved.[20,21,30]

In ordinary clinical practice, the surgical approach to mixed GGO partly depends on the surgeon's personal choice because of the debate of perspectives on these pulmonary nodules. Among different perspectives, the main one is how to determine the parameters which predict the invasiveness of lung cancer.[14] Researchers have tried multiple ways to screen low invasive lung cancer suitable for sublobectomy. In addition to the CTR and the maximum tumor diameter used in JCOG and other studies, the maximum standardized uptake value (SUVmax) of PET has also facilitated the selection of patients with a good prognosis after sublobar resection.[2] In addition, the model of quantifying invasiveness with computed tomography texture features was created to guide surgical extent.[31] Apart from indicators of radiology before surgery, perioperative blood detection can also be used to determine the malignancy of pulmonary nodules, but this is still at an exploratory stage.[32] In the near future, the more private individualized combined multi-omics models may provide a more individualized surgical plan.

In conclusion, we proved the feasibility of sublobectomy in stage IA1-2 invasive lung adenocarcinoma with a consolidation tumor ratio ≤ 0.25.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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