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ORIGINAL ARTICLE

Optimal sublobar resection for c-stage I non-small cell lung cancer: significance of margin distance to tumor size ratio and margin cytology (Supplementary analysis of KLSG-0801): complete republication

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Abstract

Background Sublobar resection for lung cancer is associated with a higher risk of recurrence than that of lobectomy; we evaluated the factors considered to be predictors of recurrence.

Methods By analyzing multicenter prospective studies of sublobar resection for patients with c-stage I non-small lung cancer who were unable to undergo lobectomy (KLSG-0801), we investigated the relationship between (1) tumor location (TL) and margin distance from the stump (MD), (2) the MD/tumor size (TS) ratio and prognosis, (3) and the margin cytology (MC) and prognosis.

Results The correlation between TS and MD was statistically significant in cases of easily resectable regions defined by Lewis' classification ($n=18$). However, there was no correlation in difficult-to-resect regions ($n=14$). Among cases of recurrence, the MD/TS ratio was less than 1. The 3-year survival rate was 100% for patients with MD/TS > 1 ($n=12$), 59.7% for patients with MD/TS ≤ 1 ($n=20$) ($p=0.06$), 88.1% in cases of negative MC ($n=18$), and 20% in cases of positive MC ($n=5$) ($p=0.001$).

Conclusion Cases with positive MC had a significantly worse prognosis than those with negative MC. It may be difficult to secure an MD greater than the TS in a difficult-to-resect region according to Lewis' classification.

Keywords Non-small cell lung cancer · Stage I · Margin distance · Tumor size · Margin cytology

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Objective

With the aging of the population, there is an increasing need for a less invasive treatment for lung cancer than lung lobectomy, which is the standard treatment for non-progressive disease [1].

Previously, we reported in a multicenter prospective study (KLSG-0801) that a sublobar pulmonary resection for patients, with limited physical preservation for lobectomy, obtained a safe, favorable treatment result in terms of anti-tumor effect. However, there are many reported cases of local recurrence after sublobar pulmonary resection: thus, control of local recurrence is essential to improve prognosis. From the consideration of KLSG-0801, it was suggested that a sufficient margin distance is important for sublobar resection. Therefore, we examined the relationship of tumor localization with margin distance, margin cytology, margin distance/tumor diameter ratio, and prognosis using the cases of KLSG-0801.

Subjects and methods

We performed a supplemental analysis using eligible cases ($n=32$) of a multicenter prospective study of sublobar pulmonary resection for c-stage I non-small cell lung cancer among patients with limited physical preservation for lobectomy (KLSG-0801) [2, 3]. The accrued cases were patients with predicted postoperative forced expiratory volume in 1 s (ppo-FEV1) less than 800 ml after lobectomy, or patients whose lesions were judged by a certificated thoracic surgeon to be difficult to treat by lobectomy, but not difficult to treat by sublobar pulmonary resection, regardless of comorbidity. On the other hand, cases where the lesion showed ground grass opacity in more than 75% of the area, or cases with active malignant disease other than the original lung cancer, were excluded.

Patient backgrounds are shown in Table 1. Tumor and operative factors, i.e., diagnosis, pathological stage, tumor localization (Lewis' classification [4]), tumor size (TS), shortest distance from the excision margin to tumor (MD) and margin cytology (MC) are shown in Table 2. Measurements of MD were carried out according to the methods of Goldstein et al. as shown in Fig. 1 [5]. Tumor localization was classified as either easily resectable (apex, edge, or lingual) or difficult to resect (large ovoid surface (LOS), deep in the fissure (DIF), or base) as shown in Fig. 2. The excision type (Type A, B-1, B-2, C) defined as the method applied by the automatic suturing device was determined in accordance with the classification of Sawabata [6].

A supplementary analysis was performed using the cases of KLSG-0801 approved by the institutional review board (IRB) of Osaka University Medical Hospital. The relationship between TS and MD was examined by determining the correlation coefficient and regression line for each tumor localization. To analyze prognosis, survival curves were obtained with overall survival and recurrence-free survival as endpoints, and significant differences were determined by the Wilcoxon test. All analyses were conducted using StatView5.0 (Japan SAS, Tokyo, Japan).

Table 1 Patients' characteristics

Sex (male, female)	30, 2
Age (median)(range)	74 (61–85)
Clinical stage (IA, IB)	30, 2
Comorbidity (+ : −)	31, 1
PS (0 : 1)	19, 13
Dyspnea (Hugh–Jones I:II:III)	12, 18, 2
FEV1 (mL) (median) (range)	1800 (790–3030)
%FEV1 (median) (range)	61.5 (27.8–114)

Results

The selected cases comprised 30 males and 2 females, and their median age was 74 years (61–85 years). Comorbid disease was present in 31 of 32 patients (Table 1). The median TS was 2.0 cm (1.0–3.5 cm) and the median MD was 1.6 cm (0.5–3.5 cm). Tumor localization according to the Lewis' classification was easy for 18 cases (6 cases of apex, 11 cases of edge, 1 case of lingual), difficult for 14 cases (2 cases of basal, 12 cases of LOS). In addition, the excision type, according to the method used by the automatic suturing instrument, was type A for 24 cases (75%) and type B2 for 7 cases (22%). In most cases, limited pulmonary resection using an automatic suturing instrument was performed mainly (Table 2). In the cases of easily resectable regions

Table 2 Tumor and surgical characteristics

Pathological stage (IA, IB)	25, 7
Pathological diagnosis (AD, SQ, other)	15, 14, 3
Tumor localization (Lewis' classification: easy, difficult)	18, 14
Surgical procedure (wedge, segmentectomy)	23, 9
Stapling (type A, B-I, B-II, C)	24, 1, 7, 0
Wedge (type A, B-I, B-II, C)	21, 0, 2, 0
Segmentectomy (type A, B-I, B-II, C)	3, 1, 5, 0
Tumor size (cm) (median) (range)	2.0 (1.0–3.5)
Margin distance (cm) (median) (range)	1.6 (0.5–3.5)
Margin cytology (positive, negative, not assessed)	5, 18, 9
TS/MD (>1, $\leqq 1$)	12, 20

AD adenocarcinoma, *SQ* squamous cell carcinoma

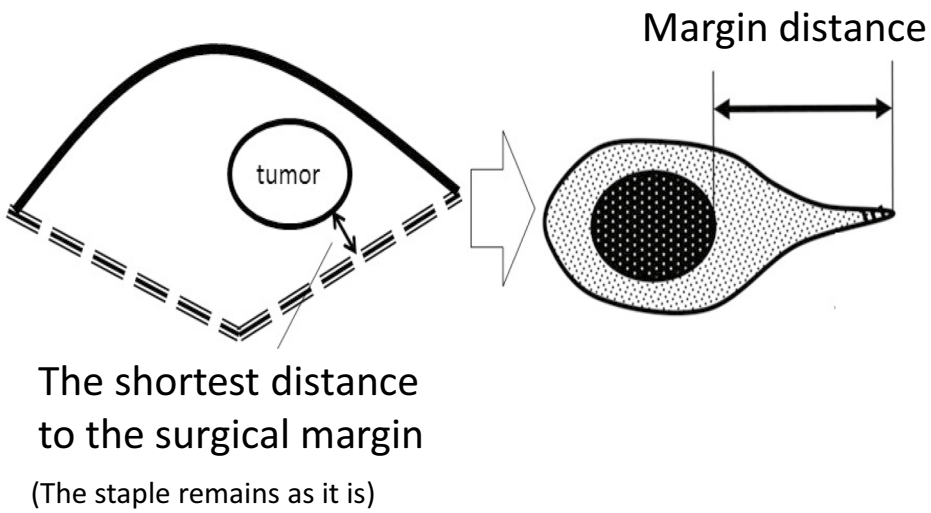

Fig. 1 Method used to measure margin distance

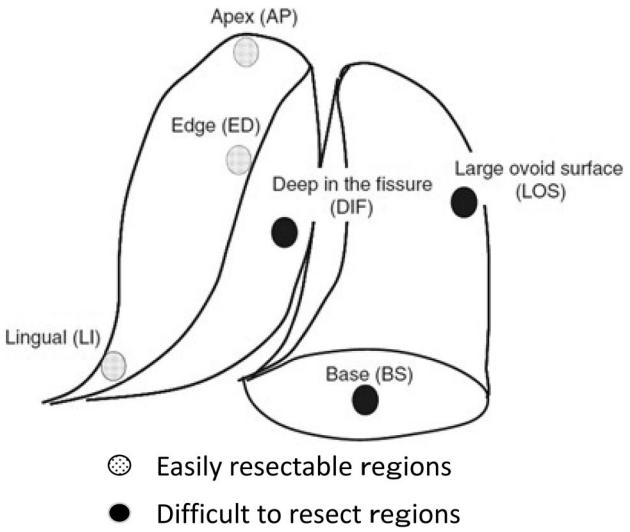

Fig. 2 Tumor location by Lewis' classification

according to Lewis' classification, the relationship between TS and MD tended to become stronger as TS increased (correlation coefficient = 0.53, $p = 0.04$) (Fig. 3a). In cases of difficult-to-resect regions in Lewis' classification, there was no correlation between TS and MD (correlation coefficient = − 0.07, $p = 0.70$), and sufficient MD could not be secured even with increased TS. (Fig. 3b). The median observation period was 39 months (5–71 months), and the outcomes were survival, death from original disease, and death from other disease in 23, 4, and 5 cases, respectively. There were 9 cases of recurrence. The patterns of recurrence were local recurrence without distant metastasis in 7 cases (ipsilateral lung: 3, pleura: 2, mediastinum lymph node: 1, surgical margin: 1), simultaneous local (pleura) and distant (liver) recurrence in 1, and distant metastasis (contralateral lung) in 1, while no recurrence was seen in 23 cases. In 8 of 9 cases of recurrence, MD/TS was ≤ 1. Table 3 shows background factors of cases with MD/TS ≤ 1 and MD/TS > 1. TS was significantly larger when MD/TS ≤ 1 ($p = 0.01$), while MD was significantly shorter when MD/TS ≤ 1 ($p = 0.006$). The 3-year recurrence-free survival rate (YRFS) was 66.2% when MD/TS ≤ 1 and 91.7% when MD / TS > 1 ($p = 0.05$, Fig. 4a).The 3-year overall survival rate (YSR) was 59.7% when MD/TS ≤ 1 and 100% when MD / TS > 1 ($p = 0.06$, Fig. 4b), and those patients with MD/TS ≤ 1 had poor prognosis. Table 4 shows the background factors of MC-positive and -negative cases. There was no difference in background factors between the two groups. For MC-positive and -negative cases, the survival values were, respectively, 20% and 88.2% for 3-YRFS ($p = 0.01$, Fig. 5a), and 20% and 88.1% for 3-YSR ($p = 0.001$, In Fig. 5b). Thus, the MC-positive cases had a significantly worse prognosis than in MC-negative cases.

Discussion

The standard treatment for non-advanced non-small cell lung cancer (NSCLC) is lobectomy associated with lymph node dissection up to the mediastinum, while sublobar resection is chosen in cases with high-risk factors related to the standard operation. Historical retrospective studies have reported that the 5-year overall survival rate (YSR) of patients undergoing a limited operation ranges from 20 to 69% and the 5-year recurrence-free survival rate (YRFS) ranges from 14 to 25%, indicating a high potential of local recurrence and shorter survival than in cases treated with lobectomy [7–13]. However, the annual report of the Japanese Association for Thoracic Surgery noted that sublobar pulmonary resection is extremely safe, so it is reasonable to conclude that this

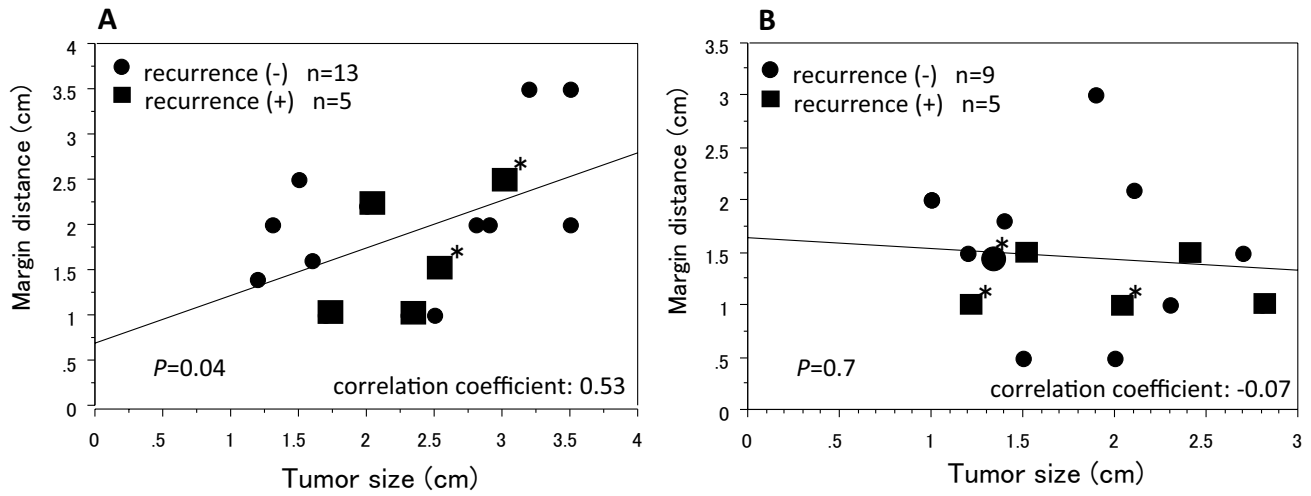

Fig. 3 Relationship between tumor size and margin distance. **a** Lewis' classification: easy; **b** Lewis' classification: difficult; astersik margin cytology, positive

Table 3 Patients' characteristics by margin distance (MD)/tumor size (TS) ratio

	MD/TS > 1($n=12$)	MD/TS ≦ 1($n=20$)	p value
Sex (male, female)	11,1	19,1	0.87
Age (median) (range)	74 (50–85)	75 (50–83)	0.76
%FEV1 (median) (range)	65.2 (29.9–84.5)	59.4 (27.8–114)	0.63
PaO_2	85.5 (70.5–98.6)	79.5 (68.3–106)	0.41
Pulmonary resection (wedge, seg)	7,5	16,4	0.39
Stapling (type A, B-I, B-II)	7,1,4	17,0,3	0.13
Tumor histology (AD, SQ, Other)	5,5,2	10,9,1	0.89
Pathological stage (IA, IB)	11,1	14,6	0.15
Location (easy, difficult)	6,6	12,8	0.58
Tumor size (cm) (median) (range)	1.4(1.0-3.2)	2.3(1.0-3.5)	0.01
Margin distance (cm)(median)(range)	2.0(1.4–3.5)	1.5(0.5–3.5)	0.006
Margin cytology (positive, negative)	1,9	4,9	0.21

AD adenocarcinoma, *SQ* squamous cell carcinoma, *Seg* segmentectomy

operation method has crucial clinical implications for high-risk patients [1].

On the other hand, in previous multicenter prospective phase II studies of stereotactic body radiation therapy (SBRT) for patients with limited physical preservation for lobectomy, the 3-YSR has ranged from 43 to 83%, the 3-YRFS from 92 to 98%, and the incidence of grade 3 adverse effects or greater from 3 to 28% [14–16]. Therefore, SBRT is considered to be an acceptable medical treatment.

In contrast, in KLSG-0801, grade 3 or greater adverse effects occurred in 2 cases (6.3%): and the 3-year surgical margin recurrence-free survival rate, 3-year local recurrence-free survival rate, and 3-YSR were 96.9%, 75.0%, and 79.0%, respectively. Thus, it appears that sublobar pulmonary resection for patients with limited physical preservation for lobectomy is equivalent to SBRT [2, 3]. However, many cases of local recurrence have been reported among patients who underwent sublobar pulmonary resection because of limited physical preservation for lobectomy.

Several risk factors for resected stump recurrence after sublobar pulmonary resection have been described, including positive stump cytology, vascular invasion, localization of the tumor and the insufficient distance to the resection stump [5, 17, 18]. Goldstein et al. reported that the mean microscopic wedge resection specimen margin distances in cases with and without residual adenocarcinoma in the lobectomy specimens were 0.7 and 2.4 mm, respectively ($p < 0.001$) [5]. Furthermore, Mohiuddin et al. reported that patients with a 10 mm margin distance had a 45% lower local recurrence risk than those with a 5 mm distance (hazard ratio, 0.55; 95% confidence interval, 0.35–0.86) [19].

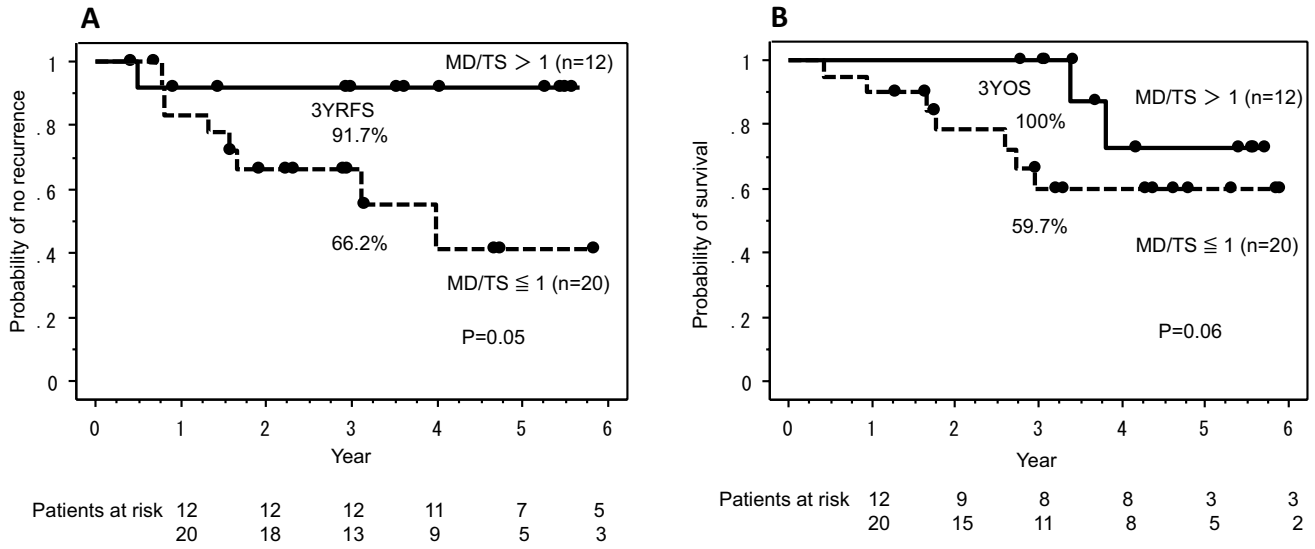

Fig. 4 Relationship between margin distance/tumor size and prognosis. **a** Recurrence-free survival(RFS): **b** Overall survival(OS). *MD* margin distance, *TS* tumor size

Table 4 Patients' characteristics by margin cytology

	Margin cytology		
	Positive ($n=5$)	Negative ($n=18$)	p value
Sex (male, female)	3:2	18:0	0.19
Age (median) (range)	70 (50–83)	74 (60–85)	0.13
%FEV1 (median) (range)	52.9 (46.3–88.2)	61.5 (28.2–114)	0.93
PaO2	83.0 (81.1–88.8)	81.0 (70.5–98.0)	0.94
Pulmonary resection (wedge, seg)	4, 1	13, 5	0.72
Stapling (type A, B-I, B-II)	4, 0, 1	14, 0, 4	0.91
Tumor histology (AD, SQ, Other)	4, 1, 0	7, 9, 2	0.25
Pathological stage (IA, IB)	4, 1	16, 2	0.6
Location (easy, difficult)	2, 3	9, 9	0.69
Tumor size (cm) (median) (range)	1.5 (1.0–3.0)	2.0 (1.0–3.2)	0.62
Margin distance (cm) (median) (range)	1.5 (1.0-2.5)	1.8 (0.5–3.5)	0.5
Margin distance/tumor size (median)	0.83 (0.60–1.15)	1.00 (0.25–2.00)	0.73

AD adenocarcinoma, *SQ* squamous cell carcinoma, *Seg* segmentectomy

So, it is important to secure a sufficient margin distance in sublobar pulmonary resection.

The optimum surgical margin distance for sublobar pulmonary resection has been reported to be either equal to/greater than the tumor diameter or 15 mm [18, 19]. Furthermore, there are reports that the positivity rate of margin cytology is high in cases with an insufficient margin distance [5]. The margin distance/tumor size ratio has also been previously reported to be a risk factor of recurrence at the surgical margin, or as a prognostic factor [18]. There has also been a report of positive margin cytology as a negative prognostic factor for surgical margin recurrence [20].

Moreover, in this study, we found that 8 out of 9 cases of recurrence had a margin distance/tumor size ≤ 1, which was particularly evident in cases of surgical margin recurrence and positive margin cytology. Regarding the prognosis, although there was no significant difference in 3-YSR between cases with margin distance/tumor size > 1 (100%) and those with margin distance/tumor size ≤ 1(59.7%), the prognosis was poorer for patients in the latter group. Based on Table 3, margin distance/tumor size ≦ 1 was significantly larger in tumor size and short margin distance. There is a possibility that the prognosis may deteriorate for patients with margin distance/tumor size ≦ 1. For margin cytology, the prognosis was significantly poorer in the positive cases than in the negative cases.

When the margin distance/tumor size was compared to the tumor localization with Lewis' classification, 12 out of

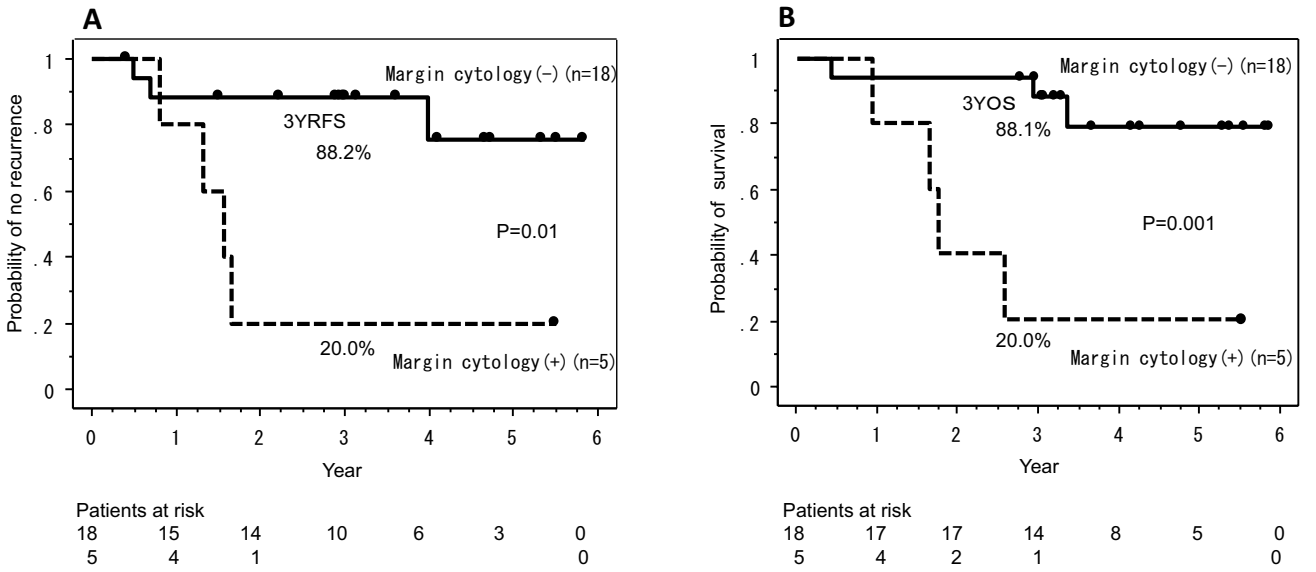

Fig. 5 Relationship between margin cytology and prognosis. **a** Recurrence-free survival(RFS); **b** overall survival (OS)

18 cases in easily resectable regions and 8 out of 14 in difficult-to-resect regions had margin distance/tumor size ≤ 1. In this study, pulmonary resection using an automatic suturing instrument was performed in most cases. Using this method, easily resectable regions in Lewis' classification showed a trend in which the margin distance increases as the tumor size increases. On the other hand, in difficult-to-resect regions defined by Lewis' classification, a margin distance equal to the tumor diameter was not obtained even when the tumor size was increased. Considering that the width of the automatic suturing instrument is about 10 mm, it is difficult to manually achieve a sufficient margin distance when using such an instrument to perform pulmonary resection in a difficult-to-resect region according to Lewis' classification, when using type A and B-2 method in Swawabata's classification. Therefore, we suggest that a new surgical procedure should be devised, such as pulmonary resection without using an automatic suturing instrument. Possible options include excision using an energy device and suturing or reinforcement of excision margin, or segmentectomy instead of wedge resection.

In sublobar pulmonary resection, it is possibility to select cases with excellent treatment outcomes by considering tumor size and localization. For difficult-to-resect cases in Lewis' classification, devising a better surgical procedure and securing a sufficient margin distance are expected to improve outcome. Furthermore, tumor diameter and tumor localization may be useful for deciding between surgery and SBRT for clinical stage I lung cancer, but the clinical significance of these factors must be further clarified. Based on these considerations, a multicenter prospective study of wedge resection for c-stage I (cT1N0M0) non-small cell lung cancer patients (ILO-1502, KLSG-1606) is ongoing, with the aim of identifying factors of local recurrence in sublobar pulmonary resection, and to show the necessity of establishing an appropriate surgical procedure [21, 22].

Conclusion

In sublobar pulmonary resection for lung cancer, cases with positive cytology margins had a significantly worse prognosis than those with negative margins. It is difficult to secure a margin distance equal to or greater than the tumor size. Therefore, it is necessary to devise a surgical procedure, such as a new pulmonary resection method that does not use an automatic suturing instrument, or segmentectomy instead of wedge resection.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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