Optimal Surgical Margin to Avoid Locoregional Recurrence for Non-small Cell Lung Cancer Larger than 2.0 cm: A Retrospective Study

Shigeki Suzuki (shgeki1209@yahoo.co.jp)
Sagamihara Kyodo Hospital: Sagamihara Kyodo Byoin https://orcid.org/0000-0002-8520-9393

Akio Kazama
Sagamihara Kyodo Hospital: Sagamihara Kyodo Byoin

Takao Shigenobu
Saiseikai Utsunomiya Hospital: Saiseikai Utsunomiya Byoin

Hiroyuki Sakamaki
Sagamihara Kyodo Hospital: Sagamihara Kyodo Byoin

Yohei Masugi
Keio University: Keio Gijuku Daigaku

Atsushi Tajima
Saiseikai Utsunomiya Hospital: Saiseikai Utsunomiya Byoin

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Abstract

Background. A parenchymal surgical margin of“the clinical tumor size or more” or “2.0 cm or more” has been widely recognized as the optimal margin distance to avoid locoregional recurrence after sublobar resection for non-small cell lung cancer (NSCLC) of 2.0 cm or less. However, the safe margin distance to avoid locoregional recurrence for NSCLC larger than 2.0 cm remains unclear.

Patients and Methods. Among 1,338 patients with resected primary lung cancers at two institutions between 2007 and 2016, 85 clinical N0M0 patients with NSCLCs larger than 2.0 cm who underwent sublobar resection were extracted. We classified these 85 NSCLCs as ground glass opacity (GGO)-dominant type or solid-dominant type according to computed tomography (CT) findings. Clinicopathological characteristics and the association between locoregional recurrence and margin distance were evaluated.

Results. The median clinical tumor size was 2.5 (2.1-4.9) cm. Based on CT findings, 14 tumors (16%) were considered GGO-dominant type and 71 (84%) were solid-dominant type. No lymph node metastasis, lymphatic permeation or vascular invasion was pathologically confirmed in GGO-dominant type. All GGO-dominant tumors were resected with a margin distance the size of the solid part on CT or more, resulting in no local recurrence, whereas, solid-dominant tumors recurred locally even if they were resected with a margin distance of “the clinical tumor size or more”.

Conclusions. The optimal surgical margin for NSCLC larger than 2.0 cm was “the size of the solid part on CT or more” for GGO-dominant type, but undefinable for solid-dominant type.

Introduction

As thin-section computed tomography (CT) has become more popular, ground glass nodules, which are lung nodules that show ground glass opacity (GGO), are being detected more frequently. GGO is defined as a hazy region of increased density that does not obscure underlying bronchovascular structures. In most cases, GGO represents a pathologically less-invasive carcinoma, while a solid component represents alveolar collapse and fibrosis, which implies cancer progression [1–5].

Recently, the size of the solid component in lung adenocarcinoma has been recognized as a better predictor of survival and tumor aggressiveness than the total tumor size [6–8]. Moreover, in the 8th edition of the Tumor–Node–Metastasis (TNM) classification of lung cancer [9], the size of the solid component should be used to assign the T category [10]. In lung adenocarcinoma showing GGO, previous studies revealed that a consolidation/tumor ratio (CTR) of 0.5 or less was an important cut-off value for predicting pathological invasiveness [11–14]. Moreover, the Japan Clinical Oncology Group (JCOG) 0201 study revealed that radiological early lung adenocarcinoma could be defined as adenocarcinoma of 3.0 cm or less with a CTR of 0.5 or less [15, 16].

Although the current gold standard for the surgical treatment of lung cancer is lobectomy, selected patients undergo sublobar resection based on the finding in retrospective studies that the prognosis after segmentectomy is not inferior to that after lobectomy in patients with GGO-dominant lung cancer of 2.0 cm or less [17–21]. In daily practice, sublobar resection is sometimes performed for other reasons such as low lung function, even for tumor larger than 2.0 cm. NCCN guidelines underscore that sublobar resection can be applied to both high- and low-risk surgical candidates, while lobectomy is recommended for large (> 2.0 cm) tumors if an adequate surgical margin is not obtainable [22]. Regarding the adequate surgical margin to avoid locoregional recurrence after sublobar resection, a margin distance of “the clinical tumor size or more” or “2.0 cm or more” is recommended for lung cancer of 2.0 cm or less [22–25], whereas that for lung cancer larger than 2.0 cm remains unclear.

In the present study, we focused on NSCLCs larger than 2.0 cm resected by sublobar resection and then analyzed the correlation between locoregional recurrence and margin distance to clarify the optimal surgical margin to avoid locoregional recurrence after sublobar resection.

Patients And Methods

Patients

Between January 2007 and December 2016, 1,338 consecutive patients with primary lung cancer underwent complete resection at two institutions. With the approval of the respective Institutional Review Boards, we reviewed the records for all patients; ultimately, 572 patients with clinical N0M0 NSCLC > 2.0 cm and ≤ 5.0 cm were selected. Patients who had undergone preoperative chemo- or radiotherapy or who had a history of lung cancer during the previous five years were excluded. As a result, 85 patients who underwent sublobar resection were eligible for this study. An overview of the study population selection and the effects of the various exclusion criteria are shown in Fig. 1. Most of the patients had some reason for undergoing limited resection such as poor lung function, comorbidity or advanced age.

Radiological tumor evaluation on thin-section CT

Chest contrast-enhanced CT scans at 5 mm collimation were used to determine the clinical staging of all patients. In addition, thin-section CT images at 1 mm collimation were used to evaluate primary lesions. The solid part was defined as an area of increased opacification that completely obscured the underlying bronchovascular structures. CTR was calculated by dividing the solid part by the maximum tumor diameter measured using the lung window setting.

Clinicopathological characteristics and surgical margin distance

The medical record of each patient was reviewed for age, gender, maximum tumor diameter on CT (clinical tumor size), maximum diameter of the solid part of the tumor on CT (solid part size), CTR, operative mode, adjuvant chemotherapy, histology, maximum pathological tumor diameter (pathological

tumor size), maximum diameter of invasive area of the tumor (invasive part size), lymph node metastasis, vascular invasion, lymphatic permeation, and pleural invasion. Histological type and predominant subtype in adenocarcinoma were described according to the 2015 World Health Organization (WHO) classification of cell types [26]. Surgical margin distance was recorded by pathologists in the pathological report. In our two institutions, margin distance was measured macroscopically from the closest resection line to the edge of the tumor as the gross cut-surface margin in the largest dimension based on a collapsed specimen with staples removed and the margin inked.

Patient follow-up

Patients were evaluated at 3-month intervals for the first two years and at 6-month intervals thereafter as outpatients. The follow-up evaluation included a physical examination, chest radiography, blood examination and annual chest to abdomen CT. Whenever any symptoms or signs of recurrence were detected, further evaluations were conducted, including brain magnetic resonance imaging and integrated positron emission tomography. When a single lung nodule appeared after surgery for lung cancer, it was difficult to accurately differentiate recurrence from new primary lesion. We performed lung biopsy if possible, and then diagnosed according to the Martini and Melamed criteria [27]. Observations were censored at the last follow-up when the patient was alive or lost to follow-up. The date of recurrence was defined as the date of histological proof or, in cases that were diagnosed based on clinical and radiological findings, the date of identification by a physician. Locoregional recurrence was defined as any recurrence in the ipsilateral hemithorax.

Standards of surgical margin based on CT findings and local recurrence

We divided the 85 clinical N0M0 NSCLCs into GGO-dominant type (CTR $\leq$ 0.5) and solid-dominant type (CTR > 0.5) according to CTR. We assumed the following four standards of surgical margin distance to avoid locoregional recurrence: 1) the clinical tumor size or more, 2) the solid part size or more, 3) 2.0 cm or more, and 4) 3.0 cm or more. To test whether these standards were adequate or not, we counted the number of cases of locoregional recurrence under the respective standards in each type of GGO. Because of the small number of cases, we assessed the association between the number of cases of locoregional recurrence and the surgical margin, not in terms of statistical significance or the recurrence rate, but rather whether there was recurrence or not.

Results

Clinicopathological findings

The clinicopathological characteristics of the 85 patients are summarized in Table 1. In this cohort, 60 patients were diagnosed as adenocarcinoma (6 adenocarcinomas in situ (AIS), 2 minimally invasive adenocarcinomas (MIA), 13 lepidic adenocarcinomas, 19 papillary adenocarcinomas, 9 acinar adenocarcinomas, 8 solid adenocarcinomas and 3 micropapillary adenocarcinomas) and 25 were diagnosed as non-adenocarcinoma (19 squamous cell carcinomas, 3 large cell carcinomas and 3 large

cell neuroendocrine carcinomas). The median age was 74 (56–90) years. The median clinical tumor size was 2.5 (2.1–4.9) cm and the median solid part size was 2.2 (0–4.0) cm. On the other hand, the median pathological tumor size was 2.5 (2.0–5.0) cm and the median invasive part size was 2.2 (0-4.7) cm. Based on preoperative CT findings, 14 tumors (16%) were assessed as CTR ≤ 0.5 and 71 (84%) were assessed as CTR > 0.5. Segmentectomy and wedge resection were performed in 41 (48%) and 44 patients (52%), respectively. Hilar and/or mediastinum lymph node dissection was performed in 46 (54.1%) patients. Concerning pathological characteristics, only one case of lymph node metastasis (1.2%), 22 cases of lymphatic permeation (25.9%), 14 cases of vascular invasion (16.4%) and 30 cases of pleural invasion (35.2%) were confirmed pathologically.

Table 1
Clinicopathological Characteristics of Patients with NSCLC Larger than 2.0 cm (N = 85)

Characteristics	N
Age, years	74 (56–90)
Sex	
Male	60 (70.5)
Female	25 (29.5)
Clinical tumor size, mm	25 (21–49)
Solid part size, mm	21.5 (0–40)
CTR	
≦ 0.5	13 (15.3)
>0.5	72 (84.7)
Operative mode	
Segmentectomy	41 (48.2)
Wedge resection	44 (51.8)
Lymph node dissection	46 (54.1)
Adjuvant chemotherapy	4 (4.7)
Histology	
Adenocarcinoma	60 (70.5)
Non-adenocarcinoma	25 (29.5)
Squamous cell carcinoma	19 (22.3)
Large cell carcinoma	3 (3.6)
LCNEC	3 (3.6)
Pathological tumor size, mm	25 (20–50)
Invasive part size, mm	21.5 (0–47)
Lymph node metastasis	1 (1.2)
Lymphatic invasion	22 (25.9)
Vascular invasion	14 (16.4)

Values are n (%) or median (interquartile range)

Characteristics	N
Pleural invasion	30 (35.2)
Values are n (%) or median (interquartile range)	

Clinicopathological findings according to the type of GGO

The clinicopathological characteristics according to the type of GGO are shown in Table 2. The characteristics for each type did not differ significantly with respect to the clinical tumor size, surgical mode, pathological tumor size, lymph node metastasis or vascular invasion. AIS and MIA were seen in 6 (46.2%) and 2 (15.4%), respectively, in GGO-dominant type, whereas they were not observed in solid-dominant type. Lymph node metastasis, vascular invasion, lymphatic permeation and pleural invasion were not detected in GGO-dominant type. No recurrence was observed in patients with GGO-dominant type, whereas recurrence was observed in 26 of 72 (36.1%) patients with solid-dominant type.

Table 2
Characteristics of NSCLC Larger than 2.0 cm According to the Proportion of GGO

Characteristics	GGO-dominant (N = 13)	Solid-dominant (N = 72)	p^a
Clinical tumor size, mm	23 (21–49)	24 (21–41)	0.931
Solid part size, mm	3 (0–15)	22 (12–40)	< 0.001
CTR	0.13 (0-0.50)	1.0 (0.53-1.0)	< 0.001
Operative mode			0.259
Segmentectomy	8 (61.5)	34 (47.2)	
Wedge resection	5 (38.5)	38 (52.8)	
Histology			< 0.001
Adenocarcinoma	13 (100)	47 (65.3)	
AIS	6 (46.2)	0 (0)	
MIA	2 (15.4)	0 (0)	
Lepidic	4 (30.8)	9 (12.5)	
Papillary	1 (7.7)	18 (25)	
Acinar	0 (0)	9 (12.5)	
Solid	0 (0)	8 (11.1)	
Micropapillary	0 (0)	3 (4.2)	
Non-adenocarcinoma	0 (0)	25 (34.7)	
Pathological tumor size, mm	25 (20–45)	25 (20–50)	0.342
Invasive part size, mm	3 (0–35)	22 (4–47)	< 0.001
Lymph node metastasis	0(0)	1 (1.4)	0.804
Lymphatic permeation	0(0)	22 (30.6)	0.018
Vascular invasion	0 (0)	14 (19.4)	0.114
Pleural invasion	0 (0)	30 (41.7)	0.015

Values are n (%) or median (interquartile range)

[a] Chi-square test or one-way analysis of variance. Significance was defined as a *p*-value of less than 0.05.

AIS adenocarcinoma in situ; *CTR*: consolidation/tumor ratio; *GGO*: ground glass opacity; *MIA*: minimally invasive adenocarcinoma; *NSCLC*: non-small cell lung cancer.

Characteristics	GGO-dominant (N = 13)	Solid-dominant (N = 72)	p^a
Recurrence after surgery	0 (0)	26 (36.1)	0.034
Values are n (%) or median (interquartile range)			
[a] Chi-square test or one-way analysis of variance. Significance was defined as a *p*-value of less than 0.05.			
AIS adenocarcinoma in situ; *CTR*: consolidation/tumor ratio; *GGO*: ground glass opacity; *MIA*: minimally invasive adenocarcinoma; *NSCLC*: non-small cell lung cancer.			

Rate and Type of Recurrences

The details of the type of recurrence are shown in Table 3. The median follow-up period was 45 (1-177) months. Recurrence was observed in 26 (30.6%) patients including 17 locoregional recurrences (3 lymph node metastases, 2 pleural disseminations, 9 pulmonary metastases in the same lobe, 3 pulmonary metastases in another lobe) and 9 distant metastases.

Table 3
Rate and Type of Recurrence After Sublobar Resection in Patients with NSCLC Larger than 2.0 cm

Type of recurrence	N (%)
Absent	59 (69.4)
Present	26 (30.6)
Type of recurrence	
Distant	9 (10.6)
Locoregional	17 (20)
Same lobe	9 (10.6)
Another lobe	3 (3.5)
Lymph node	3 (3.5)
Pleural dissemination	2 (2.4)
NSCLC non-small cell lung cancer.	

Locoregional recurrence under the respective standards of surgical margin

Locoregional recurrence in patients with GGO-dominant type or solid-dominant type under the four standards of surgical margin is shown in **Table 4**, where the number of recurrences is shown as “number of recurrences/number of cases that did or did not meet the respective standard of surgical margin”.

Locoregional recurrence was observed under all standards of surgical margin in solid-dominant type, whereas no locoregional recurrence was observed in GGO-dominant type in any cases.

The details of 13 GGO-dominant cases are shown in Table 5. Five wedge resections and 8 segmentectomies were performed. The average surgical margin was 1.7 (range:0.5– 5.2) cm. For solid dominant tumor (data not shown), the average surgical margin in patients with and without recurrence was 1.9 (range:0.3-5.0) cm and 1.5 (range:0.5-5.0) cm, respectively. All of the GGO-dominant cases were resected with a margin distance of the size of the solid part or more.

Table 5
Details of CT Findings and Surgical Margin Distance in All GGO-dominant Cases

	Laterality/Segment	Clinical tumor size (cm)	Solid part size (cm)	Operative mode	Margin distance (cm)
1	R / S2	2.1	0	Segmentectomy	0.5
2	L / S3	2.1	0.4	Segmentectomy	0.8
3	L /S6	2.1	0	Segmentectomy	1.1
4	L /S3	2.1	1.0	Wedge resection	1.3
5	R / S2	2.2	0	Wedge resection	0.9
6	L / S6	2.2	0	Segmentectomy	2.1
7	L / S3	2.3	0.7	Wedge resection	1.1
8	R / S8	2.4	0	Segmentectomy	1.3
9	L / S5	2.4	0.3	Segmentectomy	1.5
10	R / S2	2.5	0	Wedge resection	2.5
11	L / S1 + 2	3.0	0.8	Wedge resection	2.0
12	L / S10	3.8	0.5	Segmentectomy	1.8
13	L / S1 + 2	4.9	1.5	Segmentectomy	5.2

CT computed tomography, *GGO* ground glass opacity, *L* left, *R* right, *S* segment.

Discussion

In lung cancer of 2.0 cm or less, a safe surgical margin to avoid locoregional recurrence after sublobar resection is widely recognized as “the clinical tumor size or more”. However, no consensus has been

reached in lung cancer larger than 2.0 cm. Since the size of the solid component is considered to be very important, we examined the optimal surgical margin to avoid locoregional recurrence after sublobar resection in NSCLC larger than 2.0 cm. We demonstrated that a sufficient surgical margin distance to avoid locoregional recurrence was “the size of the solid part or more” for GGO-dominant type, but was undefinable for solid-dominant type.

Based on the results shown in Table 2, most pathological characteristics indicated that patients with GGO-dominant tumor had a better outcome than those with solid-dominant tumor. Regarding pathological invasiveness, neither lymph node metastasis, lymphatic permeation nor vascular invasion was observed in GGO-dominant tumors. Because we included only cN0M0 NSCLC in this study, there were few lymph node metastases even in solid-dominant tumor. Moreover, the size of the invasive part of solid-dominant type was significantly larger than that of GGO-dominant type ($p < 0.001$). Tsutani et al. reported that the size of the invasive part was significantly associated with malignant behavior and recurrence in lung adenocarcinoma [6]. Regarding the predominant subtype in adenocarcinoma, several studies have shown that micropapillary and solid adenocarcinoma were associated with poor survival [28–32]. In our study, while micropapillary and solid adenocarcinoma were not observed in GGO-dominant type, they were observed in 4.2% and 11.1% of solid-dominant type, respectively. We thought that these pathological characteristics of GGO-dominant type as mentioned above might support the notion that the minimum surgical margin distance required to avoid locoregional recurrence in GGO-dominant type was smaller than that in solid-dominant type.

In our study, there was no recurrence in GGO-dominant tumor (**Table 4**), suggesting that we may be able to avoid locoregional recurrence if we achieve complete resection. Moon et al. reported that there was no locoregional recurrence if they could achieve R0 resection in GGO-dominant NSCLC of 3.0 cm or less (HR 3.87, $p = 0.027$) [33]. However, we previously reported that, while lymph node metastasis was not observed, lymphatic permeation (7.5%) and vascular invasion (11.3%) were observed in 53 GGO-dominant NSCLC larger than 3.0 cm that were resected by lobectomy [34]. As such, the surgical margin should be considered, even if the target lesion for surgery is GGO-dominant type, to achieve R0 resection by sublobar resection.

Our suggestions for the optimal surgical margin for NSCLC are shown in Fig. 2, which was made by combining the results in this study for NSCLC larger than 2.0 cm with current standards for NSCLC of 2.0 cm or less based on previous studies [23, 24] From the results that all GGO-dominant tumors larger than 2.0 cm were resected with a margin distance of the size of the solid part or more and there was no recurrence, we thought that this could be regarded as a standard surgical margin to avoid locoregional recurrence for GGO-dominant tumor. In contrast, for a solid-dominant tumor, locoregional recurrence occurred even if the tumor was resected with a margin distance of the clinical tumor size or more, which is why we thought that a standard surgical margin to avoid locoregional recurrence for solid-dominant type was undefinable. It may be better to add postoperative radiation therapy or chemotherapy to sublobar resection to avoid locoregional recurrence in solid-dominant tumor larger than 2.0 cm.

This study was limited by its retrospective nature and the small number of cases because we focused on relatively rare cases that underwent sublobar resection for large tumor, which was contrary to the current gold standard for the surgical treatment of lung cancer. To our knowledge, previous studies to determine the optimal surgical margin in NSCLC included only about 30% tumors larger than 2.0 cm that underwent sublobar resection (**Additional** Table 1) [23–25, 35–37]. If possible, we will accumulate more cases and validate our results and theories in a larger population in the near future. As another limitation, 39 of the 85 (45.8%) patients did not undergo lymph node dissection. Three patients recurred in lymph node after surgery, however those patients had undergone lymph node dissection and were assessed as pathological N0. In other words, none of the patients without lymph node dissection showed lymph node recurrence after sublobar resection, suggesting that this limitation had little influence on our results. As for operative mode, lymph node dissection and adjuvant chemotherapy, we performed a univariate analysis to verify the influence of these factors on our results (**Additional** Table 2). As a result, none of these factors was significantly associated with locoregional recurrence. We could not perform a multivariate analysis because of the small number of events.

In conclusion, the optimal surgical margin to avoid locoregional recurrence after sublobar resection in NSCLC larger than 2.0 cm was “the size of the solid part or more” for GGO-dominant tumor, while it was undefinable for solid-dominant tumor. We believe that our results represent important findings for the daily treatment of large tumor showing GGO, particularly in patients with low lung function. Moreover, our results should help future multicenter prospective trials to determine indications for sublobar resection for large tumor showing GGO.

Abbreviations

AIS: Adenocarcinomas in situ; CT: Computed tomography; CTR: Consolidation/tumor ratio; JCOG: Japan Clinical Oncology Group; MIA: Minimally invasive adenocarcinoma; NSCLC: Non-small cell lung cancer; TNM: Tumor–Node–Metastasis; WHO: World Health Organization

Declarations

Authors’ contributions

SS wrote the main manuscript and participated in the study design and data analysis. TS interpreted the patient data. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

All patients provided written informed consent before the operation, and this study was approved by the ethics committee of the two hospitals.

Consent for publication

Written informed consent was obtained from the patients for publication of research article

Competing interests

The authors declare no conflicts of interest.

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Figures

Fig. 1

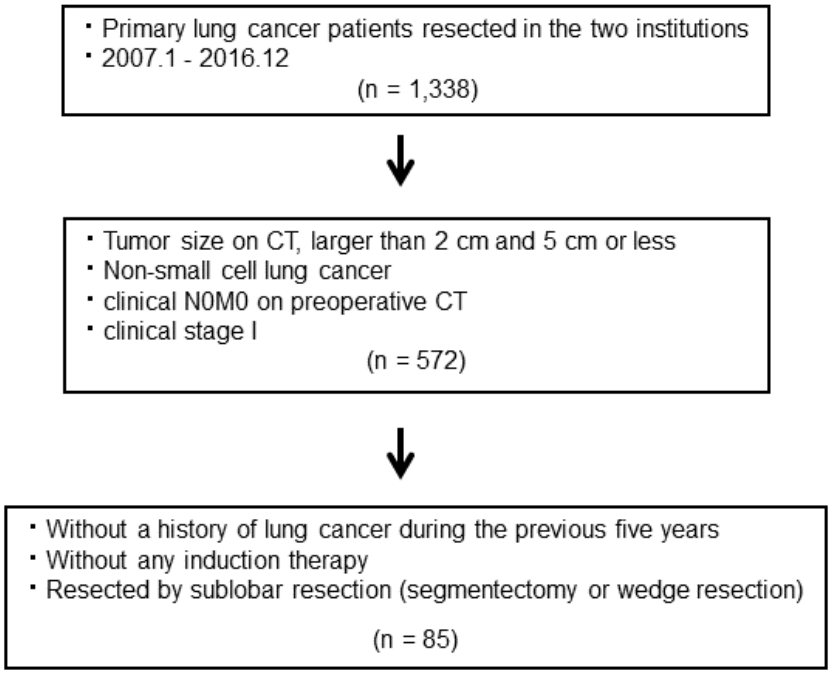

Figure 1

Schema for the study population.

Fig. 2

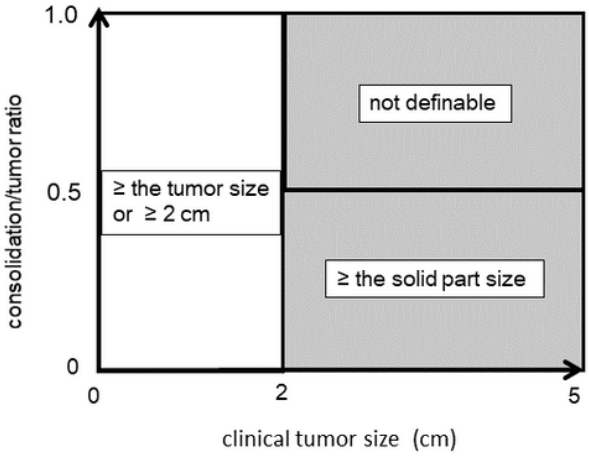

Figure 2

Our suggested optimal surgical resection margin for non-small cell lung cancer to avoid locoregional recurrence after sublobar resection. The optimal surgical margin distance was “the size of the solid part or more” for ground glass opacity-dominant type, and was undefinable for solid-dominant type.

Supplementary Files

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