Feasibility of limited resection for peripheral small-sized non-small cell lung cancer: A retrospective single-center center-based study

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Abstract

Purpose: This study aimed to establish new criteria for limited resection of non-small cell lung cancer (NSCLC) based on computed tomography findings and maximum standardized uptake value (SUVmax).

Methods: Between December 2007 and December 2015, 611 patients underwent lung cancer surgery; of these 70 with cT1aN0M0 who underwent limited resection, were enrolled. Criteria for undergoing intentional limited resection (ILR) were (1) tumor ground-glass opacity (GGO) ratio of ≥0.75 and (2) tumor SUVmax ≤1.5. Patients who met criteria (1) and (2) underwent partial resection and those who only met criteria (2) underwent segmentectomy as ILR. The control group was subjected to limited surgery without meeting the criteria.

Results: Overall, 45 and 25 patients who met our criteria were included in the ILR and control groups, respectively. In the ILR group, 13 patients underwent partial resection and 32 underwent segmentectomy; in the control group, 18 patients underwent partial resection and 7 underwent segmentectomy. According to our criteria, no relapsed cases occurred in the ILR group, although six patients showed recurrence of lung cancer in the control group. The 5-year overall survival (OS) rates in the ILR and control groups were 100% and 67.7%, respectively, and the relapse-free survival (RFS) rates were 100% and 61.6%, respectively. Log-rank test showed that this difference was statistically significant (OS: $P<0.0001$, RFS: $P<0.0001$).

Conclusions: SUVmax may serve as a predictive marker of recurrence to determine the treatment strategy for patients with NSCLC. Patients with low GGO ratio and low SUVmax may be cured by limited resection.

Keywords: Non-small cell lung cancer; limited resection; SUVmax; segmentectomy

Introduction

The standard surgical procedure for non-small cell lung cancer (NSCLC) is lobectomy with lymph node dissection or sampling. Furthermore, limited resection, including segmental resection or wedge excision, is performed in patients who cannot undergo lobectomy because of their poor cardiorespiratory function (Bennett and Smith 1979; Miller and Hatcher Jr 1987) or in elderly patients because it is associated with low complication rates (Miller and Hatcher Jr 1987; Kilic et al. 2009). Recently, due to the introduction of the low-dose computed tomography (CT) screening in high-risk patients, an increase in the incidence of early stages of NSCLC has been reported (Yendamuri et al. 2013). Furthermore, an increasing number of tumors have been shown to have ground-glass opacity (GGO) component on CT scans, which made it difficult to identify the tumors on X-ray (Asamura et al. 2003; Sakurai et al. 2004) .

In terms of treatment for these small tumors and tumors with large GGO components, there have been increasing reports of intentional limited resection (ILR) as an attempt to achieve both therapeutic efficacy and preservation of pulmonary function (Sagawa et al. 2018; Zhong et al. 2018). In addition, some prospective randomized clinical trials are underway to determine whether ILR could be the standard procedure for small lung cancer (Aokage et al. 2017; Nakamura et al. 2009b). According to these reports, the tumor diameter and the ratio of the GGO component could be important criteria for ILR; however, in these studies, they used only CT imaging findings of tumors as criteria for ILR eligibility.

Since recently, positron emission tomography (PET) examination have been widely used, and there have been increasing number of reports suggesting that 18F-fluorodeoxyglucose (FDG) uptake was associated with prognosis in lung cancer patients (Kishimoto et al. 2014; Umakoshi et al. 2018; Wang et al. 2020; Li et al. 2020). Furthermore, in a retrospective study evaluating the prognosis based on the maximum standardized uptake value (SUVmax) in GGO, the combination of SUVmax and GGO ratio was suggested to be a predictor of prognosis in lung cancer patients (Uehara et al. 2013).

In this study, we aimed to retrospectively evaluate the relationship between the GGO ratio, SUVmax, and the prognosis in NSCLC patients. To this end, we developed new criteria which were based on GGO ratio and primary tumor's SUVmax to determine whether patients with NSCLC were eligible for ILR. We further evaluated postoperative prognosis and recurrence and examined the effect of adding the SUVmax of primary tumor to the criteria for ILR.

Patients and Methods

Patients

Between January 2007 and December 2015, 611 patients underwent surgery for lung cancer at our institution. The patients were clinically staged according to the seventh edition of the Union for International Cancer Control TNM classification (Sobin et al. 2009). Among these patients, 243 patients (40.3%) were diagnosed with clinical stage IA (cT1a/bN0M0) NSCLC. Twenty-six patients with history of surgery for lung cancer were excluded. Further, 137 patients who underwent surgery other than segmentectomy or partial lung resection were also excluded. In addition, two patients with small cell lung cancer, two diagnosed as microscopic residual disease, two with multiple lung cancer, and four who had some of their medical records missing were excluded. Finally, 70 patients who underwent segmentectomy or partial lung resection were included in this study (Fig. 1).

Based on the previous study performed at our institution, we found that lung cancer patients with low SUVmax in a primary tumor were less likely to have lymph node metastasis (Hida et al. 2012). Therefore, the two following criteria were set for performing sublobar resection: (1) tumor GGO ratio of ≥0.75 and (2) primary tumor SUVmax of ≤1.5 (≤1.0, until 2008). GGO ratio was calculated using the following equation as an area ratio: GGO ratio = [(maximum diameter of the tumor) (minimum diameter of the tumor) – (maximum diameter of tumor consolidation) (minimum diameter of the tumor consolidation)]/(maximum diameter of the tumor) (minimum diameter of the tumor). From 2007, partial resection was performed for Stage IA lung cancer patients who met the criteria of (1) and (2), and segmentectomy was performed for patients with stage IA lung cancer that did not meet the criteria of (1) but met the criteria of (2). These patients were designated into the ILR group, and those who underwent limited resection for other reasons, such as poor operability, were considered as a control group (Fig. 2). As a result, the ILR group comprised 45 cases and the control group 25 cases. All patients provided informed consent for the procedure and provided written informed consent for institutional storage of their personal data in a scientific database. The medical ethics committee of the Hokkaido University School of Medicine approved this study protocol (approval number: #019-0349).

SUVmax Criteria

SUVmax of the primary tumor was evaluated using FDG-PET or FDG-PET/CT. Between 2000 and 2008, we used an FDG-PET Siemens ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN, USA), while after 2009, we used an FDG PET/CT Biograph 64 TruePoint with TrueV PET/CT scanner (Siemens Japan, Tokyo). Based on the examination results of the differences in SUVmax among models using a phantom, cases with SUVmax ≤1.0 until 2008 and cases with an SUVmax ≤1.5 from 2009 were used as criteria for ILR.

Statistical Analyses

All statistical analyses were performed using JMP software (version 14.0; SAS Institute Inc., NC, USA). Inter-group comparisons were performed using the χ^2 test or Fisher's exact test, as appropriate. Survival outcomes were plotted using the Kaplan-Meier method and compared using the log-rank test. Overall survival (OS) was defined as the time from surgery until death, regardless of the cause of death. Relapse-free survival (RFS) was defined as the time from surgery until the first instance of recurrence or death. Differences were considered statistically significant at two-sided *P*-values of <0.05.

Results

Patient Characteristics

The patient characteristics and clinical findings are summarized in Table 1. The tumors were classified according to the World Health Organization International Histological Classification of Tumors (Seifert 1988) as adenocarcinoma in 58 patients (82.9%), squamous cell carcinoma in 10 (14.3%), mucoepidermoid carcinoma in one (1.4%) and large cell carcinoma in one (1.4%). The median tumor size was 14 mm (range: 6–20). In terms of surgical approaches, the resections involved segmentectomy in 39 patients (55.7%) and partial resection in 31 patients (44.3%).

Pathological Diagnoses Comparison Between ILR and Control Groups

Based on the criteria described above, we divided the patient cohort into two groups: the ILR and the control groups. The patient characteristics and comparison between two groups are summarized in Table 2.

There was no significant difference in the age or in the size of the primary tumor between the two groups. There was a significantly higher number of female patients in the ILR group than in the control group (*P*=0.0057). In addition, the number of patients who were diagnosed with adenocarcinoma was significantly higher in the ILR than in the control group *P*<0.0001). Because this cohort was divided into two groups based on GGO ratio and SUVmax, it was obvious that there was a significant difference between the two groups in these two parameters (GGO ratio: *P*<0.0001, SUVmax: *P*=0.0003). Regarding the operative procedure, there was a significantly higher number of patients who underwent segmentectomy in the ILR group (*P*=0.0009); for this reason, the number of patients who underwent nodal dissection was also significantly higher in the ILR group (*P*=0.0329). No regional lymph node metastases were found in either group.

Survival Rate

The OS and RFS outcomes were analyzed in both groups and compared between the two. The 5-year OS rates in the ILR and control groups were 100% and 67.7%, respectively, and the RFS rates were 100% and 61.6%, respectively. Kaplan-Meier survival curves were greater in the ILR group than in the control group for both OS and RFS; and based on the log-rank test, this difference was statistically significant (OS: $P<0.0001$, RFS: $P<0.0001$) (Fig. 3).

Postoperative recurrence was observed in six patients in the period of investigation. Three of them died due to the recurrence of lung cancer and one other patient died due to the stroke. Apart from these, there were two cases in which secondary lung cancer appeared. In one case, secondary lung cancer appeared 3.5 years after the surgery and the final diagnosis was made by surgical resection. In another case, the cancer appeared 6.5 years after the surgery and the final diagnosis was made by imaging studies. The characteristics and clinical findings of postoperative recurrence cases are shown in Table 3. Three of the six patients underwent segmentectomy and three others underwent partial resection. The GGO ratios were low in all recurrent cases; only one had GGO component, but the others were all solid tumors. SUVmax was higher than those defined in our criteria in all cases. Regarding the site of recurrence, hilum or mediastinal lymph node recurrence were observed in four cases, and distant metastases were detected in five.

We divided all patients into eight groups based on three factors; surgical procedure, GGO ratio, and SUVmax value and examined the breakdown of recurrent cases (Table 4). Although there were no cases in which the GGO ratio and SUVmax were high and segmental resection was performed, no recurrence was observed, regardless of the surgical procedure or SUVmax in all cases with high GGO ratio.

In patients with low GGO ratio and high SUVmax, recurrence was observed in 3 out of 12 partial resections and in 3 out of 7 segmentectomy cases. Conversely, in patients with low GGO ratio and low SUVmax, no recurrence was observed in 4 patients who underwent partial resection or in 13 patients who underwent segmental resection as ILR.

Discussion

In this study, we aimed to identify criteria for stratifying patients who were eligible for limited resection and those that were not eligible for limited resection. Our findings demonstrated that none of the patients who underwent ILR after meeting the criteria based on GGO rate and SUVmax relapsed. From previous reports, it is clear that it was not correct to consider only the tumor size to determine whether to perform limited resection, and it generally tended to be based on tumor size and GGO ratio (Tsutani et al. 2013b; Kodama et al. 2016; Ye et al. 2018). According to these reports, limited surgery was performed for tumors with a tumor diameter of 2 cm or less and high GGO ratio, and most of the cases are performed partial resection and the prognosis are good (Tsutani et al. 2013b; Ye et al. 2018). The treatment for this group does not change much, on the other hand, lobectomy is selected for small tumors with low GGO ratio using these criteria. The new findings of our report are that the group for which lobectomy was selected might be able to be stratified by SUVmax value. Our report suggests that patients with low GGO ratio and low SUVmax might be cured by appropriately selected limited resection, which may be a new option for patients with low lung function.

Regarding the criteria for performing ILR, tumor diameter is one of the factors that should be considered. Some studies that have performed limited resection for lung cancer with a tumor diameter of ≤2 cm have been reported, and one meta-analysis stated that the prognosis in such cases after reduced resection was not inferior to that of lobectomy [Nakamura et al. 2005a; Yoshida et al. 2010; Okada et al. 2006). However, the subject of each report varied, and according to the guidelines, the standard surgery for lung cancer with a tumor diameter of ≤2 cm is lobectomy, while limited resection is also acceptable (Ettinger et al. 2019). This indication of limited resection based solely on the tumor diameter may not accurately reflect the malignant potential of the tumor; therefore, in recent years, there have been some reports adding the GGO ratio as an indicator for limited resection (Sagawa et al. 2018; Cho et al. 2015; Huang et al. 2018b). According to the Noguchi classification, it is well known that the recurrence rate of lung cancer in Noguchi type A and type B is extremely low, and the clinical outcomes in patients with tumors with high GGO ratio who underwent limited resection based on this knowledge were favorable (Noguchi et al. 1995). For this reason, the GGO ratio will continue to be an important index for deciding whether to perform ILR.

For SUVmax, some reports suggested that the prognosis of lung cancer was better in patients with low primary SUVmax than in those with high SUVmax and there was a report suggesting that SUVmax could be a predictor of nodal metastasis in early stage lung adenocarcinoma (Kishimoto et al. 2014; Umakoshi et al. 2018; Wang et al. 2020; Li et al. 2020, Tsutani et al. 2012a). Although SUVmax is considered as a good prognostic marker, there is some concern about variations in the FDG uptake values based on inter-institution or inter-model differences in PET instruments; furthermore, FDG uptake values can also vary depending on the size of the patient's body and the presence or absence of diabetic complications (Lasnon et al. 2013; Akamatsu et al. 2012; Boellaard 2011; Busing et al. 2013). For this reason, it is necessary to consider these variations when evaluating SUVmax. It may be difficult to establish a uniform standard; however, we believe that SUVmax may be correlated with tumor malignancy, and that adding SUVmax to the list of criteria for limited resection could help select patients for this procedure more accurately. Although our study did not find any cases with both high GGO ratio and high SUVmax, there were cases with low GGO ratio and low SUVmax. Patients with low GGO ratio and high SUVmax, as described above, were not eligible for ILR if they were stratified by criteria based on only GGO ratios; however, they were eligible for ILR by our criteria taking SUVmax into account. Therefore, using our criteria, we could identify more patients who were eligible for ILR as curative surgery.

In terms of curability, segmentectomy is considered to be a more curative operation than partial resection, and it has been reported that segmental resection has a better prognosis for lung cancer patients with tumors of 2 cm or less than partial resection (Dai et al. 2016). The major differences between segmental resection and partial resection are the possibility of systematic lymphadenectomy and the length of resection margin. We believe that these factors are related to the reason why this segmental resection is more curative. Regarding lymphadenectomy, it is impossible to remove peripheral lymph nodes from the # 12 lymph node in the case of partial resection; therefore, lymph node dissection is generally not performed. Conversely, lymphadenectomy is possible for segmental resection cases. Although some results of randomized trials that compared the effectiveness of systematic lymph node sampling suggested that they did not improve prognosis but contributed to accurate staging, this conclusion remains controversial (Darling et al. 2011; Ma et al. 2013; Huang et al. 2014a). If an accurate diagnosis of lymph node metastasis could be made, there is a possibility that there would be no difference between partial resection and segmental resection in this study, but that is a future study subject. In terms of the length of resection margin, several reports suggested the importance of resection margins in cases with small but solid or high SUVmax tumors (Moon et al. 2017). In our study, segmental resection for tumors with a low GGO rate could have secured enough margins to prevent recurrences.

One of the limitations of our study is a question of whether the choice of the control group was appropriate. It is clear from previous reports that the outcomes in the control group were below standards. As a matter of course, the patients in the ILR group had received treatment aimed at a radical cure, and those in the control group had to undergo palliative surgery because of the poor operability, which made them ineligible for the standard surgery. If the patient could not be cured by the limited resection performed on the ILR group, the prognosis was considered to be close to that in the current control group; therefore, we selected such a control group as a comparison group. Furthermore, this study has additional limitations that should be considered. For instance, due to the small retrospective nature of the study, it was prone to bias. Clinical factors with significant differences such as sex, histological type, operative procedure, and nodal dissection would affect the prognosis, therefore these factors should be controlled. To determine whether our criteria were correct, trials designed to randomize patients who meet our criteria of limited resection into standard and limited-operation groups and to demonstrate that they are not inferior to standard-of-reduction surgery are needed.

In any case, it is necessary to determine the treatment strategy by considering the tumor growth rate and its malignant potential, rather than making decisions based on the simple stage diagnosis at the time of the examinations. The search for such indicators is urgent, and our report suggests that SUVmax might be useful as a recurrence predictor after limited surgery.

To summarize, in this study, we analyzed the feasibility of our criteria for performing limited resection on the basis of CT findings and SUVmax. Our results suggested that SUVmax might serve as a predictive marker of lung cancer recurrence after surgery to determine the optimal treatment strategy. Furthermore, patients with low GGO ratio and low SUVmax may be cured by appropriately selected limited resection. In the ILR group, no relapsed cases were reported suggesting that our criteria may be useful in determining patient’s eligibility for undergoing limited resection.

Declarations

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Conflicts of interest

All the authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

Ethics approval

The study was conducted in consent to the Declaration of Helsinki and was approved by the medical ethics committee of the Hokkaido University School of Medicine (approval number: #019-0349)

Consent to participate

Informed consent was obtained from all patients and all clinical investigations were conducted according to the ethical and legal standards.

Consent for publication

All authors have read and approved the manuscript for publication.

Availability of data and material

Not applicable

Code availability

Not applicable

Authors' contributions

YH and KK contributed to the conception of the study. MA, YH and KK contributed to design the study. MA conducted the research. MA, TK and AF analyzed the data and MA wrote the manuscript. The final manuscript was read and approved by all authors.

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Tables

Table 1 Baseline Patient Characteristics.

Characteristic	n=70
Sex	
Male	37
Female	33
Age (years)	
Median (range)	66.5 (36–82)
Histological type	
Adenocarcinoma	58
Squamous cell carcinoma	10
Others	2
Size of primary tumor (mm)	
Median (range)	14 (6–20)
Operative procedure	
Segmentectomy	39
Partial resection	31

Table 2 Comparison of Patients Characteristics Between the ILR and Control Groups

Characteristic		ILR group n=45	Control group n=25	*P*-value
Sex				0.0057*
	Male	18	19	
	Female	27	6	
Age (years)				0.1587
	Median (range)	64 (36–81)	69 (50–82)	
Histological type				<0.0001*
	Adenocarcinoma	44	14	
	Squamous cell carcinoma	0	10	
	Others	1	1	
Size of primary tumor (mm)				0.0953
	Median (range)	1.5 (0.8–2.0)	1.2 (0.7–2.0)	
GGO ratio				<0.0001*
	Median (range)	100 (0–100)	0 (0–100)	
SUVmax				<0.0001*
	Median (range)	0.8 (0–1.5)	3.3 (0.6–19.4)	
Operative procedure				0.0009*
	Segmentectomy	32	7	
	Partial resection	13	18	
Nodal dissection				0.0175*
	ND0	21	20	
	ND1	3	0	
	ND2	21	5	

*$P<0.05$

ILR, intentional limited resection; SUVmax, maximum standardized uptake value

Table 3 Characteristics of Patients with Recurrent Cases.

No.	Age	Sex	Operative procedure	Nodal dissection	GGO ratio	SUVmax of primary tumor	Relapse-free survival	Sites of recurrence
1	62	M	Partial resection	ND0	0	1.19*	36M	Mediastinal lymph node Brain
2	58	M	Partial resection	ND0	0	3.6	2.5M	Hilum lymph node
3	69	F	Partial resection	ND0	40	3.6	10M	Lung (bilateral)
4	62	F	Segmentectomy	ND0	0	3.3	37M	Lung (ipsilateral) Mediastinal lymph node
5	80	M	Segmentectomy	ND0	0	4	8M	Hilum lymph node Brain, Liver
6	81	M	Segmentectomy	ND2	0	9	31M	Lung (ipsilateral)

* This case occurred before 2008, criteria of SUVmax: 1.0

GGO, ground-glass opacity; SUVmax, maximum standardized uptake value

Table 4 Classification by GGO Ratio, SUVmax, Operative Procedure, and Proportion of Recurrent Cases.

	GGO ratio: ≥0.75		GGO ratio: <0.75	
	Low SUVmax*	High SUVmax$	Low SUVmax*	High SUVmax$
Partial resection Recurrent cases / Total cases	0 / 13	0 / 2	0/ 4	3 / 12
Segmentectomy Recurrent cases / Total cases	0 / 19	0 / 0	0 / 13	3 / 7

*Low SUVmax, SUVmax≤1.5 (1.0≤ until 2008)

$High SUVmax, SUVmax>1.5 (>1.0 until 2008)

GGO, ground-glass opacity; SUVmax, maximum standardized uptake value

Figure Captions

Fig. 1 Flowchart for patient enrollment

Fig. 2 Flowchart for managing non-small cell lung cancer according to our criteria

GGO, Ground-glass opacity; ILR, Intentional limited resection; SUVmax, Maximum standardized uptake value

Fig. 3 Survival curves of the patients included in this study.

(a) Overall survival, (b) relapse-free survival. ILR, Intentional limited resection. *: P<0.05

Fig1

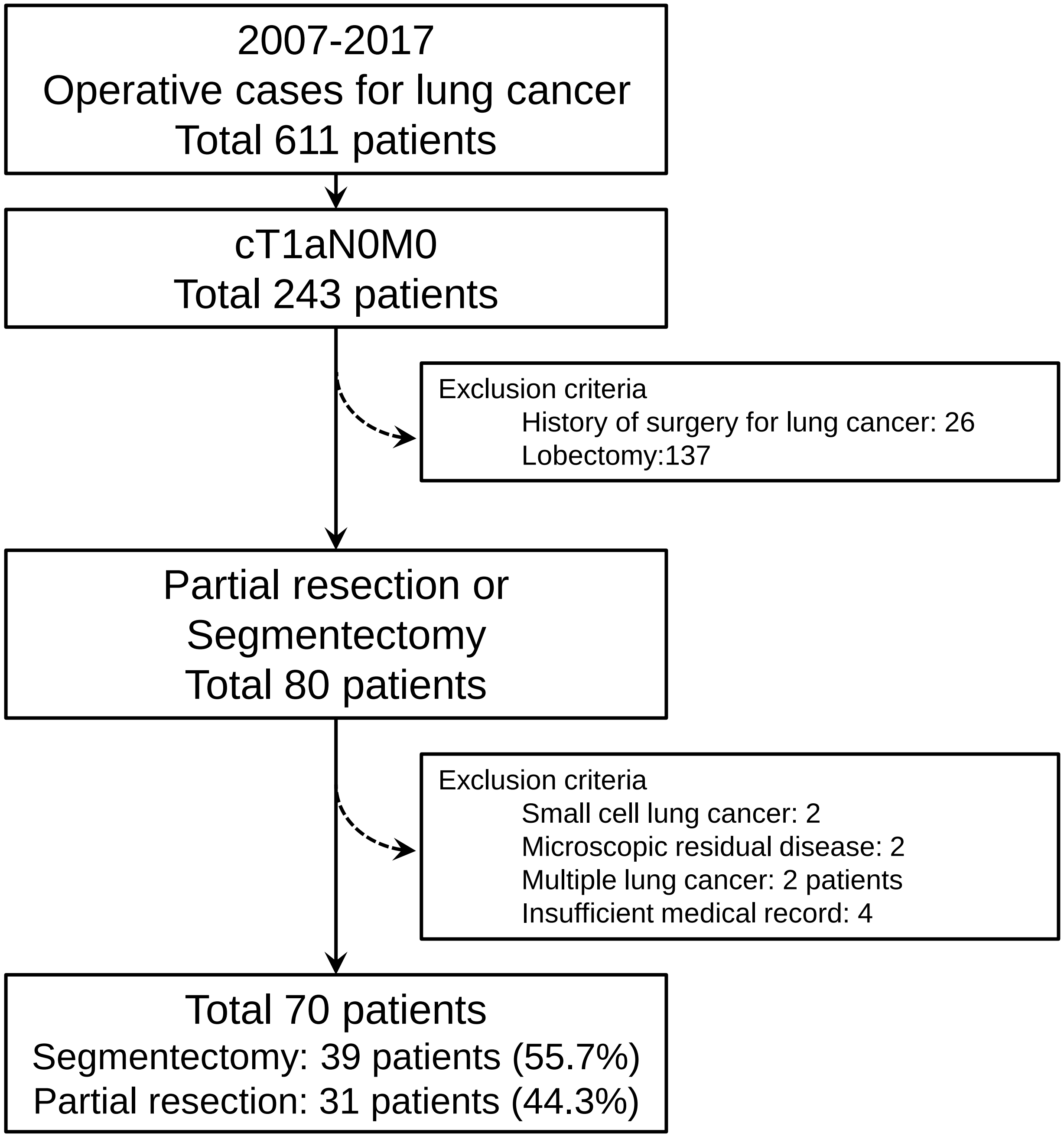

2007-2017
Operative cases for lung cancer
Total 611 patients
cT1aN0M0
Total 243 patients
Exclusion criteria
History of surgery for lung cancer: 26
Lobectomy:137
Partial resection or
Segmentectomy
Total 80 patients
Exclusion criteria
Small cell lung cancer: 2
Microscopic residual disease: 2
Multiple lung cancer: 2 patients
Insufficient medical record: 4
Total 70 patients
Segmentectomy: 39 patients (55.7%)
Partial resection: 31 patients (44.3%)

Fig2

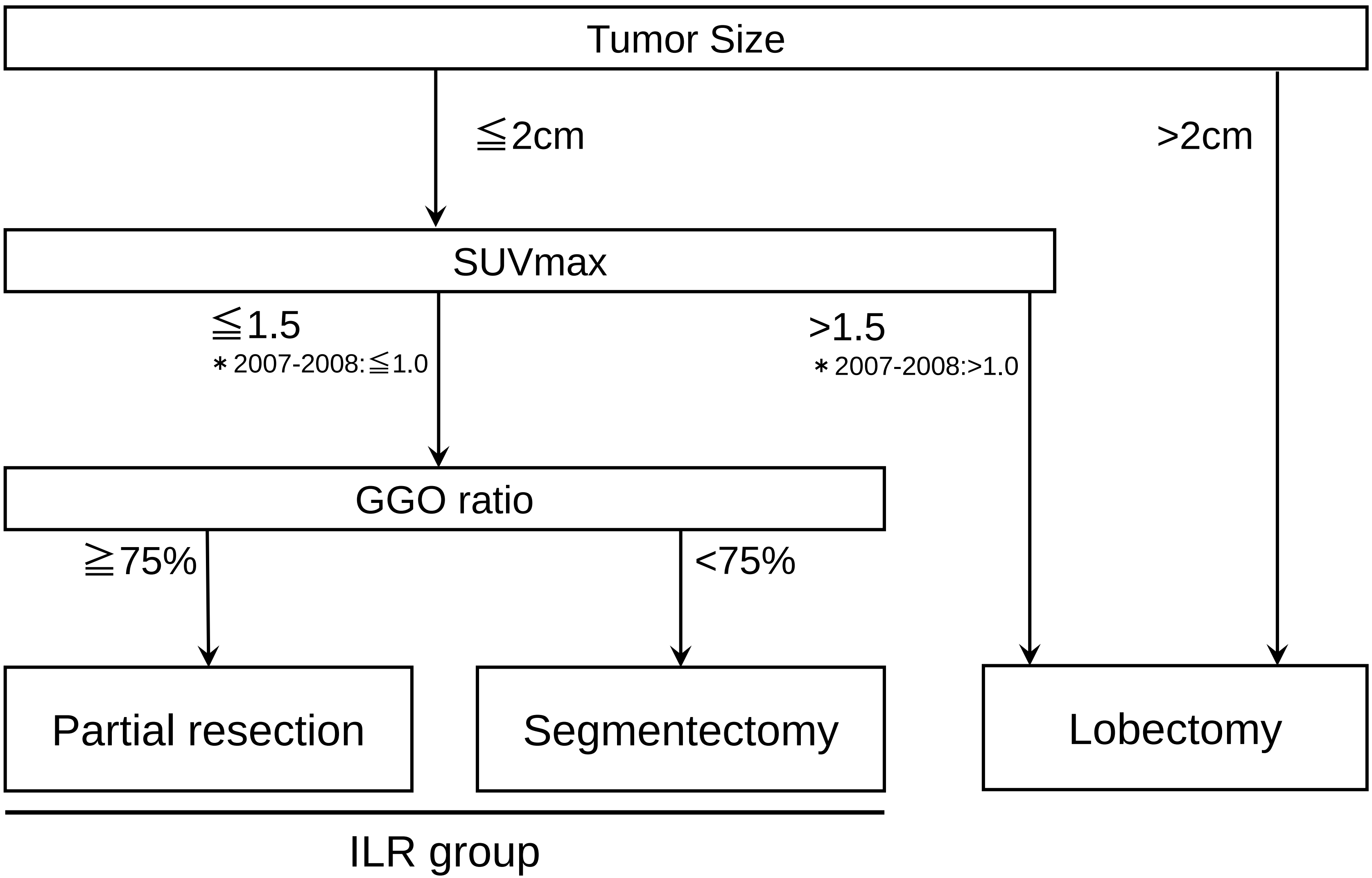
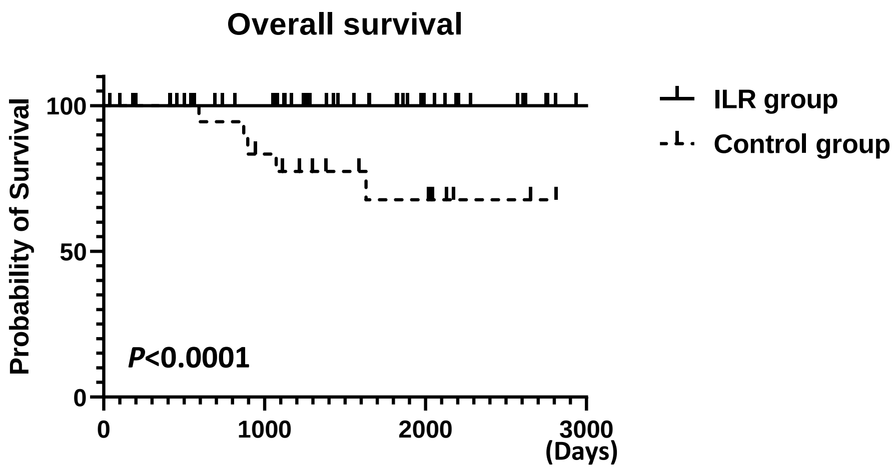

Tumor Size
≦2cm
>2cm
SUVmax
≦1.5
＊2007-2008:≦1.0
>1.5
＊2007-2008:>1.0
GGO ratio
≧75%
<75%
Partial resection
Segmentectomy
Lobectomy
ILR group

Fig3

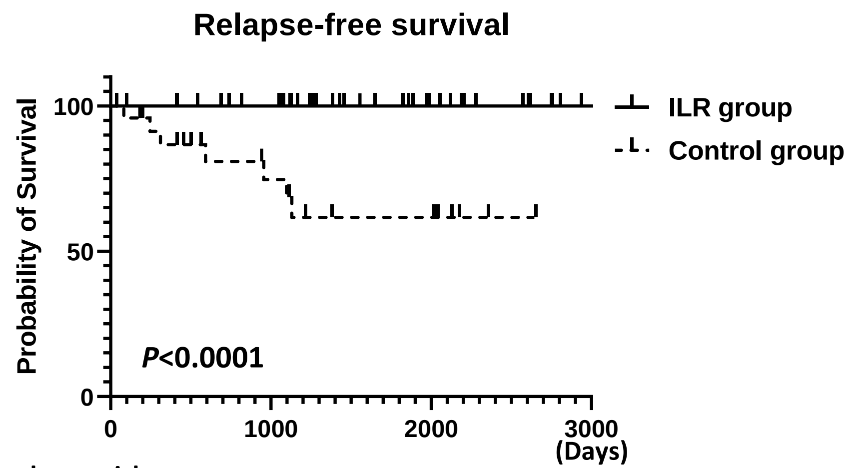
a



Number at risk

ILR	45	43	39	26	16	11	4
Control	25	21	15	10	8	2	1

b



Number at risk

ILR	45	43	39	26	16	11	4
Control	25	18	13	8	8	3	1