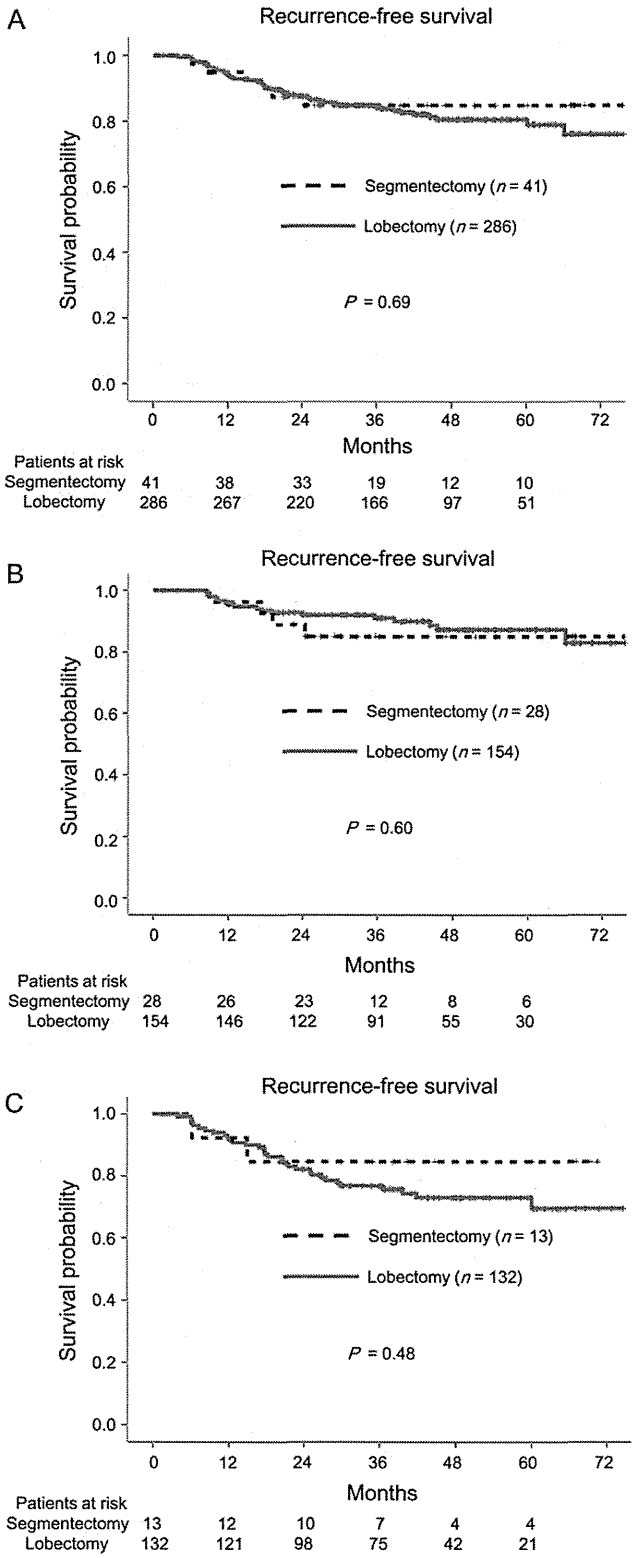

Figure 2: RFS curves for patients with solid-dominant tumours who underwent lobectomy and those who underwent segmentectomy. (**A**). In all cohorts, 3-year RFS rates of 84.4% (mean RFS of 64.7 months; 95% confidence interval [CI], 61.9–67.5 months) and 84.8% (mean RFS of 66.4 months; 95% CI, 59.5–73.1 months) were identified for patients who underwent lobectomy and those who underwent segmentectomy, respectively ($P = 0.69$). (**B**) In patients with mixed GGO tumours, 3-year RFS rates of 91.0% (mean RFS of 68.7 months; 95% CI, 65.6–71.8 months) and 85.0% (mean RFS of 66.8 months; 95% CI, 59.0–74.7 months) were identified for patients who underwent lobectomy and those who underwent segmentectomy, respectively ($P = 0.60$). (**C**) In patients with pure solid tumours, 3-year RFS rates of 76.8% (mean RFS of 59.4 months; 95% CI, 54.9–63.9 months) and 84.7% (mean RFS of 61.4 months; 95% CI, 49.6–73.2 months) were identified for patients who underwent lobectomy and those who underwent segmentectomy, respectively ($P = 0.48$).

Table 4: Univariate and multivariate analysis of RFS

Variables	HR (95% CI)	*P*-value
Univariate analysis		
Age	1.02 (0.99–1.05)	0.11
Gender, female (vs male)	1.11 (0.65–1.88)	0.70
Solid tumour size (cm)	2.07 (1..34–3.20)	0.001
SUVmax	1.17 (1.09–1.26)	<0.001
Tumour type, pure solid (vs Mixed GGO)	2.24 (1.30–3.85)	0.004
CEA (ng/ml)	1.01 (0.99–1.03)	0.36
Procedure, lobectomy (vs segmentectomy)	1.19 (0.51–2.78)	0.69
Multivariate analysis		
Age	1.02 (0.99–1.06)	0.18
Gender, female (vs male)	1.49 (0.82–2.71)	0.19
Solid tumour size (cm)	1.67 (1.01–2.88)	0.048
SUVmax	1.18 (1.08–1.29)	<0.001
Tumour type pure solid (vs mixed GGO)	1.31 (0.68–2.52)	0.42
CEA (ng/ml)	1.00 (0.96–1.04)	0.96
Procedure lobectomy (vs segmentectomy)	0.67 (0.27–1.70)	0.40

HR: hazard ratio; CI: confidence interval; SUVmax: maximum standardized uptake value; GGO: ground-glass opacity; CEA: carcinoembryonic antigen.

Table 5: Recurrence patterns between patients who underwent lobectomy and those who underwent segmentectomy

	Lobectomy (n = 286)	Segmentectomy (n = 41)	*P*-value
Local recurrence	16 (5.6%)	3 (7.3%)	0.72
Surgical stump	1	1	
Residual lung	0	1	
Pleura	3	1	
Lymph node	12	0	
Distant recurrence	26 (9.1%)	2 (4.9%)	0.55
Lung	10	1	
Bone	6	0	
Brain	3	0	
Meninges	0	1	
Adrenal grand	2	0	
Abdominal wall	1	0	
Lymph node	4	0	

Conflict of interest: none declared.

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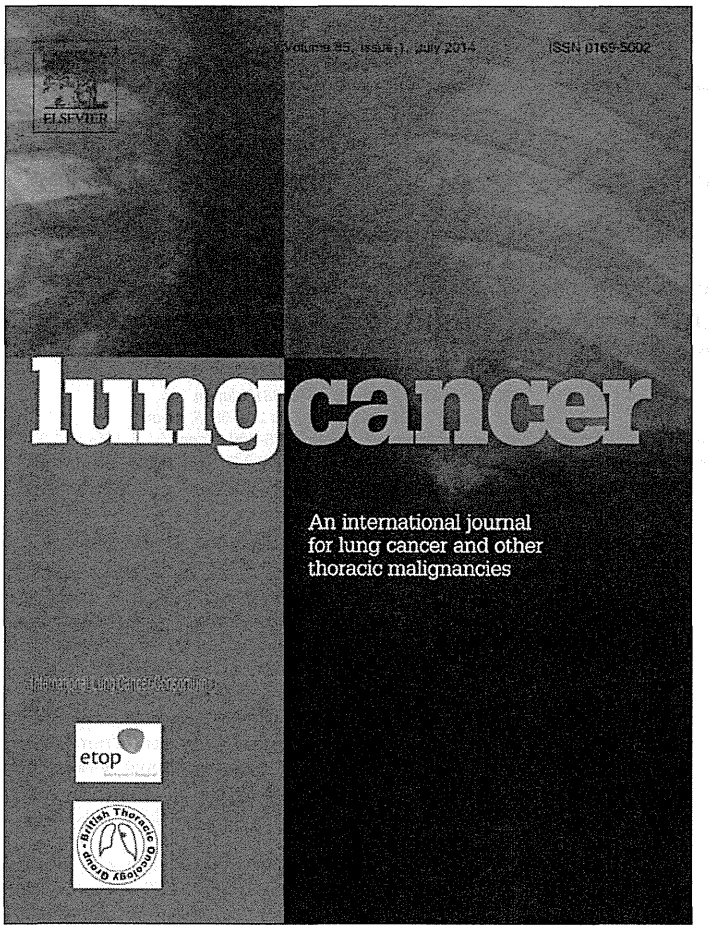

Lung Cancer 85 (2014) 40–46

Contents lists available at ScienceDirect

Lung Cancer

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Comparison between CT tumor size and pathological tumor size in frozen section examinations of lung adenocarcinoma

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ARTICLE INFO

Article history:
Received 30 December 2013
Received in revised form 18 March 2014
Accepted 24 March 2014

Keywords:
Lung cancer
Adenocarcinoma
Inflation method
Pathological tumor size
Frozen section examinations
CT tumor size
Lepidic

ABSTRACT

Objective: We examined the appropriate measurement for pathological tumor size by comparing radiological and pathological tumor size of resected lung adenocarcinoma in FSE.
Materials and methods: We reviewed records of 59 resected specimens of lung adenocarcinoma for FSE from January to December 2008. Specimens were well-inflated with saline by using an injector before cutting into segments. After selecting the tumor segment of maximal diameter, we compared three ways of measuring pathological tumor size by using paired *t*-test: (I) macroscopic tumor size (MTS), measured with a metal straight ruler, (II) microscopic frozen section tumor size (FSTS), and (III) microscopic paraffin section tumor size (PSTS). We compared each discrepancy rate (DR) [DR = (CT tumor size − pathological tumor size)/CT tumor size × 100] (%) between tumors that were air-containing type and solid-density type on CT scans, and also compared the tumors with lepidic component rates (LCR) ≥50% and LCR <50%, by using Mann–Whitney *U*-tests.
Results: FSE could diagnose malignancy with 100% accuracy. The mean CT tumor size was 18.36 mm, and the mean pathological tumor sizes (MTS, FSTS, and PSTS) were 17.81, 14.29, and 14.23 mm, respectively. FSTS and PSTS were significantly smaller than CT tumor size ($p < 0.001$). The DR calculated with PSTS was significantly larger in air-containing than in solid-density tumors, and also larger in LCR ≥50% than in LCR <50% tumors.
Conclusion: FSE with the inflation method diagnosed malignancy with 100% accuracy. The lung specimen must be sufficiently inflated to prevent tissue shrinking, and we propose MTS as the definition for pathological tumor size in FSE. The greater discordance observed between CT tumor size and microscopic tumor size was assumed to be due to shrinkage of the lepidic component in the tumor.

1. Introduction

Recent remarkable developments in diagnostic radiological imaging have allowed more frequent, easier detection of small tumorous lesions. As a result, we more frequently encounter tumors that are difficult to diagnose pre-operatively, which requires us to perform intra-operative frozen section examination (FSE) [1]. FSE is performed to confirm the presence of a tumor inside the resected specimen, to determine if the tumor is benign or malignant, to confirm that the tumor has a sufficient tumor margin, to decide the operation methodology, and to decide the exact stage [1–3]. FSE is a well-established method for definitive diagnosis, and there are few false negatives and positives when FSE is used for small-sized lung cancer [3–5].

However, deflated lung specimen results in the collapse of parenchymal tissue and distortion of lung structures, and pathologists have difficulty with differentiating minute invasive focus from

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http://dx.doi.org/10.1016/j.lungcan.2014.03.023
0169-5002/

collapse of small-sized lung adenocarcinoma. Inflation method is known to preserve the morphology of the lung specimen with high diagnostic accuracy of small-sized lung adenocarcinoma in the FSE [6]. Although FSE with inflation method plays an important role in lung adenocarcinoma operations, there are no clear methods or standards established for the preparation of resected specimens, and the technique differs by institution. Some important factors that may differ in FSE preparation include whether or not an inflation method is applied, how the lung specimen is inflated, how the embedding medium is used, and the width of the tissue segment the pathologist cuts [6–8]. There is also no standard method for measurement of characteristics such as pathological tumor size and resected tumor margin of lung specimens in FSE, and these methods differ by institution.

Although Travis et al. previously noted the possibility that estimates of tumor size for tumors that are predominately lepidic were smaller than the actual tumor size of lung adenocarcinoma [9], to our knowledge, there have not been any studies that have examined precisely how much smaller the estimates are. In this study, we determined the appropriate measurement of pathological tumor size by comparing radiological and pathological tumor measurements of resected adenocarcinoma of the lung in FSE using inflation method. Moreover, we evaluated the impact of lepidic component on pathological tumor size.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the records of 59 resected lung specimens from 58 patients for frozen section diagnoses (54 wedges and 5 segmentectomies) of lung adenocarcinoma from Kanagawa Cancer Center Hospital from January to December 2008. Cases in which tumors were positive at the cut-end were excluded. All patients provided informed consent, and the studies were performed according to the requirements of the institutional review board of Kanagawa Cancer Center.

2.2. Preparation procedures for FSE

Our preparation procedures for FSE are shown in Fig. 1. Lung specimens were well-inflated by injection of saline from the cut-end by using an 18-gauge injection needle (Fig. 1a). In order to prevent immediate saline leakage from the lung, the needle was inserted toward the subpleura and turned in some other directions inside the lung specimen so as to minimalize the number of puncture sites. Then, the pathologist (T.Y.) cut the specimen into segments 3–5 mm in width by drawing long cutting knife lightly, not pressingly (Fig. 1b) and immersed the segments in saline for a few minutes (Fig. 1c and d). We selected one or two tissue segments in which the tumor size was considered maximal, and where the tumor growth area was considered to be most predominately non-lepidic. The tumor tissue was put into a 50 mL injector which contained 10–20 mL of 50% embedding medium (Tissue-Tek O.C.T. Compound, Sakura Finetek-USA, CA), and was inflated with negative pressure (Fig. 1e and f). The tissue segment was frozen using dry ice and acetone, then a 2–4 μm cryostat section was made with a Leica CM 1900 UV Cryostat (Leica Microsystems, Wetzlar, Germany) for FSE. After FSE was complete, the tissue sections were melted at room temperature and fixed with 10% neutral buffered formalin to make permanent paraffin sections.

2.3. Measurement of pathological tumor size and CT tumor size

Pathological tumor size was measured in three ways: (I) macroscopic tumor size (MTS) measured by using a metal straight ruler, (II) microscopic tumor size measured on the frozen section (frozen section tumor size, FSTS), and (III) microscopic tumor size measured on the permanent paraffin section (paraffin section tumor size, PSTS). After the specimen was cut into segments and immersed in saline, MTS was measured where the tumor seemed to be maximal in size macroscopically. FSTS and PSTS were measured by performing stereoscopic microscopy and Leica Application Suite image analysis software (Leica Microsystems, Tokyo, Japan) (Fig. 1g and h). Chest CT images were obtained using a X-Vigor/Real CT scanner or an Aquillion CT scanner (Toshiba Medical Systems, Tochigi, Japan), and the CT tumor size was determined from high-resolution CT scans with 1–2 mm section thickness by measuring the maximum axial tumor diameter in a pulmonary window level setting (TSPW; level, −600 HU; width, 1600 HU). We also measured tumor size in a mediastinal window level setting (TSMW: level, 40 HU; width, 400 HU) on high-resolution CT scans.

2.4. Word definitions

We defined tumor shadow disappearance rate (TDR) using the following formula: $TDR = [1 - (TSMW/TSPW)] \times 100$ (%). Tumors with TDR ≥50% and TDR <50% were considered "air-containing types" and "solid-density types", respectively [10,11].

We also calculated discrepancy rate (DR) with the formula: DR = (CT tumor size − each pathological tumor size)/CT tumor size × 100 (%).

We defined the term "lepidic component rate (LCR)" as the area proportion of replacement growth pattern divided by the entire tumor on a permanent paraffin section.

2.5. Statistical analysis

The average CT tumor size and each pathological tumor size were compared by using paired *t*-tests. *T* factor migration according to the Union for International Cancer Control (UICC) guidelines, 7th edition, was assessed by using the likelihood ratio. The correlation between CT tumor size and each pathological tumor size was evaluated by using Pearson's correlation analysis. We compared DR values, which were calculated for each pathological tumor measurement and compared between air-containing type ($n = 44$) and solid-density type ($n = 15$) by using Mann–Whitney *U*-tests. Furthermore, we compared DR values between LCR ≥50% tumors ($n = 40$) and LCR <50% tumors ($n = 19$) by using Mann–Whitney *U*-tests. *p*-values less than 0.05 were considered significant.

3. Results

The clinicopathological characteristics are shown in Table 1. Of the 59 lung specimens for FSE, 28 (47.4%) were adenocarcinoma in situ (AIS), 4 (6.8%) were minimally invasive adenocarcinoma, and 27 (45.8%) were invasive adenocarcinoma. The accuracy of diagnosis of malignancy from frozen sections, based on the final diagnosis made based on the permanent paraffin section, was 100%. Air space in the tumor tissue was dilated enough to differentiate lepidic component from collapse and fibrous foci on frozen section (Fig. 2). Clinical *T* factors (cT1a, cT1b, and cT2a) were 42, 16, and 1, respectively, and the average CT tumor size ±SD was 18.36 ± 5.23 mm (range, 7–33 mm) (Fig. 3). The mean pathological tumor sizes ±SD of MTS, FSTS, PSTS were 17.81 ± 6.32 mm (range, 6–40 mm), 14.29 ± 3.66 mm (range, 5.46–21.21 mm), and 14.23 ± 4.38 mm (range, 5.17–22.92 mm), respectively. The average values for FSTS and PSTS were significantly smaller than the CT-based measurements ($p < 0.001$ for both). In regard to *T* factor migration, there were 8 (13.6%), 14 (23.7%), and 12 (22.0%) cases of down-migration when MTS, FSTS, and PSTS were used, respectively, to measure pathological tumor size, although there were

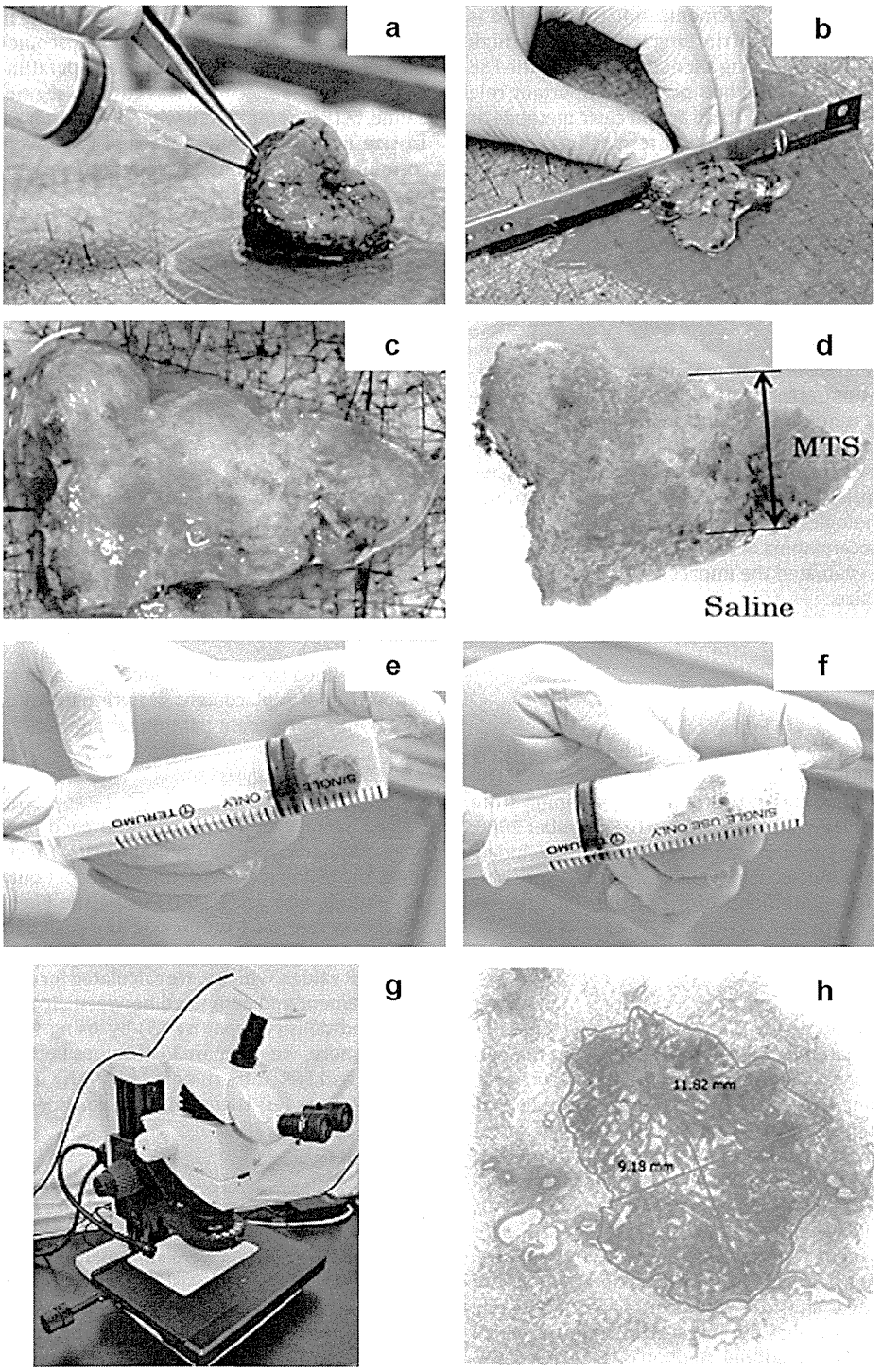

Fig. 1. Procedure for preparation of specimens for FSE. (g and h) FSTS and PSTS were measured with the Leica Application Suite stereoscopic microscope (Leica Microsystems; Tokyo, Japan). After plotting a tumor border region on frozen sections and paraffin sections, the maximum diameter in the area was measured to determine the FSTS and PSTS, respectively.

no cases of up-migration in FSTS and PSTS ($p = 0.0024$) (Fig. 3). Fig. 4 shows the correlation diagrams between CT tumor size and each pathological tumor size. According to the Pearson's correlation analysis, there were significant correlations between CT tumor size and each pathological tumor size (correlation coefficients (r) were 0.766, 0.700, and 0.682, respectively, and all were $p < 0.001$).

Fig. 5 shows the comparison of DR values between air-containing type tumors and solid-density type tumors. DR values calculated with PSTS were significantly larger in air-containing type than solid-density type specimens (27.3% versus 15.5%, $p = 0.032$). Fig. 6 shows the comparison of DR values between LCR ≥50% tumors and LCR <50% tumors. DR values calculated with

Table 1
Characteristics of the 58 patients in the study.

Fifty-eight patients with 59 specimens	
Median age (years)	67 (38–84)
Sex (male:female)	23:35
Side (right:left)	38:20
Lobe (upper:middle:lower)	39:0:20
Operative procedure for rapid diagnosis (partial resection:segmentectomy)	49:10
Pathological classification of adenocarcinoma (%)	
AIS	28 (47.4)
MIA	4 (6.8)
IA	27 (45.8)
(IA-LP:IA-AP:IA-PP:IA-SP:IA-variant)	(10:9:5:2:1)
Mean CT tumor size (mm)	18.36 (7–33)
Clinical *T* factor (%)[a]	
T1a	42 (71.2)
T1b	16 (27.1)
T2a	1 (1.7)
The accuracy of diagnosis of malignancy from frozen sections, based on the final diagnosis made based on the permanent paraffin section (%)	100

AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma; IA-LP, invasive adenocarcinoma lepidic predominant; IA-AP, invasive adenocarcinoma acinar predominant; IA-PP, invasive adenocarcinoma papillary predominant; IA-SP, invasive adenocarcinoma solid predominant.
[a] UICC 7th edition.

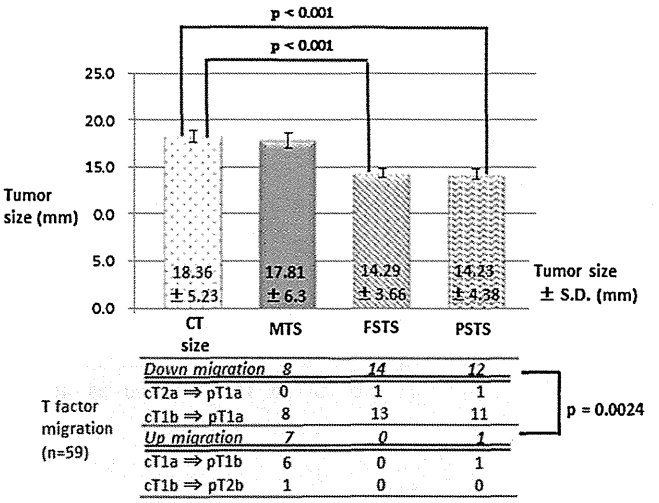

Fig. 3. Tumor size based on CT measurement and various pathological measurement techniques. The average CT tumor size ±SD was 18.36 ± 5.23 mm and the mean pathological tumor sizes ±SD of MTS, FSTS, PSTS were 17.81 ± 6.32 mm, 14.29 ± 3.66 mm, and 14.23 ± 4.38 mm, respectively. The average values for FSTS and PSTS were significantly smaller than the CT-based measurements ($p < 0.001$ for both). In regard to *T* factor migration, there were 8 (13.6%), 14 (23.7%), and 12 (22.0%) cases of down-migration when MTS, FSTS, and PSTS were used, respectively, to measure pathological tumor size, although there were no cases of up-migration in FSTS and PSTS ($p = 0.0024$).

PSTS were significantly larger in LCR ≥50% tumors than LCR <50% tumors (27.0% versus 18.6%, $p = 0.021$).

4. Discussion

4.1. Preparation methodology for FSE

It is considered that our simple inflation method, which includes injection of saline into the resected specimen and immersing the cut segment in saline, makes ambiguous and small-sized tumors more apparent in the gross specimen (Fig. 1c and d). This allows identification of all tumors, including impalpable ones, in FSE specimens. Borczuk et al. previously noted that neoplastic lesions became more apparent over time, and the lesion was often more clearly revealed upon re-examination of the gross specimen after several minutes because of drainage of excess blood and inflation of the lung by the infiltration of saline into the specimen [12]. Another inflation procedure was previously introduced that expands lung tissue by injecting diluted embedding medium into the lung, and this procedure enabled detection of minute and even non-palpable ground-glass opacity lesions much easier in FSE with a high level of diagnostic accuracy [8]. However, embedding medium is more expensive than saline and it costs even more if the lung specimen for frozen section is larger. By contrast, saline is less expensive and is easily obtainable. It is also considered that drainage excess blood by saline is necessary for the visualization and the exact measurement of MTS. Further study is necessary to examine how much effect injection of embedding medium has on each pathological tumor size compared with our saline injection method.

In this study, FSE was 100% accurate for the diagnosis of malignancy. A previous multi-center study noted that the diagnostic accuracy of FSE in thoracic surgery was 98.58% [5]. Marchevsky

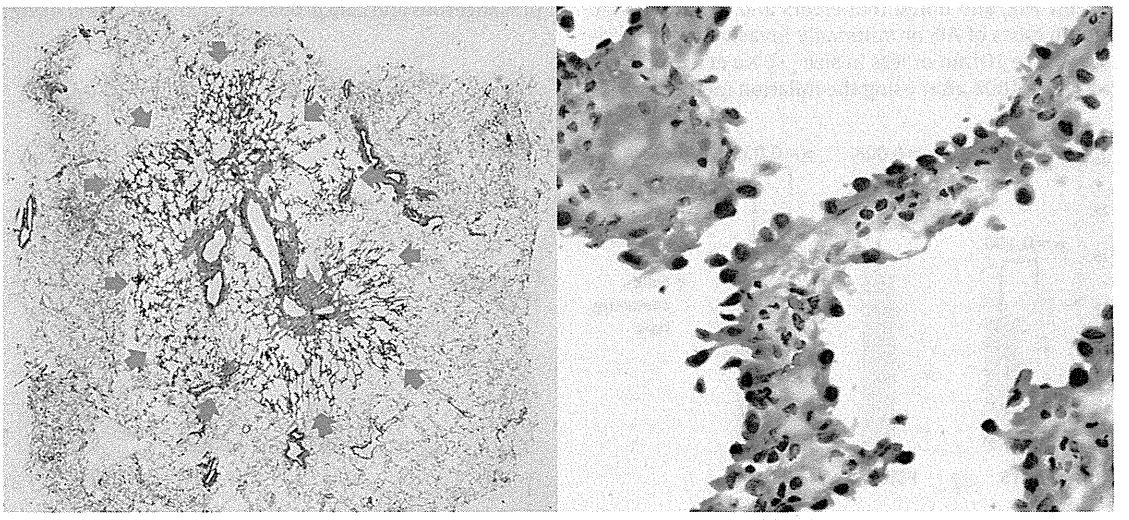

Fig. 2. The figure shows the gross appearance (left) and microscopic feature (right) in a frozen section diagnosed as adenocarcinoma in situ. Air space in the tumor was dilated enough to differentiate lepidic component from collapse and fibrous foci. Accordingly, a small adenocarcinoma in situ lesion was diagnosed readily by frozen section.

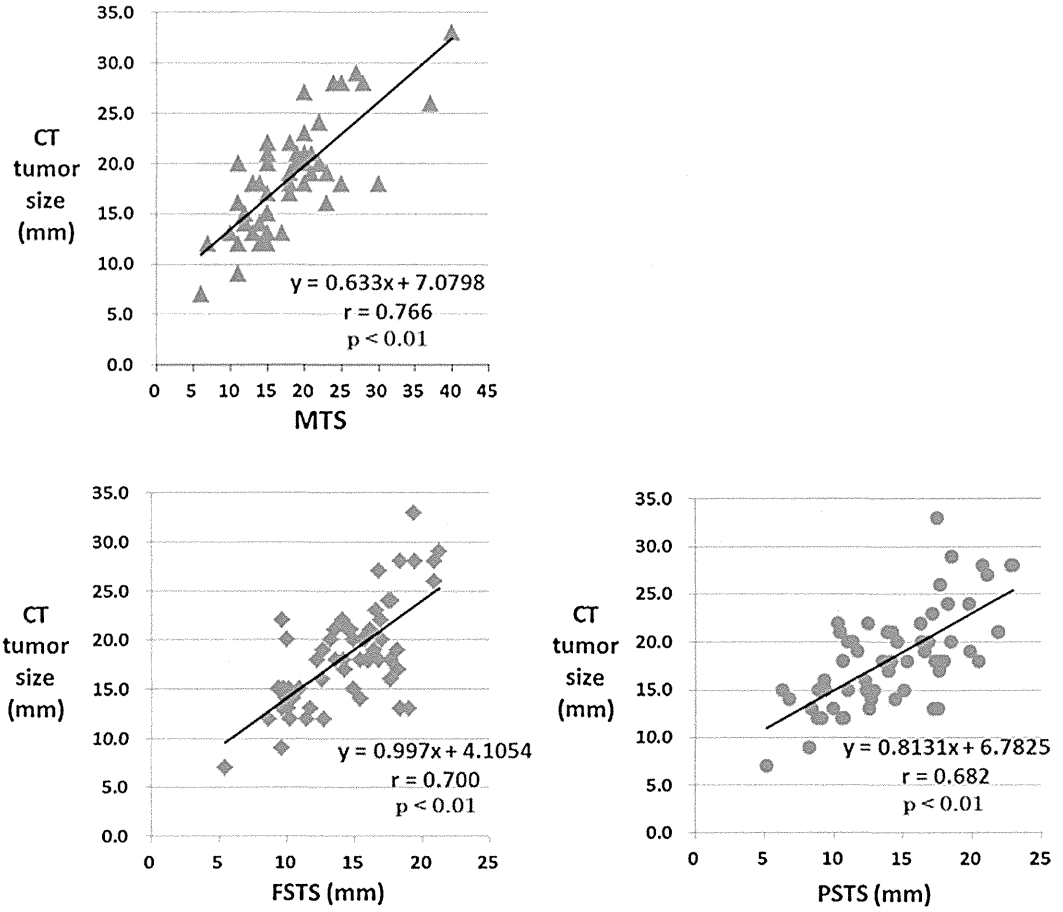

Fig. 4. Diagrams of the correlation between CT tumor size and the size indicated by each pathological measurement. According to the Pearson's correlation analysis, there were significant correlations between CT tumor size and each pathological tumor size (correlation coefficients (r) were 0.766, 0.700, and 0.682, respectively, and all were $p < 0.001$).

et al. also reported that the sensitivity for diagnosis of neoplasia was 86.9% for nodules smaller than 1.1 cm in diameter, and 94.1% for nodules 1.1–1.5 cm [1]. However, the preparation procedures for lung specimens in FSE were not described in these reports. Walts et al. reported that there were 12.1% (27 of 224) of frozen section errors and 6.3% (14 of 224) of deferrals without inflating lung specimens for FSE, and noted that errors and deferrals were more prominent in cases of AIS or minimally invasive adenocarcinoma (MIA), which are 10 mm or less in size [2]. Xu et al. reported that the accuracy was 100% after using the inflation method in FSE, although there were two false-positive cases before using the inflation method. The inflation method facilitated proper evaluation of the morphological alterations in the frozen section, and it made it easier to cut the lung specimen into segments, which reduced the chance of compression during sectioning [6]. With regard to our inflation method, it was possible to identify and diagnose minute precancerous and cancerous foci such as AAH and AIS readily on FSE

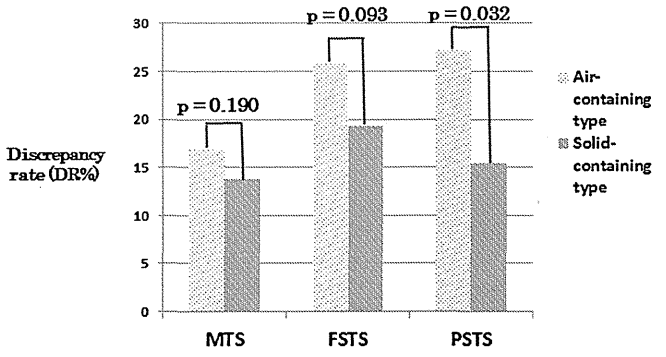

Fig. 5. Comparison of DR values between air-containing type tumors and solid-density type tumors. DR values calculated with PSTS were significantly larger in air-containing type than solid-density type specimens (27.3% versus 15.5%, $p = 0.032$).

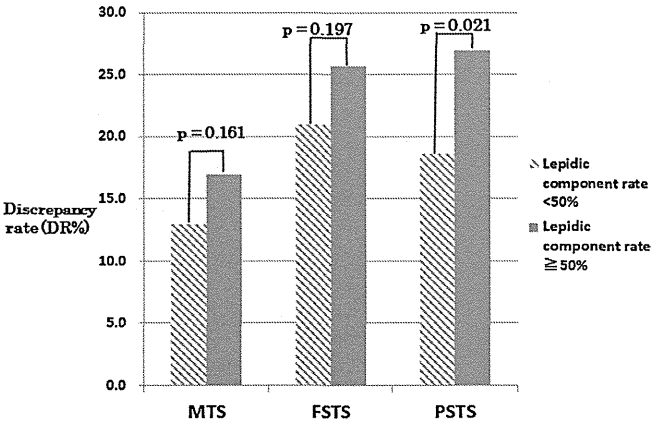

Fig. 6. Comparison of DR values between LCR ≥50% tumors and LCR <50% tumors. DR values calculated with PSTS were significantly larger in LCR ≥50% tumors than LCR <50% tumors (27.0% versus 18.6%, $p = 0.021$).

both macroscopically and microscopically (Fig. 2). In this study, all of 28 AIS lesions were detectable and diagnosed accurately on FSE by using this method (Table 1).

There is no standard method of preparation for resected specimens in FSE, and the methodology differs by institution. Moreover, the definition of pathological tumor size differs among institutions in FSE. In this study, we demonstrated that pathological tumor sizes were markedly different among MTS, PSTS, or FSTS, and clarified the necessity of unifying the pathological tumor size in FSE.

4.2. Comparison between CT tumor size and each pathological tumor size

Since there was a strong correlation between CT tumor size and each pathological tumor size (Fig. 4), and a high accuracy rate for the diagnosis of malignancy, our method of specimen preparation for FSE was considered appropriate to obtain sufficient information about the lung tumor. Among the three pathological measurement methods of tumor size, MTS correlated the best with the CT tumor size ($r = 0.766$) and its mean size was about the same as the CT tumor size (Figs. 3 and 4). Generally, in order to measure a resected margin, we cut lung specimens vertically against the resected surface. We did consider that most of the resection directions were not identical to the axial direction of the CT, but our results indicate that even if the direction varied widely, there was no significant difference between MTS and CT tumor size among the small lung adenocarcinomas.

On the other hand, the average FSTS and PSTS were significantly smaller than the CT tumor size, and caused down-migration of *T* factor (Fig. 3). As a result, we propose that the pathological tumor size for *T* factor should be defined as the MTS in small lung adenocarcinoma in FSE, and FSTS and PSTS should not be used, since patients might lose their chance to receive adjuvant chemotherapy because of the underestimation of their tumor size.

According to the TDR, the small lung adenocarcinomas (20 mm or less) were categorized as air-containing type and solid-density type, with the air-containing type having no evidence of metastasis (pleural involvement, vascular invasion, lymphatic permeation, or lymph node metastasis) and a much better prognosis than the solid-density type [10,11]. In air-containing type tumors, there is evidence of collapse, or collapse with bronchioloalveolar carcinoma, which represents a non-invasive tumor [11]. As shown in Fig. 5, DR values calculated with PSTS were significantly higher in air-containing type than solid-density type tumors ($p = 0.032$). This indicates that, if a tumor classified as air-containing type was pathologically measured using PSTS, the pathological tumor size might be underestimated by as much as 75% of the CT tumor size.

4.3. Interpretation of the discordance between PSTS and CT tumor size

Lampen-Sachar et al. used formalin fixed specimens to show that the mean CT tumor size was statistically larger than the pathological tumor size ($p < 0.001$), and concluded that CT overestimates the tumor size. The author stated that the discordance was due to differences in lung aeration and expansion, and due to the measurement of infiltration and/or edema surrounding the tumor in CT scans [13]. This result was similar to our examination in FSE. However, inflammation, fibrosis, and edema surrounding the tumor are rarely seen in the cases of peripheral small-sized adenocarcinoma which are considered to be an indication for FSE, and especially rare if the tumors were lepidic component predominant. Therefore, MTS was considered to reflect the area of adenocarcinoma accurately. It is considered that the underestimation of pathological tumor size measured with FSTS and PSTS is due to the deep cryosection of the tumor at its maximum diameter, tissue shrinkage by desiccation, and contraction that results from stuffing the tissue into a cassette.

Previously, Travis et al. noted a possibility that estimates of tumor size of lepidic predominant adenocarcinoma were smaller than the actual tumor size [9]. On the basis of this observation, we hypothesized that the lepidic component of the tumor was responsible for the contractility. As shown in Fig. 6, we found that tumors with LCR ≥50% were underestimated, giving values about 75% of the CT tumor size, if they were measured by PSTS. This agrees with the results of Fig. 5 pathologically. The reason for the contractility of the lepidic component is unknown, but we hypothesize that tumors which have abundant air space shrink more easily during preparation because of issues such as desiccation, stuffing pressure, and degeneration by the chemical solution, which are part of the preparation process for FSE. Another hypothesis is that inherent elasticity of alveoli which may cause contraction of the tissue is less affected by lepidic morphology as compared to invasive tumor.

4.4. Future tasks in the measurement of pathological tumor size

We propose the use of MTS, which approximated CT tumor size, as the pathological tumor measurement in FSE, although it may become burdensome for pathologists to measure MTS within a limited time during FSE. In the future, it is necessary to investigate the relationships between each pathological tumor size in FSE processed by our inflation method and the prognosis of lung cancer. In previous studies about the correlation between pathological tumor size and prognosis, the preparation methods for the specimens were not well-described [14–16]. Recently, several articles reported that invasive tumor size is an independent prognostic factor, and it may be a better predictor of prognosis than overall tumor size in lepidic predominant tumors [17–19]. Borczuk et al. reported that an invasion size of 5 mm or more measured by straight measurement on paraffin-fixed sections was an independent factor for poor prognosis [7]. However, many questions still remain on how to define the invasive area of the tumor, and we should clarify whether we can treat a tumor invasive size obtained with FSE in the same measured values as a tumor size obtained without FSE.

Future studies are needed for comparing the contraction rate of the tissues of FSE samples with those of paraffin fixed samples. Moreover, it is necessary to modify the inflation procedure to prevent contraction of FSTS and PSTS, which lead to misleading results about migration stage.

Recently, the significance of FSE in thoracic oncology increased, and the endeavor to standardize the methodology in FSE, including the definition pathological tumor size, is indispensable.

5. Conclusion

FSE using our inflating technique diagnosed malignancy with 100% accuracy. Moreover, there was a strong correlation between CT tumor size and the size indicated by each pathological tumor measurement. This indicates that our inflating technique of the specimen for FSE is appropriate. However, FSTS and PSTS were significantly smaller than CT tumor size, which resulted in stage migration, and pathological tumor size was considerably underestimated for tumors classified as "air-containing type" tumors or "lepidic predominant" tumors that were measured based on PSTS. We propose that the pathological tumor size should be defined as the MTS in small lung adenocarcinomas in FSE.

Conflict of interest statement

None declared.

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Featured Article

Segmentectomy versus lobectomy for clinical stage IA lung adenocarcinoma

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Background: Despite the increasing prevalence of the early discovery of small-sized non-small cell lung cancers (NSCLCs), particularly adenocarcinoma, sublobar resection has not yet gained acceptance for patients who can tolerate lobectomy.

Methods: We compared the outcomes of segmentectomy (n=155) and lobectomy (n=479) in 634 consecutive patients with clinical stage IA lung adenocarcinoma and in propensity score-matched pairs. Those who had undergone wedge resection were excluded.

Results: The 30-day postoperative mortality rate in this population was zero. Patients with large or right-sided tumors, high maximum standardized uptake value (SUVmax), pathologically invasive tumors (with lymphatic, vascular, or pleural invasion), and lymph node metastasis underwent lobectomy significantly more often. Three-year recurrence-free survival (RFS) was significantly higher after segmentectomy compared to lobectomy (92.7% *vs.* 86.9%, P=0.0394), whereas three-year overall survival (OS) did not significantly differ (95.7% *vs.* 94.1%, P=0.162). Multivariate analyses of RFS and OS revealed age and SUVmax as significant independent prognostic factors, whereas gender, tumor size and procedure (segmentectomy *vs.* lobectomy) were not. In 100 propensity score-matched pairs with variables adjusted for age, gender, tumor size, SUVmax, tumor location, the three-year RFS (90.2% *vs.* 91.5%) and OS (94.8% *vs.* 93.3%) after segmentectomy and lobectomy respectively were comparable.

Conclusions: Segmentectomy with reference to SUVmax should be considered as an alternative for clinical stage IA adenocarcinoma, even for low-risk patients.

Keywords: Adenocarcinoma; segmentectomy; sublobar resection; lung cancer; lobectomy

Submitted Nov 18, 2013. Accepted for publication Jan 22, 2014.
doi: 10.3978/j.issn.2225-319X.2014.02.10
Scan to your mobile device or view this article at: http://www.annalscts.com/article/view/3509/4452

Introduction

Sublobar resection for intentionally treating patients with small non-small cell lung cancer (NSCLC) who are able to withstand lobectomy has remained highly controversial, although lobectomy is considered a standard procedure even for sub-centimeter lung cancers. The Lung Cancer Study Group (LCSG) revealed a three-fold increase in local recurrence rates and poorer survival in patients who had undergone sublobar resection rather than lobectomy in a singular randomized phase III study published in 1995 (1). The dogma that lobectomy is the standard of care for stage I NSCLC has been upheld until recently. However, several current investigations have found equivalent outcomes of sublobar resection and lobectomy when NSCLC are ≤2 cm (2-7).

Sublobar resection consists of segmentectomy and wedge resection, which are quite different from each other as

curative surgery for lung cancer, since segmentectomy is more likely to provide sufficient margins and allows access to subsegmental and hilar lymph nodes. The present study retrospectively compared the outcomes of segmentectomy, not wedge resection and lobectomy among patients with clinical stage IA lung adenocarcinoma, and adjusted for clinical factors to minimize selection bias of patients. This analysis is an extended and updated version of our previous investigation (8).

Patients and methods

We analyzed data from 634 patients who had undergone lobectomy and segmentectomy for clinical T1N0M0 stage IA lung adenocarcinoma since October 2005. All patients were assessed using high-resolution computed tomography (HRCT) and F-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). Patients with incompletely resected (R1 or R2) or multiple tumors were excluded from the prospectively maintained database that was analyzed herein. All patients were staged according to the TNM Classification of Malignant Tumors, 7th edition (9). Platinum-based chemotherapy was administered to patients with pathological lymph node metastasis after surgery. The institutional review boards of the participating institutions approved the study and the requirement for informed consent from individual patients was waived because the study was a retrospective review of a database. Chest images were acquired by multi-detector HRCT independently of subsequent FDG-PET/CT examinations. Tumor sizes and maximum standardized uptake values (SUVmax) were determined by radiologists at each institution. Because of the heterogeneity of PET techniques and performance, we corrected inter-institutional errors in SUVmax resulting from PET/CT scanners of variable quality based on outcomes of a study using an anthropomorphic body phantom (NEMA NU2-2001, Data Spectrum Corp, Hillsborough, NC, USA) that conformed to National Electrical Manufacturers Association standards (10). A calibration factor was analyzed by dividing the actual SUV by the gauged mean SUV in the phantom background to decrease inter-institutional SUV inconsistencies. Postoperative follow-up of all patients from the day of surgery included physical examinations and chest X-rays every three months, as well as chest and abdominal CT and brain MRI assessments every six months for the first two years. Thereafter, the patients were assessed by physical examinations and chest X-rays every six months, and annual CT and MRI imaging.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences software version 10.5 (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using *t*-tests and Mann-Whitney *U* tests in all cohorts and Wilcoxon tests for propensity-matched pairs. Frequencies of categorical variables were compared using the χ^2 test and propensity-matched pairs were analyzed using McNemar tests. Propensity score matching was applied to balance the assignments of the included patients and to correct for the operative procedures (lobectomy or segmentectomy) that confounded survival calculations. The variables of age, sex, tumor size, SUVmax, side and lobe were multiplied by a coefficient that was calculated from logistic regression analysis, and the sum of these values was taken as the propensity score for each patient. Lobectomy and segmentectomy pairs with equivalent propensity scores were selected by a 1-to-1 match.

We defined recurrence-free survival (RFS) as the time from the day of surgery until the first event (relapse or death from any cause) or last follow-up, and overall survival (OS) as the time from the day of surgery until death from any cause or the last follow-up. The durations of RFS and OS were analyzed using the Kaplan-Meier method, and differences in RFS and OS were assessed using the log-rank test. Both RFS and OS were assessed by multivariate analysis using the Cox proportional hazards model.

Results

Of the 634 patients analyzed in this study, 479 and 155 underwent lobectomy and segmentectomy, respectively (*Table 1*). Patients with large tumors, right-sided tumors, pathologically invasive tumors, (presence of lymphatic, vascular, or pleural invasion), high SUVmax, and lymph node involvement were significantly more often treated by lobectomy. However, age and gender did not differ significantly between the two procedures. *Table 2* shows the segments that were removed during segmentectomy.

None of the patients died within 30 days of surgery, and tumors recurred in 54 patients at a median postoperative follow-up period of 34.2 months. Twenty recurrences were local only and 34 were distant (with or without local recurrence). Local recurrence occurred in 17 patients after

Table 1 Patient characteristics

Variables	Lobectomy (n=479)	Segmentectomy (n=155)	P value
Age	66 [30-89]	66 [31-89]	0.37
Gender			
Male	223 (46.6%)	74 (48.1%)	0.78
Tumor size (cm)	2.2 (0.7-3.0)	1.5 (0.6-3.0)	<0.001
SUVmax†	2.1 (0-16.9)	1.1 (0-9.8)	<0.001
Side			
Right	325 (67.8%)	81 (52.3%)	<0.001
Lobe			<0.001
Upper	254 (53.0%)	82 (52.9%)	
Middle	48 (10.0%)	0 (0%)	
Lower	177 (37.0%)	73 (47.1%)	
Lymphatic invasion	97 (20.3%)	10 (6.5%)	<0.001
Vascular invasion	111 (23.3%)	10 (6.5%)	<0.001
Pleural invasion	66 (13.9%)	8 (5.2%)	0.0024
Lymph node metastasis	50 (10.6%)	3 (1.9%)	<0.001

†, maximum standardized uptake value.

Table 2 Details of segmentectomy (n=155)

Site	Number
Right (n=81)	
S1	11
S1+2	1
S2	13
S3	7
S6	31
S7	3
S8	8
S9	1
S10	1
S7+8	1
S8+9	2
S9+10	1
S7+8+9+10	1
Left (n=74)	
S1+2	17
S3	9
S1+2+3	10
S1+2+3c	1
S4	5
S5	1
S4+5	7
S6	15
S8	2
S9	5
S10	1
S8+9+10	1

lobectomy (hilar lymph node, n=1; mediastinal lymph node, n=11; pleura, n=2; hilar and mediastinal lymph nodes, n=1; bronchial stump and mediastinal lymph node, n=1; mediastinal lymph node and pleura, n=1) and in three patients after segmentectomy (bronchial stump, n=1; pleura, n=1; residual lung and mediastinal lymph node, n=1).

The 3-year OS rates between patients who underwent lobectomy and segmentectomy were similar (94.1% *vs.* 95.7%, P=0.162), whereas three-year RFS rates significantly differed (86.9% *vs.* 92.7%, P=0.0394; *Figure 1*). *Table 3* shows that the multivariate analyses of RFS and OS selected age and SUVmax as significant independent prognostic factors, but not sex, tumor size, or procedure (lobectomy *vs.* segmentectomy).

Propensity score-matching based on clinical variables of age, gender, tumor size, SUVmax, side and lobe, allowed good matches of 100 lobectomy and segmentectomy pairs in terms of clinical and consequently pathological factors, except for more advanced age and higher SUVmax in the segmentectomy group (*Table 4*). Patients who underwent middle lobectomy were excluded from matching for a fair comparison, since tumors located in a middle lobe were never treated by segmentectomy. *Figure 1* shows that the three-year RFS and OS did not significantly differ between propensity score-matched patients after lobectomy or segmentectomy (91.5% *vs.* 90.2% and 93.3% *vs.* 94.8%, respectively).

Discussion

The RFS and OS curves of patients with clinical stage IA lung adenocarcinoma seemed better after segmentectomy than lobectomy, although the clinical and pathological backgrounds significantly differed and would obviously affect their survival (11-16). Multivariate analyses of the clinical background for RFS and OS demonstrated that procedure (lobectomy *vs.* segmentectomy) was not a significant prognostic factor. The clinical features or

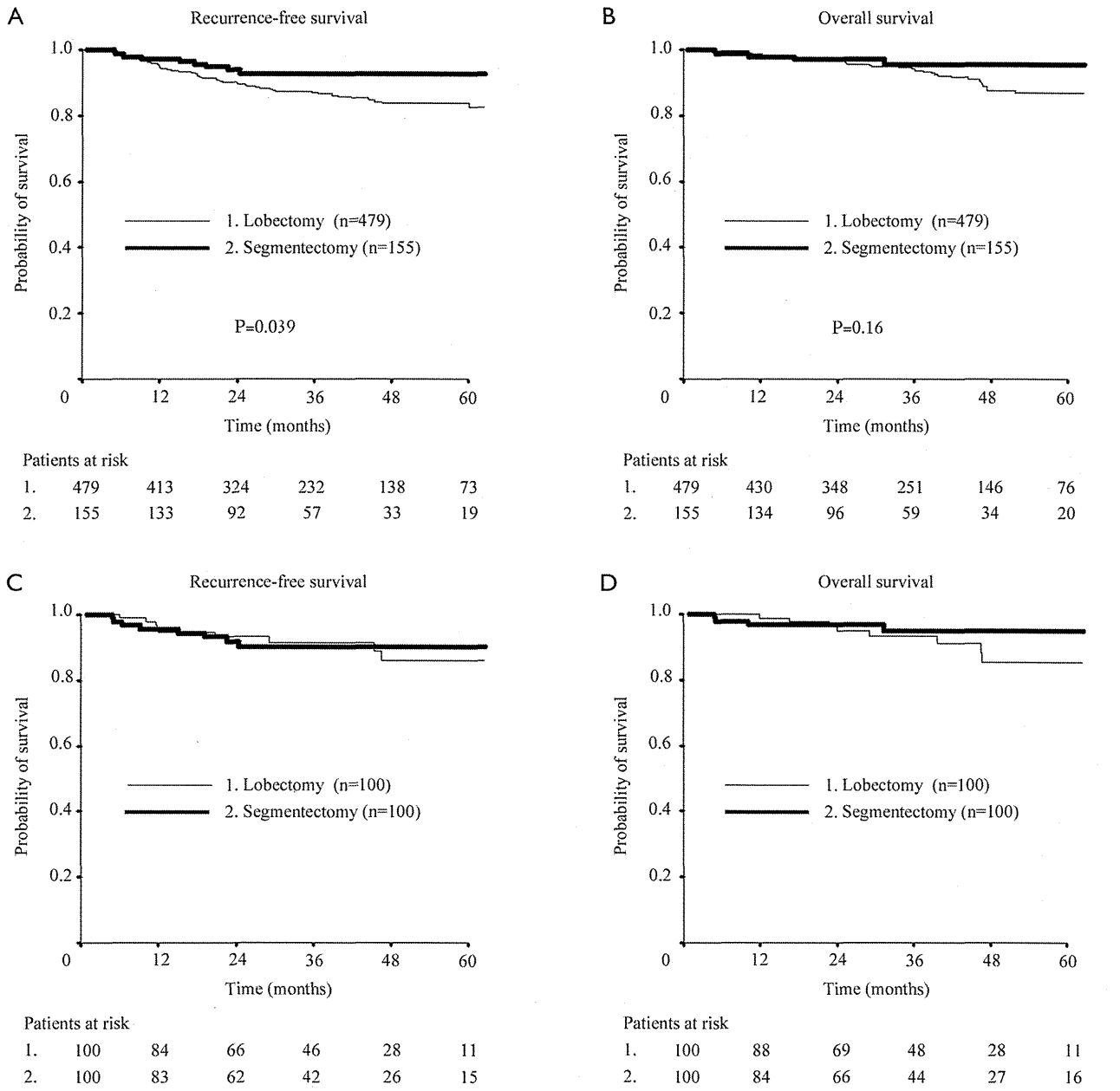

Figure 1 Recurrence-free (RFS) and overall survival (OS) curves of patients after lobectomy and segmentectomy. Three-year RFS (A) and OS (B) after lobectomy and segmentectomy were 86.9% *vs.* 92.7% (P=0.0394) and 94.1% *vs.* 95.7% (P=0.162), respectively, in all cohorts. Three-year RFS (C) and OS (D) in propensity score-matched patients after lobectomy and segmentectomy were 91.5% *vs.* 90.2% and 93.3% *vs.* 94.8%, respectively.

pathological factors of lymphatic, vascular or pleural invasion, or lymph node metastasis were similar in propensity score-matching analyses that matched for potentially confounding variables of age, sex, tumor size, SUVmax, tumor location to minimize selection bias. Only age and SUVmax significantly differed. The three-year RFS and OS rates after segmentectomy and lobectomy group were similar in the matched model, although the former

Table 3 Multivariate analyses for RFS and OS

Variables	HR (95% CI)	P value
Multivariate analysis for RFS[†]		
Age	1.04 (1.01-1.07)	0.011
Gender		
Male *vs.* female	1.20 (0.74-1.93)	0.46
Tumor size (cm)	1.36 (0.86-2.14)	0.19
SUVmax[‡]	1.17 (1.09-1.25)	<0.001
Procedure		
Lobectomy *vs.* segmentectomy	0.72 (0.34-1.52)	0.39
Multivariate analysis for OS[#]		
Age	1.05 (1.01-1.09)	0.0082
Gender		
Male *vs.* female	1.10 (0.49-1.70)	0.78
Tumor size (cm)	1.23 (0.67-2.26)	0.50
SUVmax[‡]	1.13 (1.04-1.24)	0.0068
Procedure		
Lobectomy *vs.* segmentectomy	0.68 (0.25-1.82)	0.44

RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval. [†], recurrence-free survival; [‡], maximum standardized uptake value; [#], overall survival.

Table 4 Propensity score-matched comparison of clinical and pathologic factors between patients who underwent lobectomy and segmentectomy

Variables	Lobectomy (n=100)	Segmentectomy (n=100)	P value
Clinical factors			
Age	63 [33-82]	66 [32-89]	0.030
Gender			
Male	46 (46%)	50 (50%)	0.67
Tumor size (cm)	1.6 (0.7-3.0)	1.6 (0.6-3.0)	0.28
SUVmax[†]	1.2 (0-8.7)	1.2 (0-9.8)	0.047
Side			0.27
Right	62 (62%)	53 (53%)	
Lobe			0.10
Upper	62 (62%)	50 (50%)	
Lower	38 (38%)	50 (50%)	
Pathologic factors			
Lymphatic invasion	11 (11%)	7 (7%)	0.45
Vascular invasion	9 (9%)	9 (9%)	1.0
Pleural invasion	10 (10%)	7 (7%)	0.61
Lymph node metastasis	7 (7%)	3 (3%)	0.34

[†], maximum standardized uptake value.

were significantly older and had a higher SUVmax. These data suggest that segmentectomy could be an alternative strategy for treating clinical stage IA lung adenocarcinoma when HRCT and FDG-PET/CT findings are taken into consideration.

This investigation has several limitations and the results should be interpreted with care. Information in the database analyzed herein included surgical procedures; however, further details such as indications for segmentectomy—that is, whether or not patients who were treated with segmentectomy could have tolerated lobectomy—are difficult to obtain. In addition, patients who underwent segmentectomy tended to have less invasive, smaller tumors, with small tumor size or low SUVmax, and thus a lower frequency of pathologically invasive factors such as lymphatic, vascular, pleural or nodal involvement. Therefore, we used propensity score-matched analysis to adjust the patients' backgrounds as much as possible. However, we could not compare the surgical outcomes of patients with a relatively low SUVmax, implying that patients with a high SUVmax require close scrutiny. The database also did not include information about lung function. The key advantage of segmentectomy is the preservation of lung function, and several studies have shown that segmentectomy has functional advantages over lobectomy (5,17,18).

The target tumors of most previous studies that compared the outcomes of segmentectomy and lobectomy were T1 N0 M0 NSCLC of ≤2 cm (4-6). However, the present study included patients with clinical T1b tumors of 2 to 3 cm. Patients with T1b lung adenocarcinomas with a sufficient surgical margin could be candidates for sublobar resection if selected based on HRCT and FDG-PET/CT findings (12).

The ongoing, multicenter phase III clinical trials of propriety of radical segmentectomy in the United States (CALGB-140503) and Japan (JCOG0802/WJOG4607L) should be carefully monitored. The primary end-point of the Japanese study is OS (disease-free survival in the US study), and wedge resection is not permitted as a sublobar resection, as it differs from radical segmentectomy. The Japanese study (19) aims to compare the surgical outcomes

of lobectomy and segmentectomy for T1 N0 M0 NSCLC measuring ≤2 cm, excluding radiologically less-invasive tumors such as ground-glass opacity (GGO)-dominant tumors on HRCT (20), and thus can show the true colors of segmentectomy compared with lobectomy. Segmentectomy is more procedurally demanding than either lobectomy or wedge resection, and thus incorrect outcomes of these clinical trials due to technical errors, such as recurrence at resection lines or excessive loss of lung function, might be a concern. Surgeons must carefully avoid local failure at the margin and fully expand adjacent segments to maximize postoperative lung function.

Current understanding of radical segmentectomy can be summarized as follows. Firstly, the indication for segmentectomy should be limited to T1 tumors ≤3 cm in diameter, and HRCT and PET-CT findings must be taken into consideration, particularly for T1b tumors (21-23). Whenever nodal involvement or an insufficient margin is confirmed intraoperatively, segmentectomy should be converted to lobectomy with complete nodal dissection. Secondly, radical (intentional) and compromising indications for segmentectomy must be independently discussed. The former is for low-risk patients who can tolerate lobectomy. Thirdly, segmentectomy is more valuable than wedge resection from an oncological perspective because it allows nodal dissection at the hilum. Thus, the decision of the most suitable procedure, such as whether or not to intraoperatively convert to lobectomy, should consider precise staging and the lower rate of local recurrence resulting from sufficient surgical margins. Therefore, segmentectomy must be clearly separated from wedge resection amongst the categories of sublobar resection for lung cancer. Surgeons must become adept and master segmentectomy as a keynote procedure because small lung cancers are being detected with increasing frequency.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Okada M, Mimae T, Tsutani Y, Nakayama H, Okumura S, Yoshimura M, Miyata Y. Segmentectomy versus lobectomy for clinical stage IA lung adenocarcinoma. Ann Cardiothorac Surg 2014;3(2):153-159. doi: 10.3978/j.issn.2225-319X.2014.02.10

Nishii et al. BMC Cancer 2014, 14:610
http://www.biomedcentral.com/1471-2407/14/610

BMC Cancer

RESEARCH ARTICLE Open Access

Clinicopathological features and EGFR gene mutation status in elderly patients with resected non–small-cell lung cancer

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Abstract

Background: The rapid aging of the population in Japan has been accompanied by an increased rate of surgery for lung cancer among elderly patients. It is thus an urgent priority to map out a treatment strategy for elderly patients with primary lung cancer. Although surgical resection remains standard treatment for early stage non–small-cell lung cancer (NSCLC), it is now essential to confirm the status of epidermal growth factor receptor (EGFR) gene mutations when planning treatment strategies. Furthermore, several studies have reported that *EGFR* mutations are an independent prognostic marker in NSCLC. However, the relations between age group and the molecular and pathological characteristics of NSCLC remain unclear. We studied the status of *EGFR* mutations in elderly patients with NSCLC and examined the relations of *EGFR* mutations to clinicopathological factors and outcomes according to age group.

Methods: A total of 388 consecutive patients with NSCLC who underwent complete tumor resection in our hospital from 2006 through 2008 were studied retrospectively. Formalin-fixed, paraffin-embedded tissue sections were used to isolate DNA from carcinoma lesions. Mutational analyses of EGFR gene exons 19, 20, and 21 and KRAS gene exons 12 and 13 were performed by loop-hybrid mobility shift assay, a highly sensitive polymerase chain reaction-based method.

Results: *EGFR* mutations were detected in 185 (47.7%) and *KRAS* mutations were detected in 33 (8.5%) of the 388 patients. *EGFR* mutations were found in a significantly higher proportion of patients younger than 80 years (younger group; 178/359, 49.6%) than in patients 80 years or older (older group; 7/29, 24.1%) (P = 0.008). In contrast, *KRAS* mutations were more common in the older group (6/29, 20.7%) than in the younger group (27/359, 7.5%) (P = 0.014). The older group showed a trend toward a higher rate of 5-year overall survival among elderly patients with *EGFR* mutations (100%) than among those with wild-type *EGFR* (66.2%), but the difference was not significant.

Conclusions: Our results suggest that the *EGFR* status of patients with NSCLC differs between patients 80 years or older and those younger than 80 years. *EGFR* mutation status might be a prognostic marker in elderly patients with completely resected NSCLC.

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Background

Primary lung cancer remains the leading cause of the death from malignant tumors worldwide [1]. Non–small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer [2]. Although surgical resection remains the standard treatment for early NSCLC, several molecular pathways have been shown to have prognostic significance in NSCLC. The epidermal growth factor receptor (EGFR) pathway is considered particularly important. EGFR is a membrane glycoprotein with an extracellular ligand-binding domain, a transmembrane lipophilic segment, and an intracellular domain that has tyrosine kinase activity. When a growth factor binds to EGFR, EGFR is self-phosphorylated by tyrosine kinase, and phosphorylated EGFR activates cell-signaling pathway involved in the regulation of cell cycle, apoptosis, angiogenesis, and cellular proliferation. Specific mutations of *EGFR* induce constant phosphorylation of EGFR, and increased levels of phosphorylated EGFR activate downstream signals that induce carcinogenesis [3,4]. *EGFR* mutations predict the effect of EGFR tyrosine kinase inhibitors (EGFR-TKI) [5,6]. It is now essential to confirm *EGFR* mutation status when planning treatment strategies for advanced or recurrent NSCLC.

The population of Japan is aging rapidly. In 2011 the average life-span in Japan was 83 years (males 79 years, females 86 years) [7]. Aging of the population is accompanied by a rapid increase in the incidence of primary lung cancer as well as the number of operations for lung cancer among elderly patients. Since 2009 persons 80 years or older have accounted for more than 10% of all patients in Japan. In 2011, patients 80 years old or older accounted for 11.5% of all patients [8-12]. Aging will become a global problem in the future, and knowledge acquired in Japan may contribute to solving related problems. Previous studies have suggested a relation between *EGFR* mutations and several clinicopathological factors, but whether *EGFR* status differs according to age group remains unclear. The present study assessed the status of *EGFR* mutations in elderly patients with NSCLC and examined the relations of *EGFR* mutations and clinicopathological factors to outcomes.

Methods

Patients

We retrospectively studied 388 consecutive patients with NSCLC who underwent complete tumor resection at Kanagawa Cancer Center Hospital (Yokohama, Japan) from 2006 through 2008. This study was approved by the ethics committee of the Kanagawa Cancer Center, and informed consent was obtained from all patients. The pathological diagnoses were independently made by 2 pathologists (T.N., T.Y.). Discrepancies in diagnoses were resolved by mutual agreement. The median follow-up time was 1981 days.

Assessments

Formalin-fixed, paraffin-embedded tissue sections of the resected tumors were used for DNA extraction. Mutational analyses of *EGFR* gene exons 19, 20, and 21 and *KRAS* gene exons 12 and 13 were performed by loop-hybrid mobility shift assay (LH-MSA), a highly sensitive polymerase chain reaction–based method, as described previously (Additional file 1: Table S1) [13].

Statistical analysis

Relations between *EGFR* status and categorical data were evaluated with the chi-square test. Continuous variables were compared by Student's t-test. Survival curves were plotted using the Kaplan-Meier method, and differences in survival rates were assessed using the log-rank test. $P < 0.05$ was considered to indicate statistical significance. Statistical manipulations were performed using the IBM SPSS Statistics 20 for Windows software system (IBM Corp, Armonk, NY, USA).

Results

Relations between *EGFR, KRAS* status and clinicopathological features

The patients' characteristics are summarized in Table 1. Of the 388 patients, 228 (58.8%) were men, and 160 (41.2%) were women. The mean age was 66.6 years (range, 35–90). *EGFR* mutations were detected in 185 patients (185/388, 47.7%) and *KRAS* mutations were detected in 33 (33/388, 8.5%). *EGFR* mutations were found more frequently in women (110/185, 59.5%), adenocarcinoma (183/185, 98.9%), and non-smokers (106/185, 57.3%) ($P < 0.001$). Patients with *EGFR* mutation had fewer pre-existing cardiopulmonary comorbidities than patients with wild-type ($P = 0.028$). The mean tumor diameter was smaller in patients with *EGFR* mutations (2.68 ± 0.92 cm) than in those with wild-type *EGFR* (3.35 ± 1.71 cm; $P < 0.001$). The rate of pathological T1 disease was significantly higher among patients with *EGFR* mutations (114/185, 61.6%) than among those with wild-type *EGFR* (83/203, 40.9%; $P < 0.001$). In contrast, *KRAS* mutations were not significantly related to gender, histopathological type, or smoking status. Although *KRAS* status did not correlate with pathological T factors, mean tumor diameter was larger in patients with *KRAS* mutations (3.46 ± 1.99 cm) than in those with wild-type *KRAS* (2.99 ± 1.36 cm; $P = 0.001$).

Relations between age group and clinicopathological features

We divided the patients into two groups according to whether they were 80 years or older (older group) or

Table 1 Correlations between *EGFR* mutations and clinicopathological features

Characteristics	Total	No. of patients					
		EGFR status		p^a	*KRAS* status		p^a
		Mutation	Wild-type		Mutation	Wild-type	
	(*n* = 388)	(*n* = 185, 47.7%)	(*n* = 203, 52.3%)		(*n* = 33, 8.5%)	(*n* = 355, 91.5%)	
Mean age, yr ± SD[b]	66.6 ± 10.0	65.1 ± 10.3	67.9 ± 9.57	0.462	68.6 ± 9.11	66.4 ± 10.1	0.553
Gender				<0.001			0.552
Male	228	75	153		21	207	
Female	160	110	50		12	148	
Histological type				<0.001			0.059
Adenocarcinoma	302	183	119		30	272	
Others	86	2	84		3	83	
Vascular invasion							
Ly -	314	155	159	0.172	25	289	0.429
Ly +	74	30	44		8	66	
V -	261	151	110	<0.001	23	238	0.756
V +	127	34	93		10	117	
p-stage				<0.001			
I	293	155	138		22	271	0.217
II / III	95	30	65		11	84	
T-factor				<0.001			
T1	197	114	83		14	183	0.316
T2 / 3	191	71	120		19	191	
Tumor diameter (cm)	3.03 ± 1.43	2.68 ± 0.92	3.35 ± 1.71	<0.001	3.46 ± 1.99	2.99 ± 1.36	0.001
N-factor				0.348			
N0	322	157	165		29	293	0.435
N1 / 2	66	28	38		4	62	
Smoking status				<0.001			0.107
Non-smoker	157	106	51		9	148	
Smoker	231	79	152		24	207	
Pre-existing cardiopulmonary comorbidity	203	86	117	0.028	20	183	0.319

[a]p < 0.05 statistically significant.
[b]SD, standard deviation.
EGFR, epidermal growth factor receptor; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; ND, lymph node dissection.

younger than 80 years (younger group) and compared *EGFR* status and clinicopathological features between these age groups (Table 2). The younger group comprised 359 patients (92.5%), and the older group comprised 29 (7.5%). The proportion of patients with *EGFR* mutations was significantly higher in the younger group (178/359, 49.6%) than in the older group (7/29, 24.1%; P = 0.008). In contrast, *KRAS* mutations were more common in the older group (6/29, 20.7%) than in the younger group (27/359, 7.5%; P = 0.014). The proportion of smokers was significantly lower in the younger group (208/359, 57.9%) than in the older group (23/29, 79.3%; P = 0.024). Elderly patients had more pre-existing cardiopulmonary comorbidities than younger patients (P = 0.024). Gender, histopathological type, vascular invasion, pathological stage, and tumor diameter did not differ significantly between the groups. We omitted lymph-node resection in the older group (P < 0.001). Table 3 shows the region of *EGFR* mutation according to age group. Although the study group was small, there were no exon 20 mutations in the older group.

Relations between *EGFR* status and outcomes

Kaplan-Meier curve analysis showed that *EGFR* mutation status was significantly associated with survival (Figure 1). The 5-year overall survival rate was significantly higher in patients with *EGFR* mutations (90.2%) than in those with wild-type *EGFR* (75.2%) in the younger group (P < 0.001; Figure 1A). The 5-year overall survival rate was slightly, but not significantly higher