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ORIGINAL ARTICLE

A comparison between 2- and 3-dimensional approaches to solid component measurement as radiological criteria for sublobar resection in lung adenocarcinoma ≤ 2 cm in size

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Abstract

Purpose We compared three-dimensional (3D) and two-dimensional (2D) measurements of the solid component to determine radiological criteria for sublobar resection of lung adenocarcinoma ≤ 2 cm in size.

Methods We included 233 surgical cases. The maximum size of the solid component for 3D measurement was calculated by delineating the solid component on successive axial images and reconstructing the 3D surface model.

Results The predictive performance for adenocarcinoma in situ ($n = 43$) and minimally invasive adenocarcinoma ($n = 77$) were equivalent to areas under the curve of 0.871 and 0.857 for 2D and 3D measurements ($p = 0.229$), respectively. A solid component of 5 mm had a prognostic impact on both measurements (≤ 5 mm versus > 5 mm; $p = 0.003$ for 2D and $p = 0.002$ for 3D, log-rank test). Survival rates at 5 years were 94.7–96.9% following lobectomy and sublobar resection among patients with a solid component ≤ 5 mm in size. Sublobar resection resulted in worse survival rates, with declines at 5 years of 15.8% on 2D and 11.5% on 3D measurements, than lobectomy in patients with a solid component > 5 mm in size.

Conclusions A solid component ≤ 5 mm in size is an appropriate criterion for sublobar resection for both measurements. In addition, 2D measurement is justified because of its simple implementation.

Keywords Adenocarcinoma · Computed tomography · Pathology · Solid component

Introduction

Lobectomy is currently the standard procedure for stage IA non-small cell lung cancer [1]. However, sublobar resection may be a feasible alternative for adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) as it promotes a disease-free survival rate of almost 100% among

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patients with AIS and MIA [2, 3]. Clinical trials are currently underway to evaluate sublobar resection for non-small cell lung cancer ≤ 2 cm in size [4].

The 2015 World Health Organization (WHO) classification of lung cancer defines AIS, MIA, and invasive adenocarcinoma according to the size of the invasive component for small (≤ 3 cm) lung adenocarcinoma. The eighth TNM classification of lung cancer recommends the measurement of the solid component on high-resolution computed tomography (HRCT) to define the clinical T-factor, as well as the use of multiplanar reconstructions to select the CT section that shows the largest portion of the solid component [5, 6]. Recent advances in radiographic technology allow for the three-dimensional (3D) visualization of images, and 3D measurement is expected to provide a more detailed assessment of the solid component in lung adenocarcinoma; however, evidence supporting this assumption is sparse at present.

As an alternative, two-dimensional (2D) measurement is preferable in clinical practice because it is simpler to implement than 3D measurement, which is more time-consuming, expensive, and requires additional software. To determine whether the performance of 3D measurement justifies its disadvantages, it is necessary to evaluate the clinical differences between the two methods.

We therefore conducted a retrospective study to determine appropriate radiological criteria for sublobar resection for lung adenocarcinoma ≤ 2 cm in size by comparing the 2D measurement of axial HRCT images and 3D measurement in terms of 1) the sizes of the solid components; 2) the ability of such measurements to predict the pathologies of AIS and MIA; and 3) the prognostic impact of the sizes of the solid components.

Methods

This retrospective study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research in Japan and was approved by the institutional review board at The University of Tokyo Graduate School of Medicine (No. 10257, September 10, 2013). The need for written informed consent was waived on account of the retrospective, observational nature of the research.

A search through the General Thoracic database in the Department of Thoracic Surgery at The University of Tokyo Hospital identified 983 patients who had undergone surgery for primary lung cancer between January 2001 and December 2012. We excluded 23 patients on account of the following: surgery for recurrence ($n = 8$), requirement for a 2-stage operation ($n = 8$), and a pathologic diagnosis of atypical adenomatous hyperplasia ($n = 4$) or sarcoma ($n = 3$). Among the remaining 960 patients, 504 had both clinical stage IA and adenocarcinoma histology. Of these, 347 exhibited an adenocarcinoma ≤ 2 cm in size. We further excluded 114 patients on account of the following: pathologic size > 2 cm ($n = 64$), lack of available Digital Imaging and Communications in Medicine (DICOM)-formatted data ($n = 23$), multiple synchronous lung cancers ($n = 23$), surgery for lung cancer in the previous 2 years ($n = 2$), and incomplete resection ($n = 2$). The sample size of the present study thus totaled to 233; the patients included in this study were the same as those included in another study published by our research group [7]. The patient flow chart is presented in Supplementary Fig. 1 (Online Resource 1).

Clinical data were extracted by reviewing medical charts. Variables included in the study were the sex, age, smoking history, surgical procedure, and survival. A board-certified pathologist (AS-U with 11 years of experience) who had not been informed of the clinical information reviewed the slides based on the 2015 WHO classification of lung cancer [2, 3]. The treatment strategy for each patient was discussed by a multi-disciplinary team. The preoperative assessment of a patient's candidacy for surgery included blood tests, spirometry, and electrocardiography. Although lobectomy is a routine surgery for non-small cell lung cancer, sublobar resection was performed for small-sized adenocarcinoma with predominant ground-glass opacity on HRCT. If patients with a solid nodule on HRCT were deemed to be at high risk for lobectomy, sublobar resection, including wedge resection, was recommended. Adjuvant chemotherapy, including the administration of uracil-tegafur for two years for pathologic stage IB and platinum-containing regimens for stages IIA–III, had been offered to selected patients.

Radiologic evaluations

As described in the Supplementary Text (Online Resource 2), 11 different types of helical CT scanners were used according to various protocols in this study. A contrast agent was used unless stated otherwise. All primary tumors were evaluated using HRCT with a 1- to 3-mm slice thickness. The window level and window width were set as -600 and 1400 Hounsfield units, respectively.

To assess the interobserver variability for the size of the solid component in 2D measurement, the present study recruited 2 readers with 17 and 18 years of clinical experience in thoracic imaging (YY, Reader 1; JN, Reader 2, respectively). The readers selected the axial HRCT image that displayed the largest tumor diameter, including ground glass opacity, and measured the size of the solid component independently as stated in the JCOG 0201 study [8]. HRCT images with DICOM-formatted files were reviewed using the ImageJ 1.46r software program (National Institutes of Health, Bethesda, MD, USA) [9]. To assess the intraobserver variability of the solid component's size observed in 2D,

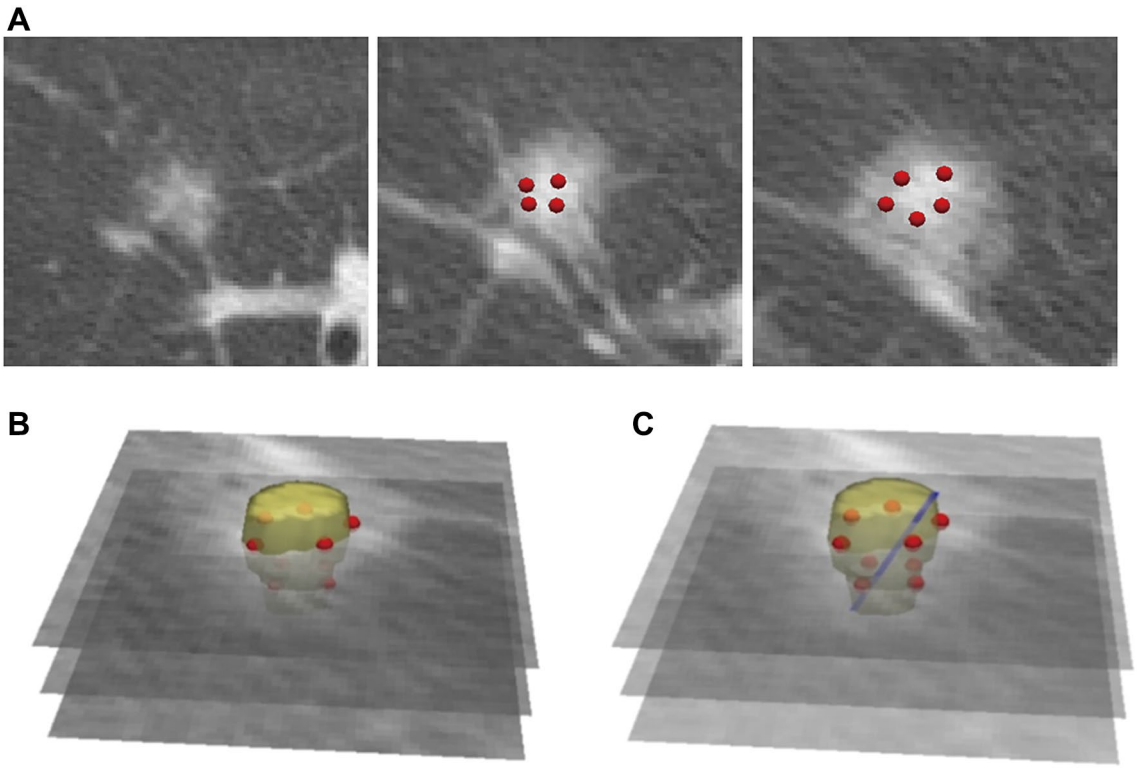

Fig. 1 Three-dimensional measurement of the size of the solid component. The borders of the solid component were manually plotted on successive axial HRCT images, as shown by the red dots (**a**). The three-dimensional surface model was reconstructed (**b**), and the maximum size of the solid component was computed (**c**)

reader 1 re-measured the size of the solid component after a three-month interval between the first and second analysis in partial accordance with the methods of a previous study [10]. HRCT images were reviewed using the Osirix v5.8.2 software program (Pixmeo SARL, Geneva, Switzerland) for the second analysis.

The HRCT findings were classified into three groups according to the definitions of established guidelines [2]: pure ground glass nodule, part-solid nodule, and solid nodule. Readers 1 and 2 evaluated the HRCT findings independently, and any discrepancies in findings were discussed to reach a final consensus diagnosis.

Three-dimensional measurement of solid component size

Reader 1 used the Osirix v5.8.2 software program to manually plot the border of the solid component on successive axial HRCT images (Fig. 1a). The 3D surface model was reconstructed (Fig. 1b) as a solid-component shape using Delaunay triangulation [11]. The maximum size of the solid component was computed as the maximum length between the vertices of the surface model (Fig. 1c).

Statistical analyses

The interobserver and intraobserver variabilities of the measurements were assessed by calculating the intraclass correlation coefficient (ICC) and displayed by Bland–Altman plots. ICC (2, 1) and ICC (1, 1) were calculated for the assessment of interobserver and intraobserver variabilities, respectively. The difference between the groups was determined by a one-way analysis of variance. Predictive performance was evaluated by a receiver-operating characteristic (ROC) analysis, calculation of the area under the ROC curve (AUROC) and estimates of sensitivity and specificity. The overall survival was defined as the period between the day of surgery and death due to any cause. Patients who were alive at the last follow-up were defined as censored cases. The survival curve was drawn using the Kaplan–Meier method, and the difference in survival between two groups was assessed using the log-rank test. All tests were two-sided, and $p < 0.05$ was defined as statistically significant. All statistical analyses were performed using the software programs JMP 10 (SAS Institute Inc., Cary, NC, USA), MedCalc v16.8 (MedCalc Software, Ostend, Belgium), and R ver. 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The patient characteristics are presented in Table 1. Both interobserver and intraobserver agreements on the sizes of the solid components were excellent, with ICCs of 0.880 (95% confidence interval [CI], 0.847–0.907) and 0.970 (95% CI, 0.961–0.977), respectively. Bland–Altman plots are presented in Supplementary Fig. 2 (Online Resource 3). The mean sizes of the solid components measured in 2D and 3D were, respectively, 2.9 mm and 3.8 mm for AIS ($n=43$), 4.7 mm and 6.5 mm for MIA ($n=77$), and 13.0 mm and 16.9 mm for invasive adenocarcinoma ($n=113$). The sizes of the solid components increased from AIS to MIA to invasive adenocarcinoma in both measurements, as shown in Supplementary Table 1 (Online Resource 4) ($p<0.001$, one-way analysis of variance).

Table 1 Patient characteristics

Variable	Number	(%)
Sex		
Male	116	49.8
Female	117	50.2
Age, years		
Median	67	
Range	34–86	
Smoking history		
Current or former	122	52.4
Never	111	47.6
HRCT findings		
Pure GGN	67	28.8
Part-solid	76	32.6
Solid	90	38.6
Procedure		
Lobectomy	157	67.4
Segmentectomy	13	5.6
Wedge resection	63	27.0
Pathology		
AIS	43	18.5
MIA	77	33.0
Invasive adenocarcinoma	113	48.5
Nodal involvement		
pNX	64	27.5
pN0	156	67.0
pN1	4	1.7
pN2	9	3.9

AIS adenocarcinoma in situ, *GGN* ground glass nodule, *HRCT* high-resolution computed tomography, *MIA* minimally invasive adenocarcinoma

Comparisons of 2D and 3D measurements

We adopted the values that Reader 1 measured using the Image J 1.46r software program in the first analysis as the sizes of the solid components recorded in 2D for the subsequent analyses. The sizes of the solid components assessed in 3D tended to be larger than those measured in 2D (Fig. 2). There was a strong correlation between the size of the solid component recorded in 2D and that observed in 3D (adjusted $R^2=0.878$, $p<0.001$). The median difference in the sizes of the solid components measured by the 2 methods (size of the solid component obtained in 3D minus the size plotted in 2D) was 1.1 mm (2.5–97.5 percentile, − 1.8 mm to 13.7 mm) in all 233 cases. The median difference in the size of the solid component between the 2 methods was 1.1 mm (2.5–97.5 percentile, − 2.2 mm to 12.0 mm) for 76 part-solid nodules on HRCT and 4.4 mm (2.5–97.5 percentile, − 1.3 mm to 16.6 mm) for 90 solid nodules.

Prediction of pathology

The predictive performances of the sizes of the solid components for AIS and MIA were equivalent between the 2D and 3D methods ($p=0.229$). The AUROC was 0.871 (95% CI 0.817–0.911) for the sizes of the solid components measured in 2D and 0.857 (95% CI 0.798–0.901) for the sizes of the solid components recorded in 3D. When a solid

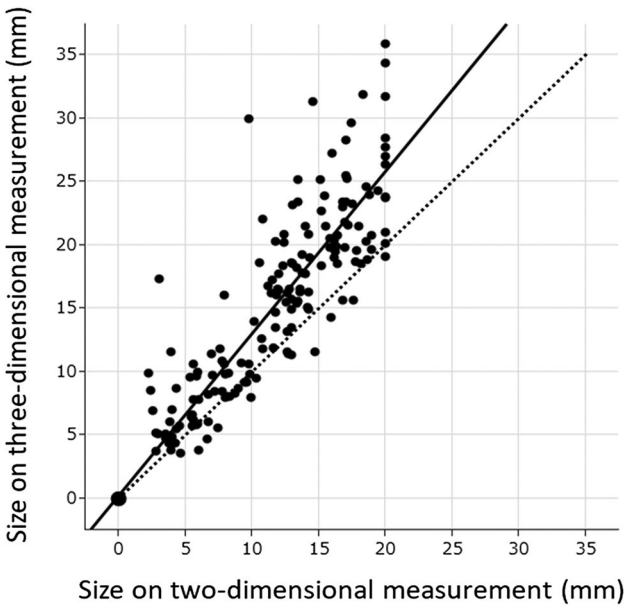

Fig. 2 Scatter plot with a 45° line. A circle indicates each case. The x axis represents the size of the solid component on two-dimensional measurement, and the y axis represents the size of the solid component on three-dimensional measurement. The solid line represents the regression line, and the dashed line represents the line $y=x$. The linear equation of the regression is $y=1.2801\,x+0.3355$

component ≤ 5 mm in size on 2D measurement was used as a radiographic criterion, the sensitivity and specificity for the prediction of AIS and MIA were 66.7% and 92.0%, respectively (Table 2). When a solid component ≤ 5 mm in size on 3D measurement was used as a radiographic criterion, the sensitivity and specificity for the prediction of AIS and MIA were 60.0% and 94.7%, respectively (Table 2). Nodal involvement was observed in 11 patients (7.6%) with a solid component > 5 mm in size on 2D measurement and in 12 patients (7.8%) with a solid component > 5 mm in size on 3D measurement.

Survival analyses

The median follow-up among the surviving patients was 6.5 years (range 11 days to 15 years), and 36 patients died. Regarding the 2D measurements, the overall survival rate at 5 years was 95.3% (95% CI 88.2–98.2) for 89 patients with a solid component ≤ 5 mm in size and 86.5% (95% CI 79.5–91.3) for 144 patients with a solid component > 5 mm in size (Fig. 3a). Regarding the 3D measurements, the overall survival rate at 5 years was 96.1% (95% CI 88.5–98.7) for 78 patients with a solid component ≤ 5 mm in size and 86.8% (95% CI 80.2–91.4) for 155 patients with a solid component > 5 mm (Fig. 3b). The difference in the overall survival according to whether the solid component was ≤ 5 mm or > 5 mm was statistically significant for both the 2D and 3D measurements ($p = 0.003$ and $p = 0.002$, respectively, log-rank test).

The overall survival rates at 5 years according to surgical procedures are presented in Fig. 4. The 5-year overall survival rates were 89.2% (95% CI, 81.9–93.8) for lobectomy ($n = 118$) and 73.4% (95% CI 51.4–87.8) for sublobar resection ($n = 26$) in 144 patients with a solid component > 5 mm in size measured in 2D ($p = 0.002$, log-rank test); 94.7% (95% CI 81.2–98.7) for lobectomy ($n = 39$) and 95.9% (95% CI 84.9–99.0) for sublobar resection ($n = 50$) in 89 patients with a solid component ≤ 5 mm in size observed in 2D ($p = 0.720$, log-rank test); 89.0% (95% CI 81.9–93.5) for lobectomy ($n = 125$) and 77.5% (95% CI, 57.8–89.7) for sublobar resection ($n = 30$) in 155 patients with a solid component > 5 mm in size recorded in 3D ($p = 0.052$, log-rank test); and 96.9% (95% CI 80.9–99.6) for lobectomy ($n = 32$) and 95.5% (95% CI 83.7–98.9) for sublobar resection ($n = 46$) in 78 patients with a solid component ≤ 5 mm in size assessed in 3D ($p = 0.580$, log-rank test).

Table 2 Relationship between the size of the solid component and pathology measured in two and three dimensions

Size	AIS and MIA	Invasive adenocarcinoma
Two-dimensional measurement		
Solid component ≤ 5 mm	80	9
Solid component > 5 mm	40	104
Three-dimensional measurement		
Solid component ≤ 5 mm	72	6
Solid component > 5 mm	48	107

AIS adenocarcinoma in situ, *MIA* minimally invasive adenocarcinoma

Discussion

The eighth TNM classification of lung cancer recommends the use of multiplanar reconstruction for the measurement of the solid component; however, the superiority of this approach over the standard 2D means of measuring the solid component on axial HRCT images remains unclear [5]. The present study examined whether 2D or 3D measurement of the solid component is more suitable as a radiological criterion for sublobar resection for lung adenocarcinoma ≤ 2 cm

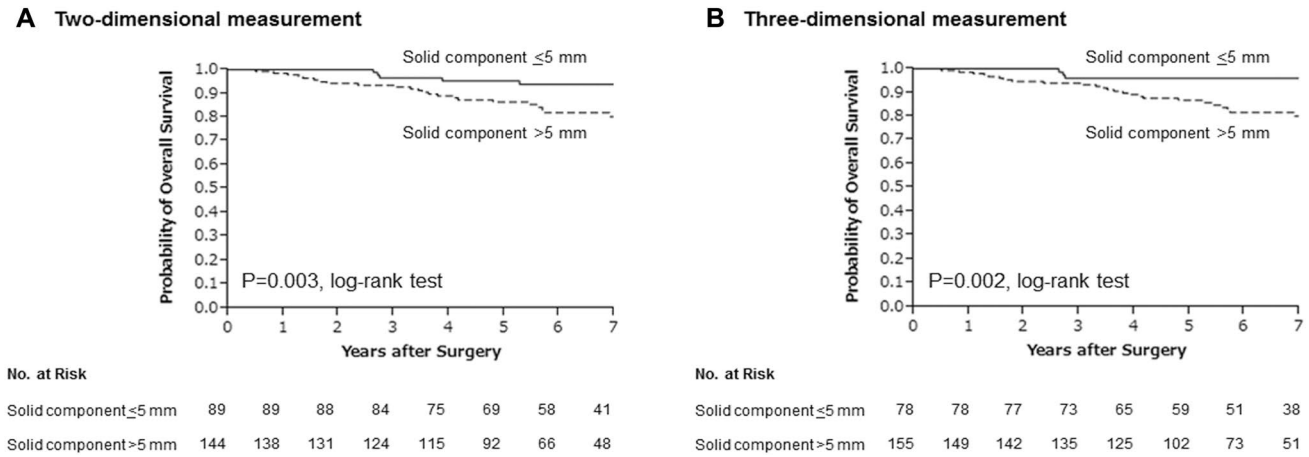

Fig. 3 The overall survival according to the size of the solid component on two-dimensional (**a**) and three-dimensional measurements (**b**)

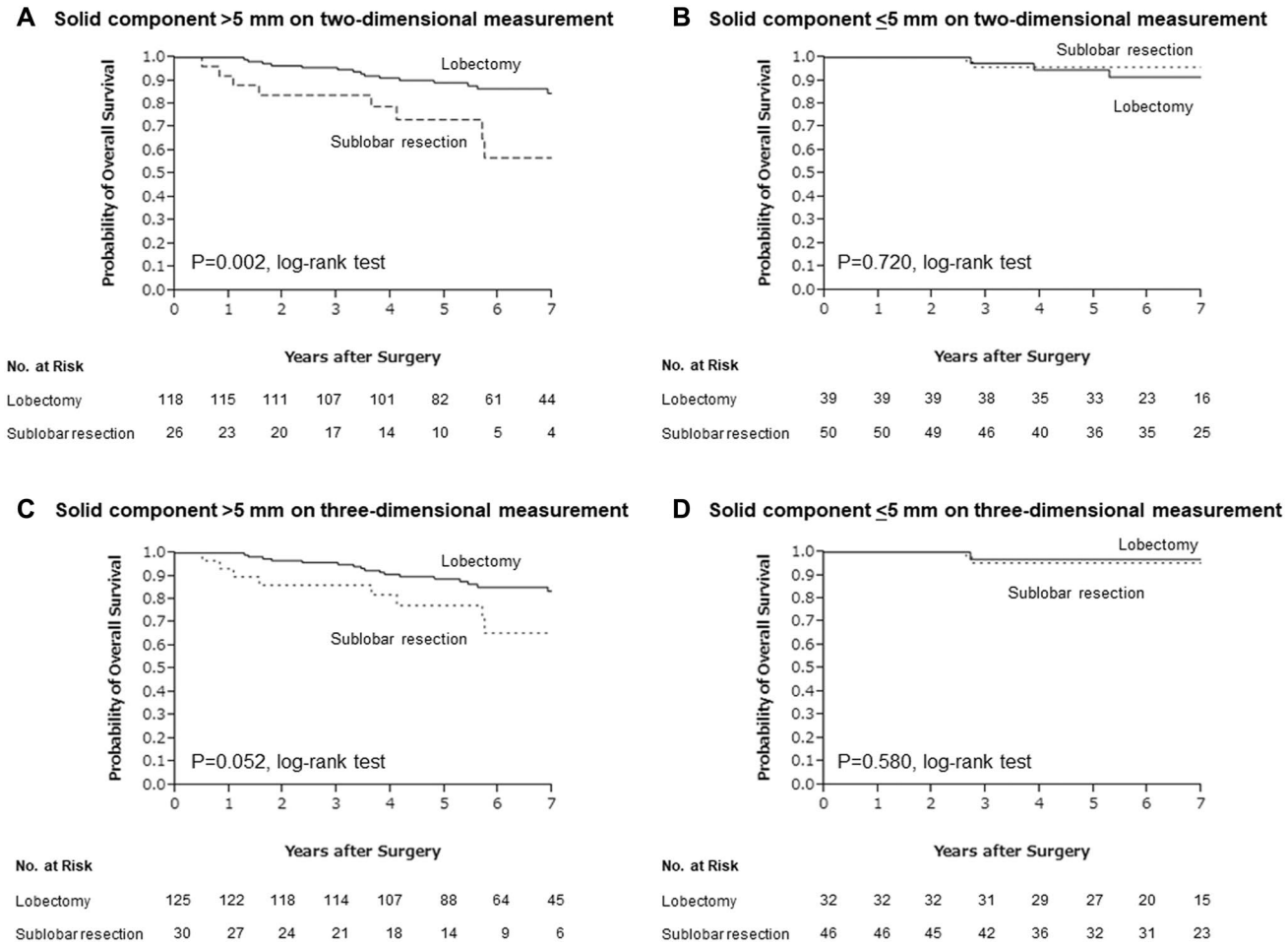

Fig. 4 The overall survival according to surgical procedures in 144 patients with a solid component > 5 mm in size on 2D measurement (**a**), 89 patients with a solid component ≤ 5 mm in size on 2D measurement (**b**), 155 patients with a solid component > 5 mm in size on 3D measurement (**c**), and 78 patients with a solid component ≤ 5 mm in size on 3D measurement (**d**)

in size. We evaluated the differences between the two methods in terms of (1) sizes of the solid components measured, (2) the predictive performance of such measurements for the pathology of AIS and MIA, and (3) the overall survival. We found that the differences between the two measurements were minimal, and a solid component ≤ 5 mm in size is an appropriate criterion for sublobar resection with both methods.

Regarding their utility for predicting AIS and MIA, the ROC curves for the size of the solid component were superimposable for both the 2D and 3D measurements. We attribute our result to a strong correlation between the sizes of the solid components recorded via the two measurements, as well as to the fact that the median difference in sizes obtained via the two methods was minimal (1.1 mm in all 233 cases). However, our results indicate a larger difference between the two methods when measuring the solid component for solid nodules than when measuring that for part-solid nodules. Furthermore, Hattori et al. found that the size of the solid component was associated with the overall survival of patients with solid nodules but not of patients with part-solid nodules. The T descriptors in the eighth edition of the TNM classification for lung cancer separate tumors into centimeter increments, from 1 to 5 cm; strict 3D measurements conducted according to these guidelines will help predict the patient survival after surgery for solid nodules on HRCT [12].

The present study further found that the size of the solid component recorded in 3D tended to be larger than that observed in 2D. Lee et al. also showed that 3D measurements overestimated the size of the invasive component on pathology relative to 2D measurements, while 2D measurements tended to yield a size similar to that of the invasive component assessed via pathology [10]. 3D measurement is expected to help improve specificity in the prediction of AIS and MIA, and given the current consensus that lobectomy is the mainstay procedure, such a clinical indicator with high specificity would be important when selecting appropriate

candidates for sublobar resection. However, when we set the cut-off value for the solid components to 5 mm, the performances of the 2D and 3D measurements became similar, with respective specificities of 92.0% and 94.7%. Furthermore, the survival rates at 5 years were equally excellent between lobectomy and sublobar resection in patients with a solid component ≤ 5 mm in size on both 2D and 3D measurements, while sublobar resection led to a deteriorations in the survival rate at 5 years (11.5–15.8%) in patients with a solid component > 5 mm in size. We believe that a solid component ≤ 5 mm in size is a reliable indication for sublobar resection, irrespective of whether 2D or 3D measurements are used.

Several limitations associated with the present study warrant mention. First, adenocarcinomas 2–3 cm in size were not included in our study, as we believe that adenocarcinomas larger than 2 cm are not suitable for sublobar resection. However, the solid component in these tumors should be measured in future studies [5]. We also excluded patients who had an adenocarcinoma with a pathological size > 2 cm. It can sometimes be difficult to measure the size and trace the edge of lung adenocarcinoma with faint and ambiguous ground-glass appearance, and we identified an unexpected extension of cancer cells along the alveolar walls that had not been recognized on preoperative HRCT. We felt that these cases hampered the exact 3D measurement and might have influenced our results. For this reason, we excluded patients who had an adenocarcinoma with a pathological size > 2 cm. However, our criteria for patient selection were deliberate and will influence the diagnostic accuracy in our study. Second, the slices of the HRCT images used in our study ranged from 1 to 3 mm, a range thicker than the recommended slice thickness of 0.6–1.5 mm [13]. Third, as in the JCOG 0201 study [8], a contrast agent was used for preoperative staging unless contraindicated. We could not estimate the influence of the contrast agent on the size of the solid components measured. Fourth, our study may not have had sufficient statistical power to detect significant differences between these two measurements because of the moderate sample size ($n = 233$); our results should thus be interpreted with reserve. Fifth, in contrast to the study by Lee et al.[10], we did not compare the size of the solid component on HRCT with the invasive size on pathology because the plane of the specimen section in pathological examinations is not consistent with the axis on HRCT. We therefore examined the correlation between the size of the solid component on HRCT and the pathological diagnosis impacting the surgical procedure and rates of survival.

In conclusion, our study demonstrated minimal difference in the sizes of the solid components measured via 2D and 3D HRCT. Furthermore, the predictive performances for AIS and MIA and the prognostic impacts of the two methods were similar. When selecting appropriate candidates for sublobar resection for lung adenocarcinoma ≤ 2 cm in size, 2D measurement of the solid component on axial HRCT is still justified.

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Compliance with ethical standards

Conflict of interest None declared.

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