Introduction

Nonsmall cell lung cancer (NSCLC) with a size of 3 cm, at maximum, is traditionally treated with a lobectomy and mediastinal lymph node dissection. However, in recent years, there has been growing interest to consider less extensive and hence more lung-sparing surgery as well as nonsurgical approaches, such as stereotactic radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) and radiofrequency ablation for these tumours.

In this review, we will give an overview of current data on which techniques may be used outside clinical trials. Indeed, in the absence of phase III randomised data and because neither sublobar resections nor SABR are clearly superior to another for the whole patient population; we have attempted to give a balanced view. Moreover, patient characteristics, tumour characteristics and local expertise should be taken into account for each individual patient.

Surgical approaches

Surgery remains the cornerstone of treatment for early stage NSCLC, and lobectomy, including systematic lymph node dissection, is considered the standard of care for patients with early stage NSCLC [1, 2]. To date, sublobar resection is performed most often as an alternative to lobectomy in patients with peripheral tumours with limited pulmonary reserve or other comorbidities [3–6]. The increased ability to identify smaller NSCLC by enhanced computed tomography (CT) screening has led many surgeons to question the appropriateness of lobectomy in all patients with small-sized NSCLC [7]. Furthermore, the growing recognition that patients with smaller tumours are a favourable subset of patients with stage I NSCLC has led to an increasing consideration of sublobar resection for patients with small-sized stage I NSCLC [8].

Several authors have identified the following three points concerning the usefulness of sublobar resection: 1) safety of the perioperative course [9, 10]; 2) effectiveness of preservation of pulmonary function compared with lobectomy [11, 12]; and 3) oncologic outcome equivalent to lobectomy [13–15]. However, these studies are clearly heterogeneous with regard to the risk status of the patients, the tumour biology and the mode of sublobar resection. In addition, a population-based analysis demonstrated that lobectomy conferred a significant survival advantage compared with segmentectomy [16]. However, a meta-analysis and a review each concluded that segmentectomy provides a survival rate similar to that with lobectomy for tumours ⩽2 cm in size, but not for larger tumours [17, 18]. Thus, the role of sublobar resection in the treatment of NSCLC has not been fully evaluated [19]. Accordingly, we need to comprehensively understand the present and updated roles of sublobar resection for patients with NSCLC.

Advantages of sublobar resection

If less lung parenchyma is removed by sublobar resection, patients should benefit from both improved perioperative outcomes (morbidity and mortality) and preserved pulmonary function.

Altorki *et al.* [9] reviewed the outcomes of 347 patients diagnosed with lung cancer who underwent lobectomy (n=294) or sublobar resection (n=53) for NSCLC in the International Early Lung Cancer Action Program from 1993 to 2011. The mortality rate was 0% for the sublobar resection group and 1.0% for the lobectomy group [9]. Schuchert *et al.* [10] also reviewed the perioperative outcomes of 182 consecutive segmentectomies and 246 lobectomies for early stage NSCLC. They reported morbidity and mortality rates of 32.4% and 1.1%, respectively, for anatomic segmentectomy, and 33.7% and 3.3%, respectively, for lobectomy [10]. One report from a Japanese survey gave a mortality rate of 0.1% for sublobar resection and 0.3% for lobectomy [20]. Thus, sublobar resection can be performed with perioperative outcomes comparable to or better than those for lobectomy. However, the initial results of the randomised, prospective American College of Surgeons Oncology Group (ACOSOG) Z0030 trials reported morbidity and mortality rates of 46% and 3%, respectively, in the setting of anatomic segmentectomy, and 37% and 1%, respectively, in the setting of lobectomy [21].

Keenan *et al.* [11] conducted a retrospective study to evaluate the degree of post-operative loss of pulmonary function among patients who underwent segmental resection or lobectomy. They concluded that segmental resection preserved pulmonary function better than lobectomy [11]. Harada *et al.* [12] also evaluated the degree of post-operative functional loss in patients who underwent segmentectomy or lobectomy. They concluded that the extent of removed lung parenchyma directly affected post-operative functional loss, even at 6 months post-surgery, and segmentectomy offered significantly better preservation of function than lobectomy [12]. No previous studies have evaluated the degree of post-operative loss of pulmonary function among patients undergoing wedge resection or lobectomy.

Thus, there is still some controversy regarding both the safety of sublobar resection and the preservation of pulmonary function by sublobar resection. Whether or not sublobar resection actually improves

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perioperative outcomes (morbidity and mortality) and preserves pulmonary function should be prospectively evaluated with an adequate number of patients.

Mode of sublobar resection

Sublobar resection generally refers to wedge resection and segmental resection (segmentectomy). Wedge resection involves the macroscopic removal of the tumour with surrounding normal lung tissue and does not follow anatomical boundaries. In contrast, segmentectomy involves the macroscopic removal of the tumour with the division of vessels and bronchi that belong to a distinct anatomical segment(s). Thus, draining lymphatics and veins of the tumour can be removed and a wider margin of resection compared with wedge resection can be achieved by segmentectomy. This is the greatest benefit with the use of segmentectomy. Theoretically, segmentectomy results in lower recurrence rates than wedge resection. In fact, several studies have demonstrated that segmentectomy is associated with a decreased risk of local recurrence compared with wedge resection [22, 23].

However, segmentectomy has some disadvantages compared with wedge resection. Since selective isolation and division of the targeted bronchovascular pedicle for each segment should be performed, segmentectomy inevitably takes longer and carries the possibility of considerable bleeding compared with wedge resection. In fact, the Japanese survey mentioned previously reported an in-hospital mortality rate of 0.3% for segmentectomy and 0.2% for wedge resection [20]. Wedge resection might be a less invasive procedure than segmentectomy. Segmentectomy also may not always be technically feasible and is best suited to the left upper lobe (lingula, apicoposterior and anterior segments) and the apical segment of both lower lobes [24, 25]. Thus, the superiority of segmentectomy over wedge resection might depend on several factors, such as the risk status of the patient or the tumour location.

While segmentectomy has been believed to be superior to wedge resection, the potential benefits and limitations of segmentectomy should be fully considered.

Indications for sublobar resection

Patients with NSCLC who are candidates for surgery are divided into two groups: standard-risk patients and high-risk patients. High-risk patients are those who have poor pulmonary reserve or other limiting factors and who could withstand thoracotomy but not lobectomy. Patients with prior resection and elderly patients, even if they have normal pulmonary function, might also be considered high risk [26–28]. The American College of Surgeons Oncology Group/National Institutes of Health inoperability criteria for lung surgery have often been used to identify high-risk patients [29]. An algorithm for the assessment of cardiopulmonary reserve before lung resection in lung cancer patients, proposed by the European Respiratory Society/European Society of Thoracic Surgery, has also been widely used [30]. However, these approaches cannot identify every high-risk patient since patients with good cardiopulmonary function are sometimes considered to be poor surgical candidates due to other non-cardiopulmonary comorbidities. As an exceptional case, some patients with a very low pre-operative forced expiratory volume in 1 s (FEV_1) or FEV_1/forced vital capacity ratio are less likely to lose pulmonary function after lobectomy and may actually see improvements [31]. The chronic obstructive pulmonary disease (COPD) index may be useful for predicting the change in FEV_1 after lobectomy. In addition to the former two major criteria, these findings should be considered in patients with severe COPD. Thus, there is still an important issue/controversy in the definition of high-risk patients.

There are two clearly different rationales for the use of sublobar resection in patients with NSCLC; an intentional limited resection and a compromised limited resection. Sublobar resection for standard-risk patients is performed as an intentional limited resection. Intentional limited resection may also include sublobar resection for patients with noninvasive or minimally invasive tumour that is sufficiently curable by limited resection. In contrast, sublobar resection for high-risk patients is performed as a compromised limited resection.

There are crucial differences in the role of sublobar resection as intentional limited resection and as compromised limited resection. In the intentional setting, patients with sublobar resection must have perioperative and oncological outcomes equivalent to those of patients with lobectomy. Patients with intentional sublobar resection must not experience special forms of loco-regional recurrence, which may not occur if they had undergone lobectomy. The importance of adequate hilar/mediastinal staging to avoid erroneous downstaging of the disease cannot be overemphasised. In contrast, oncological outcomes in the compromised setting might be inevitably worse than those in the intentional setting. Therefore, surgeons should focus on the balance between the risks and benefits when deciding upon the mode of resection. They should also consider nonsurgical therapeutic options, such as SBRT or radiofrequency ablation.

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Intentional limited resection

Only one randomised study, by the Lung Cancer Study Group [32], has compared lobectomy with intentional sublobar resection (segmentectomy or wedge resection) in patients with stage I NSCLC. The results of this study showed a three-fold increase in local recurrence for patients with sublobar resection compared to those with lobectomy, but no significant difference in overall survival [32].

Since then there have been five studies on intentional limited resection performed in Japan (table 1). KODAMA *et al.* [33] reported the results of intentional limited resection (segmentectomy) for T1 N0 M0 NSCLC at a single institution. The overall 5-year survival rate was 93% and the local recurrence rate was 8.7% [33]. TSUBOTA *et al.* [34] reported the early results of a prospective, multicentre trial of limited surgical resection (segmentectomy) for peripheral NSCLC ⩽2 cm in size. The overall 5-year survival rate was 91% and the recurrence rate was 2% [34]. OKADA *et al.* [35] also reported the results of a prospective, nonrandomised, multicentre trial that compared sublobar resection (n=305) to lobectomy (n=262) for NSCLC ⩽2 cm in size. The local recurrence rate was 4.9% in the sublobar resection group and 6.9% in the lobectomy group. The disease-free and overall survival rates were similar in the two groups, with 5-year survival rates of 85.9% and 89.6%, respectively, for the sublobar resection group and 83.4% and 89.1%, respectively, for the lobectomy group [35]. Furthermore, KOIKE *et al.* [36] retrospectively reviewed 223 patients with small (⩽2 cm in size) peripheral NSCLC who underwent intentional segmentectomy at their institution. The 5- and 10-year overall survival rates were 89.6% and 81.0%, respectively. The local recurrence rate was 3.6% [36]. More recently, TSUTANI *et al.* [37] reported the results of a multicentre trial that compared intentional segmentectomy (n=98) to lobectomy (n=383) for stage IA adenocarcinoma. The local recurrence rate was 3% in the segmentectomy group and 4.4% in the lobectomy group. The recurrence-free and overall survival rates were similar in the two groups, with 3-year survival rates of 91.4% and 96.9%, respectively, for the segmentectomy group and 87.3% and 94.1%, respectively, for the lobectomy group [37]. The most crucial point in these studies is intra-operative adequate hilar/mediastinal nodal staging by complete lymph node dissection or nodal sampling. If there were any findings during the operation, such as lymph node metastasis or a surgical margin that was insufficient for sublobar resection, the operative procedure was altered to lobectomy.

There are two ongoing randomised, phase III trials of lobectomy *versus* sublobar resection for small (⩽2 cm) peripheral NSCLC; JCOG 0802 and CALGB 140503, respectively. The Japanese phase III study is evaluating the non-inferiority in overall survival of segmentectomy compared with lobectomy in patients with small-sized (⩽2 cm) peripheral NSCLC, excluding radiologically determined noninvasive cancer. The primary end-point is overall survival. The planned sample size is 1100 patients, with 550 cases per arm [38]. In the USA, a recently initiated randomised controlled trial in approximately 1200 patients is comparing lobectomy to limited resection (segmentectomy or wedge resection) for the treatment of patients with NSCLC ⩽2 cm in size. The primary objective is to determine whether disease-free survival after sublobar resection is non-inferior to that after lobectomy in patients with small peripheral (⩽2 cm) NSCLC [39].

Sublobar resection for a tumour without metastatic potential or with low metastatic potential is also considered to be an intentional limited resection. Adenocarcinoma *in situ*, which was formerly known as bronchioloalveolar carcinoma, is a small (⩽3 cm) solitary adenocarcinoma that consists of purely lepidic growth without invasive foci. Minimally invasive adenocarcinoma is a small (⩽3 cm) solitary adenocarcinoma with invasive foci ⩽5 mm [40]. Adenocarcinoma *in situ* and minimally invasive adenocarcinoma represent a completely separate group of adenocarcinomas since they show 100%, or near-100%, disease-specific survival, respectively, if completely resected [41, 42]. Therefore, adenocarcinoma *in situ* and minimally invasive adenocarcinoma are candidates for the use of intentional sublobar resection.

KOIKE *et al.* [43] conducted a prospective, phase II study to evaluate limited resection for noninvasive bronchioloalveolar carcinoma diagnosed by intra-operative pathological examination. In their study, 44 patients underwent wedge resection and two underwent segmentectomy. Permanent pathological examination revealed that three patients had primary lung adenocarcinomas other than noninvasive bronchioloalveolar carcinoma. The predictive value of intra-operative pathological examination for noninvasive bronchioloalveolar carcinoma diagnosis was 94%. The 5-year cancer-specific survival rate was 100% [43]. Other reports have demonstrated a similar outcome [44, 45]. Ground-glass opacity with little or no consolidation on high-resolution represents adenocarcinoma *in situ* or minimally invasive adenocarcinoma. SUZUKI *et al.* [46] reported the results of the JCOG0201 study and demonstrated that radiological noninvasive peripheral lung adenocarcinoma could be defined as an adenocarcinoma ⩽2.0 cm with ⩽0.25 consolidation on high-resolution CT. In addition, the phase II trial JCOG0804 was conducted to evaluate limited surgical resection for "radiological early lung cancer" as defined by JCOG0201. Patient accrual is now complete. Over the next 10 years, this study will determine whether their criteria for early

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TABLE 1 Clinical characteristics and outcomes of patients with intentional sublobar resection

First author [ref.]	Study design	Patients n	Stage	Mean tumour size cm	Follow-up months	Mode of sublobar resection	Mortality %	Intraoperative mediastinal lymph node evaluation %	Overall 5-year survival %	Local recurrence %
Ginsburg [32]	Prospective	122	IA	Not reported	Not reported	Segmentectomy: n=82 Wedge resection: n=40	0.8	100	At 4 years: 60	18
Kodama [33]	Retrospective	46	IA	1.7	Median: 30	Segmentectomy	0	89	93	8.7
Tsubota [34]	Prospective	55	IA (T1a)	1.7	Mean: 47.2	Segmentectomy	0	100	91	2
Okada [35]	Prospective	305#	IA (T1a)	1.6	Median: 72	Segmentectomy: n=230 Wedge resection: n=30	Not reported	100	89.6	4.9
Koike [36]	Prospective	223	IA (T1a)	Not reported	Median: 70	Segmentectomy	Not reported	100	89.6	3.6
Tsutani [37]	Retrospective	98	IA	1.7	Median: 43.2	Segmentectomy	0	Not reported	At 3 years: 96.9	3

#: 45 patients converted to other procedures.

TABLE 2 Clinical characteristics and outcomes of patients with compromised sublobar resection

First author [ref.]	Study design	Patients n	Stage	Tumour size cm	Follow-up months	Mode of sublobar resection	Mortality %	Intraoperative mediastinal lymph node evaluation %	Overall 5-year survival %	Local recurrence %
Donahue [47]	Retrospective	113	Any (IA: n=63)	Mean: 2.1	Median: 24	Segmentectomy	0	100	IA: 79	IA: 12.7
Schuchert [48]	Retrospective	325	IA (T1a)	Not reported	Mean: 31.8	Segmentectomy	1.1	100	77#	5.2
El-Sherif [49]	Retrospective	207	I	Median: 1.8	Median: 31	Segmentectomy: n=85 Wedge resection: n=122	1.4	57	40	7.2
Wolf [50]	Retrospective	154	IA (T1a)	Not reported	Not reported	Segmentectomy: n=24 Wedge resection: n=130	0.6	29	59	16
Landreneau [51]	Retrospective	Open: 42 VATS: 60	IA	Open wedge resection: median 1.7 VATS: median 1.9	Open wedge resection: median 29 VATS: median 24	Wedge resection	0	0	Open wedge resection: 58 VATS: 65	Open wedge resection: 24 VATS: 16
Sienel [52]	Retrospective	87	IA	1.9	45	Segmentectomy: n=56 Wedge resection: n=31	0	100	Segmentectomy: 71¶ Wedge: 48¶	Segmentectomy: 16% Wedge: 55%

VATS: video-assisted thoracoscopic surgery. #: free from recurrence; ¶: cancer-related 5-year survival.

lung adenocarcinomas are adequate. Thus, adenocarcinoma *in situ* and minimally invasive adenocarcinoma represent ideal lesions for which limited resection gives results equivalent to lobectomy.

At present, intentional limited resection is mainly performed for small-sized NSCLC ⩽2 cm, and the favourable results of intentional sublobar resection have been based on several nonrandomised studies. We need to await the results of ongoing randomised trials that are assessing the utility of sublobar resection for small-sized NSCLC; they will likely provide important contributions to the role of intentional limited resection. Until then, lobectomy remains the standard procedure even for small NSCLC and sublobar resection should still be performed only in a clinical trial setting. In contrast, intentional limited resection is appropriate for small NSCLC that present as ground-glass opacities or semi-solid lesions, which represents adenocarcinoma *in situ* or minimally invasive adenocarcinoma under the condition of proper radiological and pathological examination.

Compromised limited resection

High-risk patients who are not eligible for lobectomy because of poor pulmonary reserve or other major comorbidities are still candidates for surgery. Sublobar resection, either segmentectomy or wedge resection, is appropriate for these patients. There have been three types of reports on the results of sublobar resection as a compromised limited resection: those that included only segmentectomy, those that included both segmentectomy and wedge resection, and those that included only wedge resection. The results of the compromised limited resection are summarised in table 2.

Donahue *et al.* [47] reported the results of anatomic segmentectomy in 113 compromised patients with NSCLC. The indications for segmentectomy were poor pulmonary function, comorbidities or the surgeon's judgment. The local recurrence rate was 12.7% and the 5-year recurrence-free survival rate was 79% for stage IA patients with T1a lesion (n=63) [47]. Schuchert *et al.* [48] also conducted a similar study with 785 patients who underwent anatomic segmentectomy. The decision to perform segmentectomy was based on tumour size, location (peripheral lesions ⩽2 cm in size), the patient's underlying cardiopulmonary status and other relevant comorbidities. The local recurrence rate was 5.2% and the 5-year recurrence-free survival rate was 77% for 325 patients with stage IA NSCLC [48]. Thus, the 5-year survival rate of patients with compromised segmentectomy seems to be 5–10% lower than that of patients with intentional segmentectomy. El-Sherif *et al.* [49] retrospectively reviewed the outcomes of 784 patients with stage I NSCLC treated with lobectomy (n=577) or sublobar resection (segmentectomy: n=85, wedge resection: n=122). Sublobar resection was performed for patients with cardiopulmonary impairment that precluded lobectomy. The local recurrence rate was 7.2% for the sublobar resection group and 4.2% for the lobectomy group. The 5-year disease-free survival rate was 40% for the sublobar resection group and 54% for the lobectomy group [49]. Wolf *et al.* [50] also retrospectively reviewed the outcomes of 238 patients with clinical T1a N0 M0 NSCLC treated with lobectomy (n=84) or sublobar resection (segmentectomy: n=24; wedge resection: n=130). Patients who underwent sublobar resection were older and had worse preoperative pulmonary function. The local recurrence rate was 16% for the sublobar resection group and 8% for the lobectomy group. The 5-year survival rate was 59% for the sublobar resection group and 80% for the lobectomy group [50].

Landreneau *et al.* [51] analysed the outcomes of a series of patients with peripheral stage IA (T1 N0 M0) NSCLC treated with open lobectomy (n=117), open wedge resection (n=42) or video-assisted thoracoscopic surgery wedge resection (n=60). Patients with a significant impairment of their physiologic condition underwent wedge resection based on the surgeon's decision. There was a trend toward increased local recurrence in the wedge resection group (16%) compared to the open lobectomy group (9%), although this difference was not statistically significant. While there was no significant difference in overall survival between patients treated with video-assisted thoracoscopic surgery wedge resection compared to open lobectomy, there was a significant decrease in overall survival for patients with open wedge resection. The 5-year survival rates were 58% for patients with open wedge resection, 65% for those with video-assisted thoracoscopic surgery wedge resection and 70% for those with lobectomy [51].

Thus, several reports have suggested that high-risk patients with wedge resection have a worse prognosis than those with segmentectomy, although there is considerable patient selection bias with regard to the physiological status of the patient and the tumour biology.

A few reports have compared segmentectomy to wedge resection for high-risk patients with NSCLC. Sienel *et al.* [52] reported the results of sublobar resection (segmentectomy: n=56; wedge resection: n=31) in patients with stage IA NSCLC. The local recurrence rate was 16% for the segmentectomy group and 55% for the wedge resection group. The cancer-related 5-year survival rate was 71% for the segmentectomy group and 48% for the wedge resection group [52].

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Several authors have reported the usefulness of adjuvant radiotherapy or brachytherapy for reducing local recurrence after sublobar resection. FERNANDO *et al.* [53] concluded that intraoperative brachytherapy might reduce local recurrence. More recently, the American College of Surgeons Oncology Group conducted a randomised study (Z4032) that compared sublobar resection alone to sublobar resection with brachytherapy for high-risk operable patients with NSCLC [54].

Patients with compromised limited resection tend to have a higher recurrence rate and a lower survival rate than those with intentional limited resection. The superiority of segmentectomy to wedge resection in these populations has not yet been clarified because there has been no formal comparison of segmentectomy to wedge resection. Furthermore, there has been no comparison of sublobar resection with nonsurgical treatment, such as SBRT or radiofrequency ablation. Prospective, randomised studies will be needed to fully delineate the utility of sublobar resection, SBRT or radiofrequency ablation in high-risk patients with NSCLC.

Stereotactic radiotherapy or stereotactic ablative radiotherapy

The gold standard for treating stage I NSCLC is a lobectomy with systematic nodal dissection [49]. However, due to comorbidities this treatment is deemed unfeasible in a significant proportion of patients, for which alternatives were sought [50–53]. Pioneered in Japan, SBRT or SABR has been introduced in clinical practice in the past decade [50–53].

In SABR, a few fractions of very high doses of radiation are delivered to small tumours that are located in lung regions able to sustain an ablative dose of radiotherapy. In most studies, so-called "central" tumours, *e.g.* those remote from the more susceptible central mediastinal structures such as the main bronchi, large vessels and the oesophagus, are not included [54]. Although some centres advocate SBRT in central tumours [55], this is the subject of an ongoing phase II trial, LUNG-TECH, led by the European Organisation for Research and Treatment of Cancer. The advantages of SABR compared with conventional irradiation are a short overall treatment time (1–2 weeks) and a very high biologically effective dose. SABR offers the possibility to minimise the time investment for treatment and toxicity, which is of obvious benefit for medically inoperable patients suffering from major comorbidities or advanced age. SABR requires highly specialised radiotherapy preparation and execution techniques including four-dimensional respiratory correlated CT scans and image-guided radiotherapy.

45 studies concerning SABR in early stage NSCLC have been reported [56]. 13 studies including 996 patients were prospective, and 32 studies including 2645 patients were retrospective.

The results of the prospective trials with SABR are summarised in table 3 [52, 57–73]. The 2-year overall survival was 65.2%, with a 2-year local tumour control rate of 90.4%. When all 45 studies on SABR, totalling 3641 patients, were considered, the 2-year overall survival was 70% (95% CI 67–92%) and the average local tumour control rate after 2 years was 91% (95% CI 90–93%) [56]. Even though the patient selection may have been different between studies and older reports used inevitably simpler techniques, neither the 2-year overall survival nor the 2-year local tumour control rate different significantly [56]. The 2-year local tumour control rate was 91% (95% CI 89–93%) for linear accelerator-based techniques, 88% (95% CI 78–94%) for Cyberknife (Accuracy Inc., Sunnyvale, CA, USA), and 80% (95% CI 68–91%) for other technologies. The 2-year overall survival was 69% (95% CI 66–71%) for linear accelerator-based techniques, 73% (95% CI 61–83%) for Cyberknife and 75% (95% CI 65–83%) for other technologies. These figures remained stable for at least 5 years [68]. After 5 years, the loco-regional recurrences rates were ~15%, with ~20% of the patients developing distant metastases [68]. Considering the robustness of these findings within many studies worldwide, it is fair to state that SBRT has been proven to be comparable to outcome of lobectomy and lymph node dissection [69, 70]. Indeed, in the International Association for the Study of Lung Cancer database, which also comprises a large, relatively non-selected group of patients, the 2-year overall survival was 68% (66–70%) [56].

The toxicity of SABR is favourable; <10% of the patients experienced important side-effects, which also makes SABR suitable for elderly and/or frail patients [68, 71]. Pulmonary function (FEV_1 and diffusing capacity of the lung for carbon monoxide (D_{LCO})) does not deteriorate after SABR, even in individuals with a poor baseline lung function [72]. Therefore, SABR is not contraindicated in patients with severe COPD [72].

Therefore, SABR has become the treatment of choice for inoperable patients with stage I NSCLC and is possibly competitive with lobectomy.

In some patients, mainly due to poor pulmonary function or other comorbidities, a pathological diagnosis of the tumour cannot be obtained. In these cases, algorithms have been developed that allow the *a priori* criteria for malignancy to be calculated. In Europe, the probability for malignancy is >95% when a lesion is new, has CT characteristics of malignancy and is 2-fluoro-2-deoxy-D-glucose (FDG) avid [74]. In the

TABLE 3 Summary of prospective trials with stereotactic radiotherapy

First author [ref.]	Study design	Patients n	Stage	Median age years	Total dose Gy	Dose per fraction Gy	2-year overall survival %	2-year local recurrence
Baumann [58]	Prospective	57	I	75	45	3	65	Not reported
Bral [62]	Prospective	40	I (n=38)	73	60	3–4	52	Not reported
Fakiris [63]	Prospective	70	I	Not reported	60–66	3	62	95
Fritz [64]	Prospective	40	I	74	30	1	63	95
Le [65]	Prospective	20	I	Not reported	15–30	1	64	70
Matsuo [66]	Prospective	101	I	77	48	4	80	93
Salazar [67]	Prospective	60	I	Not reported	40	4	Not reported	Not reported
Shibamoto [68]	Prospective	180	I	77	44–52	4	80	85
Taremi [69]	Prospective	108	I	73	48–60	3–10	63	Not reported
Timmerman [70]	Prospective	55	I	72	54	3	73	Not reported
Vahdat [71]	Prospective	20	I	75	42–60	3	90	95
Widder [72]	Prospective	202	I	76	60	3–8	72	95
Xia [73]	Prospective	43	I (n=25)	71	50	5	78	95

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absence of a clear alternative diagnosis, SABR may be delivered without pathology [74]. Nevertheless, it should be stressed that a pathological diagnosis should always be preferentially obtained whenever possible.

The prognosis of patients treated with SABR with or without a pathological diagnosis is similar [75]. This supports the use of the above-mentioned algorithm, at least in Europe where other diseases mimicking malignant coin lesions are very rare.

Historically, patients referred for SABR were the older and/or frailer patient group. With the recognised success of SABR, more borderline operable or even operable patients that refuse surgery are being treated with radiotherapy. In both cases, thorough staging is advised. Indeed, besides the detection of distant metastases by a whole-body FDG-positron emission tomography-CT scan, mediastinal and hilar lymph node involvement should be identified as it will alter the local and systemic treatment. As ~15% of the patients fail in the lymph nodes [76], endobronchial ultrasound/endoscopic ultrasound and, when appropriate, mediastinoscopy should be considered, taking into account the general condition and the comorbidities of the patient.

In particular, in patients who are potential candidates for salvage surgery early detection of local recurrences after SABR are particularly challenging. All patients show persistent and even fluctuating changes in the lungs [77]. Therefore, it is important to discuss follow-up scans multidisciplinary with experts that take into account not only tumour size, but also other morphological criteria [77]. FDG-positron emission tomography-CT scans may be falsely positive after SABR and should be interpreted in the context of other diagnostic criteria [77].

Sublobar resection, SABR or radiofrequency ablation?

In recent years, sublobar resections have gained popularity as a way to spare lung tissue. Randomised trials comparing lobectomy to sublobar resections are underway. At the time of writing, no phase III comparisons have been reported on SABR *versus* sublobar resections.

In an attempt to indirectly compare SABR to sublobar resections and radiofrequency ablation, CRABTREE *et al.* [78] compared the selection criteria and short-term outcomes of three prospective clinical trials using: SABR in the Radiation Therapy Oncology Group (RTOG) trial 0236), sublobar resection in the ACOSOG trial Z4032, and radiofrequency ablation in the ACOSOG trial Z4033. Although the patients in ACOSOG Z4033 were older (75.6±7.5 years) than those in RTOG 0236 (72.5±8.8 years) and ACOSOG Z4032 (70.2±8.5 years; $p=0.0003$), the pre-treatment FEV_1 was 61.3±33.4%, 53.8±19.6% and 48.8±20.3% for RTOG 0236, ACOSOG Z4032 and ACOSOG Z4033 ($p=0.15$), respectively. The pre-treatment D_{LCO} was 61.6±30.2%, 46.4±15.6% and 43.7±18.0% for RTOG 0236, ACOSOG Z4032 and ACOSOG Z4033 ($p=0.001$), respectively. The overall 90-day mortality for SABR, sublobar resection and radiofrequency ablation was 0%, 2.4% (five out of 211) and 2.0% (one out of 51) ($p=0.5$), respectively. Overall, the unadjusted 30-day grade 3 or more adverse events were more common with sublobar resection than with SABR (28% *versus* 9.1%, $p=0.004$), although there was no difference between the two groups at 90 days. Of the patients with clinical stage IA in ACOSOG Z4032, 29.3% had a more advanced pathological stage at surgery. A propensity-matched comparison showed no difference between SABR and sublobar resection for 30-day grade 3 or more adverse events (OR 2.37 (95% CI 0.75–9.90); $p=0.18$). Neither FEV_1 nor D_{LCO} declined after SABR or sublobar resection. There were not enough data on radiofrequency ablation outcomes to draw conclusions.

Conclusions

Lobectomy and systematic nodal dissection are still the standard for small-size (<3 cm) NSCLC. Nonrandomised trials suggest that a segmentectomy may result in local control rates that are similar to lobectomy. Nonsurgical approaches, such as SABR, consistently result in local control rates of ~90% and survival rates that are comparable to lobectomy. Short-term results for radiofrequency ablation are also comparable to sublobar resection and SABR, but there is a lack of long-term results. Until the results of randomised clinical trials become available, both SABR and sublobar resection may be offered to appropriate patients.

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E D I T O R I A L

Role of Limited Sublobar Resection for Early-Stage Lung Cancer: Steady Progress

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See accompanying articles on pages 2449 and 2456

The operative modes for pulmonary parenchymal resection include pneumonectomy, bilobectomy, lobectomy, segmentectomy, and wedge resection, according to the volume of lung parenchyma to be resected. From a technical viewpoint, with respect to the pulmonary hilum, these can be divided into nonanatomic (wedge resection) and anatomic (all other) resections. The characteristic feature of anatomic resections is that the parenchymal extent of resection is automatically determined according to the bronchovascular anatomy of the lung. For segmentectomy and wedge resection, the term sublobar resection is sometimes used. However, although sublobar resection is used to describe both approaches, both the segmental bronchus and pulmonary artery are divided at the hilum in segmentectomy, whereas in wedge resection, the extent of resection is arbitrarily determined in relation to the location of the target lesion, and the hilum remains intact. The term limited resection is also used as opposed to the term standard resection, which is essentially at least lobectomy with hilar and mediastinal lymph node sampling/dissection. Therefore, the present-day limited resection inevitably indicates sublobar resection.

In the 1930s, Churchill and Belsey[1] introduced segmentectomy for the treatment of bronchiectasis of the lingular segment, and this was called segmental pneumonectomy. In 1973, Jensik et al[2] performed various types of segmentectomy for T1 lung cancer, and reported a 5-year survival rate of 56% and a local recurrence rate of 10%. Jensik et al suggested that anatomic segmentectomy could be effectively applied to small primary lung cancers when the surgical margins were sufficient. Ever since this landmark publication, many articles have been published to either support or oppose limited, sublobar resections for lung cancer. These reports stimulated a debate regarding the optimal resection technique for early-stage non–small-cell lung cancer, which was addressed in a prospective, randomized trial conducted by the Lung Cancer Study Group (LCSG).[3] Limited pulmonary resection, including anatomic segmentectomy and nonanatomic wide wedge resections, was compared with lobectomy for stage IA lung cancer with regard to postoperative prognosis and pulmonary function. A three-fold increase in the local recurrence rate and a 30% increase in the overall death rate were observed for limited resection, and therefore this study solidified lobectomy as the procedure of choice for the treatment of T1N0 lung cancer. This is still the only randomized trial that directly compared limited resection with lobectomy, and therefore lobectomy is still considered the gold standard for lung cancer.

However, recently, there has been a surge in interest among thoracic surgeons regarding sublobar resection, and subsequent nonrandomized studies have shown that excellent outcomes can be achieved in patients with small, early lung cancer.[4] Why? Because of improvements in computed tomography (CT) imaging and the introduction of CT screening programs, smaller and pathologically earlier lung cancers are being encountered more often in our daily practice. Among the lesions that are specifically found in this context, nonsolid lesions referred to as ground-glass opacity (GGO) are a newly established clinical entity that may be a candidate for limited pulmonary resection. The pathobiologic nature of such earlier lesions is becoming better understood.[5] A new proposal for the classification of adenocarcinoma was also promulgated, in which the earlier forms of adenocarcinoma were newly defined as adenocarcinoma in situ or minimally invasive adenocarcinoma.[6] In light of this situation, it is not surprising that questions have arisen concerning whether it might be possible to manage smaller, earlier lung cancers by sublobar resection. Moreover, it has been more than 20 years since the LCSG randomized clinical trial was conducted in the 1980s.

The two articles that accompany this editorial further evaluate the role of sublobar resection. The first is by Landreneau et al,[7] who retrospectively compared operative and prognostic parameters in 392 patients who underwent segmentectomy and 800 patients who underwent lobectomy using a propensity score–matching algorithm. They found no difference between segmentectomy and lobectomy with respect to mortality/morbidity or locoregional/distant/overall recurrence rates. Furthermore, no significant differences were noted in either 5-year freedom from recurrence (70% *v* 71%) or 5-year survival (54% *v* 60%). The authors concluded that lobectomy was associated with modestly increased freedom from recurrence and overall survival, but this difference was not significant. They addressed the need for further validation by a prospective randomized trial. The second article, by Fernando et al,[8] considers the management of local recurrence after sublobar resection. One of the major concerns of surgeons regarding sublobar resection is the risk of local recurrence, especially on the resection line in the lung parenchyma. According to the report by Landreneau et al,[7] 5.5% of patients who underwent segmentectomy developed locoregional recurrence. In an attempt to reduce locoregional recurrence, a prospective randomized trial (American College of Surgeons Oncology Group [ACOSOG] Z4032) was performed to evaluate the impact of brachytherapy on the local recurrence rate after sublobar resection for non–small-cell lung cancer.[8]

Patients with high-risk operable T1 tumors were randomly assigned to undergo sublobar resection alone (n = 114) or sublobar resection with intraoperative brachytherapy on the staple line (n = 108). There was no difference in time to local recurrence or the type of local recurrence. Local progression occurred only in 7.7% of patients. The authors concluded that brachytherapy did not reduce local recurrence after sublobar resection. These two studies might be part of steady efforts in the surgical community to revise the standard mode of resection for early-stage lung cancer. However, it is quite certain that the definitive answer regarding the feasibility of sublobar resection for lung cancer can be obtained only through prospective, randomized trials.

Thus, randomized clinical trials with peripheral lung cancers no more than 2 cm in diameter as the target lesions were begun in the United States (Cancer and Leukemia Group B [CALGB] 140503) and Japan (Japan Clinical Oncology Group [JCOG] 0802) at almost the same time.[9] The JCOG 0802/West Japan Oncology Group [WJOG] 4607L trial is a prospective, randomized, multi-institutional study that intends to compare the prognosis and postoperative pulmonary function between patients with non–small-lung cancer 2 cm or less in diameter who are undergoing either lobectomy or segmentectomy. The target accrual number is 1,100 patients, and as of the end of March 2014, 1,018 patients had been enrolled. Importantly, the candidate lesions for this trial are intended to be pathologically invasive adenocarcinomas with a solid part in GGO on the CT images. As a selection criterion, a consolidation/tumor ratio of 25% to 100% is used to define invasive adenocarcinomas preoperatively. This study is coupled with the JCOG 0804/WJOG 4507L trial, which deals with noninvasive (adenocarcinoma in situ) or minimally invasive adenocarcinoma with CT images showing pure GGO with/without a minimal solid part; treatment consists of limited, sublobar resection (segmentectomy or wide wedge resection). This study is a prospective, but nonrandomized, single-arm study because no death is expected for patients with these tumors, despite differences in surgical modes. The target accrual was 330 patients; registration is already closed, and we await data maturation.

Present-day selection of the surgical mode for lung cancer should be based on solid data that demonstrate a clear advantage over the standard mode of resection (lobectomy). Several years of study are needed before we will reach a definitive conclusion regarding the appropriateness of sublobar resection for early-stage lung cancer. Until then, surgeons should be prudent in performing a sublobar resection as a radical resection for lung cancer with a curative intent.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Role of Limited Sublobar Resection for Early-Stage Lung Cancer: Steady Progress

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LETTER TO THE EDITOR

In response to the review article in *Surgery Today*: JCOG trials for small adenocarcinomas of the lung

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Abstract This letter is about the recently published review article on the segmentectomy for lung cancer. We emphasized that any prognostic and functional data on segmentectomy given without fair comparison with lobectomy are not authorized. The best way to get a definitive conclusion is undoubtedly a prospective, randomized study such as JCOG0802/WJOG4607L trial.

Keywords Lung cancer · Surgery · Segmentectomy

Dear Editor,

I read with great interest the review article entitled "Segmentectomy for c-T1N0M0 non-small cell lung cancer" by Nomori [1], which discusses the possibility of this procedure being used as radical surgery for lung cancer. As a principal investigator of the JCOG0802/WJOG4607L trial, which was mentioned in the article, I need to address the necessity for correction and some comments.

The JCOG0802/WJOG4607L trial is a prospective, randomized, multi-institutional study, designed to compare the prognosis and postoperative pulmonary function of patients with non-small lung cancer, 2 cm or less in diameter, undergoing either lobectomy or segmentectomy [2]. The target patient accrual is 1100. It is important that the candidate lesions of this trial are invasive adenocarcinomas pathologically, with a solid part seen as ground glass opacity (GGO) on CT images. As a selection criterion, a consolidation/tumor ratio of 25–100 % has been set to define invasive adenocarcinomas preoperatively. This study is coupled with the JCOG0804/WJOG4507L trial, which dealt with non-invasive or minimally invasive adenocarcinomas (MIAs) such as adenocarcinoma in situ, AIS/MIA, with CT images of pure GGO with/without a minimal solid part. They were treated with limited, sublobar resection, namely, segmentectomy or wide wedge resection. This study was a prospective, but non-randomized, single-arm study because no death was expected in relation to these tumors despite the surgical modes. The target accrual was 330, and the registration is already closed, waiting for data maturation.

First, the author wrote that the JCOG0802/WJOG4607L trial was closed in the review, which is wrong: In reality, it is still on-going. As of April 2014, 1038 patients had been registered and we expect closure in mid-2014. Second, and more importantly, the author expressed concern about the "selection bias" of this study. Needless to say, the randomized trial was planned to eliminate the bias by random assignment and a large enough number of subjects. In this sense, using the term "bias" about this trial is inappropriate. Why does the author think that such a large scaled, randomized trial contains more bias than case series by a single institute, including his own? Apparently, the JCOG0802/WJOG4607L trial is the only way to answer the definitive question about whether segmentectomy could be a comparative surgical mode of resection for small, invasive adenocarcinomas to standard, lobectomy. Third, we stress again that the JCOG0802/WJOG4607L trial targets invasive adenocarcinomas, which are traditionally resected by lobectomy in our surgical community as a gold standard procedure. Limited resection for non-invasive adenocarcinomas is dealt with in a separate study, the JCOG0804/WJOG4507L trial. As the JCOG researchers, we would like to reclaim precise and thorough understanding of the series of our efforts in establishing non-biased, scientifically fair conclusions about the nature of small

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adenocarcinomas and the role of sublobar resection for these (JCOG0201, JCOG0802, and JCOG0804) [3, 4].

In conclusion, any prognostic and functional data on segmentectomy given without fair comparison with lobectomy are not authorized. The best way to obtain a definitive conclusion is undoubtedly through a prospective, randomized study such as the JCOG0802/WJOG4607L trial.

Conflict of interest Hisao Asamura and the coauthor have no conflict of interest.

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Prognostic Importance of Volumetric Measurements in Stage I Lung Adenocarcinoma[1]

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Purpose: To perform volumetric analysis of stage I lung adenocarcinomas by using an automated computer program and to determine value of volumetric computed tomographic (CT) measurements associated with prognostic factors and outcome.

Materials and Methods: Consecutive patients (n = 145) with stage I lung adenocarcinoma who underwent surgery after preoperative chest CT were enrolled. By using volumetric automated computer-assisted analytic program, nodules were classified into three subgroups: pure ground glass, part solid, or solid. Total tumor volume, solid tumor volume, and percentage of solid volume of each cancer were calculated after eliminating vessel components. One radiologist measured the longest diameter of the solid tumor component and of total tumor with their ratio, which was defined as solid proportion. The value of these quantitative data by examining associations with pathologic prognostic factors and outcome measures (disease-free survival and overall survival) were analyzed with logistic regression and Cox proportional hazards regression models, respectively. Significant parameters identified at univariate analysis were included in the multiple analyses.

Results: All 22 recurrences occurred in patients with nodules classified as part solid or solid. Multiple logistic regression analysis revealed that percentage of solid volume of 63% or greater was an independent indicator associated with pleural invasion (P = .01). Multiple Cox proportional hazards regression analysis revealed that percentage of solid volume of 63% or greater was a significant indicator of lower disease-free survival (hazard ratio, 18.45 [95% confidence interval: 4.34, 78.49]; P < .001). Both solid tumor volume of 1.5 cm^3 or greater and percentage of solid volume of 63% or greater were significant indicators of decreased overall survival (hazard ratio, 5.92 and 9.60, respectively [95% confidence interval: 1.17, 30.33 and 1.17, 78.91, respectively]; P = .034 and .036, respectively).

Conclusion: Two volumetric measurements (solid volume, ≥1.5 cm^3; percentage of solid volume, ≥63%) were found to be independent indicators associated with increased likelihood of recurrence and/or death in patients with stage I adenocarcinoma.

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Adenocarcinoma is the most common subtype of lung cancer. In 2011, a new classification of adenocarcinoma (1) was developed to standardize diagnostic criteria and terminology applied to the wide spectrum of entities encompassed in this histologic subtype, which can range from indolent to lethal tumors. Results from several studies (2–5) have shown by using computed tomographic (CT) imaging that morphologic structure of adenocarcinoma can be predictive of tumor grade and patient prognosis. As emphasized in the recently published recommendations for subsolid nodules from the Fleischner Society (6), measurement of solid components and determination of the relative percentages of solid versus ground-glass portions of subsolid nodules are important because an increase in the extent of a solid component is associated with a higher likelihood of an invasive tumor. However, integration of this type of prognostic CT data into clinical management algorithms for adenocarcinoma has been relatively hindered by the lack of standardized methods for tumor characterization and measurement, particularly in the setting of part-solid nodules.

Volumetric measurement of nodules is a promising technique that has been shown (7–11) to be both accurate and precise for the quantification of small solid nodules. However, volumetric assessment of subsolid nodules is more challenging because of difficulties in segmentation and accurate delineation between a tumor's ground-glass margins and the adjacent normal parenchyma. By using manual measurements, de Hoop et al (12) compared diameter, volume, and mass (volume × CT value) of 52 ground-glass nodules (GGNs) that were followed as part of a lung cancer screening trial; among the three measures, they found that mass of GGN was subject to less variability and allowed earliest detection of growth in malignant nodules. Ko et al (11) reported similar growth-related results in five solid and three subsolid malignant nodules that were detected earlier with volumetric measurements obtained by using a semiautomated computer algorithm than with radiologic criteria used in current practice.

We hypothesized that volumetric measurement of solid and nonsolid components of early-stage adenocarcinoma seen by using CT imaging can provide prognostic information. The purpose of our study was to perform volumetric analysis of stage I lung adenocarcinomas by using an automated computer program and to determine the value of volumetric CT measurements associated with prognostic factors and patient outcome.

Advances in Knowledge

- Automated volumetric analysis of stage I adenocarcinoma allowed quantification of CT features associated with patient outcome.
- Radiologist and software classification of nodules into subsolid and solid subtypes showed excellent agreement ($\kappa = 0.81$).
- Volumetric measurements of tumor solid component and percentage of solid volume were associated with recurrence and/or death, whereas measurement of total tumor volume was not.

Materials and Methods

Patients

We obtained approval from our internal institutional review board; informed consent was waived for retrospective review of patient records and images. The study population consisted of 145 consecutive patients (68 men and 77 women; mean age, 63.6 years ± 9.6 [standard deviation]; range, 31–82 years) who had undergone lobectomy (n = 104) or segmentectomy (n = 41) for pathologic stage I adenocarcinoma at our hospital from April 1999 to April 2006 and had a preoperative thin-section chest CT study available for review. All patients were node-negative based on fluorine 18 fluorodeoxyglucose (FDG) positron emission tomographic (PET) staging study. Hilar and mediastinal lymph node resections were performed in 104 patients with lobectomy, and hilar lymph nodal sampling was performed in 41 patients with segmentectomy at the time of tumor resection. Individuals who had history of adenocarcinoma of the lung or other organs or who had received induction chemotherapy before surgery were excluded from the study.

After hospital discharge, all patients were evaluated at 3-month intervals. The evaluation included a physical examination, chest x-ray, and blood tests (including tumor markers). Additional thoracoabdominal CT scans were generally obtained at 6-month intervals. Recurrence was confirmed at CT and, if necessary, FDG PET imaging. The median follow-up period of all 145 patients after surgery was 6.2 years (range, 0.86–12.63 years). Complete follow-up information until death or January 2013 was available for all patients. During the follow-up period, 22 patients experienced disease recurrence with seven associated cancer-related deaths.

Implication for Patient Care

- Automated volumetric analysis of early-stage adenocarcinomas can be associated with prognosis and may be helpful in determining appropriate treatment of patients with subsolid nodules.

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Abbreviations:
FDG = fluorine 18 fluorodeoxyglucose
FWHM = full width at half maximum
GGN = ground-glass nodule

Author contributions:
Guarantors of integrity of entire study, M.Y., Y.T., S.W., H.W., T.G., K.U., O.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, M.Y., Y.T., A.N.L., E.M., K.U., T.J.; clinical studies, M.Y., Y.T., E.M., M.K., S.W., H.W., M.I., M.O., O.H., H.S., T.J.; experimental studies, M.Y., Y.T., E.M., T.G., H.S., T.J.; statistical analysis, M.Y., A.N.L., E.M., M.K., S.W., H.W.; and manuscript editing, M.Y., A.N.L., E.M., O.H., T.J., N.T.

Conflicts of interest are listed at the end of this article.

Scanning Protocols

Chest CT scans were acquired by using a four-detector row CT scanner (LightSpeed QXi; GE Healthcare, Milwaukee, Wis) and an eight-detector row CT scanner (LightSpeed Ultra; GE Healthcare). Acquisition parameters were as follows: collimation, 0.625 mm or 1.25 mm; pitch, 0.625–1.5; rotation time, 0.4–0.8 seconds per rotation; exposure parameters, 120 kV and 200 mA; field of view, 200 mm. All image data were reconstructed with a high spatial frequency algorithm at contiguous section thicknesses of 0.625 mm or 1.25 mm.

Visual Analysis

CT scans were displayed on a monitor at lung window settings (level, −700 HU; width, 1200 HU). Two independent chest radiologists (G.T. and H.S., with 9 and 13 years of experience, respectively) visually classified tumors into three subgroups: pure GGN, part-solid GGN, and solid. GGN was defined as an area that exhibited a slight, homogeneous increase in density, which did not obscure underlying vascular markings. Solid was defined as an area of increased opacity that completely obscured underlying vascular markings. The two radiologists designated the distribution of each nodule as peripheral (outer one-third of lung, but not in contact with pleura), middle (inner two-thirds of lung), or juxtapleural (in contact with pleura). Final evaluations were decided by a consensus panel, which consisted of the same two radiologists and an adjudicator (O.H., with 21 years of experience in chest radiologic imaging), as needed. By using electronic calipers, one chest radiologist (M.Y., with 12 years of experience) measured the longest diameter of the solid component and of total tumor; solid proportion was defined as the ratio of the longest diameter of the solid component divided by the longest diameter of total tumor multiplied by 100%.

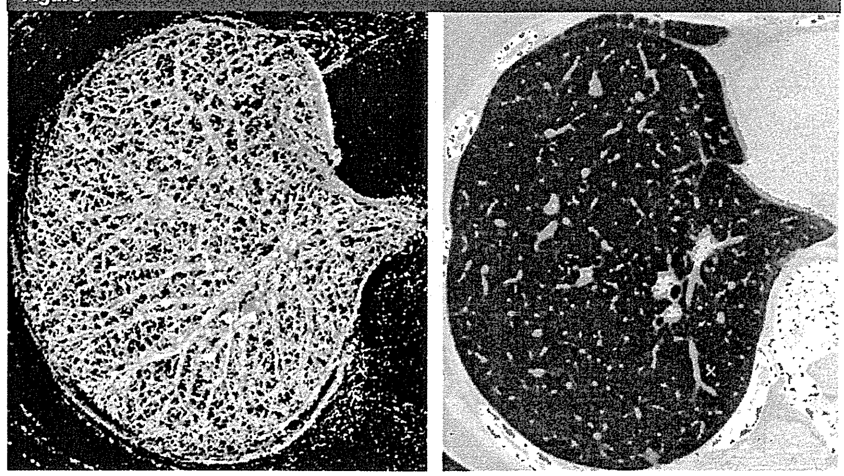
Computer Analysis

We developed our software by using commercial software (Microsoft Visual C++ 6.0; Microsoft, Redmond, Wash) on a commercially available personal computer. Incorporated in our software is a previously described (13) three-dimensional line filter that enabled the enhancement of curvilinear structures, such as vessels, in three-dimensional medical images on the basis of a combination of the eigenvalues of the three-dimensional Hessian matrix. Multiscale integration is formulated by taking the maximum among single scale filter responses, and its characteristics are examined to derive criteria for the selection of parameters in the formulation. The resultant multiscale line-filtered images provide improved segmentation and visualization of curvilinear structures. This three-dimensional line filter was used as the first step to eliminate vessels on the CT images (Fig 1). Quantitative analysis was then performed by one observer (M.Y., 12 years of experience in chest radiology) who was required to place an over-inclusive region of interest around each nodule after selecting a tumor center point (ie, a seed point) (Fig 2). The threshold value on CT between a tumor and surrounding normal lung parenchyma was automatically determined by applying CT density profile curves, one-dimensional quantitative CT values across the nodule, through the seed point at 10° intervals on each axial section (14) (Fig 3a). A CT value that corresponded to full width at half maximum (FWHM) was measured from each profile curve, and the mean FWHM from the 36 density profiles was used as threshold value (Fig 3b). FWHM is a mathematically well-defined parameter used to describe a measurement of the width of an object in imaging when that object does not have sharp edges. The width of the CT density profile curve is often decided by the FWHM (15,16). Following this approach, we used the CT value that corresponded to mean FWHM as an objective, standardized method to determine the threshold CT value between the tumor and surrounding normal lung parenchyma.

The tumor was also segmented by using a three-dimensional region-growing algorithm (17) that, after placement of an initial seed point, added in neighboring pixels with attenuation values above defined threshold value that did not contain vessels. The volume of the tumor was calculated as follows: (number of voxels within segmented region) × unit volume. Unit volume was defined as the product of x-, y-, and z-axes in a raw image.

On the basis of a previously reported threshold selection and nodule classification method (18), we used

Figure 1



a. b.

Figure 1: Images show extraction of vessels by using a multiscale three-dimensional line filter. **(a)** Volume rendering image of all vessels identified by the three-dimensional line filter. **(b)** Green areas in right lung correspond to extracted vessels.

Figure 2

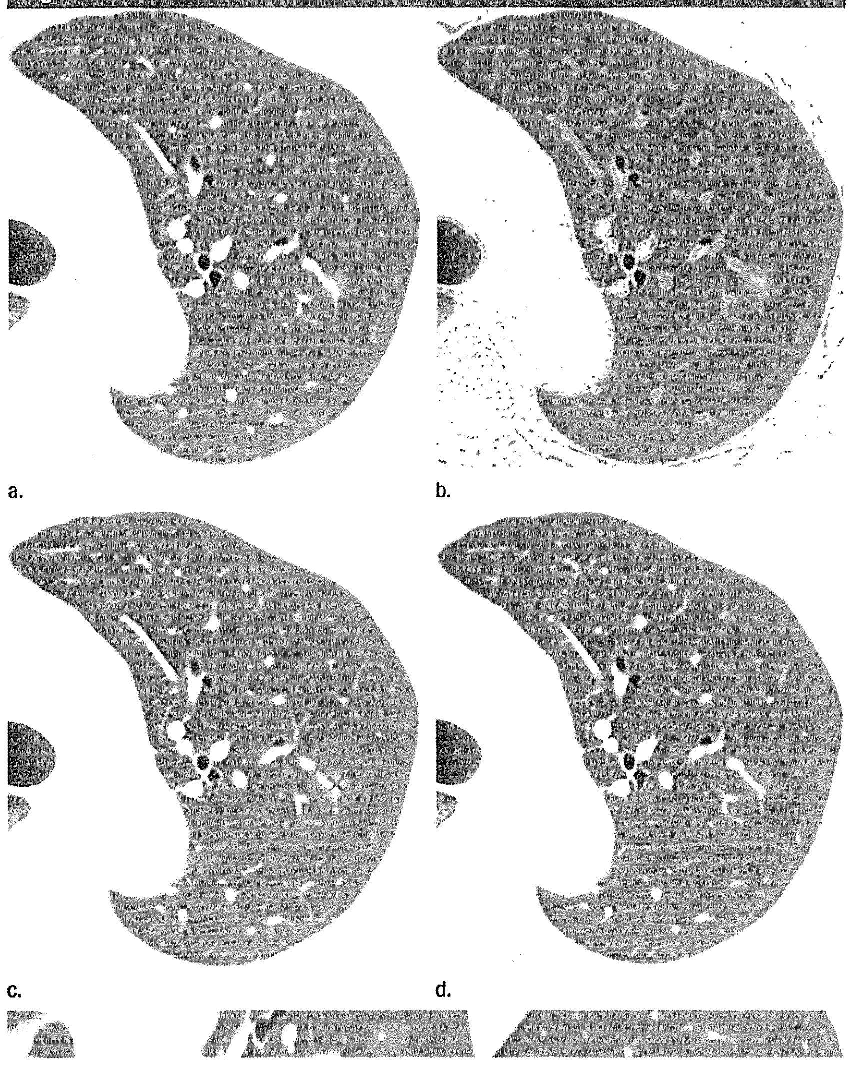


Figure 2: Images show sequential steps in volumetric analysis of a pure GGN in a 57-year-old woman. **(a)** Thin-section CT image shows a pulmonary vein traversing an 8.1-mm GGN in the left upper lobe. **(b)** Three-dimensional line filter identifies and extracts vessels (green areas). **(c)** An over-inclusive region of interest is drawn manually around the nodule in red. **(d)** Axial image, **(e)** coronal image, and **(f)** sagittal image of GGN. Nodule is automatically segmented (shown as highlighted green area) with calculation of GGN and solid components. Total volume, solid volume, and percentage of solid volume for this nodule are 0.14 cm^3, 0.00 cm^3, and 0.00%, respectively.

Figure 3

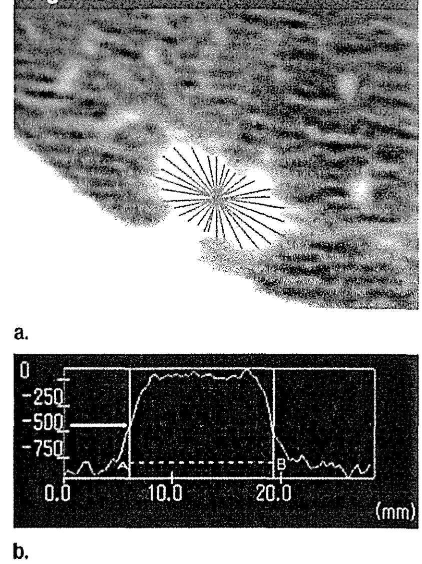


Figure 3: Threshold CT value between a tumor and surrounding normal lung parenchyma in a 60-year-old woman. **(a)** CT density profile curves are drawn through center of nodule at 10° intervals. **(b)** A representative profile curve shows CT value at FWHM is −545 HU (arrow). The mean CT value derived from all 36 profile curves on each axial section is used as the threshold CT value.

−291 HU as the threshold CT value between ground glass and solid. By using this value, each voxel of ground glass and solid included in a segmented tumor was automatically determined; total tumor volume, solid volume, and percentage of solid volume (solid volume/tumor volume × 100%) were calculated; and the nodule was classified into three subgroups (pure GGN [>98% of tumor with attenuation of −291 HU or less], part-solid GGN [2%–71.5% of tumor with attenuation greater than −291 HU], and solid [>71.5% of tumor with attenuation greater than −291 HU]) (18). Before beginning this study, we performed computer-assisted analysis of 10 nodules that were not included in this study that by qualitative evaluation consisted of pure ground-glass attenuation. In these 10 cases, percentage of solid volume ranged from 0% to 1.9% (mean, 0.8% ± 1.1% [standard deviation]); therefore, percentage of solid volume in the GGN subgroup was defined as less than 2%.

Pathologic Analysis

The presence of lymphatic, vascular, and pleural invasion was evaluated by two pathologists. Final evaluation was decided in consensus. Immunostaining methods by using D2-40 (Covance, San Diego, Calif), a lymphatic-specific monoclonal antibody, and CD31 (Dako, Glostrup, Denmark), an endothelial antigen, were performed to optimize identification of lymphatic and vascular channels, respectively (19,20).