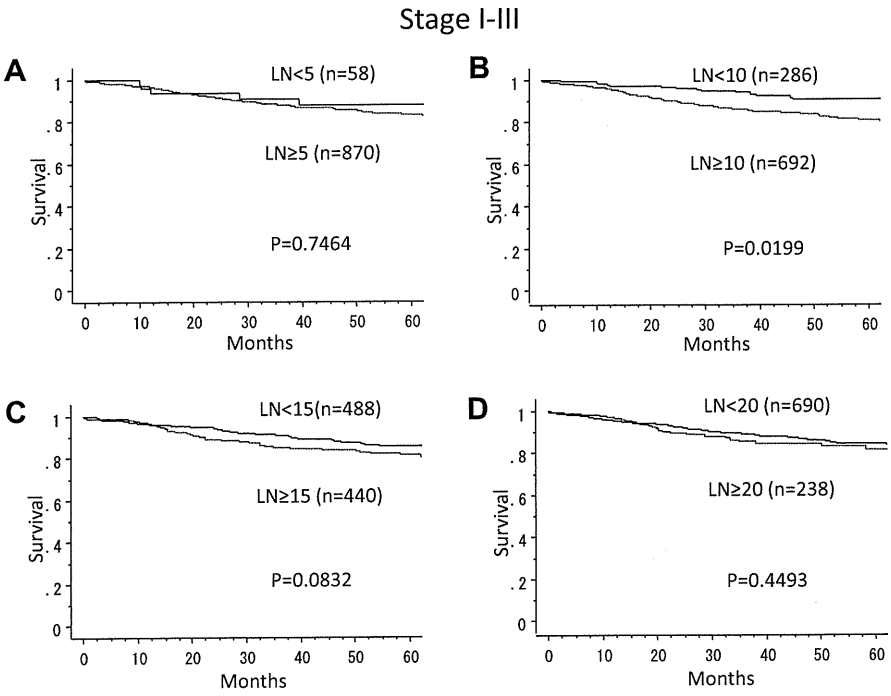

FIGURE 1. Survival curves according to the number of resected LNs at the time of complete resection in patients with stages I to III non-small cell lung cancer. *A*, LN, five nodes as cutoff. *B*, LN, 10 nodes as cutoff; a significant difference in survival was observed. *C*, LN, 15 nodes as cutoff. *D*, LN, 20 nodes as cutoff.

TABLE 2. Correlations between Overall Survival and Total Number of Resected Lymph Nodes

Valuables	*p*	HR	95% CI
5 vs. ≥5	0.7464	1.135	0.528–2.440
6 vs. ≥6	0.5464	1.233	0.624–2.437
7 vs. ≥7	0.1611	1.591	0.831–3.047
8 vs. ≥8	0.744	1.725	0.948–3.140
9 vs. ≥9	0.0217	1.783	1.088–2.923
10 vs. ≥10	0.0199	1.795	1.098–2.912
11 vs. ≥11	0.0295	1.651	1.051–2.595
12 vs. ≥12	0.0473	1.521	1.005–2.302
13 vs. ≥13	0.0907	1.394	0.949–2.050
14 vs. ≥14	0.1137	1.354	0.930–1.973
15 vs. ≥15	0.0832	1.388	0.956–2.014

HR, hazard ratio; CI, confidence interval.

RESULTS

Survival and Number of RLNs

We investigated the prognostic impact of the number of RLNs (mean number of RLNs = 15). Patients were categorized into four representative groups according to the total number of RLNs: less than 5 versus 5 or more, less than 10 versus 10 or more, less than 15 versus 15 or more, and less than 20 versus 20 or more (Figure 1). Table 2 presents each *p* value, hazard ratio (HR), and 95% CI comparing each subgroup categorized according to total number of RLNs. The largest significant difference was found in the total number of RLNs categorized between less than 10 and 10 or more ($p = 0.0199$, HR = 1.795, 95% CI = 1.098–2.912). However, even 15 or more RLNs had no significant prognostic impact on the survival of patients with NSCLC in the present series. There was no sign of incremental improvement in or impairment of survival after the resection and evaluation of 15 or more LNs for curative resection of NSCLC. There were no statistically significant differences in survival according to the total number of RLNs in cases of stage I NSCLC (Figure 2).

As shown in Table 3, the mean numbers of RLNs on both the right and left sides were significantly higher in pN1 or pN2–3 cases than in pN0 cases (right side: $p = 0.0007$, $p = 0.0002$, left side: $p = 0.0068$, $p = 0.0162$, respectively). The mean number of RLNs in cases with right-sided tumors was significantly higher than that in cases with left-sided tumors.

Survival and Number of Involved LNs

We analyzed the number of involved LNs that could provide the most appropriate indicator of OS in NSCLC. Although the incidence of LN involvement was associated with poor prognosis, the largest statistically significant increase in OS was observed between zero to three and four or more involved LNs (HR, 7.680; 95% CI, 5.051–11.655, $p < 0.0001$) (Figure 3). Although patients with no involved LNs had a better outcome than those with 1 to 3 involved LNs, there was no significant difference in survival between the two groups ($p = 0.1831$). Patients with four or more involved LNs had a significantly worse outcome than those with one to three involved LNs ($p < 0.0001$). These results suggest that four or more involved LNs would be the best benchmark of OS in NSCLC (Figure 4).

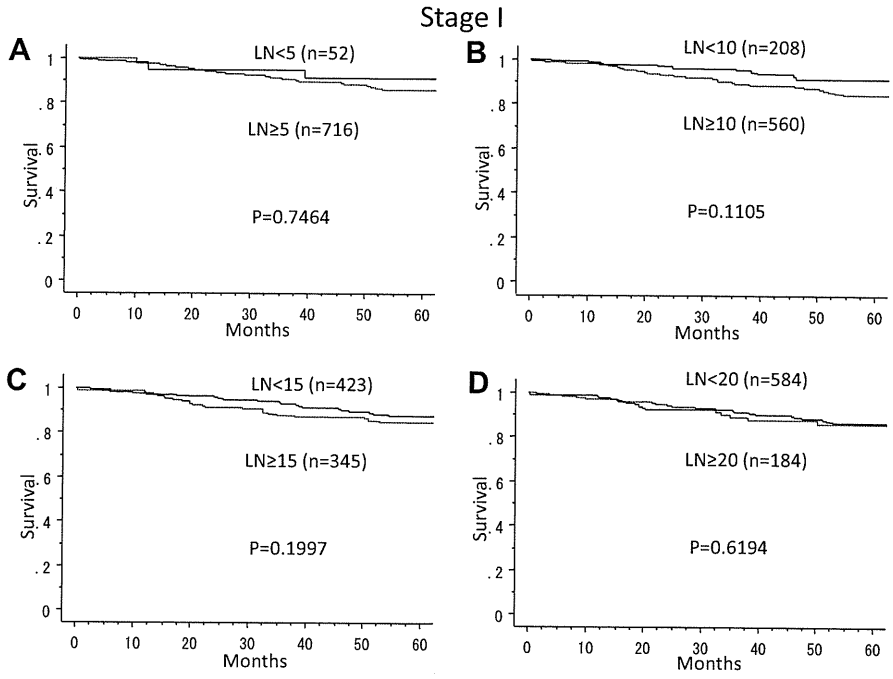

FIGURE 2. Survival curves according to the number of resected LNs at the time of complete resection in patients with stage I, non-small cell lung cancer. *A*, LN, five nodes as cutoff. *B*, LN, 10 nodes as cutoff. *C*, LN, 15 nodes as cutoff. *D*, LN, 20 nodes as cutoff. No significant difference in survival was observed in any group.

TABLE 3. Mean Number of Resected Lymph Nodes on Right or Left Side

	Mean Number	*p*
Right side lymph nodes, $n = 602$		
Total	15.5	
pN0	14.7	
pN1	18.2	0 vs. 1: $p = 0.0007$[a]
pN2–3	19.0	0 vs. 2–3: $p = 0.0002$[a]; 1 vs. 2–3: $p = 0.7199$
Left side lymph nodes, $n = 326$		
Total	14.3	
pN0	13.5	
pN1	16.6	0 vs. 1: $p = 0.0068$[a]
pN2–3	16.3	0 vs. 2–3: $p = 0.0162$; 1 vs. 2–3: $p = 0.8985$
Right vs. left		$p = 0.0323$[a]

[a] Statistical significance.

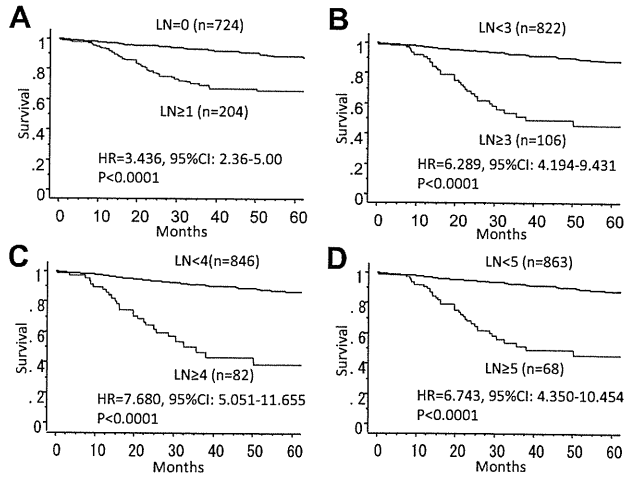

FIGURE 3. Survival curves according to the number of involved LNs at the time of complete resection in patients with stages I to III, non-small cell lung cancer. *A*, LN, one node as cutoff. *B*, LN, three nodes as cutoff. *C*, LN, four nodes as cutoff. *D*, LN, five nodes as cutoff. Although the incidence of lymph node involvement was statistically associated with poor prognosis, the largest statistically significant increase in OS was seen between zero to three and 4 or more involved LNs.

Correlations between Number of RLNs, Involved LNs and pN Status

Before analyzing the possibility of RLNs and involved LNs as possible independent prognostic factors by multivariate analysis, we examined whether RLNs, involved LNs and pN status were confounding factors. The mean and range of the total number of RLNs in our series were 15.0 and 1 to 49, respectively. The mean number of RLNs was significantly increased in pN1 or pN2–3 cases compared with pN0 cases ($p < 0.0001$ and $p < 0.0001$, respectively), whereas the mean and range of the total number of involved LNs in our pN-positive series were 4.2 and 1 to 22, respectively. The mean numbers of involved LNs in pN1 and pN2–3 cases were 2.15 and 6.56, respectively. The number of involved LNs was significantly higher in pN2–3 cases than in pN1 cases ($p < 0.0001$). These results demonstrate that each of these prognostic factors (i.e., the number of RLNs and involved LNs,

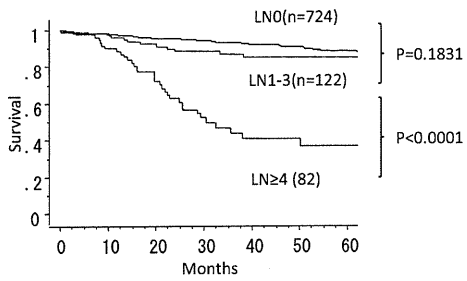

FIGURE 4. Survival curves according to the number of involved LNs at the time of complete resection in patients with stages I to III, non-small cell lung cancer. Although patients with no involved LNs had a better prognosis than those with one to three involved LNs, there was no significant difference in survival between the two groups. Patients with four or more involved LNs had a significantly worse outcome than those with one to three involved LNs.

and pN status) were confounding factors in our series. Therefore, in the subsequent multivariate survival analysis, we used the ratio between the number of involved and RLNs to reflect both factors in the multivariate analysis similarly to a previously reported method.[11]

Multivariate Survival Analysis

We performed multivariate analysis to confirm the prognostic impact of the total number of RLNs and involved LNs in NSCLC, using the ratio between the number of involved and RLNs, according to a previously observed correlation.[11] As shown in Table 4, RLNs strongly correlated with poor prognosis on multivariate analysis after adjustments for sex, age, histology, tumor factor, and surgical procedure. We therefore concluded that RLN was a strong independent prognostic factor for NSCLC (HR, 6.803; 95% CI, 4.137–11.186, $p < 0.0001$). Other independent prognostic factors identified on multivariate analysis included sex (HR, 0.620; 95% CI 0.401–0.958, $p = 0.0313$), age (HR, 1.598, 95% CI 1.090–2.341, $p = 0.0162$), and T factor (HR, 0.392, 95% CI, 0.256–0.600, $p < 0.0001$).

DISCUSSION

We set out to determine the number of LNs that should be resected, and the number of involved LNs for the accurate prediction of outcome in resectable cases of lung cancer. Opinions still vary among surgeons as to whether to remove all, some, or none of the mediastinal LNs at the time of pulmonary resection for lung cancer, and practices vary worldwide. In almost all surgical cooperative group trials in North America, LN sampling is standard, whereas systematic LN dissection is standard in Japan.

LN status is a major determinant of stage and survival in patients with lung cancer. However, the role of mediastinal lymphadenectomy in the staging and treatment of NSCLC remains controversial. The present results indicate that patient survival after complete NSCLC resection is associated with the number of LNs harvested during surgery. The largest significant difference was observed in the total number of RLNs categorized between less than 10 and 10 or more ($p = 0.0199$, HR = 1.795, 95% CI = 1.098–2.912). Patients with 10 or more RLNs had significantly worse outcomes than those with less than 10 RLNs (Figure 1), contrary to the findings of previous studies of stage I NSCLC cases.[11–13] As shown in Table 3, the mean number of RLNs on both the right and left sides was significantly higher in pN1 or pN2–3 cases than in pN0 cases (right side: $p = 0.0007$, $p = 0.0002$; left side: $p = 0.0068$, $p = 0.0162$, respectively), which may be one reason why patients with NSCLC with 10 or more RLNs had a worse outcome than those with less than 10 RLNs. According to the results of the American College of Surgeons Oncology Group (ACOSOG) Z0030 study, a higher N stage was also associated with increased LN removal (N0: 19.2 ± 10.1; N1: 22.8 ± 10.9; N2: 24.5 ± 10.8; $p = 0.043$).[12] This is possibly because surgeons tend to harvest more LNs in patients with LN-positive disease at the time of surgery, in expectation of therapeutic benefit. However, even 15 or more

TABLE 4. Univariate and Multivariate Survival Analyses

Variable	Category	n	Univariate Analysis p	Multivariate Analysis HR	95% CI	p
Sex	Men	548	0.011[a]	0.620	0.401–0.958	0.0313[a]
	Women	381				
Age (yr)	<70	690	0.0209[a]	1.598	1.090–2.341	0.0162[a]
	≥70	338				
Histopathology	Non-adenocarcinoma	244	0.015[a]	0.790	0.518–1.203	0.2719
	Adenocarcinoma	684				
T factor	T2–3	433	<0.0001[a]	0.392	0.256–0.600	<0.0001[a]
	T1	495				
Surgical procedure	Lobectomy	912	0.0136[a]	2.521	0.768–8.280	0.1273
	Pneumonectomy	16				
RLNs	<0.4	882	<0.0001[a]	6.803	4.137–11.186	<0.0001[a]
	≥0.4	46				

[a] Statistical significance.
RLNs, ratio between the number of involved and resected lymph nodes; CI, confidence interval; HR, hazard ratio.

RLNs had no significant impact on OS in patients with NSCLC in the present series, contrary to the results of a previous large study.[13] There appeared to be neither incremental improvement nor impairment of survival after resecting and evaluating 15 or more LNs with curative intent in NSCLC in the current series. One possible explanation for this is that the presence of approximately 10 dissected LNs increases the staging accuracy.

There was no significant difference in survival according to the total number of RLNs in stage I NSCLC in the current series. Recent retrospective studies from cancer registries,[14] nonrandomized trials,[15] and other institutions,[16–21] have indicated that the number of RLNs is associated with better OS.[16–19] Although LN removal may be therapeutic, the therapeutic benefit is likely to be small for patients with stage IA NSCLC, because all LNs in stage IA should be negative. The other, less likely explanation, is that a more extensive LN dissection such as systematic mediastinal LN dissection may be therapeutic, at least in stage I NCSLC.

The present analysis shows that an increasing number of RLNs during complete NSCLC resection is associated with a statistically significant difference in survival, which peaks at 10 to 14 LNs. Some studies have recommended that the minimum requirements for accurate nodal staging must include the removal of at least six LNs from hilar and mediastinal stations.[7,22,23] However, others have recommended the examination of a minimum of 10 LNs and at least three LN stations.[14,19] Although we are reluctant to recommend a definitive optimal number of LNs, the current data support the conclusion that an evaluation of nodal status should include at least 10 LNs.

Nodal involvement is the most important prognostic factor in determining survival for many malignant tumors. These factors are represented by the N category in the TNM classification and are grouped according to the anatomical location and/or number of LN involvement. In the most recently published 7th edition of the *TNM Classification of Malignant Tumors* (2009),[24] the number of involved LNs is included in the definition of pN factors in breast, stomach, esophageal, and colorectal cancer, and pN status shows a significant correlation with outcome. The nodal system in this edition in lung cancer is still based on the anatomical location of involved LNs. The Naruke map and the American Thoracic Society map have been combined into the International Association for the Study of Lung Cancer map, and the definition of the border between N1 and N2 has been changed, because of its complexity and ambiguity. However, this change is based on the anatomical location, not on the biological issue. In the current study, we predicted patient outcome after complete NSCLC resection according to the number of involved and RLNs, as previous reports have suggested.[25,26] Recently, Asamura and coworkers[27] have provocatively suggested that the number of metastatic LNs provides more accurate pathologic nodal staging than the current method of considering anatomical location of involved nodes. The largest statistically significant increase in OS was observed between zero to three and four or more involved LNs (HR, 7.680; 95% CI, 5.051–11.655; $p < 0.0001$) (Figure 2). Therefore, the current data indicate that four or more involved LNs serve as a good indicator of outcome after complete NSCLC resection. Because it is possible that the number of RLNs and involved LNs may indicate the quality of surgery in the determination of accurate staging and survival impact after complete NSCLC resection, we used RLNs as a prognostic predictor on multivariate analysis. In addition to T stage, RLNs had a strong independent effect on survival in patients with complete NSCLC resection in the present study. Indeed, the 5-year survival ratio of patients with RLNs ≥ 4 is similar to that of patients with pN2 disease in our series (data not shown). Although the nodal classification according to the number of involved LNs is simple and easy to be incorporated in the next TNM classification, there are a few limitations that are not helpful in deciding treatment preoperatively because it is mainly based on pathological assessment. However, this may change in the future with the development of new imaging device.

Our data suggested that the number of involved LNs expands pN category information and may provide additional information for the pN category of the next TNM classification. Further large-scale cohort studies, including global prospective validation analyses and multi-institutional studies are warranted.

CONCLUSION

We retrospectively evaluated the prognostic impact of the number of RLNs and involved LNs on the survival of patients with complete NSCLC resection. We found that 10 or more LNs harvested with complete LN dissection possibly influenced survival after complete NSCLC resection. Moreover, the presence of four involved LNs seemed to be a good indicator of outcome after complete NSCLC resection. The number of involved LNs was a strong independent prognostic factor in NSLC, and this may provide new information for the N categorization of the next TNM classification.

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REVIEW

Surgical implications of the new IASLC/ATS/ERS adenocarcinoma classification

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ABSTRACT: A new adenocarcinoma classification was recently introduced by a joint working group of the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS) and European Respiratory Society (ERS). A distinction is made between pre-invasive lesions, and minimally invasive and invasive adenocarcinoma. The confusing term "bronchioloalveolar carcinoma" is not used any more and new subcategories include adenocarcinoma *in situ* and minimally invasive adenocarcinoma.

Due to a renewed interest in screen-detected nodules and early-stage lung cancers of <2 cm, this classification also has profound implications for thoracic surgeons.

In this article, surgical topics are discussed: the role of a minimally invasive approach, especially video-assisted thoracic surgery, limited resection for early-stage lung cancer, the extent of lymph node dissection, the accuracy of intraoperative frozen section analysis, management of multiple lung nodules and prognostic factors in operated patients. Specific key issues are presented based on the current evidence and areas of surgical uncertainty are defined providing a basis for further studies.

Thoracic surgeons will play a major role in the application and global introduction of this new adenocarcinoma classification. The remaining controversies regarding the precise diagnosis and management of early-stage lesions will have to be resolved by multidisciplinary and international collaboration.

KEYWORDS: **Adenocarcinoma, diagnosis, lung cancer, prognosis, surgery, video-assisted thoracic surgery**

Very recently, a new adenocarcinoma classification was introduced by a joint working group of the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS) and European Respiratory Society (ERS) (table 1). A multidisciplinary article provides detailed pathological and molecular aspects, and addresses more general features related to clinical diagnosis, radiology, imaging and thoracic surgery [1]. In this article, we specifically focus on surgical implications of this classification.

Of special interest to thoracic surgeons are the new categories adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA) that represent small (⩽3 cm), solitary adenocarcinomas consisting purely of lepidic growth without invasion or with ⩽0.5 cm invasion, respectively. AIS and MIA have been introduced because they should have 100% or near-100% 5-yr disease-free survival, respectively, if completely resected. The term bronchioloalveolar carcinoma (BAC) is not used any more as it applies to five different categories in the new classification, which explains why this term has been so confusing [1].

With the advent of helical computed tomography (CT) and screening trials in high-risk populations, there is a renewed interest in small nodules, especially those with ground-glass opacity (GGO). Whether some of these lesions can be treated by limited resection, so-called sublobar resection comprising anatomical segmentectomy and wedge excision, is a prevailing question and the subject of intensive investigation. For a limited resection to be oncologically valid, a precise pre- and intraoperative diagnosis becomes imperative. Regarding preoperative diagnosis, specific criteria on chest CT, such as as percentage GGO, tumour shadow disappearance rate and histogram analysis, have been shown to have a high predictive value [2]. The role of positron emission tomography and specific

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TABLE 1 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma in resection specimens

Pre-invasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma *in situ* (⩽3 cm formerly BAC)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Minimally invasive adenocarcinoma
(⩽3 cm lepidic predominant tumour with ⩽5 mm invasion)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Invasive adenocarcinoma
Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant with mucin production
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (formerly mucinous BAC)
Colloid
Fetal (low and high grade)
Enteric

BAC: bronchioloalveolar carcinoma. Reproduced from [1] with permission from the publisher.

tumour markers has been evaluated previously [3]. The role of intraoperative frozen section analysis will also be addressed. In addition, the necessity of systematic nodal dissection is questioned for these early-stage lung cancers. Management protocols for multiple primary lung cancers have not yet been established. Prognostic histological and molecular factors of interest to thoracic surgeons are also described.

Surgical key issues are presented, based on current available evidence and obtained by general consensus of all co-authors, in table 2. For the main classification document, we made no surgical recommendations based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, because there were insufficient data in the surgical literature. One of the reasons for writing this article is to encourage studies and publications that may allow for evidence-based recommendations in the near future. We also define some areas of uncertainty that should be the subject of further investigations and recommendations (table 2).

SURGICAL APPROACH

The classical approach to performing lung resections and extensive lymph node dissection consists of a posterolateral or muscle-sparing thoracotomy. For stage I lung cancer, less invasive approaches have become available, such as as video-assisted thoracic surgery (VATS) and robotic surgery. Currently, the specific approach remains a matter of controversy. Several series suggest that there is no difference in overall survival between lobectomies performed by VATS *versus* those performed by thoracotomy for clinical stage I nonsmall cell lung cancer (NSCLC) [4, 5]. Morbidity appears to be lower with the VATS approach. A recent systematic review and meta-analysis of randomised and nonrandomised trials concluded that VATS lobectomy is an appropriate procedure for selected patients with early-stage NSCLC [6]. VATS is a standard approach for peripheral wedge resections. VATS segmentectomy is much less widely performed and requires further evaluation [7].

SUBLOBAR (LIMITED) RESECTION FOR LUNG CANCER

Although no large, prospective, randomised trials have been conducted comparing surgery and radiotherapy in early-stage NSCLC, surgical treatment has traditionally been considered the treatment of choice [8]. Historically, the first successful pneumonectomy in one stage for a lung cancer was performed in 1933 by GRAHAM and SINGER [9] in the USA. Initially, pneumonectomy was the only accepted surgical intervention for a bronchogenic carcinoma. In later years, it was shown that lobectomy provided survival rates similar to pneumonectomy if the lesion could be totally excised by lobectomy. The role of sublobar resection remained controversial and was only accepted for patients with compromised cardiopulmonary function [10].

The North American Lung Cancer Study Group performed a randomised phase III study comparing surgical outcome between lobectomy and sublobar resections, either wedge resection or segmentectomy, for clinical cT1N0 NSCLC [11]. This study showed that locoregional recurrence was three times higher in sublobar resection and that recurrence-free survival was better after lobectomy. However, overall survival was only significant at the $p<0.10$ level [12].

At the present time, the detection rate of smaller lung cancers is increasing and therefore the appropriateness of lobectomy for stage I lung cancer, especially for those tumours of ⩽2 cm (cT1a disease), is again being questioned [13, 14]. Recently, there have been numerous publications suggesting that sublobar resection for early lung cancers may be adequate surgical treatment. These studies were not randomised trials and many were retrospective [15–17]. Most reports showed no difference in survival or in locoregional recurrence between lobectomy and sublobar resection for tumours of ⩽2 cm. Tumours with a GGO appearance on CT are reported to have 100% survival at 5 yrs after resection [18–21]. However, possible delayed cut-end recurrences have been described after limited resection of GGO lesions [22].

Two recent reviews of sublobar resection concluded that well-selected use of sublobar resection, especially for pure AIS of ⩽2 cm, yields comparable survival and recurrence rates to lobectomy [23, 24]. In this way, sublobar resection is generally considered acceptable for GGO lesions or adenocarcinomas with minimal invasion. Lobectomy is still considered the standard surgical treatment for tumours of ⩽2 cm that have a solid appearance on chest CT because such tumours are invasive carcinomas. Any change in this standard care awaits the results of two randomised trials (Japan Clinical Oncology Group identifier JCOG 0802/West Japan Oncology Group identifier WJOG3406L in Japan and Cancer and Leukemia Group B identifier CALGB 140503 (www.clinicaltrials.gov identifier NCT00499330) in North America) that randomise such patients to either lobectomy or sublobar resection.

TABLE 2 Surgical key issues and areas of uncertainty

Surgical key issues
1) Small nodules (5–10 mm) that are clearly 100% pure GGO lesions on chest CT and are suspected to be AIS or MIA should be considered for CT follow-up rather than immediate resection
2) Lobectomy is the standard surgical treatment for patients with early-stage lung cancer; limited resection may be an appropriate option for AIS and MIA but results of prospective trials are awaited to determine the precise incidence of local recurrence
3) At least a lobe-specific systematic nodal dissection is advised for current intraoperative nodal staging; in some specific subgroups (cT1–2N0 or non-hilar N1), lymph node sampling, rather than systematic nodal dissection, may be appropriate
4) For small AIS or MIA, lymph node sampling or systematic nodal dissection may not be required, but no randomised studies are yet available
5) Multiple lung adenocarcinomas are considered for resection when considered to be multiple synchronous or metachronous, early-stage primary tumours rather than intrapulmonary metastases
Surgical areas of uncertainty
1) The precise role of limited resection has not yet been determined due to a lack of randomised prospective trials
2) The extent of lymph node dissection also remains controversial
3) The accuracy of frozen section in assessing the presence of invasive adenocarcinoma and the accuracy of frozen section or cytology of resection margins in sublobar resections needs to be investigated further; specific guidelines for frozen section analysis should be developed to guide intraoperative decisions
4) Treatment of multiple lesions has not been standardised
5) When there is no pleural invasion, how should one identify a tumour located deep in the lung parenchyma during VATS?
6) What is the specific value of pathological evaluation of markers for intraparenchymal nodules, such as needles or dye?
7) The role of new emerging techniques, including stereotactic radiotherapy and radiofrequency ablation, in the management of NSCLCs of ⩽3 cm needs to be defined
8) The optimal management of elderly patients with stage I–II lung adenocarcinoma needs to be defined
9) How to differentiate between multiple primary adenocarcinoma nodules of same histologic subtype and synchronous metastases
10) The role of VATS for diagnosis, staging and treatment of early lung cancer should be investigated further

GGO: ground-glass opacity; CT: computed tomography; AIS: adenocarcinoma *in situ*; MIA: minimally invasive adenocarcinoma; c: clinical; T: tumour; N: node; VATS: video-assisted thoracic surgery; NSCLC: nonsmall cell lung cancer.

Whether a purely anatomical segmentectomy provides similar or better results as a (wide) wedge excision has not yet been clearly determined. In general, when performing sublobar resections, several important factors affect the appropriateness of this intervention. These include the location (peripheral *versus* central), appearance (GGO *versus* solid) and size (T1a *versus* T1b *versus* T2) of the tumour. CT images, especially those obtained by high-resolution CT scanning with thin slices, are indispensable in evaluating these factors, and recent studies show rather good image–pathological correlations [25]. When correlating CT findings of GGO with histopathology, many of these lesions, though not all, correspond to pre-invasive, noninvasive or early forms of neoplastic growth, especially those of adenocarcinoma lineage [18–21, 26, 27]. In a recent prospective study from Japan (JCOG 0201), radiological noninvasive peripheral lung adenocarcinoma could be defined as an adenocarcinoma of ⩽2 cm with ⩽0.25 consolidation [28].

Recent guidelines and a large, randomised screening trial state that small nodules of ⩽10 mm or ⩽500 mm^3 that are clearly 100% pure GGO lesions on chest CT and that are suspected pathologically to be AIS or MIA be considered for close follow-up rather than immediate resection [25, 29]. Specific CT characteristics to be considered are size, attenuation, shape and growth rate (see table 2 for key issues 1–2).

SYSTEMATIC LYMPH NODE DISSECTION FOR EARLY-STAGE ADENOCARCINOMA

The necessity of systematic hilar and mediastinal lymph node dissection is based on the fact that nearly 20% of pulmonary adenocarcinomas ⩽20 mm and 5% of cases ⩽10 mm in size are reported to have nodal metastases [11, 14, 30]. Lobe-specific nodal dissection limits dissection to the primary nodal regions draining the involved lobe. Although there is no general consensus on this specific technique, this has been shown to be a potentially adequate alternative to complete systematic nodal dissection [17, 31, 32]. The surgeon should bear in mind that skip metastases involving mediastinal, without hilar, lymph nodes may occur in every subgroup of invasive cancers [33]. A recently reported multicentre prospective clinical trial randomising patients with intraoperatively staged T1–2N0 to nonhilar N1 NSCLC to lymph node sampling *versus* systematic nodal dissection showed that systematic nodal dissection identified occult disease in 3.8% of patients but was not associated with a benefit in overall survival [34]. These results should not be generalised to higher-stage tumours. Recent studies also show that in some specific subsets of very early-stage adenocarcinoma, especially pure GGO lesions, systematic lymph node dissection is not always required [35].

In a recent prospective study, a specific treatment algorithm was proposed [36]. Lesions of ⩽10 mm of any type or pure GGO nodules were initially observed and discussed with the patients. When size or density increased, they were subsequently resected. GGO lesions between 11 and 15 mm were treated by segmentectomy and lymph node sampling. Solid lesions between 11 and 15 mm and GGO lesions between 16 and 20 mm were removed by segmentectomy combined with lymph node dissection. Solid lesions between 16 and 20 mm were resected by lobectomy with lymph node dissection. Applying this algorithm yielded an excellent 5-yr disease-free survival rate of 98% for limited resection [36] (see table 2 for key issues 3–4).

INTRAOPERATIVE FROZEN SECTION ANALYSIS

Diagnostic accuracy

For a limited resection to be adequate oncologically, a precise pre- and intraoperative diagnosis is critical. Few articles deal with the exact procedure of intraoperative frozen section examination and its accuracy. These are summarised in table 3 [36–48]. Most papers specifically dealing with frozen section analysis of lung lesions ⩽2 cm originate from Japan. In a review by GUPTA *et al.* [41] including nodules examined over a 5-yr period, the error rate was 1.6% and deferral rate 4.4%. In the other papers summarised in table 3, predictive value ranged from 93% to 100%, but not all studies clearly mention accuracy of frozen section analysis. Most articles focus on the predictive value for noninvasive tumours. However, in some cases, the tumour was judged to be invasive, which proved not to be correct on final pathological examination [37, 40]. So, frozen section examination should also concentrate on the possible invasive nature of a nodule. The accuracy for MIAs remains to be determined, especially in countries outside Japan.

Evaluation of margins by frozen section may be problematic, especially when stapler cartridges have been used on both sides. Scraping or washing of staple lines with subsequent cytological analysis offers a possible solution [49, 50]. When a sublobar resection is performed, frozen section analysis of an interlobar, hilar or any suspicious lymph node is recommended. When positive nodes are found, a lobectomy is indicated when there is no functional cardiopulmonary limitation.

Intraoperative technique of frozen section analysis

Only five articles provide a detailed description of the specific intraoperative procedure of frozen section analysis itself [36, 37, 47, 48, 51]. As even smaller lesions can be heterogeneous, complete excision is advised to obtain an accurate result. In the article by KOIKE *et al.* [47], the lung specimen is sliced at the largest tumour diameter, a solid portion or at the site of a pleural indentation. The most suspicious portion is embedded, stained with haematoxylin–eosin and subsequently examined microscopically. YOSHIDA *et al.* [37] used modified stapler cartridges with, on one side, a single staple line to facilitate subsequent pathological examination. Specimen inflation was performed with a syringe filled with PBS, which replaces the alveolar air. After cutting the specimen into 2-mm thick slices, the pathologist looks for the site of most severe alveolar frame destruction and stromal growth, which is stained with haematoxylin–eosin and examined microscopically. In addition, a Victoria blue–van Gieson staining is added to reveal the elastic fibres of the alveolar wall. Different techniques of the inflation method are further described by MYUNG *et al.* [51] and were found to be accurate by XU *et al.* [48] in a large, recently published series.

KODAMA *et al.* [36] describe needle aspiration puncture of suspicious lesions through the thoracotomy wound. If cytological diagnosis proves to be difficult, a wide wedge resection is performed with lavage cytology of the resection margins. All fired cartridges or the specimen itself are washed and after centrifugation, the sediment is fixed with Saccomano solution and stained by the Papanicolaou method.

As frozen section examination of small lung nodules becomes increasingly important, pathologists should provide a uniform description of how to handle and examine specific tissue specimens, and which stainings should be applied in order to obtain accurate results and guide the extent of surgical resection.

TABLE 3 Accuracy of frozen section analysis for lung cancers ⩽2 cm

First author [ref.]	Study characteristics	Subjects n	Accuracy
GUPTA [41]	Retrospective review; lung nodules (5-yr period)	2405	Error rate 1.6%; deferral rate 4.4%
KONDO [40]	Retrospective; peripheral lung adenocarcinoma ⩽10 mm, subgroup Noguchi A–B	28	4/28 (14.3%) misdiagnosed as type C
MUN [39]	Retrospective; multifocal BAC ⩽20 mm	27	Frozen section in case of wedge resection, accuracy not mentioned
OHTSUKA [42]	Retrospective; pure GGO lesions ⩽20 mm	26	Frozen section if tumour was palpable, accuracy not mentioned
REGNARD [43]	Retrospective; BAC	70	Use of frozen section mentioned, accuracy not stated
TAKIZAWA [44]	Retrospective; small peripheral adenocarcinoma	27	Intraoperative assessment of lymph nodes not reliable
WATANABE [45]	Retrospective; Noguchi A–B	14	1/14 (7.1%) type C; predictive value 93%
XU [48]	Retrospective; pulmonary nodules (60.3% <2 cm)	229	Inflation method (72.1% of cases); sensitivity 100%; specificity 100%
YAMATO [38]	Prospective; small peripheral lung tumours ⩽20 mm	42	Accuracy 100%
YAMADA [46]	Retrospective; pure GGO lesions ⩽20 mm	39	Predictive value 100% (1 patient with adenocarcinoma revised to Noguchi A–B after definitive examination)
YOSHIDA [37]	Prospective; peripheral lung cancer ⩽20 mm	40	Accuracy 98%; detailed description of frozen section procedure
KODAMA [36]	Prospective; peripheral lung lesions ⩽20 mm	179	Detailed description of peroperative examination of resection margins, accuracy not mentioned
KOIKE [47]	Prospective; limited resection noninvasive BAC	46	Predictive value 94% (3/46 (6.5%) invasive adenocarcinoma); description of frozen section procedure

BAC: bronchioloalveolar carcinoma; GGO: ground-glass opacity.

MULTIPLE LESIONS

Synchronous lesions

Multifocal GGOs are often found, especially in screening programmes (18% in the Early Lung Cancer Action Program (ELCAP) trial) [52–54]. When there is no evidence of mediastinal lymph node invasion, multiple nodules are not a contraindication for surgical exploration. In the ELCAP study, nonsolitary node-negative adenocarcinomas had the same prognosis as solitary node-negative cases, suggesting that these represent multiple primary, and not intrapulmonary, metastases [52].

A standard treatment algorithm for multiple lesions has not yet been established. Several factors have to be taken into consideration: number and size of the different nodules, ipsilateral *versus* contralateral, primary *versus* metastatic lesions, and specific nature (atypical adenomatous hyperplasia, AIS or MIA). Conservative treatment with frequent follow-up is advocated for potentially benign lesions. When it is technically not possible to remove multiple, synchronous, pure GGO lesions, regular follow-up with chest CT represents an alternative approach to surgical resection [55]. For malignant nodules, several options exist, such as lobectomy for same-lobe nodules (now considered to be T3 disease), bilobectomy, lobectomy with wide wedge resection(s), multiple wide wedge resections or segmentectomies, and pneumonectomy, depending on functional capacity. Such resections can sometimes be performed by VATS [39]. One approach is to perform an anatomical resection (segmentectomy or lobectomy) for larger, more invasive or more central tumours, and removing the smaller, peripheral or less invasive tumours by wedge resection. However, such an approach has not yet been validated in clinical studies.

Metachronous lesions

For precise diagnosis of metachronous *versus* synchronous lung cancers, the classical criteria of Martini and Melamed are often used, at the present time combined with molecular genetic analysis [56]. To be considered multiple primary tumours, the interval between the two should be >2 yrs. When the interval is <2 yrs and both tumours are detected in the same lobe, different histology should be present or they should arise from foci of carcinoma *in situ*. When the interval is <2 yrs and they are found in different lobes, there should be no carcinoma cells in lymphatics common to both and no systemic metastases.

Currently, not much information is available on metachronous AIS or MIA. If the patient's cardiopulmonary function allows, the same surgical principles apply as for synchronous lesions. Recently, three second tumours were described that were clearly cut-end scar area recurrences [22]. One case could be defined as a metachronous primary cancer after thorough pathological and mutational analysis (see table 2 for key issue 5).

PROGNOSTIC FACTORS IN SURGICALLY TREATED PATIENTS

Histological prognostic features in surgically treated patients are presented in table 4.

AIS and MIA

AIS is defined as a small (⩽3 cm) solitary tumour with pure lepidic growth, lacking any invasion. If completely resected, the prognosis of surgically treated AIS is 100% [57, 58]. There was no mortality in 66 cases with >75% of lepidic growth component (LGC) [59]. Similarly, while patients having adenocarcinoma with 100% or 50–99% LGC showed 100% and 88% 5-yr survival rates, those with 1–49% or 0% LGC had worse survival, with 5-yr survival rates of 57% and 60%, respectively [60]. In contrast, vascular invasion and >25% papillary growth component were the most significant determinants of an unfavourable outcome [59]. Furthermore, in the patients with tumour size >2 cm, percentage LGC and pathological stage appeared to be two independent prognostic factors [61, 62].

MIA is currently defined as a small (⩽3 cm), solitary tumour with predominant lepidic growth and ⩽5 mm invasion. For MIA, the prognosis is near 100% survival [57, 58, 63]. In a series of 100 consecutive adenocarcinomas of the lung measuring ⩽30 mm, 21 subjects had central fibrosis of ⩽5 mm with a 5-yr survival rate of 100%, whereas the other 79 patients had a 5-yr survival of <70% [63].

Invasive adenocarcinoma

Lepidic predominant adenocarcinoma

Lepidic predominant adenocarcinomas have ~90% 5-yr survival [57].

Acinar and papillary predominant adenocarcinoma

Acinar and papillary predominant adenocarcinoma have an intermediate clinical behaviour, with 83–84% 5-yr disease-free

TABLE 4 Histological prognostic features

Histological features	Relevant histological type	Prognostic implication
Pure lepidic growth (⩽3 cm)	AIS	Excellent
Lepidic predominant (⩽3 cm) with ⩽5 mm invasion	MIA	Excellent
Invasive adenocarcinoma		
Lepidic	Lepidic predominant adenocarcinoma	Intermediate
Papillary	Papillary predominant adenocarcinoma	Intermediate
Acinar	Acinar predominant adenocarcinoma	Intermediate
Solid	Solid predominant adenocarcinoma	Poor
Micropapillary	Micropapillary predominant adenocarcinoma	Poor
Mucinous adenocarcinoma	Invasive mucinous adenocarcinoma (formerly mucinous BAC)	Poor

AIS: adenocarcinoma *in situ*; MIA: minimally invasive adenocarcinoma; BAC: bronchioloalveolar carcinoma.

survival compared with 100% for AIS and MIA and 67–70% for high-grade subtypes, such as micropapillary and solid adenocarcinoma [64]. Another study also showed an intermediate survival for 5-yr overall survival of 49–54% [65].

Micropapillary predominant adenocarcinoma

Adenocarcinomas with a micropapillary pattern (MPP), featuring small papillary tufts and lacking a central fibrovascular core, have a poor prognosis [64, 66, 67] and are associated with epidermal growth factor receptor (*EGFR*) mutation [68]. However, the prognostic impact of a MPP has not been rigorously compared with that of *EGFR* mutation status using multivariate analysis [68]. By comparing MPP-positive (n=139, 40%) with MPP-negative (n=205, 60%) patients, lymph node metastases, pleural invasion, intrapulmonary metastases and nonsmoking status were more common in the MPP type [67]. In stage I patients, 5-yr survival of the MPP-positive group (n=45) was 79%, which is significantly lower than the 93% of the MPP-negative group (n=109). In patients with Noguchi type C tumours (small adenocarcinomas ($\leqslant$2 cm) with a predominantly lepidic pattern), the 5-yr survival of the MPP-positive group (n=51) was 54%, which was significantly lower than the 100% of the MPP-negative group (n=23) (p=0.02) [69]. YOSHIZAWA *et al.* [64] found a 67% 5-yr survival for micropapillary predominant adenocarcinomas in a series of stage I adenocarcinomas.

Solid predominant adenocarcinoma

Several studies have demonstrated a poor prognosis for the solid subtype of adenocarcinoma [64, 65, 68]. In a series of 565 adenocarcinomas, those with solid adenocarcinoma with mucin components (n=239) were characterised by more males and stage IIB patients, and had poorer survival rates than those without solid adenocarcinoma with mucin components (38.6% *versus* 61.4%). In this study, 5-yr survival rates for predominantly acinar, papillary and solid adenocarcinoma with mucin components were 48.5%, 54.1% and 34.6%, respectively [65]. Using the current classification to analyse 514 stage I adenocarcinomas, YOSHIZAWA *et al.* [57] found the 5-yr disease-free survival for solid predominant adenocarcinoma to be 70% in the group of subtypes with high-grade clinical behaviour.

Invasive mucinous adenocarcinoma

Invasive mucinous adenocarcinomas represent tumours formerly classified as mucinous BAC. In resected cases, most of these tumours have an invasive component. The separation of these tumours is largely because they have the most robust molecular–histological correlation with a high percentage of *KRAS* mutations. In addition, they usually lack thyroid transcription factor-1 expression and most often show nodules of consolidation on CT scan. Frequently they form multiple nodules and can show lobar consolidation.

Signet ring and clear cell adenocarcinoma are now cytological features

Signet ring and clear cell adenocarcinoma are no longer histological subtypes, but rather cytological features that can occur in tumour cells of multiple histological subtypes, most often solid adenocarcinoma. Tumours are classified according to the histological classification, and any amount of signet ring or clear cell cytological change should be recorded with mention of the estimated percentage of tumour cells affected.

Molecular prognostic factors

Since lung cancers that look similar under a microscope sometimes show very different behaviour in patients, biomarkers that can predict patients' prognosis have been extensively investigated during the past 20 yrs.

Immunohistochemical markers for which meta-analyses have been performed include EGFR1 [70], p21 Ras [71], human EGFR2 (HER2) [72], p53 (the product of the *TP53* gene) [73, 74], Ki67 [75], Bcl2 [76] and cyclo-oxygenase 2 (Cox-2) [77]. All but p21 Ras and Cox-2 were statistically significant by meta-analysis. However, prognostic impact was generally limited, with hazard ratios being in the range of 1.13–1.57.

Similarly, there are many studies examining the prognostic impact of mutation of the *KRAS* or *TP53* genes. These show qualitative rather than quantitative differences detected by immunohistochemistry and therefore a greater impact on prognosis had been anticipated. Although these differences might be statistically significant, meta-analyses showed that their impact was not strong enough to be recommended for routine clinical use [71, 73, 74]. It was also suggested that *TP53* is prognostic in adenocarcinoma but not in squamous cell carcinoma of the lung [73, 74]. In contrast, lung cancers with *EGFR* mutations appear to have better prognosis than those without [78, 79]. However, *EGFR* mutations are known to be common in females and nonsmokers. These characteristics have been long known to be good prognostic factors.

Following the aforementioned observations, it was thought that the complexity and heterogeneity of lung cancer make it difficult to predict prognosis using a single gene. Researchers tried to create prognostic models by analysing expression of tens of thousands of genes using microarray technologies, and identified potential biomarkers and gene signatures for classifying patients with significantly different survival outcomes [80–84]. Similarly, proteomic profiling by use of mass spectrometry seems to be promising in predicting prognosis [85]. There are probably many prognostic gene signatures that are algorithm- and assay-specific. In general, overlapping of genes of prognostic importance between reports is exceptional. To address these issues, a large retrospective, multisite, blinded study was conducted to characterise the performance of several prognostic models based on gene expression for 442 lung adenocarcinomas [86]. Most methods performed better when combined with clinical data, supporting the integrated use of clinical and molecular information when building prognostic models for early stage lung cancer. The Cancer and Leukemia Group B is running a randomised phase III trial to evaluate a predictive model using a collection of gene expression profiles [83]. We will have to wait for the results of studies like this to establish the general applicability of gene signatures for routine clinical use. In lung adenocarcinoma, data from molecular studies need now to be analysed in the context of tumours classified according to this new classification and evaluated in multivariate analysis to identify the settings in which histologic *versus* genetic information provide the most useful information.

CONCLUSION

The newly introduced adenocarcinoma classification has profound surgical implications regarding surgical diagnosis and treatment of early-stage lung cancers. Initial data applying the

new classification in early-stage resected adenocarcinomas suggest substantial prognostic differences among histological subtypes that may allow for stratification of patients for adjuvant therapy [64]. However, many questions remain unanswered. When this new classification is adopted internationally, cooperative efforts to establish randomised trials will hopefully be able to solve these burning questions, providing a more tailored and uniform management of patients with early lung cancer.

STATEMENT OF INTEREST

A statement of interest for H. Asamecra can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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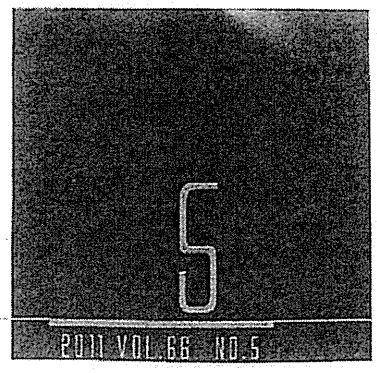
臨床外科



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肺癌の外科治療に関する臨床試験

Challenges and future directions of clinical trials about surgical strategies for lung cancer in Japan

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[ポイント]

◆縮小手術の臨床試験として，わが国のJCOG0802/WJOG4607L，JCOG0804/WJOG4507Lおよび北米のCALGB140503の3つの大規模臨床試験が進行中である．

◆術後補助化学療法の開発も進行癌と同様に，分子標的治療薬やバイオマーカーを用いた個別化治療の方向で進んでいる．

◆局所進行肺癌に対する外科治療を含む集学的治療法にはいまだ確固たるエビデンスはないが，開発が進むことは肺癌全体の予後の改善に与える影響が大きい．

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はじめに

厚生労働省がん統計によると，1998年以降，肺癌はわが国の癌死因の第1位となり，2008年には年間死亡数が66,849人に達した．この疾患に対する有効な治療法の開発と，質と安全性の向上は癌診療において特に重要性が高いと考える．2004年の罹患者数は80,106人に達し，その3～4割に手術適応があると考えられる．実際，日本胸部外科学会の2008年の「Annual report」[1]によると27,881件の原発性肺癌の手術が行われ，現在も増加の一途をたどっている．

近年，分子標的治療薬を中心とした新たな薬剤が開発されており，さらに，基礎医学の成果が臨床へ還元されるプロセスが高速化されたことによって，肺癌全体の治療成績の向上が肌で感じられるようになってきた．しかし，特に根治を目指した治療戦略を考える場合，依然として外科治療を含めた集学的治療が必要であることはいまだ異論はない．

一方，わが国では胸部CTを用いた検診の普及に伴い，早期肺癌の発見が増えている．当施設における病期別手術症例の推移をみても，2010年には1期が80％を占め，1990年の2倍に増加している．わが国では特に2 cm以下の早期肺癌の発見が多く，これらを対象とした低侵襲手術の開発と質の追及が呼吸器外科医に求められていると言っても過言ではない．さらに，高齢者肺癌の増加や，私見ではあるが，第2，第3の肺癌に対する手術を行う機会も増え，低侵襲手術に対するエビデンスの確立が今後さらに必要性を増してくると思われる．

新しい治療法の有効性と安全性を科学的に検証する手法が臨床試験である．複数の前向き第Ⅲ相試験randomized controlled trial（RCT）を経て有効性が証明されるとエビデンスレベルは高くなり，新治療がガイドラインで推奨されることになる．外科治療におけるエビデンス構築も同様であり，これからの外科医には臨床試験を理解し遂行する能力が求められている．

本稿では，肺癌に対する外科関連治療として，①低侵襲手術，②術後補助化学療法，③集学的治療に関する最新の臨床試験に関する知見を紹介し，問題点と今後の展望をついて述べる．

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低侵襲手術

肺癌における低侵襲手術は大きく3つに分けられる．①アプローチの縮小としての胸腔鏡下手術，②切除範囲の縮小としての楔状切除，区域切除，そして③リンパ節郭清の縮小としての選択的リンパ節郭清，系統的リンパ節サンプリングである．

■胸腔鏡下手術

前述の「Annual report」[1]によると，いまだ定義は曖昧であるが，肺癌手術の52%がすでに実臨床では胸腔鏡を用いて行われている．

2009年にオーストラリアのグループから，早期肺癌に対する胸腔鏡下肺葉切除術の安全性と有効性を開胸手術と比較した試験のmeta-analysisが報告された[2]．結果は，安全性では遷延性肺瘻（p＝0.71），不整脈（p＝0.86），肺炎（p＝0.09）の合併症発生率および死亡率（p＝0.49）に群間差はなく，有効性では局所再発率（p＝0.24）に差はないが，遠隔再発率（p＝0.03），5年時の全死亡率（p＝0.04）は胸腔鏡下手術群で有意に改善を認めたものとなった．しかし，この解釈には注意を要し，あくまでも両群あわせて100例以下の2つの小規模RCTと19の後ろ向き比較試験から得られたsystematic reviewであり，考察では著者らみずからがこの研究における解析の限界を指摘している．

そもそも単施設による後ろ向き試験は，胸腔鏡下手術を選択した時点ですでに相当なselection biasが存在し，これを排除することは事実上不可能である．また，試験のなかには肺葉手術に移行した症例を胸腔鏡下手術群から除いたり，さらには肺葉切除群にカウントしているのも含まれており，臨床試験の大前提であるintention-to-treat（ITT）そのものが順守されていないものもある．また，胸腔鏡下手術の定義も試験によって異なる．これらの点から，統一した基準のもとITTで胸腔鏡下手術の認容性を検討したCALGB 39802[3]のほうがより正確な情報を提供していると考える．

結局は大規模な多施設共同RCTをしない限り胸腔鏡下手術の真の有効性を科学的に証明したことにならない．なお，Clinical Trials.govで検索する限り，現在進行中の胸腔鏡下手術の有効性を検証するRCTには中国の9施設が共同で行っている試験がある．コントロール群の術式は腋窩開胸手術，primary endpointはdisease-free survival（DFS）とoverall survival（OS），予定登録数は200例と小規模なもので，2010年1月から開始されている．

■楔状切除，区域切除

肺葉切除術より小さい範囲を切除する2つの縮小手術をまとめて“sublobar resection”と表現する．従来は低肺機能や高齢者に対して消極的縮小切除として行われていた．近年の肺野末梢小型早期肺癌の発見の増加に伴い，肺葉切除が可能な患者に対しても積極的縮小切除術を行おうという流れに変わりつつある[4~7]．

現在も小型肺癌に対する標準手術は肺葉切除術であり，そのエビデンスは20年近く前にさかのぼる．米国のLung Cancer Surgical Groupによる臨床病期Ⅰ期（cⅠ期）を対象とした肺葉切除術と縮小切除術を比較したRCTでは，OSに有意差（p＝0.088）は認めないものの，DFSが縮小切除術群では有意（p＝0.016）に悪化し，局所再発は3倍に増加（6% vs. 18%）した．この結果から，依然として肺葉切除術が早期肺癌でも標準術式であると結論づけられた[8]．

しかし，上記のRCTには，①対象の多くが2 cmを超える腫瘍であった，②10～15%のリンパ節転移が予想される対象に郭清を伴わない楔状切除が許容されていた，③肺野末梢病変以外も対象としており，十分な断端の確保が担保されていなかったなどという問題が指摘されている．さらに，わが国では胸部CT検診および薄切CTの普及に伴い，当時とは明らかに生物学的悪性度の異なるgrand glass opacity（GGO）を主体とする早期肺癌が増加している．

それを踏まえ，Japan Clinical Oncology Group（JCOG）とWest Japan Oncology Group（WJOG）は2つの大規模臨床試験を，全国75施設が参加するintergroup studyとして行っている．先行する画像的非浸潤癌の特異度を検証したJCOG0201（JTO in press）の探索的研究の結果を踏まえ，胸部薄切CT画像上の最大腫瘍径におけるconsolidationの割合（25% cut off）によって2つの臨床試験に分けられる．JCOG0802/WJOG4607Lは肺野末梢小型肺癌（2 cm以下cⅠ期）を対象に，画像的浸潤癌（25%超）に対して，区域切除が肺葉切除に比べてOSにおいて非劣性であることを検証するRCTであり（図1），JCOG0804/WJOG4507Lは画像的非浸潤癌（25%以下）に対して縮小切除術（原則として楔状切除）の有効性と安全性を検証する第Ⅱ相試験である（図2）．

北米では同様の対象に縮小切除術と肺葉切除術を比

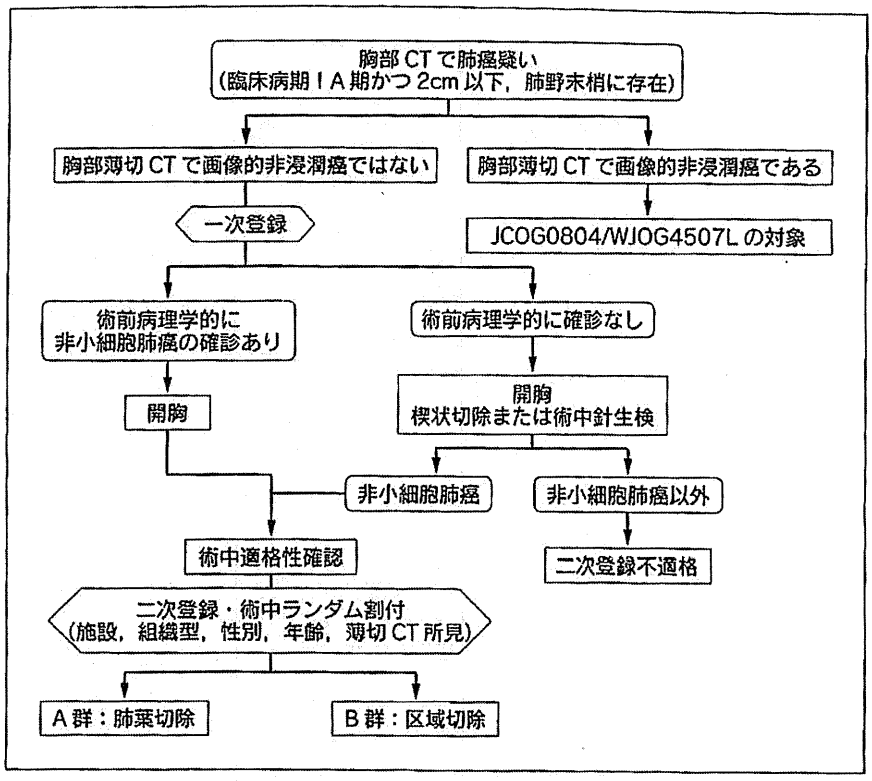

図1　JCOG0802/WJOG4607L
目的：画像的非浸潤癌を除く臨床病期ⅠA期の肺野末梢小型非小細胞肺癌（最大腫瘍径2 cm以下）を対象として，試験治療である区域切除が，現在の国際的標準治療である肺葉切除に比べて全生存期間において非劣性であることをランダム化比較試験によって検証する．
Primary endpoint：全生存期間．
Secondary endpoints：術後呼吸機能（6か月後，1年後），無再発生存期間，局所再発発生割合，有害事象，区域切除完遂割合，在院日数，ドレーン留置期間，手術時間，出血量，自動縫合器使用数．

較した大規模RCT（CALGB140503）が進行中である（図3）．表1にJCOG0802/WJOG4607Lとの比較を示すが，大きな違いは，①primary endpointがDFSであること，②pure GGOが除かれること，③術中登録前に系統的リンパ節サンプリングによるpN0を必須としていることである．両試験とも1,000例規模のRCTであり，その結果によっては呼吸器外科の教科書を変えうる臨床試験と期待される．

一方，JCOG0804/WJOG4507Lの結果によってはsurgical vs. non-surgical treatmentといったmodalityの違う治療法を比較した次期臨床試験が考えられる．JCOG0403の予後に関する最終結果によっては定位放射線治療がnon-surgical treatmentの第一候補に挙がる．

■選択的リンパ節郭清

The European Society of Thoracic Surgeons (ESTS) のガイドラインには各種リンパ節の評価方法が定義されている[9]．リンパ節郭清の意義には予後の改善と正確な病期判定の2つがあり，前者にはいまだ議論のあるところである．The American College of Surgeons Oncology (ACOSOG) のZ0030は上記を検証する目的で計画され，The American Association for Thoracic Surgery (AATS) Annual meeting 2010のplenary sessionでその最終結果が報告された．1999年6月から2004年2月にかけ，北米の63施設が参加して1,111例の早期肺癌を対象に行われた大規模RCTであり，mediastinal lymph node sampling (MLNS) 後のmediastinal lymph node dissection (MLND) がOSの改善に寄与するかを検証した優越性試験である（図4）．結果はDFS，OSともに差はなく（median survival：MLNS：8.1 vs. MLND：8.5 years），MLNS後のMLNDのOS改善効果は証明されなかった．

この試験はデザイン上の問題も指摘されており，

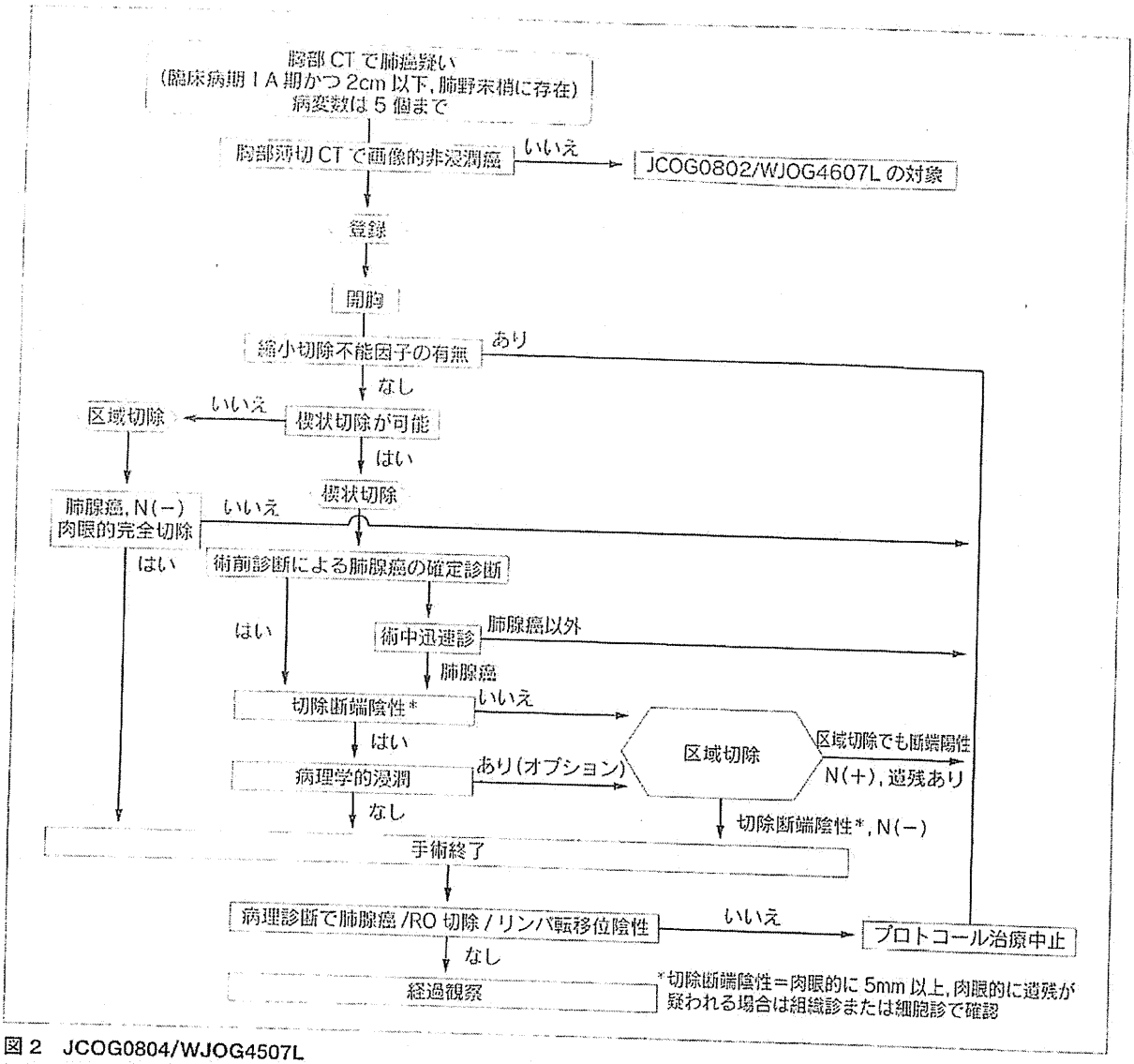

図2　JCOG0804/WJOG4507L

目的：術前の胸部薄切（thin section）CT画像に基づく2cm以下の肺野末梢の早期肺癌に対する縮小切除術（原則として楔状切除）の有効性と安全性を検討する．

Primary endpoint：無再発生存期間

Secondary endpoints：全生存期間，局所再発発生頻度，術後呼吸機能（努力性1秒量，努力性肺活量），縮小切除完遂割合，有害事象．

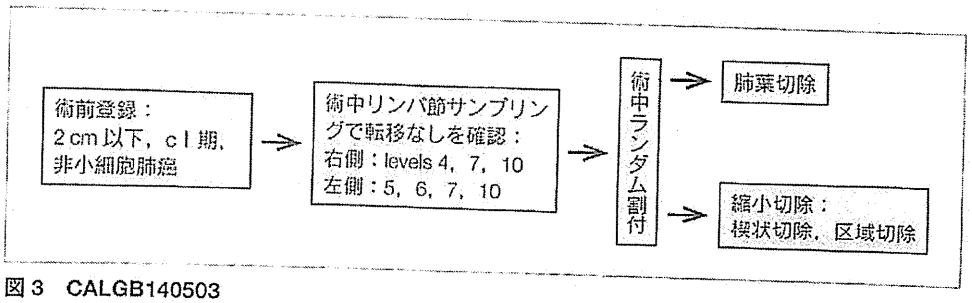

図3　CALGB140503

Primary endpoint：無再発生存期間

Secondary endpoints：全生存期間，局所再発割合，遠隔再発割合，術後6か月1秒率．