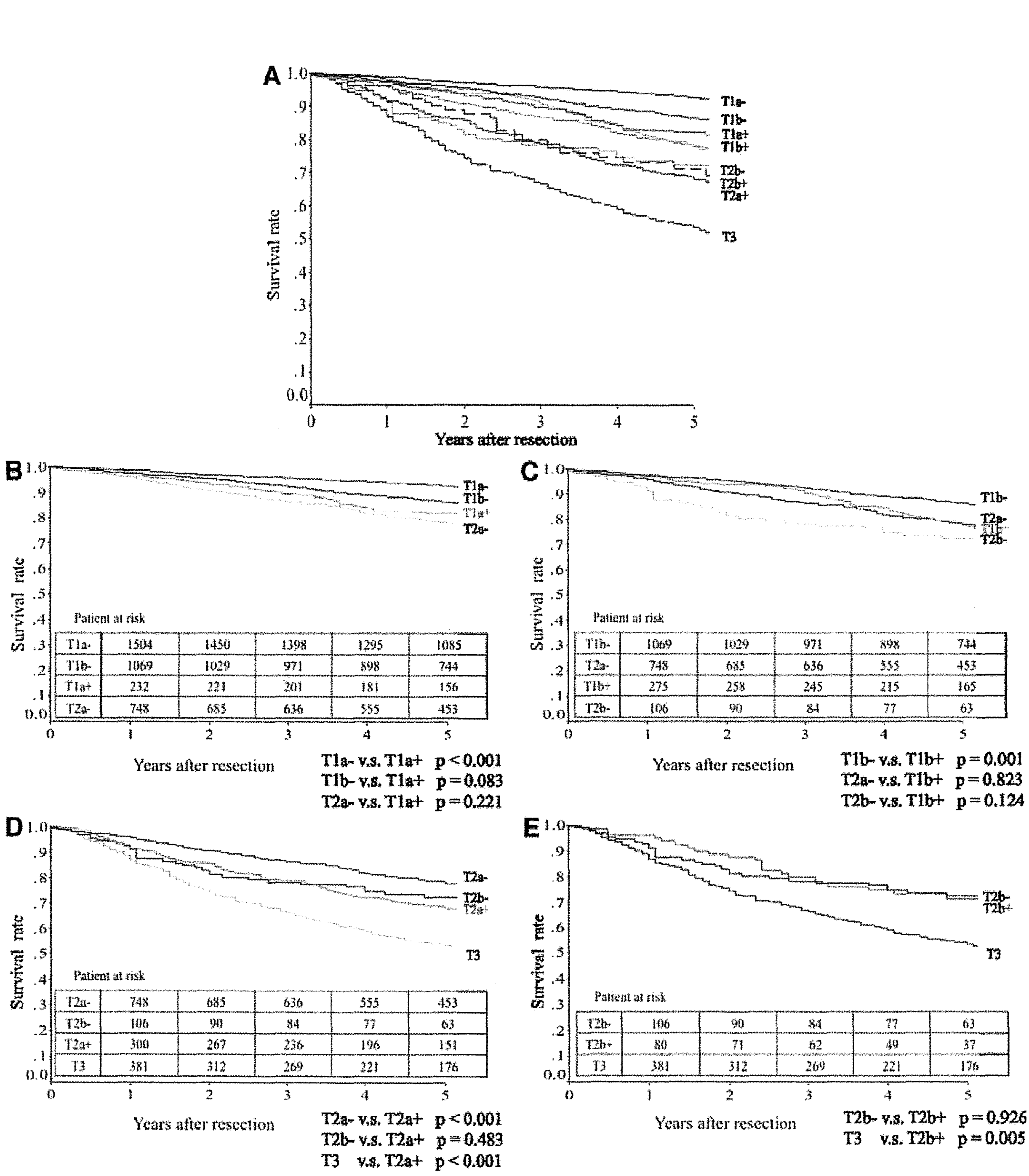

FIGURE 2. (*A*) Survival curves stratified by T stage and VPI status. (*B*) Survival curves of T1a/VPI–, T1b/VPI–, T2a/VPI–, and T1a/VPI+. (*C*) Survival curves of T1b/VPI–, T2a/VPI–, T2b/VPI–, and T1b/VPI+. (*D*) Survival curves of T2a/VPI–, T2b/VPI–, T2b/VPI–, and T2a/VPI+.(*E*) Survival curves of T2b/VPI–, T3, and T2b/VPI+.

tumors with VPI and T2a tumors without VPI ($p = 0.823$) or T2b tumors without VPI ($p = 0.124$).

Figure 2*D* shows the survival impact of VPI on T2a tumors. T2a tumors with VPI had a significantly poorer prognosis than T2a tumors without VPI ($p < 0.001$). There were no significant survival differences between T2a tumors with VPI and T2b tumors without VPI ($p = 0.483$). T2a tumors with VPI had a significantly better prognosis than T3 tumors ($p < 0.001$).

Figure 2*E* shows the survival impact of VPI on T2b tumors. There were no significant survival differences between T2b tumors with VPI and T2b tumors without VPI ($p = 0.926$). T2b tumors with VPI had a significantly better prognosis than T3 tumors ($p = 0.005$).

DISCUSSION

VPI is known to be a poor prognostic factor of NSCLC patients and is defined as a factor to upgrade T1a/T1b tumors to T2a in the 7th Edition of the TNM Classification for Lung and Pleural Tumours.[11,12,14] Travis et al.[13,17,18] recommend the use of elastic stains when invasion beyond the elastic layer is not clear on evaluation of HE sections. Although the Japan Lung Cancer Society also recommends using not only HE staining, but also elastic staining such as Victoria-blue van Gieson staining in VPI evaluation, the JJCLCR did not collect data regarding staining or how extensively VPI was evaluated in each participating institution. This is a major limitation of the present study.

In the present study, PL1 patients had a significantly poorer prognosis than PL0 patients, consistent with many previous reports.[1-10] PL2 patients had a significantly poorer prognosis than PL1 patients. The survival difference between PL1 and PL2 patients remains controversial. Kawase et al.[10] analyzed a cohort of more than 2700 patients, using the current VPI definition and elastic staining in all cases for VPI diagnosis, and reported no survival differences between PL1 and PL2 patients. Moreover, several other researchers have reported similar results.[2,6,9] In contrast, Sakakura et al.[4] reported significant differences in survival between PL1 and PL2 patients, but they did not describe whether or not they used elastic stains in diagnosing VPI status. In the data of the JJCLCR registry, it is not clear in what portion of the accumulated cases elastic staining was employed, and there remains some uncertainty regarding the determination of pleura invasion. Some PL0 patients might have been miscategorized as PL1 without the use of elastic staining, which may have led to the significant survival difference observed between PL1 and PL2 patients. To conclude whether or not a difference between PL1 and PL2 survival is valid, it is necessary to study more patients with VPI diagnoses made with the help of elastic staining.

To analyze the prognostic impact of VPI on T-status classification in the current cohort, we defined VPI to include PL1 and PL2 patients, as defined by the 7th edition of the TNM Classification for Lung and Pleural Tumours. T1a with VPI had a significantly poorer prognosis than T1a without VPI, but there were no significant survival differences between T1a with VPI and T1b without VPI, or between T1a with VPI and T2a without VPI. To summarize, T1a with VPI had prognosis similar to that of T1b/T2a without VPI, which suggests it is credible to upgrade T1a with VPI to T2a.

T1b with VPI had a significantly poorer prognosis than T1b without VPI, but there were no significant survival differences between T1b with VPI and T2a without VPI or between T1b with VPI and T2b without VPI. To summarize, T1b with VPI had a similar prognosis to T2a/T2b without VPI, which suggests it is reasonable to upgrade T1b with VPI to T2a, as described in the 7th edition of the TNM Classification for lung cancer.[11,12]

The most significant information of the present study is the outcome of T2a with VPI. T2a with VPI had a significantly poorer prognosis than T2a without VPI. There were no significant survival differences between T2a with VPI and T2b without VPI. T2a with VPI had a significantly better prognosis than T3. To summarize, T2a with VPI had a similar prognosis to T2b without VPI, which suggests T2a with VPI should be upgraded to T2b.

TABLE 2. T-Classification Comparison

Tumor Diameter, cm	VPI Ctatus	7th Edition T-Classification	Our Proposal
<2	–	T1a	T1a
<2	+	T2a	T2a (or T1b)
2.1–3	–	T1b	T1b
2.1–3	+	T2a	T2a
3.1–5	–	T2a	T2a
3.1–5	+	T2a	T2b
5.1–7	–	T2b	T2b
5.1–7	+	T2b	T2b

VPI– = PL0, VPI+ = PL1 or PL2.
VPI, visceral pleural invasion.

In the current cohort, there were no significant survival differences between T2b with VPI and T2b without VPI. T2b with VPI had a significantly better prognosis than T3. To summarize, T2b with VPI had a prognosis similar to that of T2b without VPI, which suggests there is no need to upgrade T2b with VPI. These suggestions are summarized in Table 2, and they include some differences from the conclusions of previous publications.[2,8,10]

A major limitation of the current study is that we do not know how thoroughly VPI was evaluated including elastic staining, in each participating institution. The differences observed may have been attributable to misdiagnoses of VPI status due to the lack of elastic staining use. However, the recommendation of the 7th edition of the TNM classification, that is, to upgrade T-classification according to VPI status, was determined on the basis of the results of some retrospective studies of small cohorts, in contrast to the large number cohort accumulated by the IASLC Lung Cancer Project. Moreover, the IASLC Lung Cancer Project also lacks detailed information on VPI status evaluation methodology. Therefore, we consider that a worldwide large-scale study that is limited to patients whose VPI status is diagnosed using elastic staining is necessary to determine the true impact on survival of pleural invasion and VPI.

In conclusion, in addition to the current TNM Classification recommendations—to upgrade tumors of 3 cm or less with VPI to T2a—tumors greater than 3 cm and 5 cm or less with VPI should be upgraded to T2b. However, more detailed further research is necessary for the next edition of the TNM classification for lung and pleural tumours, using a large-scale database with VPI status diagnosed using elastic staining.

ACKNOWLEDGMENTS

Supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, Japan.

The authors thank Roderick J. Turner and Professor J. Patrick Barron, chairman of the Department of International Medical Communications at Tokyo Medical University, for their editorial review of this manuscript. The authors also thank Dr. Kanji Nagai, MD, PhD, of the Division of Thoracic Oncology at the National Cancer Center Hospital East, Kashiwa, Chiba, Japan, for his scientific advice.

REFERENCES

1. Shimizu K, Yoshida J, Nagai K, et al. Visceral pleural invasion is an invasive and aggressive indicator of non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2005;130:160–165.
2. Shimizu K, Yoshida J, Nagai K, et al. Visceral pleural invasion classification in non-small cell lung cancer: a proposal on the basis of outcome assessment. *J Thorac Cardiovasc Surg* 2004;127:1574–1578.
3. Kang JH, Kim KD, Chung KY. Prognostic value of visceral pleura invasion in non-small cell lung cancer. *Eur J Cardiothorac Surg* 2003;23:865–869.
4. Sakakura N, Mori S, Okuda K, et al. Subcategorization of lung cancer based on tumor size and degree of visceral pleural invasion. *Ann Thorac Surg* 2008;86:1084–1090.
5. Satoh Y, Ishikawa Y, Inamura K, Okumura S, Nakagawa K, Tsuchiya E. Classification of parietal pleural invasion at adhesion sites with surgical specimens of lung cancer and implications for prognosis. *Virchows Arch* 2005;447:984–989.
6. Shim HS, Park IK, Lee CY, Chung KY. Prognostic significance of visceral pleural invasion in the forthcoming (seventh) edition of TNM classification for lung cancer. *Lung Cancer* 2009;65:161–165.
7. Manac'h D, Riquet M, Medioni J, Le Pimpec-Barthes F, Dujon A, Danel C. Visceral pleura invasion by non-small cell lung cancer: an underrated bad prognostic factor. *Ann Thorac Surg* 2001;71:1088–1093.
8. Yoshida J, Nagai K, Asamura H, et al.; Japanese Joint Committee for Lung Cancer Registration. Visceral pleura invasion impact on non-small cell lung cancer patient survival: its implications for the forthcoming TNM staging based on a large-scale nation-wide database. *J Thorac Oncol* 2009;4:959–963.
9. Yilmaz A, Duyar SS, Cakir E, et al. Clinical impact of visceral pleural, lymphovascular and perineural invasion in completely resected non-small cell lung cancer. *Eur J Cardiothorac Surg* 2011;40:664–670.
10. Kawase A, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Visceral pleural invasion classification in non-small cell lung cancer. *J Thorac Oncol* 2010;5:1784–1788.
11. Goldstraw P (Ed). Staging Manual in Thoracic Oncology. Denver: IASLC; 2009.
12. International Union against Cancer. Sobin LH, Gospodrowicz MK, Wittekind CH (Eds), TNM Classification of Malignant Tumours, 7th Ed. New York: Wiley-Liss; 2009.
13. Travis WD, Brambilla E, Rami-Porta R, et al.; International Staging Committee. Visceral pleural invasion: pathologic criteria and use of elastic stains: proposal for the 7th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2008;3:1384–1390.
14. Osaki T, Nagashima A, Yoshimatsu T, Yamada S, Yasumoto K. Visceral pleural involvement in nonsmall cell lung cancer: prognostic significance. *Ann Thorac Surg* 2004;77:1769–73; discussion 1773.
15. Sawabata N, Miyaoka E, Asamura H, et al.; Japanese Joint Committee for Lung Cancer Registration. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. *J Thorac Oncol* 2011;6:1229–1235.
16. Travis WD, Brambilla E, Müller-Hermelink H, Harris C (eds). Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press; 2004.
17. Taube JM, Askin FB, Brock MV, Westra W. Impact of elastic staining on the staging of peripheral lung cancers. *Am J Surg Pathol* 2007;31:953–956.
18. Butnor KJ, Vollmer RT, Blaszyk H, Glatz K. Interobserver agreement on what constitutes visceral pleural invasion by non-small cell lung carcinoma: an internet-based assessment of international current practices. *Am J Clin Pathol* 2007;128:638–647.

European Journal of Cardio-Thoracic Surgery 43 (2013) 795–799
doi:10.1093/ejcts/ezs419 Advance Access publication 24 July 2012

ORIGINAL ARTICLE

Pulmonary metastasectomy for osteogenic and soft tissue sarcoma: who really benefits from surgical treatment?

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Received 12 April 2012; received in revised form 2 June 2012; accepted 8 June 2012

Abstract

OBJECTIVES: Surgical resection is widely accepted as a beneficial treatment of pulmonary metastases originating from osteogenic and soft tissue sarcomas despite adequate validation. The factors associated with the selection of patients who receive pulmonary metastasectomy (PM) are controversial and not well known. In this study, we aimed to identify the prognostic factors associated with survival after treatment with PM and to disclose the candidates who profit from PM being performed on patients with osteogenic and soft tissue sarcomas.

METHODS: We retrospectively reviewed the variables and survival outcomes in 52 consecutive patients who underwent PM to treat lung metastases originating from osteogenic and soft tissue malignancies from April 1996 to January 2011. Prognostic factors associated with overall survival after the first PM were evaluated using univariate and multivariate analyses.

RESULTS: Fifty-eight PM procedures were performed in 52 patients as the first PM including 6 bilateral diseases. Wedge resection was the most frequently performed PM procedure (84%), and video-assisted thoracic surgery was introduced in 34 (59%). The median follow-up of the patients was 33 months and the 5-year survival rate after the first PM was 50.9%. Forty-eight (92%) patients underwent complete resection during the first PM. Thirty-three patients (62%) experienced relapse after the first PM. Among those patients, 20 received redo surgeries for pulmonary relapse, and the 5-year survival rate in this group was 49.7%. According to univariate analyses, the use of complete resection, the number of metastatic nodules (one or two) and the length of the disease-free interval prior to the first PM were each found to be significant favourable factors. According to a multivariate analysis, the use of complete resection and the number of metastatic nodules were both found to be independent prognostic factors associated with overall survival. Although our cohort included 15 patients with poor prognostic factors (29%), 5 patients who underwent redo surgery survived >22 months.

CONCLUSIONS: The survival of those patients with one or two pulmonary nodules and those who underwent complete resection was favourable following the treatment of osteogenic and soft tissue sarcomas with PM. Redo surgery may also provide some survival benefit in patients with poor prognostic factors.

Keywords: Pulmonary metastases • Pulmonary metastasectomy • Osteosarcoma • Soft tissue sarcoma

THORACIC

INTRODUCTION

The lungs are one of the most common organs targeted by metastatic malignancies. It is widely believed that malignant diseases with pulmonary metastases are so advanced that the prognoses of patients are unfavourable. In cases of orthopaedic sarcoma, especially those originating in the extremities, it has been reported that ~20% relapse in the lungs [1, 2]. Patients with osteogenic and soft tissue sarcomas sometimes develop metastatic nodules in peripheral lung areas, which cannot be sufficiently treated with therapies other than surgical resection. Because of surgical accessibility concerns and drug-resistant characteristics in the selected population, pulmonary metastasectomy (PM) has come to be accepted as a potentially effective treatment.

Although a number of retrospective analyses have reported the outcomes and efficacy of PM, the true benefits of this treatment have not been disclosed due to the heterogeneity of the disease. Others have reported 5-year survival rates of 15–52% and have suggested that the number of nodules, the length of the disease-free interval (DFI) prior to PM, the histology of the primary tumour and the size of the pulmonary nodule are each prognostic factors associated with survival outcomes [3–5]. Controversies still remain among the reports regarding these prognostic factors. In addition, we have acknowledged that ~40% of patients who underwent PM to treat osteogenic and soft tissue sarcomas experienced relapses in the lungs. Treatment with repeated PM has also recently been introduced without an adequate investigation of its efficacy.

We review here our experience with PMs performed for osteogenic and soft tissue sarcomas and aim to investigate the prognostic factors associated with the selection of patients.

PATIENTS AND METHODS

Patients

From April 1996 to January 2011, 52 consecutive patients underwent surgical resection at Nagoya University Hospital to treat pulmonary metastases originating from orthopaedic sarcomas. In all patients, the primary tumours were pathologically diagnosed prior to pulmonary resection. However, preoperative diagnoses of the pulmonary nodules were made based on the radiological findings of chest computed tomography (CT).

Whether or not surgery was deemed to be indicated was determined based on the background, respiratory function, the length of the DFI after treatment of the primary site, number of pulmonary nodules and location of the tumour in the lungs of each patient. In all 52 patients, the primary and distant sites, except for the lungs, were controlled, and PMs were performed with the intention of completing radical resections.

Investigated variables

The data regarding gender, age, histology and sites of the primary tumours were reviewed as variables for the patient characteristics. Furthermore, the following six clinical variables were investigated for each patient: the length of the pre-PM DFI before the first PM (pre-DFI), the laterality of the lung nodules, the type of PM procedure, the number of metastatic pulmonary nodules, the completeness of PM, the frequency of PM, the length of the post-PM DFI after PM (post-DFI) and the prognosis (survival, recurrence). In the univariate analysis of the number of metastatic pulmonary nodules, the patients were classified into two groups: patients with one or two nodules, and patients with three or more nodules.

Statistical analyses

The overall survival rate of each patient was measured from the date of the first PM until either death or the last day of the follow-up. The length of the DFI (pre-DFI) was calculated from the day of treatment of the primary tumour to the day of the first PM. Survival curves were created using the Kaplan–Meier method. Univariate analyses were performed using the log-rank test based on the Kaplan–Meier method to assess the prognostic significance of the individual factors. A multivariate analysis was performed on the significant variables of the univariate analyses using the Cox regression hazard model to access the independent prognostic values of the potential factors. These statistical analyses were completed using the SPSS software for Windows (version 12.0; Chicago, IL, USA). In both univariate and multivariate analyses, $P < 0.05$ was considered to be significant.

RESULTS

The characteristics of the 52 patients are shown in Table 1. The majority of the patients were male (65%). The median age of the patients was 41 years. Forty-two percent of the patients were younger than 40 years of age, and only four patients older than 70 years of age were included. The most dominant histological type of primary tumour observed was osteosarcoma (42%), and the remaining half of the patients suffered from soft tissue sarcomas. Most of the patients (85%) had unilateral diseases, and approximately half of the patients (54%) had solitary lung nodules. The maximum number of metastatic nodules occurring in one patient was 10. During surgery, two unexpected pulmonary nodules were found in two cases, and multiple pleural disseminated nodules were disclosed in three cases. Fifty-eight PM procedures were performed in 52 patients as the first PM including six bilateral diseases of one-staged surgery. Wedge resection was the most frequently performed PM procedure (84%). Video-assisted thoracic surgery was introduced in 34 procedures (59%), and the rest were performed through thoracotomy. Complete resection was accomplished in 92% of the patients. On the other hand, PMs were incomplete in four patients. Three were due to unexpected pleural dissemination, and one was due to a positive surgical margin in the bronchus. Postoperative complications were identified in four patients; pneumonia, prolonged air leakage, wound infection and arrhythmia in one each. Thirty-six (69%) of 52 patients received chemotherapy after the first PM, and 49 (94%) experienced chemotherapy during their overall treatment course. The median length of the DFI before the first PM (pre-DFI) was 13.3 months, including one synchronous case.

Table 1: Patient characteristics

Variables	$n = 52$	%
Gender (male/female)	34/18	
Age (year, median/range)	41/7–74	
Histology		
Osteosarcoma	22	42
MFH	7	14
Liposarcoma	6	12
Synovial sarcoma	4	8
Others	13	24
Primary site		
Extremities	37	72
Trunk	15	28
Unilateral	44	85
Number of nodules (1/2/3/4/5/10)	28/9/8/4/2/1	
First PM procedure		
Wedge resection	49	84
Segmentectomy	5	9
Lobectomy or more	4	7
Complete resection	48	92
Pre-DFI (months; median/range)	13.3/0–130	
Recurrence after the first PM	33	62

Of 48 patients who underwent complete resection of the pulmonary metastases, 15 survived to be free of disease after the first PMs. Each of these patients had unilateral diseases with one or two metastatic nodules, and the median survival time (MST) of this group was 50 months. However, 33 patients experienced relapses of the lung metastases. Among these patients, 20 underwent repeated PM for recurrent lung disease. Despite such aggressive surgical treatment, re-recurrence was observed in 13 patients (65%) with short DFI intervals after the first PMs were performed (post-DFI, median: 6.9 months). Thirteen patients did not meet the criteria for repeated PM, including patients with

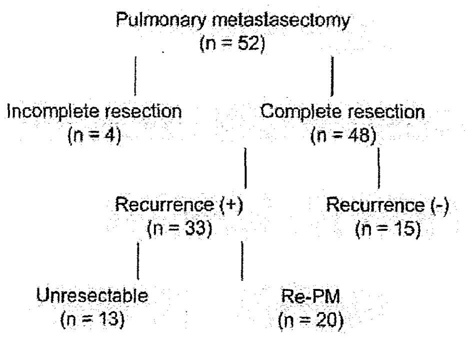

Figure 1: The enrolment and survival outcomes of the patients with pulmonary metastases originating from osteogenic and soft tissue sarcomas.

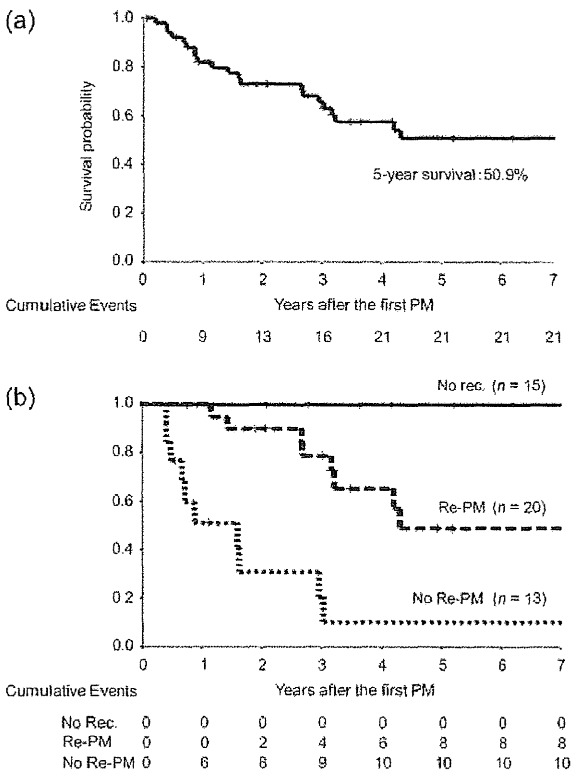

Figure 2: (a) The overall survival of the patients after the first PMs who received surgery to treat lung metastases originating from osteogenic and soft tissue sarcomas. (b) The overall survival curves according to the frequency with which PM was performed. No rec.: no recurrence; Re-PM: repeated PM.

three or more metastatic nodules and shorter pre-DFI (median: 9.7 months) at the first PMs (Fig. 1). Redo PMs were not performed for these patients due to extrathoracic recurrence in four, multiple pulmonary metastases in four, pleural dissemination in two, intrathoracic recurrence involving the subclavian vessels in one, and hilar lymph node metastasis in one. One patient refused redo surgery for her metastatic pulmonary disease.

The MST and 5-year survival rate of all 52 patients was 33.3 months and 50.9%, respectively (Fig. 2a). The MST and 5-year survival rate of the 20 patients who underwent repeated PM was 38.3 months and 49.7%, respectively, while those of the 13 patients who did not undergo repeated PM was 8.7 months and 10.3%, respectively (Fig. 2b).

The univariate analyses demonstrated that the number of metastatic nodules, the length of the pre-DFI and the use of complete resection were each significant prognostic factors associated with the overall survival after the first PMs were performed (Table 2). A multivariate analysis showed that the number of metastatic nodules and the completeness of resection were both independent prognostic factors, while the length of the pre-DFI was not significant (Table 3).

In our present population, we identified 15 patients with unfavourable factors. The MST and 5-year survival rate in this group was 11 months and 15.6%, respectively. Although all of these patients experienced recurrences after the first PMs were performed, five patients (33%) who underwent repeated PM achieved longer survival times. We did not identify any trends in characteristics, including histology, history of chemotherapy, length of pre-DFI or length of post-DFS in these patients (data not shown).

DISCUSSION

It is widely accepted that treatment with PM offers a potential cure for patients with metastatic malignancies, despite a lack of validation with prospective studies. The large cohort study conducted by the International Registry of Lung Metastases reported a 5-year survival rate of 36% in patients who underwent complete resection of pulmonary metastases compared with that of 7% in patients who underwent incomplete resection [6]. Regarding PM performed to treat metastases of sarcomatous histology, limited numbers of retrospective studies report beneficial effects of PM or increased patient survival rates. Although others have reported 5-year survival rates of 15–52% in patients selected to received PM and have also identified several prognostic factors, including the use of complete resection of the pulmonary metastases, the length of the DFI prior to PM (pre-DFI), the number of nodules, tumour diameter and the use of redo surgery, controversies remain among these reports [3–5, 7–12]. A report from Massachusetts General Hospital (MGH), which is one of the most recent retrospective studies and included 97 patients, showed that resectability, laterality, the length of the DFI, the number of metastases and the use of redo surgery were important factors in determining whether patients were selected to receive PM [13]. This report documented a 50.1% overall survival rate in carefully selected patients and also commented on the presence of selection bias.

In the present study, we reported that having a small number of nodules, especially fewer than three, and undergoing complete resection, were found to be favourable prognostic factors associated with overall survival in PM patients. Concerning the number of metastatic nodules, some reports have supported our results [3, 11, 14], while others have demonstrated that fewer than two or five nodules predict favourable outcomes [13, 15]. Our cohort included 15 patients who underwent resection of three or more metastatic nodules and who had 5-year survival rates as low as 15.6%. The majority of these patients had short pre-DFI and post-DFI of <12 months, and all of these patients experienced relapse. After conducting statistical analyses and detailed case investigations, we conclude that whether PM is performed should be carefully decided in patients in whom three or more nodules are diagnosed prior to surgery.

Table 2: Univariate analyses of the factors associated with overall survival after PM

Variables	Survival (month)	3-year survival (%)	5-year survival (%)	*P*-value
Gender				
Male	33.3	63.6	50.3	0.99
Female	22.8	70.7	53.0	
Age				
<40	36.4	70.7	50.0	0.94
≥40	35.5	62.5	51.6	
Histology				
Osteosarcoma	38.0	65.2	50.3	0.62
Non-osteosarcoma	32.0	64.7	49.9	
Primary site				
Extremities	41.9	63.1	52.6	0.84
Trunk	13.9	75.7	28.4	
Laterality				
Unilateral	36.4	70.1	53.2	0.28
Bilateral	19.2	38.1	38.1	
Number of nodules				
<2	38.3	78.6	63.1	<0.001
≥3	10.5	31.2	15.6	
PM procedure				
Limited resection	36.4	69.1	51.7	0.45
Lobectomy or more	32.2	40.0	40.0	
Complete resection				
Yes	27.6	70.0	54.2	<0.001
No	6.2	0.0	0.0	
Pre-DFI				
<12 months	17.2	35.8	30.5	0.003
≥12 months	38.3	85.1	65.1	
Redo PM				
Yes	38.3	77.0	53.8	0.34
No	19.2	59.7	49.6	

DFI: disease-free interval; PM: pulmonary metastasectomy.

Table 3: A multivariate analysis of the factors associated with overall survival rates after the first PM

Variables	Hazard ratio	95% CI	*P*-value
Number of nodules	1.16	1.10–2.503	0.016
Pre-DFI	0.997	0.98–1.015	0.759
Complete resection (yes/no)	0.15	0.035–0.596	0.007

DFI: disease-free interval; CI: confident interval.

The completeness of resection is another independent prognostic factor that has been identified by previous reports. Suzuki *et al.* [12] reported that the 5-year survival rate in patients who underwent incomplete resection was 8.3%, and no patients survived 5 years in the report published by Kim *et al.* [13] from MGH. There were no 3-year survivors in our four cases of incomplete resection. Because resectability is a factor confirmed by surgical or postoperative pathological findings, it may not be useful for surgeons to utilize resectability as a prognostic factor to predict a patient's survival preoperatively. However, since an accurate preoperative diagnosis of resectability is not given in some cases even with current diagnostic modalities, our results promote the use of PM in patients with potentially resectable disease.

Several reports have demonstrated the DFI interval between the treatment of the primary tumour and the first PM to be one of the factors predicting a patient's survival outcome [4, 13]. Kim *et al.* [13] have suggested that a DFI exceeding 12 months is an independent prognostic factor. On the other hand, Smith *et al.* and Garcia *et al.* have reported DFI of >25 months in patients with soft tissue sarcomas and >20 months in patients with bone sarcomas, respectively [4, 16]. In the present study, although the survival of patients with pre-DFI of >12 months, who consisted of half of our population, was favourable, this factor did not reach a level of statistical significance due to a lack of power. A larger series study may prove this factor to be significant. Unfortunately, the cut-off values for the pre-DFI interval used to determine whether or not PM should be performed still remain controversial.

Currently, redo surgery is also considered to be an important treatment for achieving longer survival times for PM patients. Several studies have suggested that re-recurrent patients who undergo redo PM have a survival advantage compared with those who undergo single PM [13, 17, 18]. Furthermore, Blackmon *et al.* [19] have demonstrated that survival rates improve in accordance with the frequency with which PM is performed. According to those reports, it is possible that cases of redo surgery include patients with longer DFI, who might have less-aggressive tumours. Although our analysis did not demonstrate a statistically significant impact of redo surgery on the survival of PM patients, five patients who underwent redo surgery survived >22 months despite having unfavourable factors.

Our data showed that undergoing complete resection and having fewer than three metastatic nodules were both independent favourable predictors of overall survival. Although our study included some limitations of patient selection bias and a small series, our results suggest that whether PM is performed in patients with three or more pulmonary nodules should be carefully considered and strong efforts for complete resection should be made. Even if patients who undergo PM to treat osteogenic and soft tissue sarcomas experience relapse in the lungs, aggressively performing redo PM in selected patients may also improve survival.

Conflict of interest: none declared.

REFERENCES

[1] Belal A, Salah E, Hajjar W, El-Foudeh M, Memon M, Ezzat A *et al.* Pulmonary metastatectomy for soft tissue sarcomas: is it valuable? J Cardiovasc Surg (Torino) 2001;42:835–40.
[2] Saltzman DA, Snyder CL, Ferrell KL, Thompson RC, Leonard AS. Aggressive metastasectomy for pulmonic sarcomatous metastases: a follow-up study. Am J Surg 1993;166:543–7.
[3] Predina JD, Puc MM, Bergey MR, Sonnad SS, Kucharczuk JC, Staddon A *et al.* Improved survival after pulmonary metastasectomy for soft tissue sarcoma. J Thorac Oncol 2011;6:913–9.
[4] Smith R, Pak Y, Kraybill W, Kane JM III. Factors associated with actual long-term survival following soft tissue sarcoma pulmonary metastasectomy. Eur J Surg Oncol 2009;35:356–61.
[5] Weiser MR, Downey RJ, Leung DH, Brennan MF. Repeat resection of pulmonary metastases in patients with soft-tissue sarcoma. J Am Coll Surg 2000;191:184–90.
[6] Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P *et al.* Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. J Thorac Cardiovasc Surg 1997;113:37–49.
[7] Gossot D, Radu C, Girard P, Le Cesne A, Bonvalot S, Boudaya MS *et al.* Resection of pulmonary metastases from sarcoma: can some patients benefit from a less invasive approach? Ann Thorac Surg 2009;87:238–43.
[8] Kimura H, Suzuki M, Ando S, Iida T, Iwata T, Tatesaki S *et al.* Pulmonary metastasectomy for osteosarcomas and soft tissue sarcomas. Gan To Kagaku Ryoho 2004;31:1319–23 (in Japanese).
[9] Rehders A, Hosch SB, Scheunemann P, Stoecklein NH, Knoefel WT, Peiper M. Benefit of surgical treatment of lung metastasis in soft tissue sarcoma. Arch Surg 2007;142:70–5.
[10] Suemitsu R, Yoshino I, Tomiyasu M, Ondo K, Ueda H, Iwamoto Y *et al.* Outcome of a pulmonary metastasectomy for an orthopedic malignancy. Jpn J Thorac Cardiovasc Surg 2005;53:420–5.
[11] Suri RM, Deschamps C, Cassivi SD, Nichols FC III, Allen MS, Schleck CD *et al.* Pulmonary resection for metastatic malignant fibrous histiocytoma: an analysis of prognostic factors. Ann Thorac Surg 2005;80:1847–52.
[12] Suzuki M, Iwata T, Ando S, Iida T, Nakajima T, Ishii T *et al.* Predictors of long-term survival with pulmonary metastasectomy for osteosarcomas and soft tissue sarcomas. J Cardiovasc Surg (Torino) 2006;47:603–8.
[13] Kim S, Ott HC, Wright CD, Wain JC, Morse C, Gaissert HA *et al.* Pulmonary resection of metastatic sarcoma: prognostic factors associated with improved outcomes. Ann Thorac Surg 2011;92:1780–6.
[14] Tronc F, Conter C, Marec-Berard P, Bossard N, Remontet L, Orsini A *et al.* Prognostic factors and long-term results of pulmonary metastasectomy for pediatric histologies. Eur J Cardiothorac Surg 2008;34:1240–6.
[15] Chen F, Miyahara R, Bando T, Okubo K, Watanabe K, Nakayama T *et al.* Prognostic factors of pulmonary metastasectomy for osteosarcomas of the extremities. Eur J Cardiothorac Surg 2008;34:1235–9.
[16] Garcia Franco CE, Torre W, Tamura A, Guillen-Grima F, San-Julian M, Martin-Algarra S *et al.* Long-term results after resection for bone sarcoma pulmonary metastases. Eur J Cardiothorac Surg 2010;37:1205–8.
[17] Burt BM, Ocejo S, Mery CM, Dasilva M, Bueno R, Sugarbaker DJ *et al.* Repeated and aggressive pulmonary resections for leiomyosarcoma metastases extends survival. Ann Thorac Surg 2011;92:1202–7.
[18] Chen F, Fujinaga T, Sato K, Sonobe M, Shoji T, Sakai H *et al.* Significance of tumor recurrence before pulmonary metastasis in pulmonary metastasectomy for soft tissue sarcoma. Eur J Surg Oncol 2009;35:660–5.
[19] Blackmon SH, Shah N, Roth JA, Correa AM, Vaporciyan AA, Rice DC *et al.* Resection of pulmonary and extrapulmonary sarcomatous metastases is associated with long-term survival. Ann Thorac Surg 2009;88:877–84; discussion 84–5.

THORACIC ONCOLOGIC

European Journal of Cardio-Thoracic Surgery 43 (2013) 799–800
doi:10.1093/ejcts/ezs448

EDITORIAL COMMENT

Forty years on: pulmonary metastasectomy for sarcoma

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Keywords: Pulmonary metastases • Pulmonary metastasectomy • Osteosarcoma • Soft-tissue sarcoma

We searched the literature for evidence concerning pulmonary metastasectomy for sarcoma. A systematic review includes data on 1357 patients from 18 surgical follow-up studies [1]. The report from Nagoya University in this issue [2] is characteristic of the genre: a 15-year experience is described of a mixed series of 52 consecutive patients with bone or soft-tissue sarcoma. The majority (28 of 52) had a solitary metastasis, and most of the rest had two or three metastases (17 of 52). Overall survival was 51% five years after the first pulmonary metastasectomy.

From the 1970s, rather than being an occasional individualized decision, as it was for other cancers, pulmonary metastasectomy has become an established practice in the care of

European Journal of Cardio-Thoracic Surgery 43 (2013) e92
doi:10.1093/ejcts/ezs627 Advance Access publication 12 December 2012

IMAGES IN CARDIO-THORACIC SURGERY

Solitary fibrous tumour of the mediastinal pleura: the origin detected with three-dimensional computed tomography angiography

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Received 28 August 2012; received in revised form 15 October 2012; accepted 2 November 2012

Keywords: Solitary fibrous tumour of the mediastinal pleura • 3D-CT angiography

We present an intrathoracic mass suspected of originating in the mediastinum on three-dimensional computed tomography (3D-CT) angiography. Although the origin was not determined on CT (Fig. 1), 3D-CT angiography clearly demonstrated the feeding artery (Fig. 2). The vessel was easily identified during operation, and the tumour was diagnosed as a solitary fibrous tumour.

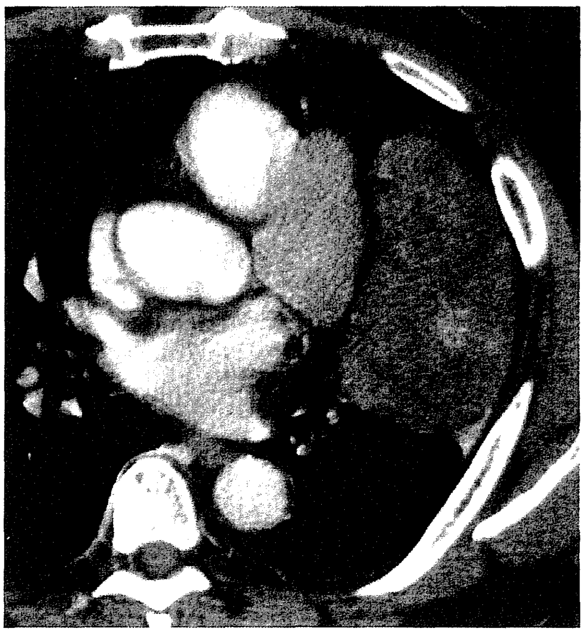

Figure 1: Contrast-enhanced computed tomography demonstrated a well-circumscribed, smooth and inhomogeneous mass in the left thorax.

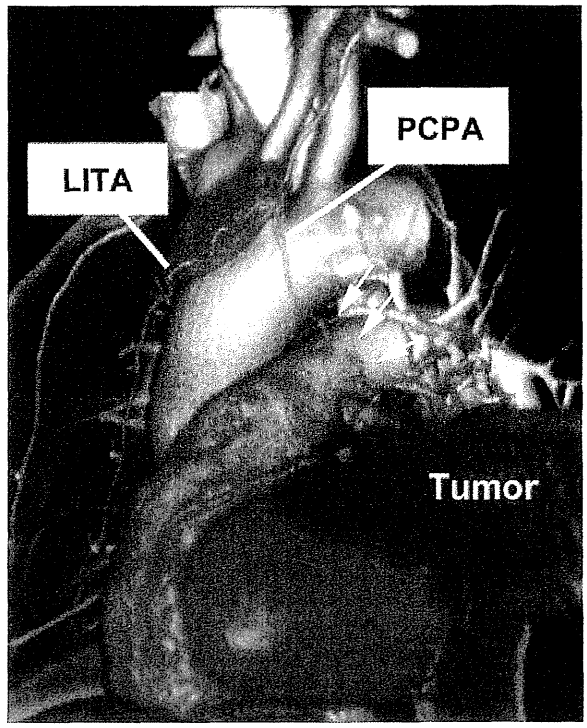

Figure 2: Three-dimensional computed tomography angiography showed that the blood supply to the lesion was continuing from a pericardiacophrenic artery (PCPA), which was a branch of the left internal thoracic artery (LITA), not from the lung or the chest wall.

Lung Cancer 81 (2013) 410–415

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Planning of segmentectomy using three-dimensional computed tomography angiography with a virtual safety margin: Technique and initial experience

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ARTICLE INFO

Article history:
Received 30 December 2012
Received in revised form 12 April 2013
Accepted 3 June 2013

Keywords:
Segmentectomy
Three-dimensional computed tomography (3DCT)
Non-small cell lung carcinoma
Safety margins
Resection planning

ABSTRACT

Objectives: In preoperative segmentectomy simulation for primary lung cancer, it is important to identify the intersegmental pulmonary veins and the relationship between them and the surgical safety margin. We have adopted a method that incorporates a virtual safety margin into three-dimensional computed tomography angiography images in order to plan adequate segmentectomy for lung cancer patients. In this study, we describe the new preoperative planning technique and review cases in which we performed segmentectomy based on its results.
Methods: We reviewed clinical, radiological, and pathological records and selected patients who underwent segmentectomy for a primary lung cancer lesion with a diameter of 2 cm or less. These segmentectomies were planned using preoperative three-dimensional computed tomography angiography with a virtual safety margin.
Results: A total of 17 primary lung cancers in 16 patients (11 male and 5 female, aged 52–82 years) were removed by segmentectomy, planned using the new technique. In 6 of 17 tumors (35%) were non-solid type adenocarcinomas, 3 tumors (18%) were partly solid type adenocarcinomas, 6 tumors (35%) were solid type adenocarcinomas and 2 tumors (12%) were squamous cell carcinomas. Pathological examination revealed no positive surgical margins and no lymph node metastases in any patients.
Conclusions: Three-dimensional computed tomography angiography with a virtual safety margin was able to non-invasively visualize the three-dimensional distances and the relationships between the primary tumor and intersegmental pulmonary veins. It was able to aid in the preoperative planning of a suitable segmentectomy procedure for patients with a primary lung cancer lesion of 2 cm or less in diameter.

1. Introduction

Patients with lung cancer often have cardiopulmonary complications such as chronic obstructive pulmonary disease (COPD), interstitial pneumonia, and ischemic heart disease. Segmentectomy preserves pulmonary function to a greater degree than lobectomy; its use for lung cancer has therefore been increasing for both non-solid and solid tumors [1–3]. In preoperative segmentectomy simulation, it is important to identify the intersegmental pulmonary veins, i.e., those that divide the pulmonary segments [4–6]; the branching patterns of the pulmonary arteries and veins exhibit a great deal of variety from patient to patient [7]. The efficacy of three-dimensional computed tomography angiography (3D-CTA) for the preoperative assessment of both the pulmonary arteries and pulmonary veins has been reported, although it is difficult for 3D-CTA alone to recognize the relationship between the intersegmental veins and the surgical safety margin, currently defined as 2 cm from the primary tumor [4–6,8,9]. We have therefore adopted a method for lung cancer patients that merges a virtual safety margin with 3D-CTA images. We previously reported on 2 patients who underwent segmentectomy, based on this technique, for primary lung cancer [10].

In the present study, we describe the new preoperative planning technique. In addition, we performed a retrospective review of patients who underwent segmentectomy using 3D-CTA with a virtual safety margin to examine the reliability of using this technique to plan for segmentectomy.

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http://dx.doi.org/10.1016/j.lungcan.2013.06.001

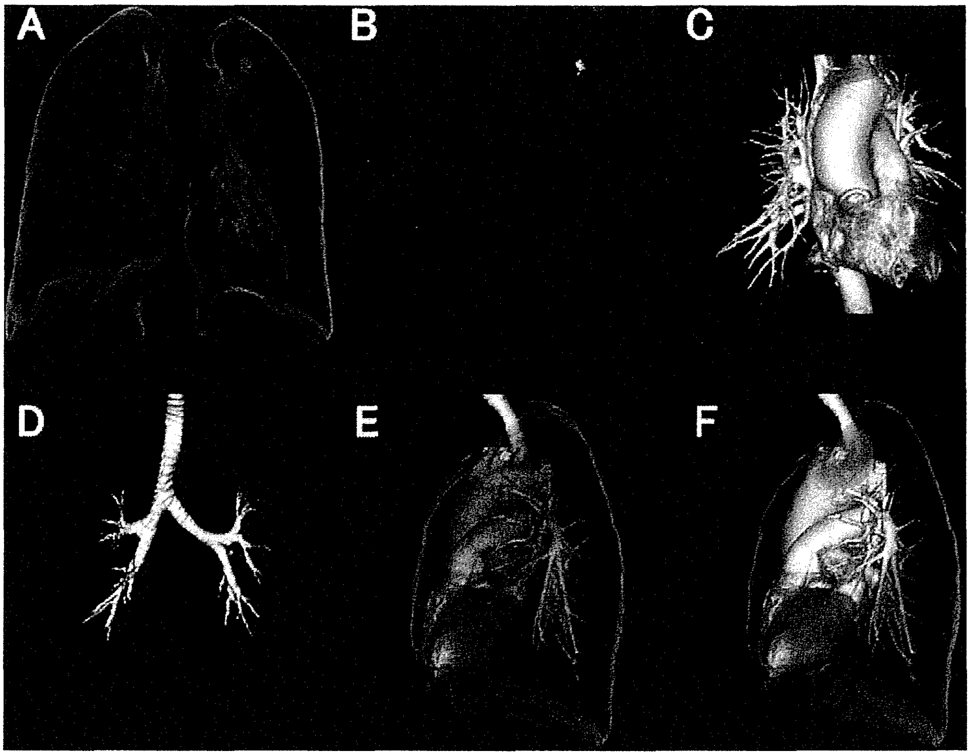

Fig. 1. Construction of three-dimensional computed tomography angiography (3D-CTA) with a virtual safety margin. The lung (A), the primary tumor in the left upper lobe (B), the pulmonary vessels (C), and the trachea and bronchi (D) are separately segmented and color coded by CT value (Hounsfield units). (E) All organs and the primary tumor are merged into the 3D-CTA image. (F) The left upper lobe with the primary tumor is removed from the image to improve visualization of the lobular distribution of bronchi and vessels. Finally, the virtual 3D safety margin (blue sphere) is merged with the 3D-CTA image. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

2. Patients and methods

2.1. Patients

This retrospective study was approved by the institutional review board of our institution with a waiver for informed consent. Since 2011, all preoperative 3D-CTA with a virtual safety margin for segmentectomy at our institution have been determined by a chest radiologist (S.I.) with 18 years of experience reading thoracic CTs. We searched clinical, radiological, and pathological records and selected patients for inclusion who underwent segmentectomy between April 2011 and July 2012 for a primary lung cancer lesion, 2.0 cm or less in diameter. Any lymph node and distant metastases were not detected by preoperative enhanced CT, FDG-PET, and intraoperative lymph node sampling. We reviewed the patients' age, sex, tumor size (maximal diameter), internal opacity on thin-section CT, histological type, and pathological stage based on the Union for International Cancer Control 7 (UICC-7) staging guidelines. Internal opacity was classified into 3 types: solid, partly solid, and non-solid. The solid type was defined as a tumor containing no ground-glass opacity on thin-section CT, the partly solid type was defined as a tumor with a ratio of maximum consolidation diameter to maximum tumor diameter of ≥25%, and the non-solid type was defined as having a ratio of <25% [1].

2.2. Computed tomography

3D-CTA data were obtained using a 64-channel multi-detector row CT (Aquilion 64, Toshiba Medical Systems Corp., Tokyo, Japan). Patients were scanned in the craniocaudal direction with inspiratory apnea. The scanning parameters were set to a voltage of 120 kV with auto-milliamperage (maximum, 450 mA). The gantry rotation time was 0.5 s. The slice thickness and reconstruction interval were 1 mm and 0.8 mm, respectively, using a standard algorithm. Vascular access was obtained using a 20-G needle in the cubital vein. For vessel enhancement, 96 mL of a non-ionic contrast medium (Optiray 320: 320 mg I/mL ioversol, Tyco Healthcare Japan, Inc., Tokyo, Japan; or Iopamiro 370: 370 mg I/mL iopamidol, Bayer HealthCare, Tokyo, Japan) was used at a flow rate of 3.0 mL/s. Ioversol was used in patients with a body weight of ≤60 kg and iopamidol was used in patients with a body weight of >60 kg. The injection of the contrast medium was immediately followed by 24 mL of saline at the same flow rate, using a double-barrel power injector (Dual Shot GX, Nemoto Kyorindo Co., Ltd., Tokyo, Japan). The scan delay was evaluated by an automatic bolus tracking system with a circular region of interest (ROI) localized on the descending aorta at the level of the tracheal bifurcation. Scanning started automatically when the attenuation at the ROI reached 150 Hounsfield units (HUs).

2.3. Three-dimensional computed tomography angiography with a virtual safety margin

The thin-section CT images were transferred to a commercial 3D workstation (Ziostation, Amin, Inc., Tokyo, Japan), where the chest radiologist constructed the thoracic 3D-CTA. The lung, the primary tumor, the pulmonary vessels, and the trachea and bronchi were separately segmented and color coded by CT value, as defined by the tissue's Hounsfield units (Table 1 and Fig. 1). These volume-rendered images were then merged into the 3D-CTA. Next, the lobes containing the primary tumors were removed from the 3D lung images to improve visualization of the lobular distribution of

Table 1
Values used for 3D-CTA segmentation.

Structure	CT value (Hounsfield units)
Lung	<−400
Trachea and bronchus	<−900
Pulmonary vessels	>70
Primary tumor (solid type)	>−100
Primary tumor (non-solid type)	>−700

CT, computed tomography; 3D-CTA, three-dimensional computed tomography angiography.

bronchi and vessels. Finally, the virtual safety margin was merged with the 3D-CTA image. The safety margin was defined as a sphere, extending 2 cm outside the primary tumor; for example, the margin was 6 cm in diameter for a primary tumor of 2 cm. The center of the virtual safety margin was manually matched to the center of the tumor using the 3D workstation. The chest radiologist interpreted the relationship between the margin and the intersegmental veins and used this to recommend the minimal extent of segmentectomy for each patient. In cases where the intersegmental veins ran through the safety margin, the veins were designated for removal. It took about 1.5 h to construct 3D-CTA with a virtual safety margin and to report the recommendation per patient. The 3D images and the radiologist's report were delivered to the intra-institutional picture archiving and communication system; the surgeons had this information available at the preoperative conference and in the operating room. Each patient's procedure was planned based on the radiological report and the 3D-CTA image with a virtual safety margin; the actual operating procedure was adjusted, if necessary, based on the surgical findings. After thoracotomy, the surgeons touched the primary tumor directly and confirmed eventually the enough resection margin ≥2 cm. In addition, the actual surgical margins that were the shortest distance between the tumor and the surgical cut surface were measured on the formalin-fixed specimen.

2.4. Assessment of 3D-CTA with a virtual safety margin

We compared the planned procedure with the actual segmentectomy procedure performed in each patient. We also evaluated the postoperative pathologic findings, with particular attention to whether there was residual tumor on the specimen's surgical margin. The tumor size on preoperative CT was compared with the actual size of the pathological specimen using Pearson's correlation coefficient.

3. Results

Of 226 thoracic surgeries for primary lung cancer conducted at our institution in the study timeframe, a total of 17 tumors in 16 patients qualified for this study, as they were removed by segmentectomy planned with preoperative 3D-CTA with a virtual safety margin (Table 2). The patients comprised 11 males and 5 females, aged 52 to 82 years. One patient had 2 simultaneous cancers in the left upper and lower lobe and underwent each segmentectomy on a same operation (Cases 5 and 11). The tumor size on preoperative thin-section CT ranged from 1.0 to 2.0 cm in maximal diameter, while that of the surgical specimens ranged from 0.7 to 2.3 cm. There was a strong correlation between the CT image size and that of the surgical specimens ($r = 0.75$; $p < 0.001$). Sixteen tumors located in peripheral area within 2.5-cm of the chest wall and one tumor (Case 6) located in the intermediate area. The internal opacity was non-solid in 6 tumors, partly solid in 3 tumors, and solid in 8 tumors. The reason to plan the segmentectomy for solid type tumors were previous or simultaneous lung cancer in 5 patients (Case 10, 11, 12, 15, 17), complication of COPD in one patient (Case 16), and advanced age in one patient (Case 13). Remaining one patient (Case 14) chose for segmentectomy instead of lobectomy after fully discussing the risk and benefits with the surgeons.

In 10 of 17 tumors (59%) segmentectomy was performed without deviation from the preoperative plan. In 5 tumors (29%), segmentectomy was performed with a wider margin than the preoperative plan called for. In 4 of these 5 cases (Cases 6, 7, 9, 11), left S1 + 2 segmentectomy was planned but left upper division segmentectomy was actually performed; the upper division segmentectomy was chosen in these cases as it was surgically more facile due to a single intersegmental dissection surface than S1 + 2 segmentectomy [4]. In Case 4, left S3 + S4 segmentectomy was planned but left S3 + S4 + S5 was performed due to the small volume of residual S5 and the risk of torsion. In 2 cases (12%), a more limited segmentectomy was performed (Cases 3 and 14) because the radiologist did not take subsegmental resection into consideration when making surgical recommendations.

The actual surgical margins ranged from 1.5 to 5.0 cm (median 3.3 cm) on formalin-fixed specimen. Pathological examination revealed no residual tumor cells at the surgical margins and no lymph node metastases in any patients. The pathological stages were T1aN0M0 ($n = 14$), T2a(pl1)N0M0 ($n = 2$), and T3a(pl3)N0M0 ($n = 1$). One patient was hospitalized for 20 days after surgery because of drug-induced liver dysfunction; no other patients experienced complications.

Table 2
Patient characteristics.

Case	Sex	Age	Internal opacity	Size (cm)	Side	Planned procedure	Actual procedure	Pathology	Actual margin (cm)
1	F	68	NS	1.4	Right	S1	S1	W/D AC	3.0
2	M	70	NS	1.5	Left	S1 + 2	S1 + 2	W/D AC	1.5
3	F	71	NS	1.7	Right	S1 + S2	S1 + S2a	W/D AC	3.0
4	F	73	NS	1.8	Left	S3 + S4	S3 + S4 + S5	M/D AC	2.0
5	M	68	NS	1.9	Left	S6	S6	W/D AC	2.0
6	M	70	NS	2.0	Left	S1 + 2	S1 + 2 + S3	W/D AC	4.0
7	M	70	PS	1.2	Left	S1 + 2	S1 + 2 + S3	W/D AC	5.0
8	F	53	PS	1.5	Right	S1 + S2	S1 + S2	W/D AC	1.5
9	M	63	PS	2.0	Left	S1 + 2	S1 + 2 + S3	M/D AC	Not available
10	M	70	SOL	1.0	Right	S6	S6	M/D AC	2.5
11	M	68	SOL	1.0	Left	S1 + 2	S1 + 2 + S3	M/D AC	3.5
12	M	52	SOL	1.1	Left	S1 + 2 + S3	S1 + 2 + S3	M/D AC	4.0
13	F	82	SOL	1.2	Left	S1 + 2 + S3	S1 + 2 + S3	M/D AC	4.5
14	M	60	SOL	1.3	Right	S6 + S10	S6 + S10a	M/D AC	2.0
15	M	67	SOL	1.5	Right	S6	S6	M/D SCC	3.5
16	M	56	SOL	1.6	Left	S1 + 2 + S3	S1 + 2 + S3	M/D SCC	5.0
17	M	62	SOL	1.8	Left	S1 + 2	S1 + 2	M/D AC	3.5

M/D AC, moderately differentiated adenocarcinoma; M/D SCC, moderately differentiated squamous cell carcinoma; NS, non-solid; PS, partly solid; SOL, solid; W/D AC, well-differentiated adenocarcinoma; S2a, posterior subsegment of S2; S10a, posterior subsegment of S10.

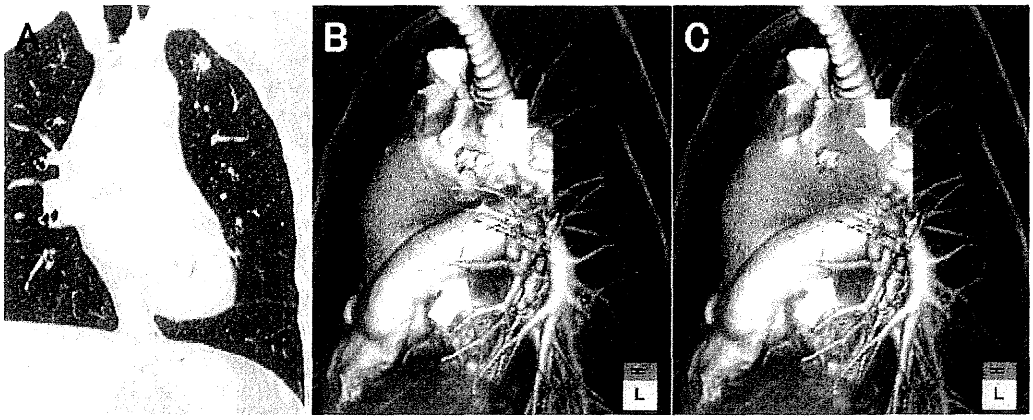

Fig. 2. An 82-year-old female. (A) A solid lung cancer in the left S1 + 2 segments is seen on coronal CT; the maximal tumor diameter is 1.2 cm. (B) 3D-CTA of the left upper lobe. The relevant intersegmental veins are V3b, between S3 and S4 (yellow arrow), and V1b, between S1 + 2 and S3 (white arrow). (C) 3D-CTA with the virtual safety margin. Because V3b is running through the margin but V1b is running within it, S1 + 2 + S3 segmentectomy is necessary. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 2 displays images for Case 13, an 82-year-old female. She had a solid lung cancer in the left S1 + 2 segments; the maximal tumor diameter was 1.2 cm. Based on 3D-CTA with a virtual safety margin and given her advanced age, we planned and performed segmentectomy of the left upper division. The pathologic findings confirmed the diagnosis of moderately differentiated adenocarcinoma, pT1aN0M0; the surgical margins were negative for tumor cells. She had no postoperative complications.

Fig. 3 displays the images for Case 1, a 68-year-old female. She had a non-solid lung cancer located in the right S1 segment with a maximal tumor diameter of 1.4 cm. Based on 3D-CTA with a virtual safety margin, we planned and performed right S1 segmentectomy. The pathologic findings confirmed the diagnosis of well-differentiated adenocarcinoma, pT1aN0M0; the surgical margins were negative. She had no postoperative complications.

Fig. 4 displays the images for Case 9, a 63-year-old male. He had a partly solid lung cancer located in the left S1 + 2 segments; the maximal tumor diameter was 2.0 cm. The radiologist suggested left S1 + 2 segmentectomy because the intersegmental vein between S1 + 2 and S3 appeared distant enough from the virtual safety margin. The surgeon eventually selected segmentectomy of the left upper division (S1 + 2 + S3). The pathologic findings confirmed the diagnosis of moderately differentiated adenocarcinoma, pT2a(pl1)N0M0; the surgical margins were negative. He had no postoperative complications.

4. Discussion

3D-CTA with a virtual safety margin is a non-invasive method of visualizing not only the branching of bronchi and pulmonary arteries and veins, but also the three-dimensional distances and relationships between the primary tumor and the intersegmental pulmonary veins. This technology could therefore be useful in preoperative planning of a suitable segmentectomy procedure in lung cancer patients. We found that thoracic surgeons were usually able to perform segmentectomy according to the preoperative plan. In the present study, no positive surgical margins were observed.

Segmentectomy could increase the risk of locoregional recurrence at the resection line, compared with lobectomy [3,11–13]; inadequate safety surgical margins and incomplete lymph node clearance are identified as the main causes for this recurrence. Because there are intersegmental veins but no pleura between segments, a sufficient surgical margin must be secured by segmentectomy. As the lung parenchyma is dissected along the intersegmental vein, this vein should not pass through the safety margin; however, during surgery on a contracted lung it can be

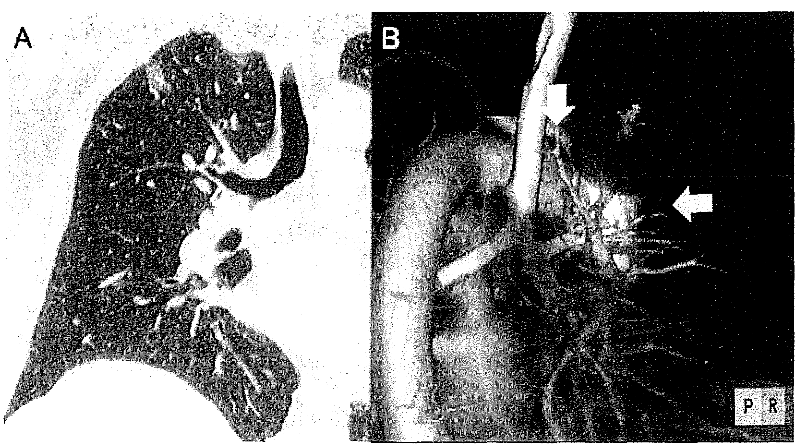

Fig. 3. A 68-year-old female. (A) A non-solid lung cancer in the right S1 segment is seen on coronal CT; the maximal tumor diameter is 1.4 cm. (B) 3D-CTA with the virtual safety margin. The relevant intersegmental veins are V1b, between S1 and S3 (yellow arrow), and V2a, between S1 and S2 (white arrow). Because both intersegmental veins are running outside of the virtual safety margin, S1 segmentectomy is able to be performed. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

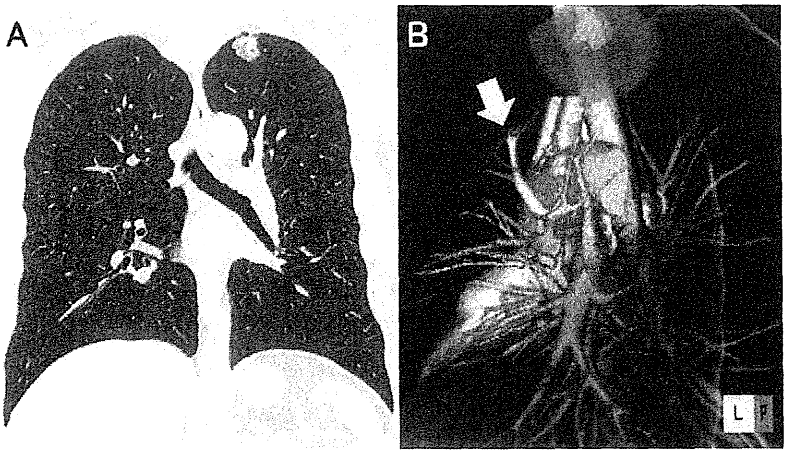

Fig. 4. A 63-year-old male. (A) A partly solid lung cancer in the left S1 + 2 segments is seen on coronal CT; the maximal tumor diameter is 2.0 cm. (B) 3D-CTA with the virtual safety margin. The relevant intersegmental vein is V3b, between S1 + 2 and S3 (yellow arrow). Because the intersegmental vein is running outside of the virtual safety margin, S1 + 2 segmentectomy is able to be performed. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

difficult for surgeons to recognize the relationship between the safety margin and the intersegmental veins. Preoperative planning to decide on a minimal resection extent is therefore important in segmentectomy.

We adopted a distance of 2 cm from the tumor surface as our virtual surgical margin [10]. Safety margins of 2 cm or larger are usually adequate to prevent local recurrence when the tumor is smaller than 2 cm [8,9]. In our study, 14 tumors could keep the actual surgical margins of at least 2 cm. Although the margins of 2 tumors were 1.5 cm, the reason may be that the distance was measured on the deflated and fixed specimens. Furthermore, no residual tumor cells were seen at the surgical margins for any type of tumor, whether solid, non-solid, or partly solid. Small tumors with a diameter of $\leq$2 cm and non-solid tumors are radiologically determined to be non-invasive cancer [1,8]. Partly solid and solid tumors are supposed to have invasive potential, even if they are small in size; adequate surgical safety margins for these invasive small tumors are controversial. Based on our limited results, a virtual surgical margin of 2 cm from the tumor surface may be adequate for not only non-solid tumors, but also partly solid and solid lung cancers that measure $\leq$2 cm in maximum diameter on thin-section CT. Further case evaluations are needed to verify this observation.

Seven patients in this study underwent an actual segmentectomy procedure different from the preoperative procedure planned using the virtual 3D safety margin. In 4 cases, the left S1 + 2 segmentectomy suggested by the radiologist was modified to a left upper division segmentectomy. Because the left upper division segmentectomy is typical procedure of segmetectomy, it has been performed more than S1 + 2 segmentectomy in our institution even if the safety margin is sufficient (Fig. 4). Although the virtual safety margin indicates the minimal extent of resection, the actual procedure should be determined by the surgeon in real time, as many other factors can affect the surgery.

Obtaining a virtual safety margin is simple and non-invasive; the primary tumor and the spherical safety margin are superimposed on a 3D-CTA image. At most of the hospital, the contrast enhanced CT is scanned routinely to evaluate hilar and mediastinal lymph node enlargement in lung cancer patients. We think that most 3D workstations are able to create this margin because it requires only basic workstation functions. In the present study, a chest radiologist constructed the 3D-CTA and manually merged it with a virtual safety margin. This was time-consuming work, but in the near future computers may be able to automatically construct a virtual safety margin when 3D-CTA is performed.

This retrospective study is limited by being an initial report; we were not able to examine the long-term outcomes or prognoses of these segmentectomy patients. Long-term follow up is essential to determine whether 2 cm is an adequate virtual surgical margin [14]. It is also necessary to investigate the usefulness of this method in patients with tumors >2 cm in diameter.

In conclusion, 3D-CTA with a virtual safety margin is able to non-invasively visualize three-dimensional distances and relationships between primary tumors and intersegmental pulmonary veins. It aids in the preoperative planning of suitable segmentectomy procedures for patients with primary lung cancer, when the tumor is 2 cm or less in diameter.

Funding

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas from the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Conflict of interest

None of the authors have any conflicts of interest associated with this study.

References

[1] Nakamura K, Saji H, Nakajima R, Okada M, Asamura H, Shibata T, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol 2010;40:271–4.

[2] Keenan RJ, Landreneau RJ, Maley Jr RH, Singh D, Macherey R, Bartley S, et al. Segmental resection spares pulmonary function in patients with stage I lung cancer. Ann Thorac Surg 2004;78:228–33.

[3] Nomori H, Mori T, Ikeda K, Yoshimoto K, Iyama K, Suzuki M. Segmentectomy for selected cT1N0M0 non-small cell lung cancer: a prospective study at a single institute. J Thorac Cardiovasc Surg 2012;144:87–93.

[4] Oizumi H, Kanauchi N, Kato H, Endoh M, Suzuki J, Fukaya K, et al. Anatomic thoracoscopic pulmonary segmentectomy under 3-dimensional multidetector computed tomography simulation: a report of 52 consecutive cases. J Thorac Cardiovasc Surg 2011;141:678–82.

[5] Oizumi H, Endoh M, Takeda S, Suzuki J, Fukaya K, Sadahiro M. Anatomical lung segmentectomy simulated by computed tomographic angiography. Ann Thorac Surg 2010;90:1382–3.

[6] Shimizu K, Nakano T, Kamiyoshihara M, Takeyoshi I. Segmentectomy guided by three-dimensional computed tomography angiography and bronchography. Interact Cardiovasc Thorac Surg 2012;15:194–6.

[7] Yamashita H. Variations in the pulmonary segments and the bronchovascular trees. In: Yamashita H, editor. Roentgenologic anatomy of the lung. Tokyo: Igaku-shoin; 1978. p. 70–107.

[8] Suzuki K, Koike T, Asakawa T, Kusumoto M, Asamura H, Nagai K, et al. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). J Thorac Oncol 2011;6:751–6.
[9] Swanson SJ. Segmentectomy for lung cancer. Semin Thorac Cardiovasc Surg 2010;22:244–9.
[10] Iwano S, Usami N, Yokoi K, Naganawa S. Segmentectomy simulation using a virtual three-dimensional safety margin. Ann Thorac Surg 2012;93:e37–9.
[11] El Sherif A, Gooding WE, Santos R, Pettiford B, Ferson PF, Fernando HC, et al. Outcomes of sublobar resection versus lobectomy for stage I non-small cell lung cancer: a 13-year analysis. Ann Thorac Surg 2006;82:408–15.
[12] Sienel W, Stremmel C, Kirschbaum A, Hinterberger L, Stoelben E, Hasse J, et al. Frequency of local recurrence following segmentectomy of stage IA non-small cell lung cancer is influenced by segment localisation and width of resection margins—implications for patient selection for segmentectomy. Eur J Cardiothorac Surg 2007;31:522–7.
[13] Miller DL, Rowland CM, Deschamps C, Allen MS, Trastek VF, Pairolero PC. Surgical treatment of non-small cell lung cancer 1 cm or less in diameter. Ann Thorac Surg 2002;73:1545–50.
[14] Nakao M, Yoshida J, Goto K, Ishii G, Kawase A, Aokage K, et al. Long-term outcomes of 50 cases of limited-resection trial for pulmonary ground-glass opacity nodules. J Thorac Oncol 2012;7:1563–6.

Role of lymphatic invasion in the prognosis of patients with clinical node-negative and pathologic node-positive lung adenocarcinoma

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Objective: Some patients with clinical T1 N0 M0 lung adenocarcinoma have pathologic lymph node metastasis. However, neither the precise prognosis nor the factors predictive of the prognosis of such patients have yet been identified.

Methods: Our study included 609 patients with clinical T1 N0 M0 lung adenocarcinoma; 568 (93.3%) pathologic node negative [pN(–)] and 41 (6.7%) pathologic node positive [pN(+)] patients, diagnosed after complete surgical resection. The association between prognosis and pathologic findings was analyzed retrospectively.

Results: pN(+) patients had a significantly lower lepidic growth component ratio (10% vs 50%), a higher lymphatic invasion (LI) rate (68% vs 11%), vessel invasion rate (59% vs 14%), and visceral pleural invasion rate (29% vs 9%), compared with pN(–) patients (all *P*s < .001). Surprisingly, 13 of 41 (32%) pN(+) patients showed no LI. In pN(–) patients, a multivariate analysis of recurrence-free survival revealed that lower lepidic growth component ratio, and lymphatic, vessel, and pleural invasion were significantly correlated with a poor prognosis (P = .008, .045, .031, and .024). However, in pN(+) patients, the multivariate analysis of recurrence-free survival showed that only LI was a significant independent prognostic factor (P = .037). The 5-year recurrence-free survival rates were as follows: 91.2% for pN(–)/LI(–) patients, 68.2% for pN(–)/LI(+) patients, 63.5% for pN(+)/LI(–) patients, and 41.9% for pN(+)/LI(+) patients. LI status stratified the prognosis not only in patients with no nodal metastasis but also in those with metastasis.

Conclusions: LI, which is not always present in node-positive adenocarcinoma, is an important prognostic variable in patients with node involvement. (J Thorac Cardiovasc Surg 2014;147:1820-6)

Fluorescence deoxyglucose (FDG) positron emission tomography (PET) is commonly used for preoperative assessment of primary tumors, lymph nodes, and distant metastasis to determine staging and treatment strategy,[1-3] thereby improving the accuracy of the definition of clinical stage IA compared with only computed tomography assessment.[1] This has changed the population of patients with clinical stage IA lung adenocarcinoma.[1,4-7] However, some clinical lymph node-negative [cN(–)] patients show positive pathologic lymph node [pN(+)] metastasis. It is speculated that a cN(–) but pN(+) status indicates an initial lymph node metastatic condition, because the accumulation of FDG in the lymph node could be significantly higher in patients with massive lymph node metastasis. Therefore, cN(–)/pN(+) patients may have a better prognosis than cN(+)/pN(+) patients, or a similar prognosis to cN(–)/pN(–) patients. In addition, no studies have identified the prognostic factors in cN(–)/pN(+) patients.

In our study, we evaluated the clinicopathologic findings and prognosis of patients with clinical T1 N0 M0 lung adenocarcinoma according to lymph node status, or other pathologic status. First, we examined the pathologic findings to identify predictive factors for recurrence-free survival (RFS) among patients with clinical stage IA lung adenocarcinoma. Multivariate analysis revealed that lymphatic invasion (LI) status was a predictive factor, both in patients with and without node involvement. Next, we assessed the prognosis of patients with and without lymph node involvement according to LI status. The results highlight the importance of the LI status in patients with clinical T1 N0 M0 lung adenocarcinoma.

MATERIALS AND METHODS

Patient Population

Our study included 611 patients who underwent complete surgical resection of clinical stage IA lung adenocarcinoma at the Hiroshima University

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Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication Aug 5, 2013; revisions received Oct 22, 2013; accepted for publication Nov 22, 2013; available ahead of print Feb 7, 2014.

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0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2013.11.050

Abbreviations and Acronyms

CT = computed tomography
FDG = fluorescence deoxyglucose
GGO = ground glass opacity
HU = Haunsfield unit
LC = lepidic component
LI = lymphatic invasion
OS = overall survival
PET = positron emission tomography
RFS = recurrence-free survival
SUV = standardized uptake value

Hospital (Hiroshima, Japan), the Kanagawa Cancer Centre (Yokohama, Japan), the Cancer Institute Hospital (Tokyo, Japan), and the Hyogo Cancer Centre (Akashi, Japan) between April 2007 and December 2010. Approval was given by the institutional review boards of the participating institutions, all of which waived the requirement for informed consent from individual patients for this retrospective review of the prospective database. Two patients were excluded because they lacked a lepidic component (LC) ratio. The data from the remaining 609 patients were analyzed retrospectively. High-resolution computed tomography (CT) and FDG-PET/CT, followed by a curative R0 resection were performed for all patients staged according to the TNM Classification of Malignant Tumours.[8] Endobronchial ultrasonography or mediastinoscopy was not performed routinely because all patients underwent preoperative high-resolution CT and FDG-PET/CT; the high-resolution CT results showed no swelling of mediastinal or hilar lymph nodes and FDG-PET revealed no accumulation of FDG in those lymph nodes. Lymph node swelling was defined when the diameter of a minor axis is larger than 10 mm. Sublobar resection was performed in cases of complete removal of the disease with appropriate surgical margins for a peripheral T1a N0 M0 tumor. Wedge resection without lymph node assessment was performed for ground glass opacity (GGO) tumors on high-resolution CT, which was regarded as a node-negative and noninvasive tumor in a prospective study.[9] Segmentectomy with hilar and mediastinal lymph node dissection were performed for a GGO-mixed tumor. If lymph node involvement was detected on an intraoperative frozen section of any lymph node, the procedure was converted to a standard lobectomy. All other patients underwent a standard lobectomy. The inclusion criteria included preoperative staging determined by high-resolution CT and FDG-PET/CT, curative surgery without any induction therapy, and a definitive histopathologic diagnosis of lung adenocarcinoma. Patients with incompletely resected tumors (R1 or R2), and those with multiple tumors or previous lung surgery, were excluded from the data set.

Pathology Studies

Sections were fixed with 10% formalin and embedded in paraffin. Consecutive 4-μm sections were cut and 1 slice per 5 mm was examined under a microscope for the pathologic assessment. Histologic diagnosis and staging was based on the latest edition of the World Health Organization classification scheme.[10] The histologic type of adenocarcinoma and the presence of lymphatic involvement were determined using hematoxylin-eosin stained tissue. If the findings could not be determined by hematoxylin-eosin staining alone, immunohistochemical staining was carried out as necessary. An LC ratio was defined as the proportion of LC area relative to the entire tumor. LI and blood vessel invasion were assessed by immunohistochemistry for D2-40, which stains lymphatic ducts, and Van Gieson staining of the elastic fiber of the vessels. LI and blood vessel invasion were determined when spreading through or penetration was detected as an extension of a malignant neoplasm. To evaluate pleural invasion, elastic tissue fibers were subjected to Van Gieson staining. Pleural invasion was determined if cancer cells had invaded beyond the elastic layer, including invasion into the visceral pleural surface, or neighboring organs. Histologic examinations were determined by pathologists from each institution for the purposes of this study.

HRCT

A 16-row multidetector CT was used to obtain chest images. For high-resolution images of the tumors, the following parameters were used: 120 kVp, 200 mA, 1 to 2 mm section thickness, 512 $\times$ 512 pixel resolution, 0.5 to 1.0 second scanning time, a high spatial reconstruction algorithm with a 20 cm field of view, and mediastinal (level, 40 Haunsfield unit [HU]; width, 400 HU) and lung (level, −600 HU; width, 1600 HU) window settings. GGO was defined as a misty increase in lung attenuation that did not obscure underlying vascular markings. CT scans were reviewed and tumor sizes determined by radiologists from each institution.

FDG-PET/CT

Patients were instructed to fast for at least 4 hours before intravenous injection of 74 to 370 MBq FDG and then to relax for at least 1 hour before the FDG-PET/CT scan. For imaging, Biograph Sensation 16 (Siemens Healthcare, Erlangen, Germany), Aquiduo (Toshiba Medical Systems Corporation, Tochigi, Japan), or Discovery ST (GE Healthcare, Little Chalfont, United Kingdom) integrated 3-dimensional PET/CT scanners were used. Low-dose nonenhanced CT images of 2 to 4 mm section thickness were taken from the head to the pelvis of each patient. An anthropomorphic body phantom (NEMA NU2-2001; Data Spectrum Corp, Hillsborough, NC) was used to minimize variations in standardized uptake values (SUVs) among the institutions.[11,12] The original SUV_{max} values were determined by radiologists from each institution for the purposes of this study. On FDG-PET/CT images, all lymph nodes in the thorax with FDG uptake no greater than the normal background activity of the mediastinal blood pool—the SUV_{max} of which was <1.5, regardless of size—were considered cN0. A lymph node where the SUV_{max} was ≥ 1.5 or more was considered "suspicious for malignancy." However, even lymph nodes with high FDG uptake, when they showed higher attenuation than mediastinal structures (great vessels) or benign calcification (central, nodular, diffuse, or popcorn-like), were also considered benign.[13]

Follow-up Evaluation

All patients who underwent lung resections were followed-up from the day after surgery. Postoperative follow-up procedures, including a physical examination and chest radiograph every 3 months and chest and abdominal CT examinations every 6 months, were performed for the first 2 years. Thereafter, a physical examination and chest radiograph were performed every 6 months, and a chest CT examination was performed annually.

Statistical Analyses

Patients with clinical stage IA lung adenocarcinoma were included in the analysis. A Mann-Whitney *U* test was used to compare continuous variables and the χ^2 test or Fisher exact test was used for categorical variables. RFS was defined as the length of time after primary surgical treatment for a cancer ends that the patient survived without any sign or symptom of the cancer. Recurrence was defined as patients having symptoms caused by recurring cancer and suspicious lesions that were diagnosed as recurrent tumors by biopsies. If suspicious lesions were not diagnosed as recurrence, by biopsy, the "recurrence" was comprehensively and clinically defined by radiographic findings, including CT and FDG-PET/CT. RFS and overall survival (OS) curves were calculated using the Kaplan-Meier method. Univariate survival analysis was performed using the log-rank test for comparisons of curves. A Cox regression model was used to calculate *P* values and hazard ratios in the univariate and multivariate analyses. The prognostic analysis was performed during August 2012. All statistical analyses were

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performed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan),[14] which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria). More precisely, it is a modified version of R Commander (version 1.6-3), which includes statistical functions frequently used in biostatistics.

RESULTS

Clinical Outcomes in Patients With Lung Adenocarcinoma

The median follow-up time was 41.6 months. Lobectomy, segmentectomy, and wedge resection were performed in 375, 97, and 137 patients, respectively. The 30-day mortality rate was 0%. As shown in Table 1, 41 patients (6.7%) had lymph node metastasis in the clinical stage IA lung adenocarcinoma cohort. No significant difference between pN(–) and pN(+) patients was detected in terms of age, sex, and carcinoembryonic antigen value, whereas a marginal difference was seen for tumor size on preoperative high-resolution CT. Regarding the clinical variables, lower GGO ratios and higher SUV_{max} were observed in the N+ group compared with the N– group. In terms of pathologic variables, a lower LC ratio and higher positive rate of LI, blood vessel invasion, and pleural invasion were detected in pN(+) patients. Thirteen of 41 pN(+) patients showed no LI. As shown in Figure 1, *A*, clinical stage IA lung adenocarcinoma patients with lymph node metastasis had a lower RFS rate than those without lymph node metastasis ($P < .001$).

Univariate and Multivariate Analyses of Prognosis According to Pathologic Variables, by Lymph Node Status

Univariate and multivariate analyses of the clinical and pathologic variables were performed to ascertain the most important predictive factor. Univariate analyses were performed on RFS and OS, whereas further analyses, including multivariate analyses, were performed on RFS because OS was more immature than RFS. The pathologic variables included LC ratio, LI status, blood vessel invasion status, pleural invasion status, and lymph node status. For the LC ratio, 30% was used as a threshold because this is the borderline for cT1 N0 M0 lung adenocarcinoma classified as a high- or low-grade malignancy.[2] Univariate analysis revealed that pN(+) patients with LI positive status [LI(+)] had a marginally poorer prognosis ($P = .059$), whereas a lower LC ratio and LI+ status, blood vessel invasion, pleural invasion, or lymph node metastasis was significantly correlated with a poor prognosis in both all patients in this cohort, and in pN(–) patients (Table 2). Additionally, multivariate analysis showed that only LI positive status was a prognostic factor in pN(+) patients ($P = .037$), whereas a lower LC ratio and positive LI status, blood vessel invasion, pleural invasion, or lymph node metastasis were prognostic factors in both all patients and pN(–) patients (Table 3).

TABLE 1. Clinicopathologic findings in patients with clinical stage IA lung adenocarcinoma with or without lymph node metastasis

Finding	Node negative (n = 568)	Node positive (n = 41)	*P* value
Age			
Median	66	65	.33
Interquartile range	60.75-73	56-73	
Sex			
Female	322 (57%)	22 (54%)	.19
Male	246 (43%)	19 (46%)	
CEA			
Median	2.5	3.6	.25
Interquartile range	1.5-3.6	1.1-113.8	
Size*			
Median	2.0	2.2	.060
Interquartile range	1.5-2.4	2.55-4.2	
GGO† ratio			
Median	40	0	<.001
Interquartile range	10-80	0-10	
SUV max			
Median	1.5	3.6	<.001
Interquartile range	0.9-2.6	2.3-4.9	
LC ratio			
Median	50	10	<.001
Interquartile range	10-90	0-20	
Lymphatic invasion			
Negative	507 (89%)	13 (32%)	<.001
Positive	61 (11%)	28 (68%)	
Blood vessel invasion			
Negative	488 (86%)	17 (41%)	<.001
Positive	80 (14%)	24 (59%)	
Pleural invasion			
Negative	515 (91%)	29 (71%)	<.001
Positive	53 (9%)	12 (29%)	

CEA, Carcinoembryonic antigen; *GGO*, ground-glass opacity; *SUV*, standardized uptake value; *LC*, lepidic component. *Tumor size on the high-resolution computed tomography scan. †GGO ratio on the high-resolution computed tomography scan.

Next, we assessed the RFS of pN(–) and pN(+) patients according to their LI status. In both pN(–) and pN(+) patients, RFS rates were lower in LI(+) status compared with LI negative status [LI(–)] ($P < .001$ and $P = .059$) (Figure 1, *B* and *C*). The 3-year RFS and OS rates for each group was as follows: pN(–)/LI(–) 93.4% and 96.7%, pN(–)/LI(+) 70.8% and 85.1%, pN(+)/LI(–) 84.6% and 92.3%, and pN(+)/LI(+) 47.9% and 75.0%, respectively (Table 2 and Figure 1, *B-F*). No significant difference was detected between the pN(+)/LI(–) and pN(–)/LI(+) patients for RFS ($P = .62$; Figure 1, *D*), whereas pN(+)/LI(–) and pN(–)/LI(–) patients, pN(+)/LI(+) and pN(–)/LI(–) patients, and pN(+)/LI(+) and pN(–)/LI(+) patients exhibited significantly different RFS values ($P = .022$, <.001, and .011, respectively).

Clinicopathologic Findings in N+ Patients

In N+ patients, there were no significant differences between the LI(–) and LI(+) groups in terms of age, sex,

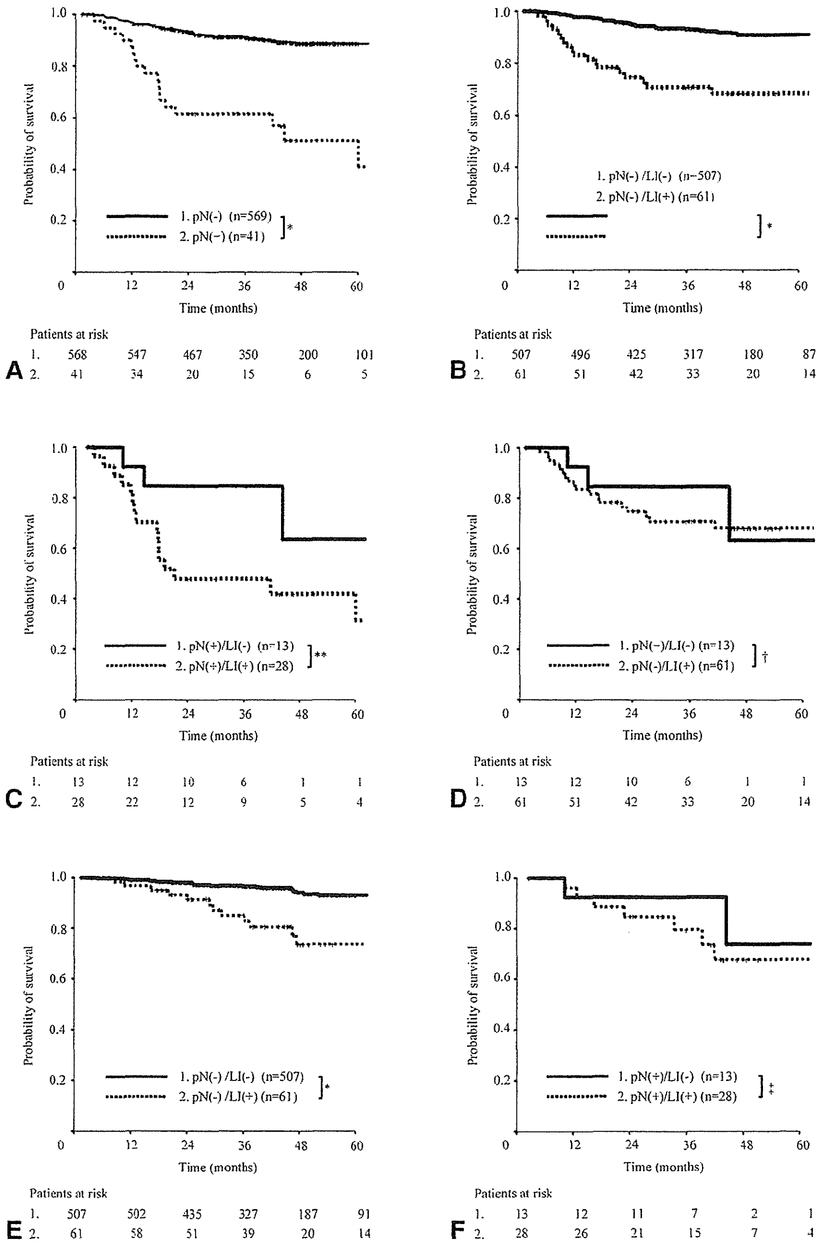

FIGURE 1. Kaplan-Meier recurrence-free survival (A-D) and overall survival (E and F) curves in patients with clinical stage IA lung adenocarcinoma according to pathologic lymph node status and lymph node metastasis and lymphatic invasion (*LI*) status. A, Patients are classified into pathologic lymph node metastasis negative (pN[−]) and positive (pN[+]) groups. B, The pN(−) patients are classified into a lymphatic permeation negative (pN[−]/LI[−]) group and a lymphatic permeation positive (pN[−]LI[+]) group. C, The pN(+) patients are classified into a lymphatic permeation negative (N[+]LI[−]) group and a lymphatic permeation positive (N[+]LI[+]) group. D, Recurrence-free survival curves of pN(+)LI(−) and pN(−)LI(+) patients are shown. E, The pN(−) patients are classified into a pN(−)/LI(−) group and a pN(−)LI(+) group. F, The pN(+) patients are classified into an N(+)LI(−) group and an N(+)LI(+) group. **P* < .001; ***P* = .059; †*P* = .62; ‡*P* = .48.

carcinoembryonic antigen values, preoperative tumor size, and SUV_{max} values. Regarding pathologic findings, LI status had no association with the LC ratio, blood vessel invasion, and pleural invasion. Additionally, LI status had no correlation with lymph node metastasis status, both single or multiple station metastases (Table 4).

DISCUSSION

In this study, pN(+)/LI(−) patients had a better prognosis than pN(+)/LI(+) patients, whereas there were no significant differences in the RFS between pN(+)/LI(−) and pN(−)/LI(+) clinical stage IA lung adenocarcinoma patients at the participating institutions. LI status, which is

TABLE 2. Univariate log-rank analysis of recurrence-free survival (RFS) and overall survival (OS) according to various factors in patients with lung adenocarcinoma

	All		Node negative		Node positive	
Pathologic variable	3-y RFS rate (%)	P value	3-y RFS rate (%)	P value	3-y RFS rate (%)	P value
LC ratio						
≥30	95.2	<.0001	95.9	<.0001	57.1	.93
<30	78.2		81.4		60.5	
Lymphatic invasion						
Negative	93.1	<.0001	93.4	<.0001	84.6	.059
Positive	63.7		70.8		47.9	
Blood vessel invasion						
Negative	93.1	<.0001	94.3	<.0001	58.8	.93
Positive	63.7		71.0		60.6	
Pleural invasion						
Negative	93.1	<.0001	92.6	<.0001	57.1	.42
Positive	68.6		74.6		65.6	
Lymph node metastasis						
Negative	90.9	<.0001	90.9	—	—	—
Positive	59.9		—		59.9	
	All		**Node negative**		**Node positive**	
	3-y OS rate (%)	P value	3-y OS rate (%)	P value	3-y OS rate (%)	P value
LC ratio						
≥30	97.0	<.0001	97.3	<.0001	75.0	.76
<30	90.9		92.0		84.5	
Lymphatic invasion						
Negative	96.6	<.0001	96.7	<.0001	92.3	.490
Positive	83.5		85.1		75.0	
Blood vessel invasion						
Negative	96.4	<.0001	96.7	<.0001	88.2	.55
Positive	86.5		88.1		81.0	
Pleural invasion						
Negative	94.9	.0042	95.9	<.0001	100.0	.29
Positive	92.7		91.2		77.3	
Lymph node metastasis						
Negative	95.5	<.0001	95.5	—	—	—
Positive	83.6		—		83.6	

LC, Lepidic component; *RFS*, recurrence-free survival; *OS*, overall survival.

not always positive in N+ patients, is a significant predictive factor in patients with pathologic lymph node metastasis, whereas the lymph node metastasis status is a strong prognostic factor in patients with clinical T1 N0 M0 lung adenocarcinoma.

It is reasonable that lymph node metastasis occurs after cancer cells invade the lymphatic vessels around the tumors; however, 13 of 41 (31.7%) patients with lung adenocarcinoma, whose LI status was negative, exhibited metastasis to regional lymph nodes. One possible explanation is the difficulty in examining all slices of a specimen; some of the slices, including the tumor, could be pathologically assessed. This could be missed if tumors had only slight LI, and the LI status would be determined as negative. Therefore, "no pathologic LI" could either mean no massive LI, just a slight invasion, or it could mean that there was indeed no LI. This is especially the case in pN+ patients, where "no pathologic LI" indicates a slight LI. Slight invasion means the initial period of lymphatic vessel invasion and lymph node metastasis; therefore, patients with slight invasion had a better prognosis than those with massive invasion after complete surgical resection. In pN+ patients the N1 rate was higher in pN(+)/LI(–) patients compared with pN(+)/LI(+) patients, albeit nonsignificantly so. This suggests that pN(+)/LI(–) is indicative of initial lymph node metastasis, as described above.

In pN+ patients, the N2:N1 ratio was higher in pN(+) LI(+) than pN(+)LI(–) patients, although the difference was not statistically significant. The number of pN+ patients was too small to draw any conclusion; however, the tumors that showed massive LI had a higher tendency to progress to N2 disease than LI(–) tumors. Patients with