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Proposal on incorporating blood vessel invasion into the T classification parts as a practical staging system for stage I non-small cell lung cancer

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ABSTRACT

Background: We investigated blood vessel invasion (BVI) as a possible negative prognostic factor in patients with stage I non-small cell lung cancer (NSCLC) according to the 7th edition of the TNM classification.
Methods: Between 1999 and 2007, a total of 694 consecutive patients with pathological stage I NSCLC underwent complete resection with systematic lymph node dissection at Tokyo Medical University Hospital. All sections of the specimens were stained by Elastica van Gieson to visualize elastic fibers and were examined to determine the prognostic symptoms of BVI. We statistically analyzed the association between BVI and clinicopathologic factors, as well as clinical outcomes.
Results: BVI was detected in 201 patients with stage I NSCLC (29.0%). The 5-year overall survival (OS) rates of the non-BVI and BVI patients were 90.5% and 66.0%, respectively ($p < 0.0001$). BVI was found to be a significant independent prognostic factor by multivariate survival analysis in stage IA and stage IB NSCLC (HR 2.591, $p < 0.001$; HR 2.347, $p = 0.009$, respectively). The 5-year OS rate of patients with BVI was significantly worse than that of patients without BVI in the T1a (94.5% vs 87.5%, $p < 0.0001$), T1b (82.7% vs 65.9%, $p < 0.0001$), and T2a (90.9% vs 61.8%, $p < 0.0001$) subgroups.
Conclusion: We identified the presence of BVI as an independent poor prognostic factor in patients with stage I NSCLC. In the future revision of the TNM staging system, the routine use of elastic fiber stains in pathological evaluations of lung cancer for BVI determination might be recommended, and tumors with BVI should be upstaged to the higher current T staging.

1. Introduction

Non-small cell lung cancer (NSCLC) is one of the most common cancers and a major cause of cancer-related deaths. Pathological stage (p-stage) I NSCLC was observed in about 65% of all surgical cases [1], and these patients have the best chance of cure by surgery alone. Within the stage I designation, however, some clinicopathological characteristics may be associated with poor long-term survival. The 5-year overall survival (OS) rates in resected stage IA and IB NSCLC range from 84% to 87% and from 66% to 74%, respectively, as shown in large-scale Japanese lung cancer studies [1,2], although the 5-year OS rates were approximately more than 95% in p-stage I patients with breast cancer, colon cancer or gastric cancer.

Many studies have been reported to determine various prognostic factors other than the pathological stage, such as sex [3], age [3], smoking history [4], serum level of carcinoembryonic antigen (CEA) [5], extent of operation [3], tumor differentiation [6], tumor size [7], and number of involved lymph nodes [8]. In addition, blood vessel invasion (BVI) has been shown to be a strong independent predictor for p-stage I disease in most studies that adopted this factor as a variable for analyses [7,9–12]. Although BVI has been taken into account in the supplementary TNM staging, BVI is not a descriptor of the T component of the TNM classification. The objective of the present study was to evaluate BVI impact on survival and propose a method of incorporating BVI into T status, in relation with the 7th TNM classification.

2. Materials and methods

2.1. Patient selection

A total of 1234 consecutive patients underwent complete pulmonary resection between January 1999 and December 2007 at

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Tokyo Medical University Hospital. We defined complete resection as lobectomy or more extensive lung resection with systematic ipsilateral hilar and mediastinal lymph node dissection and with no evidence of residual cancer either macroscopically or microscopically. Of these patients, 847 were pathologically proven to have stage I NSCLC. We excluded patients who had received preoperative chemotherapy, radiotherapy or both, or who had been given a diagnosis of low-grade malignant diseases, including carcinoid, mucoepidermoid carcinoma, and adenoid cystic carcinoma. The remaining 694 patients who were pathologically confirmed to have stage I NSCLC were enrolled in this study. We also reviewed 35 patients with surgically resected pathological node-negative stage IIA NSCLC in order to compare the survival and recurrent rates.

We reviewed the medical records of each patient regarding their clinicopathologic information including age, gender, smoking history, tumor location, operation procedure, histologic type, tumor size, blood vessel invasion, lymphatic permeation, and visceral pleural invasion (VPI). Disease stages were based on the 7th edition of the TNM Classification for Lung and Pleural Tumors of the Union for International Cancer Control (UICC).

After resection, the patients were examined at 3-month intervals for 3 years, then at 6-month intervals for the next 2 years, and thereafter at 1-year intervals, in general. The evaluations included physical examination, chest roentgenogram, chest computed tomography (CT), and tumor marker measurement. Abdominal CT and brain MRI as well as bone scintigraphy were performed every year. Patients with cancer recurrence were carefully divided into 2 groups according to the site of initial relapse: locoregional or distant. The median follow-up period was 4.6 years. The Institutional Review Board of our hospital approved the protocols for data collection and analyses, and waived the need to obtain written informed consent from each patient.

2.2. Histopathologic studies

Histopathologic studies were performed according to World Health Organization criteria. After fixing the specimens in 10% formalin and embedding them in paraffin, sections were stained with hematoxylin and eosin and by Elastica van Gieson (EvG) staining to visualize elastic fibers. Detailed examinations of BVI were routinely performed at our institution. Blood vessels were identified by the presence of erythrocytes in the lumen or an endothelial cell lining or the presence of elastic tissue around larger vessels. Sections stained by EvG were examined for the presence of BVI. The presence of BVI was determined by identifying conspicuous clusters of intravascular cancer surrounded by an elastic fiber layer (Fig. 1). On the other hand, lymphatic permeation was determined to be present when tumor cells floating in lymphatic vessels with no supporting smooth muscles or elastic fibers were identified. We confirmed that lumens within the bronchovascular bundle, subpleural, and intralobular pleural space were lymphatic vessels by immunostaining with anti-D2-40 antibody.

2.3. Statistical analysis

Overall survival (OS) and recurrence-free survival (RFS) were estimated using the Kaplan–Meier method, and differences in survival rates were determined by log-rank analysis. OS was defined as the time elapsed from the date of pulmonary resection to the date of death. RFS was defined as the time elapsed from the date of pulmonary resection to the date of the first recurrence or last follow-up showing no recurrence. The last follow-up observation was censored if the patient was alive or lost to follow-up. Univariate analysis was conducted among the different groups. Categorical variables were analyzed using the chi-square test. Differences between 2 groups were tested using the Mann–Whitney

Fig. 1. Elastica van Gieson staining of a tumor with blood vessel invasion (BVI). The presence of BVI was determined by identifying conspicuous clusters of intravascular cancer surrounded by an elastic layer (original magnification, 400×).

U test. Multivariate analysis was performed by the Cox proportional hazards model using the significant factors identified from univariate analysis to examine the association between survival and potential prognostic factors. All *p*-values were two-sided and *p*-values of <0.05 were considered to indicate a statistically significant difference. All statistical calculations were performed using StatView for Windows version 5.0 (SAS Institute Inc., Cary, NC, USA).

3. Results

The characteristics of the patients are shown in Table 1a. BVI was detected in 201 patients (29.0%). The 5-year OS rates of non-BVI and BVI patients were 90.5% and 66.0%, respectively (Fig. 2). The relationship between clinicopathological prognostic factors and BVI is shown in Table 1b. BVI prevalence was significantly higher in men, ever smokers, non-adenocarcinoma, positive lymphatic permeation, positive visceral pleural invasion, and p-stage IB ($p < 0.05$). Tumor size was significantly larger in BVI tumors than in non-BVI tumors ($p < 0.0001$).

In patients with p-stage IA tumors, men, over 70 years old, ever smokers, tumor size over 2 cm in diameter, non-adenocarcinoma, and the presence of BVI were statistically significant poor prognostic factors. Multivariate survival analysis showed that a tumor size over 2 cm in diameter and the presence of BVI were statistically significant independent prognostic factors, as well as ages over 70 years old and non-adenocarcinoma (hazard ratio [HR] = 2.096, $p = 0.0040$; HR = 2.591, $p = 0.0004$, respectively)

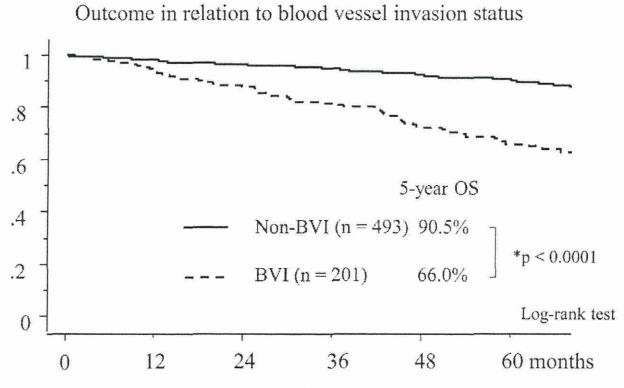

Fig. 2. Survival curves for blood vessel invasion (BVI) and non-BVI. *p < 0.05.

Table 1a
Patient characteristics (stage I, $n = 694$; stage IIA, $n = 35$).

Variable	Number (%)				p value (stage IA vs stage IB)
	All ($n = 694$)	Stage IA ($n = 423$)	Stage IB ($n = 271$)	Stage IIA (T2bN0) ($n = 35$)	
Sex					<0.0001*
Men	371 (53.5)	200 (47.3)	171 (63.1)	32 (91.4)	
Women	323 (46.5)	223 (52.7)	100 (36.9)	3 (8.6)	
Median age (range)	66.0 (22–86)	65.0 (22–86)	67.0 (38–86)	69.0 (48–86)	0.0381*
Smoking history					0.0030*
Never smoker/unknown	315 (45.4)	211 (49.9)	104 (38.4)	5 (14.3)	
Ever smoker	379 (54.6)	212 (50.1)	167 (61.6)	30 (85.7)	
Tumor location					0.9999
Right	451 (65.0)	275 (65.0)	176 (64.9)	25 (71.4)	
Left	243 (35.0)	148 (35.0)	95 (35.1)	10 (28.6)	
Operation procedure					0.5355
Lobectomy	669 (96.4)	406 (96.0)	263 (97.0)	33 (94.3)	
Bilobectomy	25 (3.6)	17 (4.0)	8 (3.0)	2 (5.7)	
Histological type					0.0002*
Adenocarcinoma	568 (81.8)	365 (86.3)	203 (74.9)	18 (51.4)	(Ad vs non-Ad)
Squamous cell carcinoma	97 (14.0)	47 (11.1)	50 (18.4)	15 (42.9)	
Large cell carcinoma	22 (3.2)	8 (1.9)	14 (5.2)	2 (5.7)	
Others	7 (1.0)	3 (0.7)	4 (1.5)	0 (0)	
Median tumor size (cm) (range)	2.3 (0.4–5.0)	1.9 (0.4–3.0)	3.5 (0.6–5.0)	6.0 (5.1–7)	<0.0001*
BVI	201 (29.0)	73 (17.2)	128 (47.2)	13 (37.1)	<0.0001*
Lymphatic permeation	237 (34.1)	101 (23.8)	136 (50.2)	17 (48.6)	<0.0001*
VPI	122 (17.6)	0 (0)	122 (45.0)	13 (37.1)	–
pT factor					–
T1a	263 (37.9)	263 (62.2)	0 (0)		
T1b	160 (23.1)	160 (37.8)	0 (0)		
T2a	271 (39.0)	0 (0)	271 (100)		

Ad, adenocarcinoma; non-Ad, other histological types; BVI, blood vessel invasion; VPI, visceral pleural invasion.
* $p < 0.05$.

Table 1b
Patient characteristics in the 2 groups according to clinicopathologic factors ($n = 694$).

Variable	Number (%)		p-Value [non-BVI vs BVI]
	Non-BVI ($n = 493$)	BVI ($n = 201$)	
Sex			<0.0001*
Men	228 (46.2)	143 (71.1)	
Women	265 (53.8)	58 (28.9)	
Age			0.0705
≤70 years old	143 (29.0)	73 (36.3)	
>70 years old	350 (71.0)	128 (63.7)	
Smoking history			<0.0001*
Ever Smoker	229 (46.5)	150 (74.6)	
Never smoker/unknown	264 (53.5)	51 (25.4)	
Tumor location			0.9302
Right	321 (65.1)	130 (64.7)	
Left	172 (34.9)	71 (35.3)	
Histological type			<0.0001*
Ad	434 (88.0)	134 (66.7)	
Non-Ad	59 (12.0)	67 (33.3)	
Operation procedure			0.8225
Lobectomy	476 (96.6)	193 (96.0)	
Bilobectomy	17 (3.4)	8 (4.0)	
Median tumor size (cm) (range)	2.0 (0.4–5.0)	3.0 (0.7–5.0)	<0.0001*
Lymphatic permeation			<0.0001*
present	101 (20.5)	136 (67.7)	
absent	392 (79.5)	65 (32.3)	
VPI			<0.0001*
present	52 (10.5)	70 (34.8)	
absent	441 (89.5)	131 (65.2)	
p-stage			<0.0001*
IA	350 (71.0)	73 (36.3)	
IB	143 (29.0)	128 (63.7)	

Non-BVI, without blood vessel invasion; BVI, with blood vessel invasion; Ad, adenocarcinoma; non-Ad, other histological types; VPI, visceral pleural invasion.
* $p < 0.05$.

(Table 2a). In patients with p-stage IB tumors, men, ever smokers, non-adenocarcinoma, the presence of BVI, and the presence of lymphatic permeation were significant poor prognostic factors. Multivariate survival analysis showed that the presence of BVI was a significant independent prognostic factor, as well as men and the presence of lymphatic permeation (HR = 2.347, $p = 0.0088$) (Table 2b).

Thus, we analyzed the OS of p-stage IA patients stratified by tumor size (≤2 cm, T1a; >2 cm, T1b) and BVI status (presence or absence) (Fig. 3a), and we also analyzed the OS of p-stage IB patients stratified by BVI status (Fig. 3b).

In the p-stage IA patient cohort, subgroup analysis of the patients revealed 5-year OS rates of 94.5%, 87.1%, 82.7%, and 65.9% for patients with T1a/non-BVI, T1a/BVI, T1b/non-BVI, and T1b/BVI, respectively (Fig. 3a). The differences in survival were statistically significant between patients with T1a/BVI and T1a/non-BVI tumors, and between patients with T1b/BVI and T1b/non-BVI tumors ($p < 0.001$ and $p = 0.034$, respectively). There was no significant difference in the survival rates between the T1a/BVI and T1b/non-BVI subgroups ($p = 0.2604$). On the other hand, in the p-stage IB patient cohort, subgroup analysis of the patients revealed 5-year OS rates of 90.3% and 61.5% for patients with T2a/non-BVI and T2a/BVI tumors, respectively, with statistically significant difference ($p < 0.001$) (Fig. 3b).

We also analyzed the prognosis of T1b, T2a and T2b tumors (Table 3). There was no significant difference in survival between the patients with T1b/non-BVI and T2a/non-BVI tumors ($p = 0.0753$). There was no significant difference in survival between patients with T1b/BVI and T2a/BVI tumors, and between patients with T2a/BVI and T2b tumors ($p = 0.7364$ and $p = 0.2394$, respectively).

The patients with T1a/BVI tumors had lower RFS than the patients with T1b/non-BVI, with no significant difference ($p = 0.2090$) (Fig. 3c). However, in RFS curves, similar relationships to OS curves were observed among these subgroups with each pathological stage tumor (Fig. 3c and d).

Table 2a
Univariate and multivariate analyses of prognostic factors in stage IA patients.

Variable	UVA	MVA		
	p-Value	Hazard ratio	95%CI	*p*-Value
Sex: men (vs women)	0.0159*	1.205	0.5921–2.451	0.6076
Age: >70 (vs ≤70)	0.0125*	1.852	1.091–3.145	0.0226*
Smoking history: ever smoker (vs never smoker)	0.0059*	1.290	0.601–2.770	0.5134
Operation procedure: bilobectomy (vs lobectomy)	NS (0.1968)		Not included in MVA	
Tumor location	NS (0.387)		Not included in MVA	
Tumor size: >2 cm (vs ≤2 cm)	0.0007*	2.096	1.266–3.472	0.0040*
Histologic type: non-Ad (vs Ad)	<0.0001*	2.899	1.624–5.176	0.0003*
BVI: present (vs absent)	0.0001*	2.591	1.529–4.386	0.0004*
Lymphatic permeation: present (vs absent)	NS (0.4553)		Not included in MVA	

UVA, univariate analysis; MVA, multivariate analysis; Ad, adenocarcinoma; non-Ad, other histological types; BVI, blood vessel invasion.
* $p < 0.05$.

Table 2b
Univariate and multivariate analyses of prognostic factors in stage IB patients.

Variable	UVA	MVA		
	p-Value	Hazard ratio	95%CI	*p*-Value
Sex: men (vs women)	<0.0001*	3.690	1.475–9.259	0.0052*
Age: >70 (vs≤70)	NS (0.7117)		Not included in MVA	
Smoking history: ever smoker (vs never smoker)	0.0007*	1.016	0.475–2.037	0.9657
Operation procedure: bilobectomy (vs lobectomy)	NS (0.5782)		Not included in MVA	
Tumor location	NS (0.6533)		Not included in MVA	
Tumor size: >3 cm (vs≤3 cm)	NS (0.0665)		Not included in MVA	
Histologic type: non-Ad (vsAd)	0.0006*	1.226	0.716–2.101	0.4575
BVI: present (vs absent)	<0.0001*	2.347	1.239–4.464	0.0088*
Lymphatic permeation: present (vs absent)	<0.0001*	2.288	1.279–4.082	0.0053*
VPI: present (vs absent)	NS (0.8943)		Not included in MVA	

UVA, univariate analysis; MVA, multivariate analysis; Ad, adenocarcinoma; non-Ad, other histological types; BVI, blood vessel invasion; VPI, visceral pleural invasion.
* $p < 0.05$.

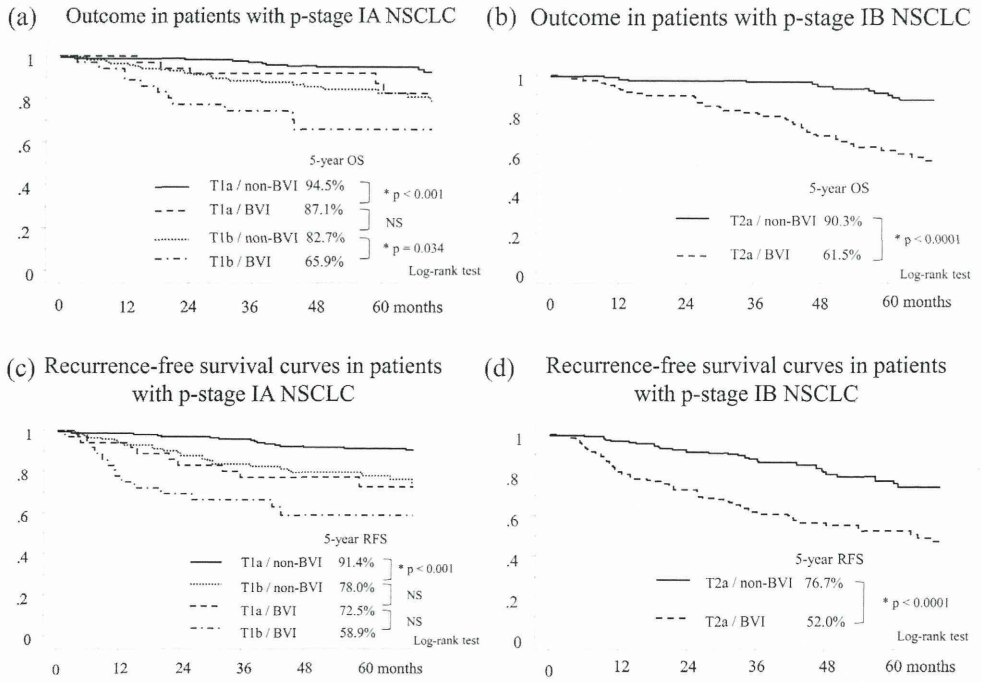

Fig. 3. (a) Survival curves and 5-year overall survival (OS) rates stratified by T-factor (T1a or T1b) and blood vessel invasion (BVI) status in patients with p-stage IA non-small cell lung cancer (NSCLC). (b) Survival curves and 5-year OS rates stratified by BVI status in patients with p-stage IB NSCLC. (c) Recurrence-free survival (RFS) curves and 5-year RFS rates stratified by T-factor (T1a or T1b) and blood vessel invasion (BVI) status in patients with p-stage IA non-small cell lung cancer (NSCLC). (d) RFS curves and 5-year RFS rates stratified by BVI status in patients with p-stage IB NSCLC. *$p < 0.05$.

Table 3
Proposal on incorporating vascular invasion into T classification.

Group	n	5yOS	p-value	7th Edition stage (N0M0)	Our proposal stage (N0M0)
T1a/non-BVI	227	94.5%	< 0.0001	IA	IA
T1a/BVI	38	87.5 %	NS (0.2604)	IA	**IB**
T1b/non-BVI	125	82.7%	0.034	IA	**IB**
T1b/BVI	39	65.9%	0.0002	IA	**IIA**
T2a/non-BVI	145	90.9%	< 0.0001	IB	IB
T2a/BVI	130	61.8%	NS (0.2394)	IB	**IIA**
T2b	36	68.7%		IIA	IIA

NS (0.0753)
NS (0.7364)

T-factor and stage in bold in our proposal differ from those in the 7th edition classification. Non-BVI, without blood vessel invasion; BVI, with blood vessel invasion; 5y OS, 5-year overall survival rate.

4. Discussion

The TNM stage classification was developed as a benchmark for prognosis and treatment options. For patients with stage I lung cancer, however, survival outcomes vary, thus stage I NSCLC comprises a heterogeneous group with different prognoses [13]. BVI has been shown to be a strong independent predictor for p-stage I disease as a variable for analyses [7,9–12,14], with only few exceptions [15,16]. In several other malignancies, BVI has similarly been shown to predict poor outcome [17–19], and its value has been commonly recognized to the point that it is included in the AJCC staging system for testicular cancer [20]. The first studies about the prognostic role of BVI in lung cancer date back to the late 1950s [21]. Despite the numerous reports of BVI as a negative prognostic factor and that BVI has been taken into account in the supplementary TNM staging, BVI has not yet been incorporated into the T classification component.

One possible reason may be that there is a lack of standardization of evaluating BVI. Many variations regarding the method of BVI assessment exist, although in most studies BVI was defined as the presence of neoplastic structures inside the lumen of a vessel. Ichinose et al. reported that venous invasion was one of the significant prognostic factors among patients with completely resected NSCLC [22]. On the other hand, arterial invasion was reported to be strongly associated with 5-year survival in patients with stage I NSCLC [23]. Arterial and venous invasion has not yet been studied pathologically separately in our institute, because discrimination was not always possible. Some studies evaluated BVI by staining with hematoxylin and eosin alone or in combination with EvG stain or by staining with Victoria blue hematoxylin and eosin, which can lead to significant heterogeneity. The reported detection rates of BVI in pathological stage I NSCLC case without any elastic fiber stains were 11–17% [15,24]. In contrast, those with elastic fiber stains ranged from 21% to 56% and were higher than those without [9,16,25]. We uniformly used hematoxylin and eosin and EvG stains on all tumors and the detection rate was 28.9% for patients with pathological stage I, which was similar to previous studies [9,16,25]. These findings suggest that elastic fiber staining helps pathologists to identify BVI more accurately in almost all cases. In the latest 7th edition of the TNM classification, VPI is clearly defined and T1 tumors remain to be upgraded to T2a when the visceral pleural elastic layer is invaded. Elastic fiber staining is also helpful in identifying VPI. We therefore recommend the routine use of elastic fiber stains in pathological evaluations of lung cancer, not only for VPI determination, as recommended in the TNM classification, but also for BVI determination, especially in patients with stage I NSCLC, to reflect more accurate, prognosis.

In this series, we showed that the 5-year OS rate of BVI patients was significantly lower than that of non-BVI patients (Table 3). These results indicate that T1a tumors with BVI should be classified as T1b, T1b tumors with BVI as T2a, and T2a tumors with BVI as T2b. This would also be consistent with other tumors with BVI being upgraded to the next T level. Our proposal on incorporating BVI into T classification can be framed to yield a better staging system for stage I NSCLC.

BVI is one of the steps leading to metastatic diffusion, and this may be the reason that BVI is associated with a poorer prognosis. Tumor cells from the primary neoplasm may penetrate these new vessels and escape from the primary site to distant organs. The relationship between tumor vessels, intravascular tumor cell invasion, and metastases has been studied in animal models [26]. In our series, there were 44 patients and 74 with recurrence in stage IA and stage IB, respectively. Among these patients, the patterns of initial recurrence included distant metastasis in 31 patients (70.5%) and in 58 (78.3%), respectively (data not shown). Classified by BVI status, recurrence developed in 17 (23.3%) of stage IA patients with BVI, and recurrence in 27 (7.7%) of these patients with non-BVI, with significant difference ($p = 0.0004$, data not shown). However, there were high rates of distant metastasis in both groups, and there were no significant differences in initial recurrence patterns. In the stage IB patients, recurrence developed in 51 (39.8%) of patients with BVI, and recurrence in 23 (16.1%) of patients with non-BVI, with a significant difference ($p < 0.0001$, data not shown). However, there were high rates of distant metastasis in both groups, and there were no significant differences in initial recurrence patterns. Surgery is considered to be the standard treatment for early-stage NSCLC. However, distant metastasis occurred in nearly 60–70% of recurrence patients with stage I NSCLC after complete resection [27,28]. Micrometastasis of the tumor is generally regarded as the cause of recurrence; therefore systemic chemotherapy after surgery is a rational strategy to reduce the risk of recurrence and metastasis.

Recent randomized controlled trials have demonstrated the survival benefit varied with stage and the usefulness of platinum-based adjuvant chemotherapy in p-stage II to IIIA NSCLC patients [29–31]. For stage IB adenocarcinoma patients, based on a large adjuvant trial on oral uracil-tegafur (UFT), UFT adjuvant

chemotherapy is recommended as the standard treatment in Japan [32]. Although surgery alone remains the standard treatment for patients with stage IA disease, recent Japanese studies also showed that oral UFT may improve survival in patients with p-stage IA showing a tumor size of 2–3 cm [32,33]. Recently, the proposed IASLC/ATS/ERS classification of lung adenocarcinoma identified histological categories with prognostic differences that may be helpful in identifying candidates for adjuvant therapy and was associated with BVI [34,35], but there might be some lack of preparation to incorporate the classification into the staging system. In the present study, when we divided the study population stratified by BVI, the patients with BVI have worse survival than those without BVI (Table 3). This classification can incorporate the prognostic impact of BVI status into the 7th edition T classification reasonably well, and patients with each stage of NSCLC with BVI may therefore be good candidates for adjuvant chemotherapy. BVI is an important parameter to venture postoperative poor prognostic groups in a strategical staging system.

Due to the retrospective analysis in a single institute, which evaluated cases from 1999, and due to a small sample size compared with T2b patients, making it impossible to draw any statistically significant conclusions in these subgroups, our proposal is not complete. Furthermore, it is difficult to evaluate BVI in the clinical staging setting. However, our data clearly indicate that BVI has a very strong prognostic impact. Prospective multi-institutional studies are mandatory to further validate the prognosis of BVI in resected stage I NSCLC.

In conclusion, despite the limitations mentioned above, we have demonstrated the prognostic power of BVI as a single independent pathologic marker for NSCLC, and our results have indicated that T1a tumors with BVI should, unlike in the 7th TNM classification, be classified as T1b, T1b tumors with BVI as T2a, and T2a tumors with BVI as T2b. In future revisions of the TNM staging system, we recommend the routine use of elastic tissue stains in pathological evaluations of lung cancer for BVI determination, and we believe that tumors with BVI should be upstaged to the above T stages. As this will affect staging criteria, additional studies employing standard methodology to assess BVI are needed to further clarify the underlying reasons why tumors with BVI have an unfavorable prognosis.

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Conflict of interest statement

None declared.

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Virtual segmentectomy based on high-quality three-dimensional lung modelling from computed tomography images

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Abstract

OBJECTIVES: The aim of this study was to demonstrate the feasibility and efficacy of a novel simulation software called, virtual segmentectomy.

METHODS: We developed the segmentectomy simulation system, which was programmed to analyse the detailed 3D bronchovascular structure and to predict the appropriate segmental surface and surgical margin, based on lung modelling from CT images.

RESULTS: We have attempted this novel technique for 3 cases of pulmonary metastases and 1 case of multiple lung cancer. For validation, the predicted resection margin was compared with the actual resected specimen. The surgical surface, as estimated by the simulation, was compared with the surface of the specimen and a surgical video. To test its feasibility, the operation time, blood loss, durations of chest tube placement and hospitalization as well as pathological findings were assessed.

CONCLUSIONS: Preoperative simulation and intraoperative guidance by virtual segmentectomy could contribute significantly to determining the most appropriate anatomical segmentectomy and curative resection.

Keywords: 3D computed tomography • Surgical techniques • Lung segmentectomy • Simulation • Computer applications

INTRODUCTION

New technologies can considerably improve preoperative planning, enhance the surgeon's skill, and simplify the approach to complex surgical procedures. Recently, surgical simulation based on preoperative 3D computed tomography (CT) scan has been developed in the fields of head and neck surgery, neurosurgery, orthopaedic surgery and general surgery.

Because of the increasing detection of early small lung cancer lesions due to the expansion of low-dose CT screening, sublobar resections of the lung, including segmentectomy and wedge resection, are becoming common procedures [1]. However, segmentectomy is a complicated operative procedure because of its anatomical complexity, including the high variability of vascular and bronchial structures and the technical difficulty in obtaining an adequate surgical margin due to tumour location and the number of tumours. There have been reports of a recently developed hepatectomy simulation software, regarding its feasibility and efficacy in the fields of both general surgery and liver transplantation [2–5]. This software was designed to analyse detailed 3D vascular structure and to predict liver resection volume and margins. We have developed a segmentectomy simulation system for thoracic called virtual segmentectomy, based on high-quality 3D lung modelling from CT images using the Fujifilm Synapse Vincent system (Fujifilm Corporation, Tokyo, Japan). In this article, we describe 2 representative cases and report the preliminary results of the preoperative and intraoperative assessment via this simulation software in 4 consecutive cases.

TECHNOLOGY

Computed tomography, 3D angiography and bronchial tree

Virtual segmentectomy, surgical simulation of a segmentectomy using 3D lung modelling, was performed with a 64-channel multidetector CT (MDCT) (Light Speed VCT, General Electric Company, CT, USA). A total of 100 ml of contrast agent was injected by a mechanical injector at a rate of 1.5–2.0 ml/s. Scanning parameters used for the contrast examination were as follows: a slice thickness of 1.25 mm, a table displacement of 39.37 mm/rot, and a reconstruction interval of 1.0 mm. Using 3D volume rendering, a solid image was constructed from 1.25-mm data slices of the contrast-enhanced CT images. These digital imaging and communication in medicine data were transferred to a workstation with the Synapse Vincent volume-rendering

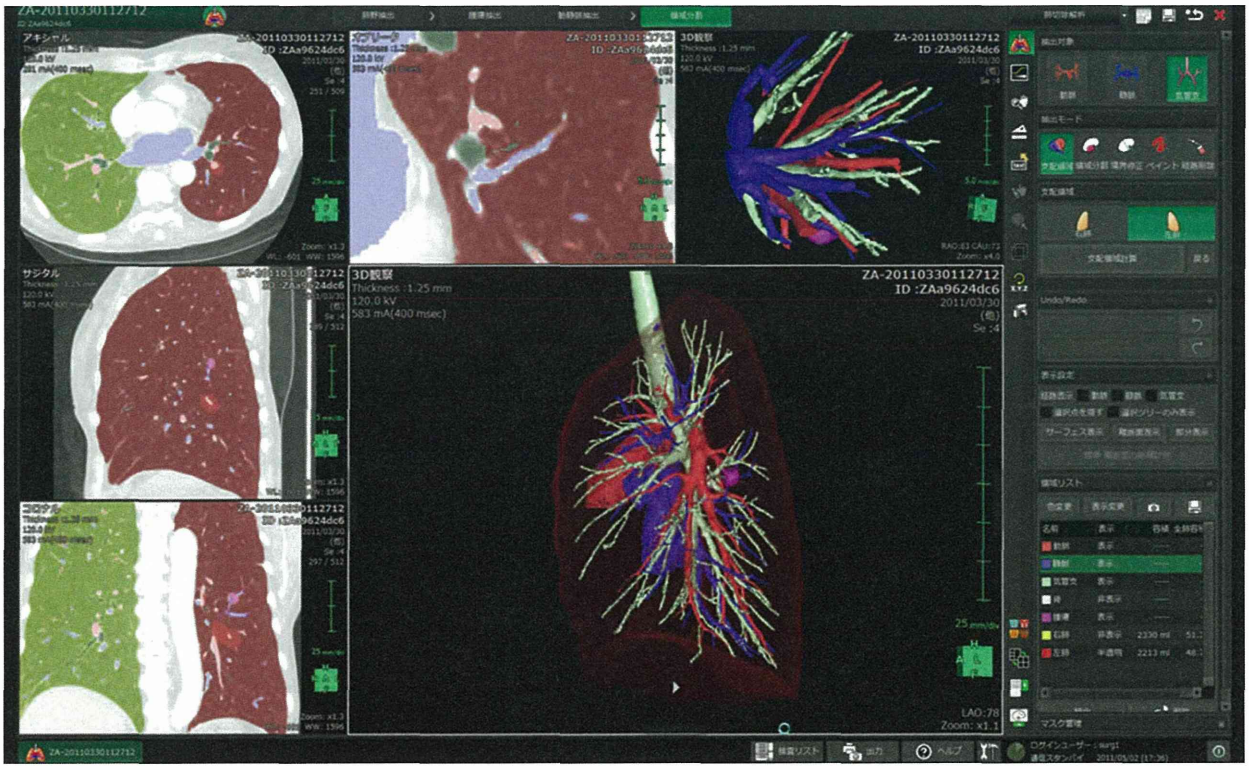

Figure 1: Interface of the lung resection analysis function packaged in Synapse Vincent (Fujifilm).

reconstruction software, which includes a novel 3D image-processing system for the preoperative simulation of segmentectomy. The procedures for 3D reconstruction of the pulmonary vessels and bronchial trees were performed automatically, then further corrected by a thoracic surgeon, taking anatomical variability into account. These procedures took only 5–10 min (Fig. 1).

Preoperative segmentectomy simulation, virtual segmentectomy

Image analysis for the preoperative segmentectomy simulation called virtual segmentectomy was performed using the novel 3D CT image-processing software, including a lung resection analysis function, packaged in Synapse Vincent, developed in collaboration between our department and Fujifilm Corporation. This software has been commercially available since April 2012 and is now being used routinely in our institution. This particular process consisted of the following steps: (i) transfer of CT images to the 3D imaging system; (ii) 3D reconstruction of the tumour, pulmonary vessels, tracheo-bronchial tree and lung parenchyma (Fig. 1); (iii) definition of the segmental bronchi based on the location of the tumour; (iv) calculation of the bronchial ventilation area using an algorithm based on the direction and diameter of the bronchi (Figs 2B and 3B); (v) determination of the sites of resection of the pulmonary vessels, bronchi and inter-segmental veins (Figs 2C and 3E); (vi) calculation of the extent of the surgical margin (Fig. 2D and E) and (vii) visualization of the appropriate segmentectomy surface (Figs 2E and 3E). The 3D CT-guided segmentectomy was initiated by detaching the pulmonary arteries and veins from the pulmonary parenchyma along the shortest route to the target segmental bronchi, according to the preoperative virtual segmentectomy and intraoperative visualization guidance, with an appropriate inter-segmental plane surface (Fig. 3C–E). We performed those operations with double monitor guidance: one was a thoracoscopy television monitor, and the other was a 3D imaging system allowing 3D lung structure and virtual segmentectomy, with which we could reconstruct 3D imaging during operations (Fig. 4).

The simulation system was implemented as a plug-in in the processing workstation (Dell Precision T5500, Windows 7 Professional, 64-bit, 12GB, DDR3 RDIMM).

3D CT-guided segmentectomy

We performed 3D CT-guided segmentectomy for video-assisted thoracoscopic surgery (VATS)-assisted mini-thoracotomy under guidance from both a television monitor and visualization of virtual segmentectomy. Basically, we applied a surgical approach with a combination of muscle-sparing mini-thoracotomy (incision, 4–10 cm) and another incision for an access port of a thoracoscope for video assistance and used mainly direct visualization for the resection of lung parenchyma. The surgeon directly observed the proximal region of the target lobe and individually ligated and dissected the pulmonary arteries and veins from the pulmonary parenchyma along the shortest route to the intended segmental bronchi, according to preoperative virtual segmentectomy and intraoperative 3D CT guidance (Figs 2E, 3C–E). After the segmental bronchi involved with the diseased segment were isolated and divided, the lung was ventilated using selective jet ventilation through a double-lumen tube or directly through mini-thoracotomy into the orifice of the targeted segmental bronchi. The diseased segment was inflated while the preserved segments appeared to collapse and a line formed between the inflated and deflated lung parenchyma, showing the anatomical