antibody that recognizes the ERα carboxy-terminus, staining was found in the cytoplasm and cell membrane [4]. This membrane-bound ERα comprises variant isoforms that lack the amino-terminus, because they cannot be detected by antibodies that recognize the ERα amino-terminus. In this study, we used this antibody for membrane-bound ERα (mERα).

The other well known female-related factor is mutation of the epidermal growth factor receptor (*EGFR*). *EGFR* tyrosine kinase inhibitors (EGFR-TKIs) produce a dramatic clinical response in a significant proportion of patients with lung cancer [5]. In 2004, response to EGFR-TKIs was ascribed to the presence of some type of gene mutations in the tyrosine kinase domain of *EGFR* [6,7]. The *EGFR* mutations in lung cancer associated with sensitivity to EGFR-TKIs occur more frequently in women, nonsmokers, Asians, and with adenocarcinomas [8,9].

Estrogen directly stimulates the transcription of estrogen-responsive genes of lung cells and transactivates the EGFR pathway. Stimulation of ER has been reported to increase the activity of the EGFR signal, and EGFR signal increases the activity of the ER [10]. Strong nuclear expression of ERß has been shown to be correlated with the presence of *EGFR* mutation, and the favorable prognostic significance of ERß expression has been shown to be influenced by the presence of *EGFR* mutation in lung adenocarcinoma [11]. However, to date, no report has described the correlation between mERα expression and *EGFR* mutation.

Based on these data from previous studies, we investigated the association between the expression of mERα and *EGFR* mutation in lung adenocarcinoma. In addition, we restricted the tumor size of the adenocarcinomas to tumors measuring less than 3 cm in diameter, because *EGFR* mutation is considered an early event in the pathogenesis of lung adenocarcinoma [12]. The purpose of this study was to clarify the correlations between the expression of mERα and *EGFR* mutation and clinicopathological factors, in relation to the prognosis of the patients. In addition, using immunohistochemistry to determine the expression of vascular endothelial growth factor (VEGF) and Ki-67, we studied the tumor proliferative activity and angiogenesis in adenocarcinomas showing mERα expression and *EGFR* mutation.

Methods

Study population

Fifty-one patients with lung adenocarcinoma measuring less than 3 cm in diameter, who underwent surgical resection (lobectomy or segmentectomy) with systematic lymph node dissection, at the Kawasaki Medical School Hospital between 2007 and 2009 were enrolled in this study. None of the patients had received either radiotherapy or chemotherapy prior to surgery. The histological diagnosis of the tumors was based on the criteria of the World Health Organization, and the tumor, nodule, metastasis (TNM) stage was determined according to the criteria in 2009. Written informed consent was obtained from each patient for the study of the excised tissue samples from the surgical specimens. This study was conducted with the approval of the institutional Ethics Committee of Kawasaki Medical School. Follow-up information up to recurrence, or March 2012, was obtained from medical records.

All patients underwent fluorodeoxyglucose positron emission tomography (FDG-PET) before the surgery. The PET and computer tomography (CT) examinations were performed with a dedicated PET/CT scanner (Discovery ST Elite; GE Healthcare, Japan), at 115 minutes after intravenous injection of 150 to 220 MBq of ^{18}FDG (FDGscan, Universal Giken, Nihon Mediphysics, Tokyo, Japan). The regions of interest (ROI) were placed three-dimensionally over the lung cancer nodules. Semiquantitative analysis of the images was performed by measuring the maximal standardized uptake value (SUV_{max}) of the lesions.

EGFR mutation analysis

Analysis to detect *EGFR* mutations was performed in the resected, paraffin-embedded lung cancer tissues by a peptide nucleic acid-locked nucleic acid (PNA-LNA) PCR clamp method [13]. For this study, the PNA-LNA PCR clamp assay was performed at Mitsubishi Kagaku Bio-clinical Laboratories, Inc, Tokyo, Japan.

Table 1 The patient characteristics

Characteristics	Number of patients	%
Age		
<70	31	60
≥70	20	40
Sex		
Male	23	48
Female	28	52
Tumor differentiation		
well	32	68
moderate	14	22
poor	5	10
Lymphnode metastasis		
negative	43	87
positive	8	13
Pathological stage		
IA	32	62
IB	11	22
II(A+B)	3	6
III(A+B)	5	10
Adjuvant chemotherapy		
Yes	13	35
No	38	65

Table 2 Association of membrane-bound ERα (mERα) expression / *EGFR* mutation status and clinicopathological variables

		mERα expression			*EGFR* mutation		
Characteristics	**n**	**Negative**	**Positive**	**p-value**	**Mutant**	**Wild**	**p-value**
Patients, number	51	27	24		26	25	
Age(mean), year		66.6	66.4	0.717	67.5	65.4	0.391
Sex				0.921			0.036
Male	23	12	11		8	15	
Female	28	15	13		18	10	
Smoking				0.615			0.124
smoker	21	12	9		8	13	
never-smoker	30	15	15		18	12	
Tumor size(mean), mm		20.1	23.6	0.051	24.1	19.4	0.017
PET SUVmax		4.16	8.00	0.005	4.94	5.01	0.711
Tumor differentiation				0.019			0.691
well	32	21	11		17	15	
moderate/poor	19	6	13		9	10	
Vascular invasion				0.001			0.006
negative	35	21	11		13	22	
positive	16	3	13		13	3	

Immunohistochemical staining

Immunohistochemical analyses were performed in the resected, paraffin-embedded lung cancer tissues. After microtome sectioning (4 μm), the slides were processed for staining using an automated immunostainer (Nexes; Ventana, Tucson, AZ, USA). The streptavidin-biotin-peroxidase detection technique using diaminobenzidine as the chromogen was applied. The primary antibodies were used according to the manufacturer's instructions (ERα:, clone HC-20, Santa Cruz Biotechnology, Santa Cruz, CA, 1/500 dilution; VEGF:, clone A-20, Santa Cruz Biotechnology, Santa Cruz, CA, 1/300 dilution; Ki-67: clone MIB-1, Dako Cytomation, Kyoto, Japan, 1/100 dilution). The slides were examined by two investigators who had no knowledge of the corresponding clinicopathological data. The expression of each marker protein was examined and evaluated according to the original protocol reported previously.

ERα expression was categorized into eight grades according to previously described immunohistological scores [14]. Initially, six degrees of the proportional scores for positive staining were assigned according to the proportion of positive tumor cells (0, none; 1, < 1/100; 2, 1/100 to 1/10; 3, 1/10 to 1/3; 4; 1/3 to 2/3; 5, > 2/3). Next, an intensity score was assigned, which represented the average intensity in the tumor cells showing positive tumor staining (0, none; 1, weak; 2, intermediate; 3, strong). The proportional and intensity scores were then added to obtain a total score, ranging from 0 to 8. For the statistical analysis, ERα expression was judged as positive when the score was ≥ 4. VEGF expression was judged as positive when more than 20% of the cancer cell cytoplasm showed positive staining [15]. The labeling index of Ki-67 was measured by determining the percentage of cells with positively stained nuclei. Ki-67 expression was judged as positive when more than 10% of the cancer cell nuclei showed positive staining [16].

Statistical analysis

Statistical analysis was performed for examining significant differences among the groups and possible correlations between presence/absence of mERα expression/*EGFR* mutation and the clinicopathological features using Fisher's exact test or the chi square (χ^2) test as appropriate. An unpaired *t*-test was used for comparison of the continuous data. Multivariate analyses were performed using logistic regression analysis. To explore the association between recurrence-free survival (RFS) and the presence of mERα expression/*EGFR* mutation, a Kaplan-Meier survival analysis was performed by stratifying significant predictor variables identified in the Cox proportional hazards model. All the statistical analyses were conducted using SPSS software (Version 17.0; SPSS Incorporation, Chicago, IL, USA). All statistical tests were two-sided, and probability values < 0.05 were regarded as statistically significant.

Results

Clinical characteristics

The characteristics of the patients are summarized in Table 1. The patients ranged in age from 46 to 83 years (mean, 66.8). There were 23 men and 28 women. The median follow-up period was 34 months (range 3 to 54 months).

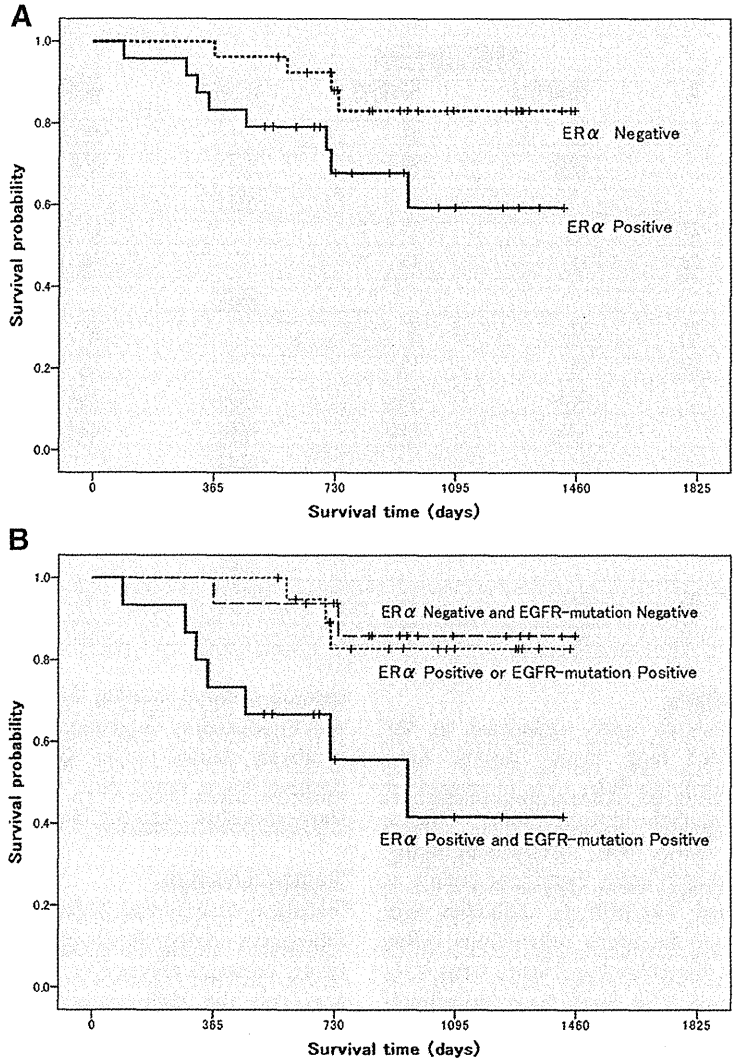

Figure 1 A. Kaplan-Meier curve for recurrence-free survival according to the presence or absence of membrane-bound ERα expression. The RFS tended to be worse in patients showing elevated mERα expression level in the tumor cells than that of the patients not showing tumor-cell mERα expression ($P = 0.076$, log-rank test). **B.** The RFS of the patients in the double-positive group was significantly worse than that of the other patients ($P = 0.003$, log-rank test).

Relationship between mERα expression and the clinicopathological characteristics

Of the 51 patients, 24 exhibited marked increase of the immunoreactivity of the tumor cells for mERα, whereas the remaining 27 showed no increase of mERα expression. Significant associations of the mERα expression level in the tumor cells were observed with the tumor differentiation grade ($P = 0.019$), presence or absence of vascular invasion ($P = 0.001$), and the SUV_{max} on FDG-PET ($P = 0.005$), but not with age ($P = 0.717$), sex ($P = 0.921$), smoking status ($P = 0.615$) or tumor size ($P = 0.051$) (Table 2). The RFS tended to be worse in patients showing elevated mERα expression level in the tumor cells than that of the patients not showing tumor-cell mERα expression; however, the association was not statistically significant ($P = 0.076$, log-rank test; Figure 1A).

Relationship between the mutation status of EGFR and the clinicopathological characteristics

Of the 51 patients, 26 had *EGFR* mutation, whereas the remaining 25 had wild-type *EGFR*. Significant associations of the *EGFR* mutation status were observed with sex ($P = 0.036$), tumor size ($P = 0.017$) and presence or absence of vascular invasion ($P = 0.006$), but not with age ($P = 0.319$), smoking status ($P = 0.124$), SUV_{max} on

Table 3 Relationship between membrane-bound ERα (mERα) expression or *EGFR* mutation and VEGF or Ki-67 expression

	mERα expression			*EGFR* mutation		
Factor	**Negative**	**Positive**	**p-value**	**Mutant**	**Wild**	**p-value**
VEGF						
negative	17	2	<0.001	9	10	0.691
positive	10	22		17	15	
Ki-67						
negative	21	8	0.001	13	16	0.313
positive	6	16		13	9	

FDG-PET ($P = 0.711$) or tumor differentiation grade ($P = 0.691$) (Table 2).

Associations of mERα expression and EGFR mutation with VEGF and Ki-67 expression

mERα expression was significantly correlated with VEGF expression ($P < 0.001$) and Ki-67 expression ($P = 0.001$). However, the presence of EGFR mutation was not correlated with either VEGF expression or Ki-67 expression (Table 3).

Relationships between mERα expression, EGFR mutation and clinicopathological characteristics

We categorized the 51 patients according to the presence or absence of mERα expression and *EGFR* mutation status as follows: Group-1 (n = 15): both mERα expression and *EGFR* mutation (double-positive); Group-2 (n = 20): either mERα expression or *EGFR* mutation (single-positive); Group-3 (n = 16): neither mERα expression nor *EGFR* mutation (double-negative). Significant association of the double-positive status was observed with sex ($P = 0.036$), presence of vascular invasion ($P < 0.001$), VEGF expression ($P = 0.018$) and Ki-67 expression ($P = 0.003$), but not with age ($P = 0.097$), tumor differentiation grade ($P = 0.150$), SUV_{max} on FDG-PET ($P = 0.168$) (Table 4). The RFS of the patients in the double-positive group was significantly worse than that of the other patients ($P = 0.003$, log-rank test; Figure 1B).

Table 5 Prognostic value of recurrence-free survival

Variable	Univariate analysis		Multivariate analysis	
	Unfavorable / favorable	**p-value**	**HR (95%CI)**	**p-value**
Sex	male / female	0.821		
Tumor differentiation	moderate+poor / well	0.006	1.96 (0.77-5.00)	0.157
Pathological stage	IB-IIIA / IA	0.005	2.74 (0.63-11.83)	0.178
double positive	Yes/ No	0.003	4.02 (1.13-14.22)	0.031

double positive: membrane-bound ERα expression positive and *EGFR* mutation positive.
HR: hazard ratio.
95%CI: 95% confidence interval.

Table 4 Relation among membrane-bound ERα (mERα) expression, *EGFR* mutation and clinicopathological characteristics

Characteristics	**mERα negative & *EGFR* wild**	**mERα positive or *EGFR* mutant**	**mERα positive & *EGFR* mutant**	**p-value**
Patients, number	16	20	15	
Age (mean), year	67.9	63.7	69.7	0.097
Sex				
Male	23	8	15	0.036
Female	28	18	10	
PET SUVmax	5.03	5.34	7.77	0.168
Tumor differentiation				0.150
well	11	17	7	
moderate+poor	5	3	8	
Vascular invasion				<0.001
negative	15	16	4	
positive	1	4	11	
VEGF expression				0.018
negative	10	7	2	
positive	6	13	13	
Ki-67 expression				0.003
negative	11	15	3	
positive	5	5	12	

A univariate analysis revealed that tumor differentiation grade ($P = 0.006$), pathological stage ($P = 0.005$) and double-positive status ($P = 0.003$) were independent risk factors influencing the RFS. However, a multivariate analysis identified only double-positive status as an independent risk factor influencing the RFS ($P = 0.031$) (Table 5).

Discussion

There have been several reports of cross-talk between ER (ERα or ERß) and EGFR status (protein expression or gene mutation). This is the first report focusing on mERα and *EGFR* mutation. In the present study, we found that patients with lung adenocarcinoma who had both mERα expression and *EGFR* mutation showed significantly poorer outcomes.

One of the factors peculiar to sex reported to be involved in lung cancer development is estrogen. For example, treatment with estrogen plus progestin in postmenopausal women did not increase the incidence of lung cancer, but increased the number of deaths from lung cancer, in particular deaths from non-small-cell lung cancer (NSCLC) [17]. ER enhances transcription in response to estrogens by binding to estrogen response elements and utilizing activator protein sites [18,19]. ERα exerts an augmenting effect on cell proliferation. On the other hand, ERß exerts a suppressive effect on cell proliferation via inhibition of ERα transcriptional activity [20,21]. The differential roles of ERα and ß in lung carcinogenesis and their biological properties are still controversial. In our study, mERα expression was significantly correlated with VEGF and Ki-67 expression. Therefore, we suggest that mERα may exert an augmenting effect on angiogenesis and cell proliferation.

Some recent studies have suggested the existence of bidirectional signaling between EGFR and ER [22,23]. In addition, two clinical studies have suggested the existence of cross-talk between ER and EGFR. First, Kawai *et al.* demonstrated that the combined overexpression of mERα and EGFR protein in patients with NSCLC was predictive of poorer outcomes [24]. They showed that while overexpression of either mERα or EGFR was also predictive of poor outcomes, combined overexpression of mERα and EGFR was an independent prognostic factor, suggesting the existence of cross-talk between mERα and EGFR. Overexpression of EGFR has been observed and its prognostic significance confirmed in various cancers. In NSCLC, Salvaggi *et al.* showed that overexpression of EGFR was correlated with a poor prognosis [25]. However, the factor that is most strongly associated with from EGFR-TKI therapy has been identified as *EGFR* mutation, but not EGFR protein expression [9]. In the present study, for the treatment of patients with NSCLC, we studied *EGFR* mutation but not EGFR protein expression. Second, Nose *et al.* demonstrated that the favorable prognostic significance of overexpression of ERß was influenced by the presence of *EGFR* mutation in lung adenocarcinoma [11]. They showed that the status of *EGFR* mutation did not affect the RFS, but that ERß expression was associated with a favorable prognosis. To date, several studies have identified ER as a prognostic factor in lung cancer. In general, ERα expression seems to be associated with a poor prognosis, and ERß expression with a favorable prognosis [14,24,26-28].

An important finding of the present study was that mERα expression and the categorized status of ERα expression/*EGFR* mutation was significantly correlated with the expression of Ki-67 and VEGF. Immunostaining with the Ki-67 antibody is a widely accepted method for evaluating the proliferative activity in a variety of human tumors. Tumors showing a high expression index of Ki-67 are frequently more aggressive than tumors showing a low Ki-67 expression index [16]. On the other hand, the VEGF family of proteins modulates angiogenesis, which is essential for tumor growth and metastasis. Expression of VEGF has been shown to be associated with tumor angiogenesis, metastasis, and prognosis in several cancers, including NSCLC [15]. To the best of our knowledge, no reports to date have shown a correlation between the expression of ER and VEGF or Ki-67. Our results using tissues from patients with lung adenocarcinoma tumors measuring less than 3 cm in diameter indicate that double marker positivity was significantly correlated with the expression of Ki-67 and VEGF.

Conclusions

This study demonstrated that the presence of mERα expression together with *EGFR* mutation is an independent prognostic factor in patients with lung adenocarcinoma, suggesting the existence of cross-talk between mERα expression and *EGFR* mutation.

Abbreviations

CT: Computer tomography; EGFR: Epidermal growth factor receptor; EGFR-TKI: EGFR tyrosine kinase inhibitor; ER: Estrogen receptor; FDG-PET: Fluorodeoxyglucose positron emission tomography; mERα: Membrane-bound estrogen receptor; NSCLC: Non-small-cell lung cancer; PCR: Polymerase chain reaction; PNA-LNA: peptide nucleic acid-locked nucleic acid; RFS: Recurrence-free survival; ROI: Regions of interest; SUV_{max}: maximal standardized uptake value; TNM: Tumor, nodule, metastasis; VEGF: Vascular endothelial growth factor.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Study concept and design: KS, MN. Data acquisition: SS, AM, KY. Data analysis and interpretation: KS, TY. Statistical analysis: KS, YH. Manuscript preparation: KS Manuscript review: MN. All authors have read and approved the final manuscript.

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Extended indications for robotic surgery for posterior mediastinal tumors

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Extended indications for robotic surgery for posterior mediastinal tumors

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Abstract

Previously, we evaluated use of the da Vinci Surgical System for anterior and middle mediastinal tumors in clinical cases, focusing on feasibility, safety, and appropriate settings. In this study, we evaluated extending the indications for robotic surgical treatment of posterior mediastinal tumors to include those located adjacent to the upper vertebrae or aorta. Three patients with mediastinal tumors located immediately adjacent to the vertebrae or aorta, underwent resection with the da Vinci Surgical System. All resected tumors were benign histologically. Robotic surgery enabled treatment of tumors located in the posterior mediastinum, which are very difficult to reach, making resection with the conventional video-assisted thoracoscopic surgery technique extremely difficult. All procedures were performed safely, smoothly, and extremely precisely. Crucial to the success of these operations were the appropriate placement and angle of the special da Vinci surgical ports in relation to the target and the patient's position, which varied according to the tumor location.

Keywords

mediastinal neoplasms, robotics, surgical procedures, minimally invasive, thoracic surgery, video-assisted

Introduction

We previously reported the use of the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA, USA) and its later version, the da Vinci S Surgical System (dVS), for various types of mediastinal tumors in clinical practice.[1] We also reported the appropriate settings according to tumor location, which are important in robotic surgery, especially in the space of the anterior and middle mediastinum.[2] In this report, we evaluated the feasibility and safety of extended indications for the dVS system in the surgical treatment of posterior mediastinal tumors located in difficult-to-reach areas. Video-assisted thoracoscopic surgery (VATS) is less invasive than a standard thoracotomy, however VATS has the problem of difficulty of manipulation in narrow spaces, such as the upper and lower thoracic spaces (near the apex or diaphragm) and immediately adjacent to the vertebrae and the aorta. The da Vinci and dVS systems have been used in very few cases of mediastinal tumors in Japan;[3,4] use of the new dVS for posterior mediastinal tumors has not yet been reported in Japan. We set out to establish a procedure for resection of posterior mediastinal tumors located in areas difficult to reach by the VATS technique.

Patients and Methods

Three patients, who underwent posterior mediastinal tumor dissection between March 2010 and April 2011, gave written informed consent to receive robotic surgery using the dVS. The institutional review committees of both institutions gave permission for these studies. These representative posterior mediastinal tumors were selected to assess the merits of the procedure. The tumors were located adjacent to the vertebrae in case 1, close to the upper thoracic vertebrae in case 2,

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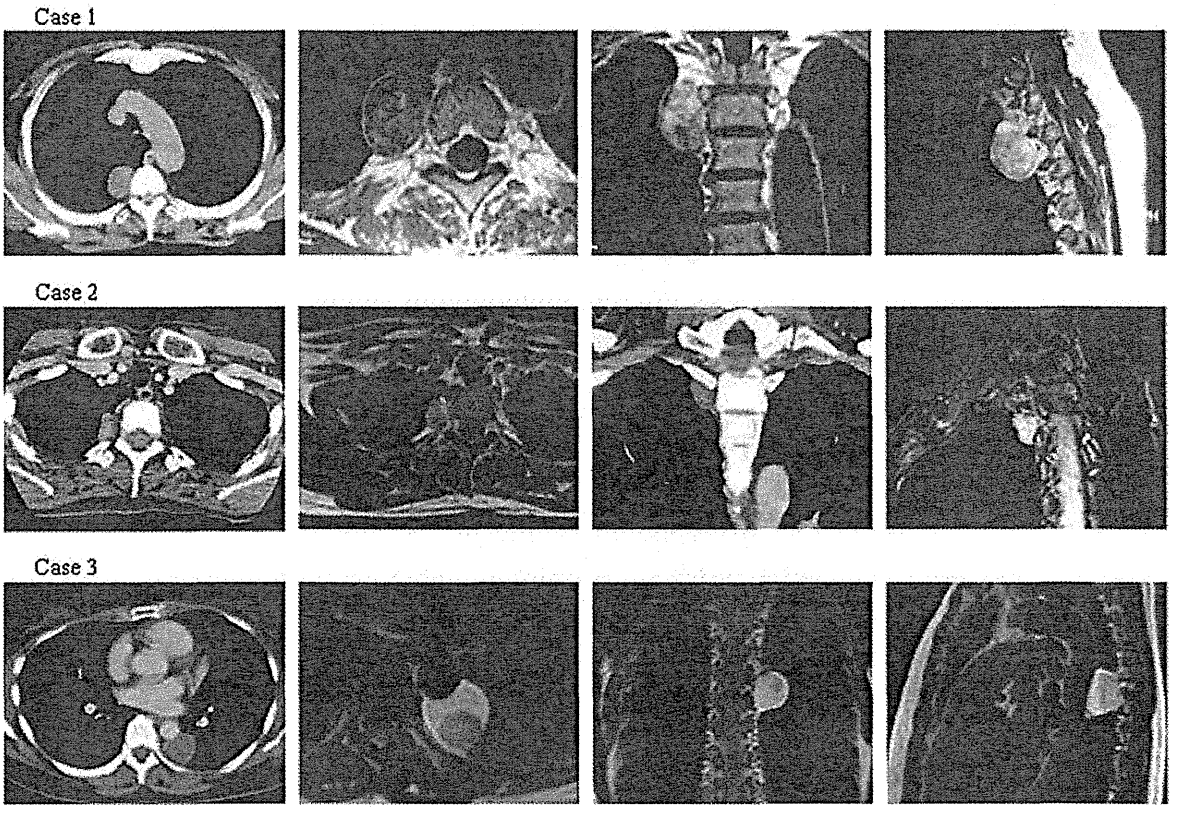

Figure 1. Chest computed tomography and magnetic resonance images showing the various posterior mediastinal tumors in 3 patients.

and in a narrow space between the aorta and the vertebrae in case 3 (Figure 1).

The dVS consists of a surgeon's console connected to the body of the da Vinci Surgical System, a manipulator unit with 3 instrument arms, including a central arm to guide the endoscope camera, to which the surgeon's movements are transmitted (Figure 2).[1,2] Typically, three 2-cm incisions and one 1-cm incision for accessory port access are made. A central 3-dimensional camera incision is made in the 6th intercostal space on the anterior-axillary line. Another 2 incisions are made in the appropriate intercostal spaces on the axillary line, depending on the location of the tumor. An additional 1-cm incision is made for accessory port access. To widen the narrow working space, CO_2 inflation of the thoracic space (high-flow; 8–10 mm Hg) was carried out during the dVS procedure. Tumor dissection was performed by 3 specialists in thoracic surgery, certified by the manufacturer to use the dVS.

Results

All 3 resected tumors were histologically classified as benign: schwannoma or bronchogenic cyst (Table 1). The time to set up the dVS, the procedure time from roll out to start of use, and other perioperative details are listed in Table 1. The surgical procedure caused no complication in any patient. For these procedures, the semilateral prone position, which enables an approach from the posterolateral side in cases where emergency access is required, was found to be optimal. During the procedure, the lower limbs of the patient were made to flex downward so that pelvis did not disturb the movement of the instrument arms, as shown in Figure 3. The operating surgeon (surgeon 1) manipulated the dVS from the console, located apart from the operating table, but pointing in the same direction as the camera. The table surgeons (surgeons 2 and 3) worked on the setting and replacement of instrument arms (Figure 2). Details of the positioning of all units are shown in Figure 2. The direction of the dVS, dVS arm position, and instrument arm placement depended on the location of the posterior mediastinal tumors, as shown in Figure 4A. Accurate setup of the dVS was crucial to the success of these operations, and this varied according to the location in the posterior mediastinum, as shown in Figure 4B and Table 2.

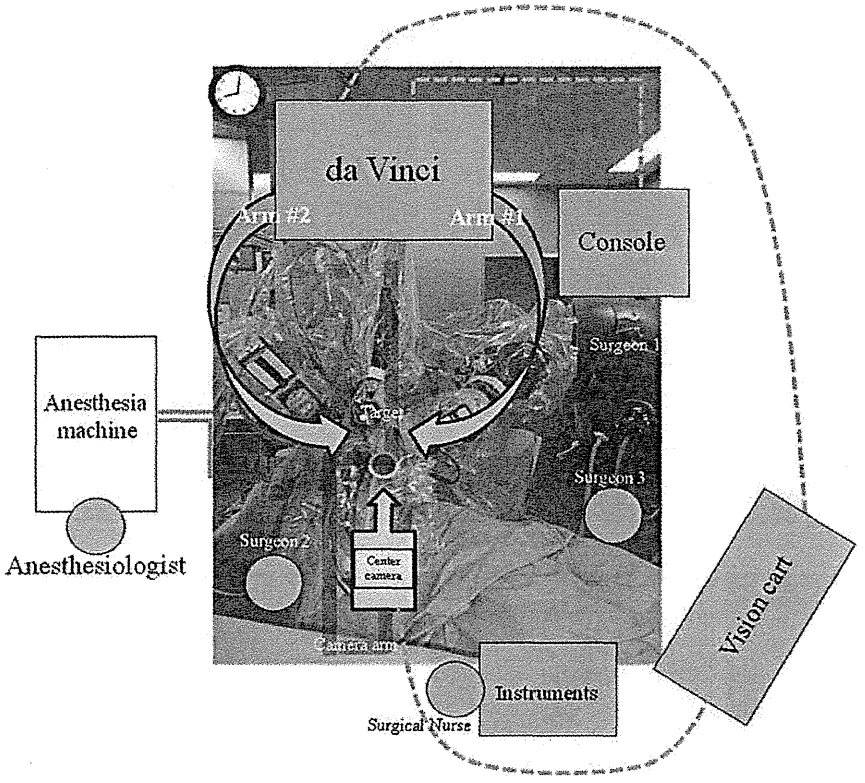

Figure 2. Appropriate positioning of the da Vinci S Surgical System (dVS), other instruments, thoracic surgeons, anesthesiologist, and surgical nurse. The direction of the patient was based on clock position. The dVS consists of a surgeon's console connected by wires to the body of the dV, and a manipulator unit with 3 instrument arms. The dVS was rolled in from the 2 o'clock direction in this figure.

Table 1. Operative and postoperative data of 3 patients with mediastinal tumors undergoing dVS resection.

Case No.	Sex	Age (years)	Diagnosis	Side	Tumor Location	Tumor Size (mm)	dVS Setup (min)	dVS Time (min)	Blood Loss (mL)	Drainage (days)	Pain Score*
1	F	57	Schwannoma	Right	Next to vertebrae (T3/4)	42 × 30 × 23	9	61	5	1	0
2	F	38	Schwannoma	Right	Apex (T2/3)	18 × 18 × 14	9	82	35	1	0
3	F	52	Bronchogenic cyst	Left	Next to aorta (T8/9)	31 × 30 × 27	8	54	5	1	0
Average							8.7	65.7	15	1	0

*On visual analog scale at discharge. dVS = da Vinci S Surgical System.

Discussion

The usefulness of the dVS in mediastinal surgery is important because of its advantages compared to a standard thoracotomy and VATS.[1,2,5–9] Although VATS is less invasive than a standard thoracotomy, there is the problem of postoperative pain caused by the inevitable leverage of instruments on the chest wall during the procedure, and the difficulty of manipulation in the mediastinum. The instrument arm used in the dVS causes less stress on the chest wall than conventional VATS, especially when highly skilled techniques are needed to operate on lesions in difficult-to-reach areas such as the upper, lower, anterior, and posterior mediastinum. The recent development of robotic surgery raises the question of whether it can yield comparable results in terms of safety and curability for thoracic diseases such as mediastinal tumors. In previous reports, we set out to determine the feasibility and safety of the dVS in performing anterior and middle

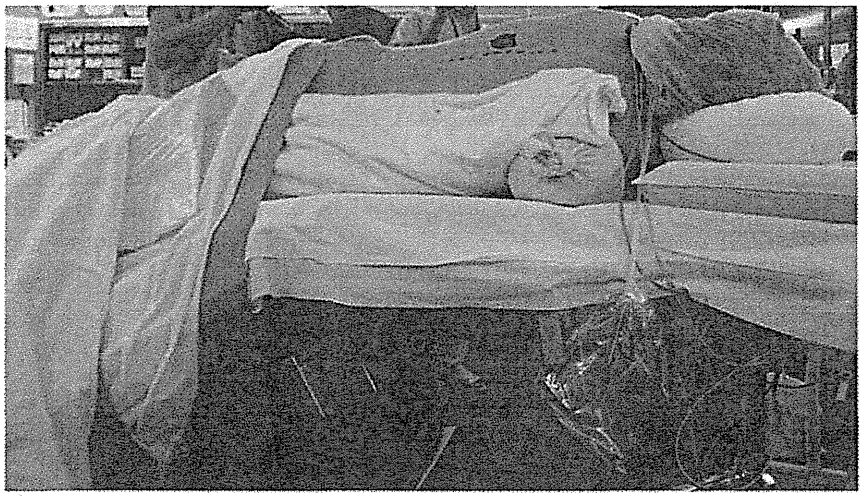

Figure 3. The patient was placed in semilateral prone position with the lower limbs flexed downward so that the pelvis did not disturb the movement of the instrument arms.

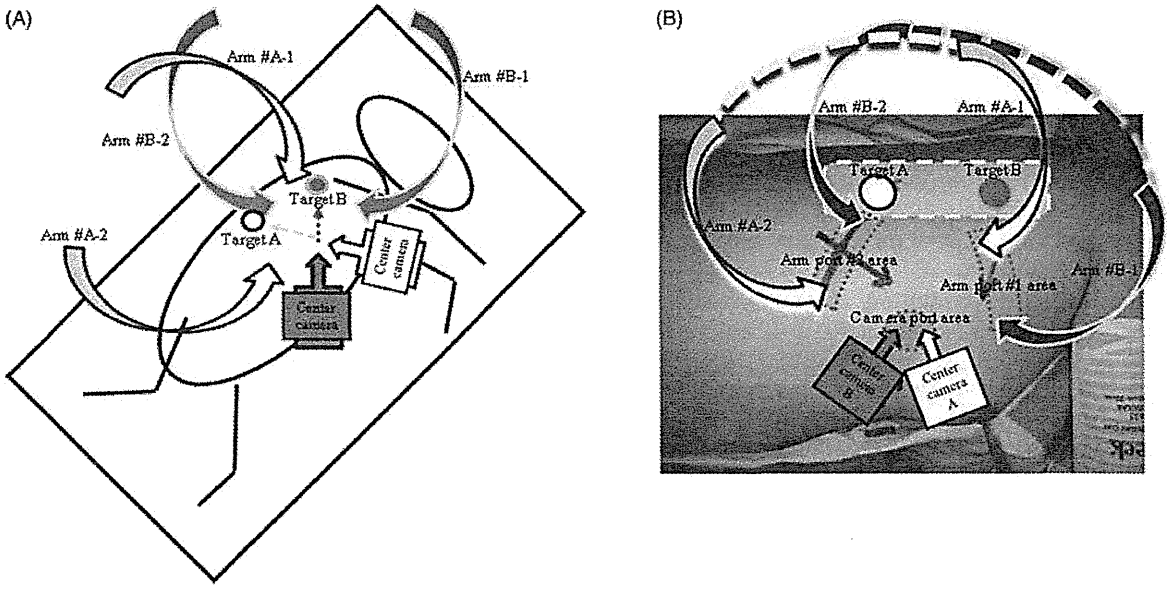

Figure 4. (A) Instrument arm ports for posterior mediastinal tumors: arm A (gray and white arrows) is placed for upper posterior tumors; arm B (dark gray arrows) is placed for lower posterior tumors. (B) Instrument arm ports for a right posterior tumor: the camera port is placed in the 6th intercostal space area on the anterior axillary line; arm 1 (A and B) is placed in the 3rd–4th intercostal space in the anterior axillary line; arm 2 (A and B) is placed in the 8th–9th intercostal space in the mid axillary line; an accessory port is placed in the 5th intercostal space in the anterior axillary line. For a left-sided tumor, arms 1 and 2 should be interchanged.

mediastinal tumor dissection, to contribute to the future establishment of operative guidelines and certification.[1,2]

Robotic surgery using the dVS has been approved in many countries for cardiovascular surgery, urology, and gynecology. However, unlike mediastinal tumors that can be located in many different sites, in other organs treated with the dVS (heart, bladder, prostate, and uterus), the tumors are generally found in similar locations. Moreover, the anatomical structures surrounding mediastinal tumors are vital (heart, aorta, lungs, pulmonary vessels, esophagus, and vertebrae). Very few institutions perform robot-assisted thoracic surgery routinely in Japan, and there are few reports of robotic posterior mediastinal tumor resection.[1,2,4,10,11]

Table 2. Positioning of patients and location of instrument arm ports in dVS resection of mediastinal tumors.

Case	Position	dVS Location	Camera Port	Camera Angle	Arm Port 1	Arm Port 2	Accessory Port
1	Left semilateral prone (45°)	Head side (10 o'clock)	6th intercostal space anterior-axillary line	Down (30°)	3rd intercostal space anterior-axillary line	9th intercostal space middle-axillary line	5th intercostal space anterior-axillary line
2	Same as above	Same as above	Same as above	Straight	Same as above	8th intercostal space middle-axillary line	Same as above
3	Right semilateral prone (45°)	Head side (2 o'clock)	Same as above	Down (30°)	9th intercostal space middle-axillary line	4th intercostal space anterior-axillary line	Same as above

dVS = da Vinci S Surgical System.

Conventional VATS is challenged by the narrow anatomical structure of the mediastinum; the most crucial aspect is the limited movement of long rigid instruments (stick surgery). However, the flexible joint movements of robotic surgery enables dissection of mediastinal tumors located in sites that are difficult to reach in the thoracic space, such as the posterior mediastinum. Dissection of posterior mediastinal tumors with this system enables an accurate, smooth, and safe surgical operation, because the range of motion of the robotic arms and wrists within small spaces is extremely extensive, as shown in Video 1 of case 1 with a schwannoma. The EndoWrist operative arm of the dVS is capable of replicating minute human wrist-like movements within the thoracic cavity. Moreover the EndoWrist system has motion scaling that eliminates physiological vibrations of the hands of the human surgeon. The endoscope of the dVS system provides a 3-dimensional high-resolution binocular view of the surgical field, and is capable of a 12-fold enlarged view. This is why maneuvers using the dVS are safer and more precise than those of conventional VATS, and curative levels similar to open thoracotomy can be obtained, but with lower complication rates. The crucial factors for successful dVS surgical procedures in thoracic surgery are selection of the appropriate placement and angle of the da Vinci surgical ports, selected in relation to the individual target and patient position, which varies according to the tumor location. Care in selecting the pre-setting according to tumor location is the most important stage for robotic surgery on such lesions. Adjustments to the position of the instrument arms are also necessary, depending on the level of the lesion.

In the instrument-port procedure, the first port was positioned for the 3-dimensional center camera placed in the 6th intercostal space on the anterior-axillary line. Another two ports for arms 1 and 2 were made (Figure 4B). Arm port 1 is usually placed in the 3rd–4th intercostal space on the anterior-middle axillary line, and arm port 2 is often placed in the 8th–9th intercostal space on the middle-posterior axillary line for right-sided posterior tumors. For tumors located in the left side of the thoracic cavity, the system and instrument ports positions were reversed, and areas for arms 1 and 2 should be changed correspondingly. The patient position on the operating table is also very important for the dVS procedure. A semilateral prone position is appropriate for resection of posterior mediastinal tumors, to avoid contacting the lung anteriorly under gravity. The lower limbs of the patient were also flexed downward so that the pelvis does not disturb the movement of the instrument arms, as shown in Figure 3. The 4th port is used as an accessory port for other devices such as those for vessel sealing and clipping, continuous suction, and washing; it was placed at least 5 cm apart from the other ports to prevent clashing of instrument arms. This accessory port was usually placed at the 5th intercostal space on the anterior axillary line. Although we used various types of surgical arm for tumor dissection, we usually attached the monopolar curved scissors on arm 1 and Maryland bipolar forceps or Cadiere forceps on arm 2. In conventional surgery, posterior tumors are dissected in stages around the surgical margin, necessitating movement of the operator or release and re-grasping of the tumor to turn it around. There is also a need to exchange monopolar and bipolar instruments; the former for tissue dissection, the latter for vascular transection and hemostasis. With the da Vinci system, these complicated aspects are eliminated because the flexibility of the tips of the robot arms allow a smooth continuous dissection, while the monopolar or bipolar features of both arms obviate the need for exchange of instruments.

Ng and colleagues[12] reported that results of VATS for posterior mediastinal tumor resection were comparable to those of conventional surgical techniques, in terms of symptomatic improvement, recurrence, and survival. Robotic surgery is associated with less postoperative pain, minimal surgical trauma, faster recovery and a rapid return to normal activities, yielding improved quality of life for patients. However, clinical data on long-term follow-up after robotic surgery are still insufficient, and should be clarified in a variety of fields. Our study found that robotic surgery using the

dVS yielded results similar to those of standard surgical procedures, at least in the perioperative period, and it appears safe, reliable, and less invasive. This instrument is better for the treatment of tumors located in difficult-to-reach areas than conventional VATS, but the positioning of all units and the location of arm ports need suitable directional settings, which depend on the tumor location.

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Conflicts of interest statement

None declared.

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ORIGINAL ARTICLE

Do tumours located in the left lower lobe have worse outcomes in lymph node-positive non-small cell lung cancer than tumours in other lobes?

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Abstract

OBJECTIVES: Although an association between prognosis and lobar location of lung cancer, particularly the left lower lobe (LLL), has been suggested, the certainty of such association remains controversial. The purpose of this study was to evaluate the impact of tumour lobar location on surgical outcomes as an independent prognostic factor for survival in our non-small cell lung cancer (NSCLC) patient series.

METHODS: We retrospectively reviewed 978 NSCLC patients who underwent complete resection in our hospital between 2000 and 2007. We statistically analysed the association between clinicopathological factors and clinical outcomes.

RESULTS: Among the 978 patients reviewed, the NSCLC was located in the LLL in 143 (14.6%) patients, and lymph node involvement was identified in 210 patients (21.5%). The 5-year overall survival rates of patients whose NSCLC was located in the LLL and in other lobes (non-LLL) were 73.1 and 74.3%, respectively, and showed no significant association ($P = 0.86$). On the other hand, the 5-year survival rates of patients whose NSCLC occurred in the LLL ($n = 33$) and non-LLL ($n = 177$) and with lymph node metastasis were 32.7 and 57.7%, respectively, and showed a significant association ($P = 0.01$). Therefore, we performed a more detailed analysis on the 210 NSCLC patients with lymph node metastasis. On multivariate analysis, we found that LLL tumour ($P = 0.02$), tumour size >3 cm ($P = 0.02$) and N status ($P < 0.001$) were significant independent predictors for survival.

CONCLUSIONS: LLL tumours with lymph node metastasis are strongly associated with mortality in NSCLC patients. The location of the primary tumour may contribute in determining the optimal management strategy and accurate prediction of prognosis.

Keywords: Lung cancer • Prognostic factor • Tumour location • Lymph node metastasis

INTRODUCTION

Lung cancer is the leading cause of cancer mortality in the world, and non-small cell lung cancer (NSCLC) comprises the majority of lung cancers. Complete resection, whenever feasible, is generally recognized as the most effective initial treatment for NSCLC. However, even with complete resection, the 5-year survival rates are disappointing and range from 79.4–83.9% for stage IA to 29.8–32.8% for stage IIIA [1–3].

Lower lobe tumours have been reported to be associated with poorer survival than upper lobe tumours [4]. On the other hand, it has also been contended that tumour location within the lungs does not independently predict survival [5]. Thus, whether the location of a tumour in the lungs is a prognostic factor remains controversial.

The purpose of this study was to evaluate the impact of tumour lobar location as an independent prognostic factor for survival in a long series of NSCLC patients at our institution.

MATERIALS AND METHODS

From January 2000 to December 2007, a total of 1145 patients underwent complete resection of NSCLC at our hospital. We excluded 167 patients who had received preoperative chemotherapy, radiotherapy or both, or who had been given a diagnosis of low-grade malignant histologies, including carcinoid, mucoepidermoid carcinoma and adenoid cystic carcinoma. The remaining 978 patients were enrolled in this study. We defined complete resection as lobectomy or more extensive lung resection with systemic ipsilateral hilar and mediastinal lymph node dissection and no evidence of residual cancer either macroscopically or microscopically. The median follow-up period was 3.8 years. The Institutional Review Board of our hospital approved the data collection and analyses, and waived the need to obtain written informed consent from each patient since all data were retrospective.

We reviewed the medical records of each patient for clinicopathological information including age, gender, pathological

nodal involvement, vessel invasion (vascular invasion and lymphatic permeation), pleural invasion (as defined in the 7th Edition of the TNM Classification for Lung and Pleural Tumors), tumour location and histologic type. Disease stages were based on the 7th Edition of the TNM Classification for Lung and Pleural Tumors of the Union for International Cancer Control. The histologic type was determined according to the 3rd Edition of the World Health Organization Classification. We used haematoxylin-eosin and Elastica van Gieson stains for the evaluation of vessel and pleural invasion.

Overall survival (OS) was estimated using the Kaplan–Meier method, and differences in survival were determined by log-rank analysis. Zero time was the date of pulmonary resection, and the end point was defined as the date of death from any cause. The last follow-up observation was censored when the patient was alive or lost to follow-up. All *P*-values were two-sided and *P*-values <0.05 were considered a statistically significant difference. Univariate analysis was conducted among the different groups.

Categorical variables were analysed using the χ^2-test. Differences between two groups were tested using Student's *t*-test. Multivariate analysis was performed using the Cox proportional hazards model to examine the association between survival and potential prognostic factors. A probability value of <0.05 was considered statistically significant. All statistical calculations were performed using SPSS for Windows version 15.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

The characteristics of the patients are shown in Table 1. The 978 patients in this study consisted of 574 men (58.7%) and 404 women (41.3%). The mean age was 65.0 years (range: 22–86). Among the 978 patients, the tumours in 143 (14.6%) patients were located in the LLL. The 143 patients with LLL tumours had a lower proportion of adenocarcinoma than the 835 patients with non-LLL tumours, and there were significant differences in histology (adenocarcinoma vs non-adenocarcinoma) between LLL and non-LLL tumours ($P = 0.02$). Tumour size was significantly larger in LLL tumours than in non-LLL tumours (mean: 3.4 and 2.9 cm, respectively; $P = 0.0001$). However, there was no

Table 1: Patient characteristics ($n = 978$)

Variable	Number (%)			*P*-value (LLL vs non-LLL)
	All ($n = 978$)	LLL ($n = 143$)	Non-LLL ($n = 835$)	
Sex (%)				
Men	574 (58.7)	85 (59.4)	489 (58.6)	0.84
Women	404 (41.3)	58 (40.6)	346 (41.4)	
Mean age (range)	65.0 (22–86)	66.0 (22–85)	64.8 (22–86)	0.19
Tumour location (%)		143 (14.7)	RUL 340 (34.8) RML 69 (7.1) RLL 212 (21.7) LUL 214 (21.9)	-
Histological type (%)				
Adenocarcinoma	726 (74.2)	93 (65.0)	633 (75.8)	0.02*
Squamous cell carcinoma	183 (18.7)	38 (26.6)	145 (17.4)	
Large cell carcinoma	50 (5.1)	7 (4.9)	43 (5.1)	
Others	19 (2.0)	5 (3.5)	14 (1.7)	
Operation procedure (%)				
Lobectomy/bilobectomy	961 (98.3)	138 (96.5)	823 (98.6)	0.08
Pneumonectomy	17 (1.7)	5 (3.5)	12 (1.4)	
Mean tumour size (cm) (range)	2.9 (0.4–15.0)	3.4 (0.7–15.0)	2.9 (0.4–13.0)	0.0001*
pT factor (%)				
T1a/T1b	472 (48.3)	69 (48.2)	403 (48.3)	0.85
T2a/T2b	441 (45.1)	63 (44.1)	378 (45.3)	
T3/T4	65 (6.6)	11 (7.7)	54 (6.4)	
pN factor (%)				
N0	768 (78.5)	110 (76.9)	658 (78.8)	0.37
N1	119 (12.2)	22 (15.4)	97 (11.6)	
N2	91 (9.3)	11 (7.7)	80 (9.6)	
P-stage (%)				
IA	420 (40.9)	63 (44.0)	357 (42.7)	0.47
IB	286 (29.2)	35 (24.5)	251 (30.1)	
IIA	118 (12.1)	22 (15.4)	96 (11.5)	
IIB	49 (5.0)	9 (6.3)	40 (4.8)	
IIIA	105 (10.7)	14 (9.8)	91 (10.9)	
Vascular invasion (%)	383 (40.9)	56 (39.2)	327 (39.2)	0.95
Lymphatic permeation (%)	453 (48.5)	71 (49.6)	382 (45.7)	0.39
Pleural invasion (%)	250 (25.6)	42 (14.9)	208 (24.9)	0.49

RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe.
*$P < 0.05$.

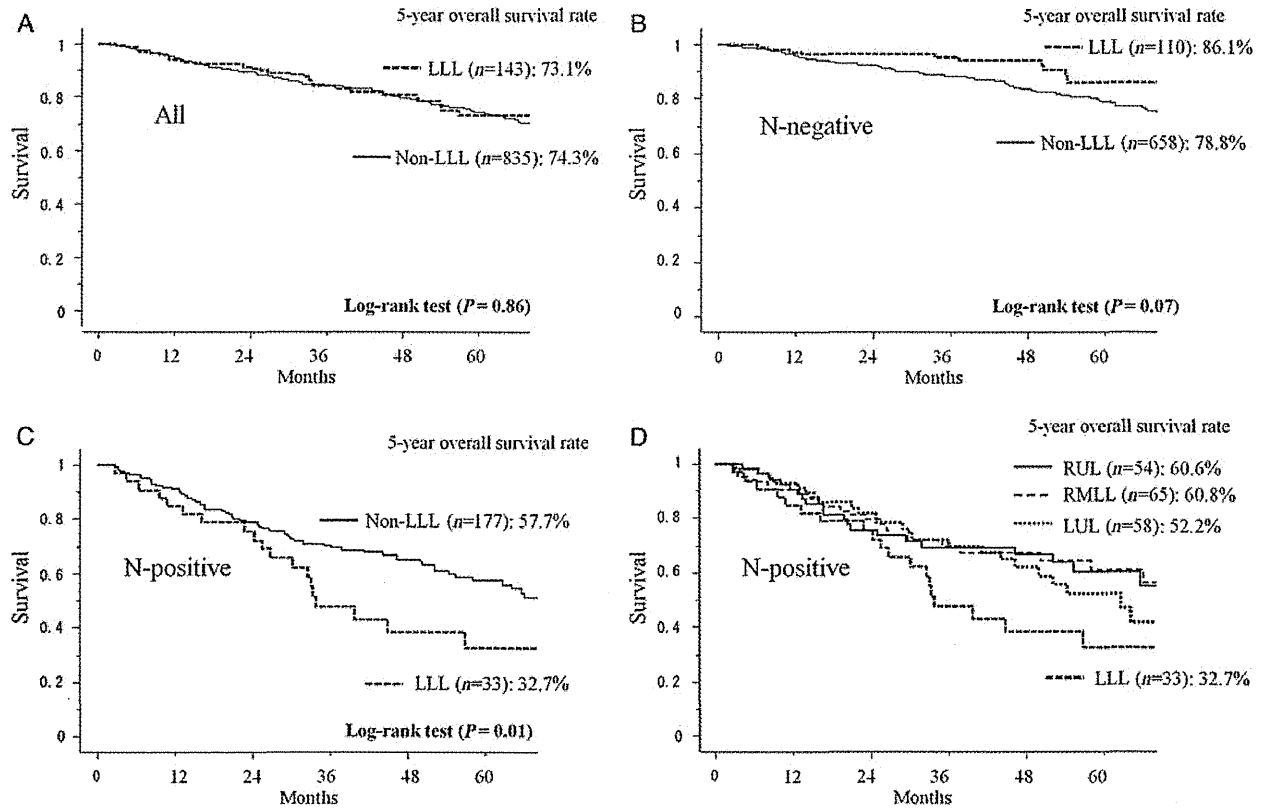

Figure 1: (A) Survival curves of all patients classified by the primary tumour site. No significant differences in survival outcomes were observed ($P = 0.86$). (B) Survival curves of all patients without lymph node metastasis classified by the primary tumour site. No significant differences in outcomes were observed ($P = 0.07$). (C) Survival curves of all patients with lymph node metastasis classified by the primary tumour site. Significant differences in outcomes were observed ($P = 0.01$). (D) Survival curves of all patients with lymph node metastasis classified by the primary tumour site. Significant differences in outcomes were observed between LLL and RUL, or RMLL ($P = 0.03$ and 0.03, respectively), and no slight differences in outcomes was observed between LLL and LUL ($P = 0.056$). RUL: right upper lobe; RMLL: right middle or lower lobe; LUL: Left upper lobe; non-LLL: other lobes; LLL: Left lower lobe.

significant difference between LLL and non-LLL tumours with regard to the several clinical factors including sex, age, operation procedure, pT factor, pN factor, p-Stage, vascular invasion, lymphatic permeation and pleural invasion.

The 5-year OS rates in patients whose NSCLC were located in the LLL and other lobes (non-LLL) were 73.1 and 74.3%, respectively ($P = 0.86$) (Fig. 1A). In 768 patients without lymph node metastasis, the 5-year OS rates for LLL ($n = 110$) and non-LLL ($n = 658$) tumours were 86.1 and 78.8%, respectively, with no significant difference ($P = 0.07$) (Fig. 1B). However, in 210 patients with lymph node metastasis, the 5-year OS rates for LLL ($n = 33$) and non-LLL ($n = 177$) tumours were 32.7 and 57.7%, respectively, showing a significant association between survival rates and tumour lobe location in NSCLC patients with nodal metastasis ($P = 0.01$) (Fig. 1C). Notably, although the 5-year OS rate of N1 patients with non-LLL (74.2%) was significantly higher than that of N1 patients with LLL (33.6%) ($P = 0.0007$), there was no significant difference in the 5-year OS rate between N2 patients with LLL (39.0%) and N2 patients with non-LLL (36.9%) ($P = 0.42$) (data not shown). Moreover, we divided all cases into four groups [right upper lobe (RUL), right middle or lower lobe (RMLL), left upper lobe (LUL) and left lower lobe (LLL)] according to tumour locations, and performed analysis for survival. In patients with lymph node metastasis, the 5-year OS rates for RUL ($n = 54$), RMLL ($n = 65$), LUL ($n = 58$) and LLL ($n = 33$) were 60.6, 60.8, 52.1 and 32.7%, respectively (Fig. 1D). There was a statistically significant difference in the 5-year OS rate between LLL and RUL, or RMLL ($P = 0.03$ and 0.03, respectively), but while the 5-year OS rate for LLL was worse than that of LUL there was no statistically significant difference ($P = 0.056$). On the other hand, in patients without lymph node metastasis, the 5-year OS rates for RUL ($n = 286$), RMLL ($n = 216$), LUL ($n = 156$) and LLL ($n = 110$) were 78.0, 78.5, 80.6 and 86.1%, respectively. There was no significant difference in the 5-year OS rates among LLL and RUL, RMLL, or LUL ($P = 0.16$, respectively) (data not shown).

We conducted a more detailed analysis on the 210 patients with lymph node metastasis to clarify the association of various prognostic factors with survival rate. Univariate analysis showed that a tumour size of >3 cm ($P = 0.01$), N2 ($P < 0.0001$), the presence of pleural invasion ($P = 0.006$) and LLL tumour ($P = 0.01$) were risk factors significantly associated with survival (Table 2). Multivariate analysis using the Cox regression model demonstrated that LLL tumour [hazard ratio (HR) = 1.84, 95% confidence interval (CI): 1.12–3.05, $P = 0.02$], a tumour size of >3 cm (HR = 1.68, 95% CI: 1.08–2.63, $P = 0.02$) and N status (HR = 2.28, 95% CI: 1.47–3.54, $P < 0.001$) were significant independent predictors for survival (Table 3).

Table 2: Univariate survival analysis in N-positive NSCLC ($n = 210$)

Variable		Number of patients	5-year survival rate (%)	*P*-value
Sex	Men	146	53.7	0.93
	Women	64	53.5	
Age	<70	139	54.3	0.12
	70	71	51.6	
Right vs left	Right	119	60.5	0.08
	Left	91	44.9	
Location	Non-LLL	177	57.7	0.01*
	LLL	33	32.7	
Histological type	Non-Ad	90	55.0	0.37
	Ad	120	52.6	
Tumour size	3 cm	86	65.2	0.009*
	>3 cm	124	45.4	
N status	N1	119	65.7	<0.0001*
	N2	91	36.6	
Pleural invasion	Absent	125	64.2	0.006*
	Present	83	37.3	
Vascular invasion	Absent	45	67.6	0.06
	Present	153	47.2	
Lymphatic permeation	Absent	26	56.2	0.66
	Present	174	52.2	

LLL: left lower lobe; non-LLL: other lobes; Ad: adenocarcinoma; non-Ad: other histological types.
*$P < 0.05$.

Table 3: Multivariate survival analysis in N-positive NSCLC ($n = 210$)

Variable	HR	95% CI	*P*-value
Location (LLL vs non-LLL)	1.84	1.12–3.05	0.02*
Tumour size (>3 cm vs 3 cm)	1.68	1.08–2.63	0.02*
N status (N2 vs N1)	2.28	1.47–3.54	<0.001*
Pleural invasion (present vs absent)	1.24	0.79–1.94	0.26

LLL: left lower lobe; non-LLL: other lobes; CI: confidence interval.
*$P < 0.05$.

DISCUSSION

The TNM stage classification was developed to provide high specificity for patients with a similar prognosis and treatment options. There are several recent reports of poor prognostic factors in lung cancer [6, 7]. In the TNM classification, the location of the primary tumour does not affect prognosis. However, several studies of prognostic factors in resected NSCLC showed that lower lobe lesions increase mortality.

Lower lobe tumours were previously shown to be associated with worse-term survival than upper lobe tumours [4]. Moreover, death within 5 years is caused more frequently by lower lobe tumours than by upper lobe tumours, the difference between the right and left lungs being largely due to the low survival rate associated with tumours of the LLL [8]. A previous study has shown that differences in survival rates are associated with lobar location, such that patients with upper lobe tumours showed better long-term survival than patients with middle lobe or lower lobe tumours [9]. Recent studies have shown that tumours located in non-upper lobes such as the right middle lobe (RML), right lower lobe (RLL) and LLL independently had an increased risk of mortality in patients with stage IB NSCLC compared with tumours located in the upper lobes [10]. Similarly, multivariate analysis of patients undergoing surgery for T2 tumours previously showed that patients with LLL tumours had significantly worse survival outcomes than those who had tumours in other lobar locations [11]. Rocha *et al.* [12] found that the presence of the primary tumour in the lower lobe was the only statistically significant factor associated with upstaging, and other factors such as patient age, smoking history, weight loss, tumour size and tumour histology were not associated with upstaging.

In our NSCLC patient series, the OS curves between LLL and non-LLL patients were similar for all patients, and no significant difference was observed ($P = 0.86$). However, in patients with lymph node metastasis, the 5-year OS rates of LLL and non-LLL patients were 32.7 and 57.7%, respectively, showing a significant difference between the two categories ($P = 0.01$). Moreover, according to the analysis between the four groups of tumour locations in patients with lymph node metastasis, LLL tumours had significantly worst survival, with only a slight difference between LLL and LUL ($P = 0.056$). When we subdivided the N category into pN1 and pN2 subgroups, the survival rate of LLL patients was significantly different from that of non-LLL patients for pN1 ($P < 0.001$), but not for pN2 ($P = 0.42$). Moreover, the 5-year OS of 33.6% in LLL patients with N1 was lower than that of 39.0% in LLL with N2, but there was no statistically significant difference ($P = 0.39$) (data not shown). In the N1 patients, there was no significant difference in the number of metastatic lymph node, in the pattern of recurrence (locoregional or distant), or in the cause of death between LLL and non-LLL groups (data not shown). We have not fully clarified the underlying reasons for this finding but we speculate that the lack of statistical significance may be, in part, due to the small number of LLL patients with pN2 ($n = 11$). These results suggest that the unfavourable prognosis of lower lobe lesions is affected by the presence or absence of lymph node metastasis. In particular, this study showed that tumour size ($P = 0.01$), N status ($P < 0.0001$), pleural invasion ($P < 0.01$) and tumour location ($P = 0.01$) accounted for significant differences between the OS curves of patients with lymph node metastasis. On multivariate analysis, LLL tumour with lymph node metastasis was shown to be an independent prognostic factor for OS, as well as tumour size and N status (HR = 1.84, 95% CI: 1.12–3.05, $P = 0.02$).

Right lung cancer spreads mainly to mediastinal ipsilateral nodes. In left lung cancer, contralateral and ipsilateral lymphatic spread occurs with the same frequency on each side [8]. The lymphatic drainage of the lungs to the mediastinal lymph nodes has been studied extensively. Various techniques of injection of dyes into the lymphatic channels of lungs from autopsy specimens of stillborn infants and adults without pulmonary disease have been used by Rouvière [13]. Notably, the dynamic study using lymphoscintigraphy in normal healthy subjects and the lymphatic drainage routes described by Hata *et al.* [14] are generally in agreement with the patterns described by Nohl-Oser [15]. Drainage from the basal segments of the RLL rarely distributed to the left side of the mediastinum. In contrast, contralateral mediastinal drainage from the left lung is relatively common,

Table 4: Summary of studies of the association between tumour location and prognosis

Authors	Journal	N	Case	Location	*P*-value
Positive association					
Iwasaki *et al.* [11]	*ICVTS* 2004	93 (total, 268) (34.7%)	T2	LLL vs others	0.0258
Ichinose *et al.* [9]	*JTCVS* 2001	N2	Stage IIIA-N2	Four primary sites (LLL, RMLL, RUL, LUL)	0.0378
Ou *et al.* [10]	*Cancer* 2007	N0	Stage IA/IB	Upper vs non-upper	0.0072/<0.0001
Bignall and Moon [8]	*Thorax* 1955	133 (total, 233)	Unknown	Four primary sites (right upper/lower, left upper/lower)	Data not shown (LLL: worst survival)
Hayakawa *et al.* [18]	*JJCO* 1996	126 (total, 141)	Stage III(A/B)s	Upper + superior segment of lower lobe vs lower lobe	0.032
Inoue *et al.* [19]	*JTCVS* 2004	N2	Stage IIIA	Upper vs middle or lower	0.0362
Negative association					
Puri *et al.* [5]	*ATS* 2010	0/144 (total, 841)	Stage I/II	Upper vs lower, right vs left	0.57/0.63, 0.78/0.71
Inoue *et al.* [19]	*JTCVS* 2004	N0, 1	StageIIIA-N2 (N0–1 data are only shown in discussion)	Upper vs middle or lower	No survival difference (data not shown)
Huhti *et al.* [20]	*EJRD* 1983	NX	Unknown	Four major lobes	Data not shown

LLL: left lower lobe; RMLL: right middle and lower lobe; RUL: right upper lobe; LUL: left upper lobe.

occurring most frequently through the subcarinal nodes, as initially pointed out by Rouvière [11] and reconfirmed by all subsequent studies. Occasionally, crossover occurs through the lower paratracheal nodes in drainage from the LLL. Nohl-Oser [15] previously reported that the metastasis rate to the right upper paratracheal nodes was 22% for LUL cancer and 40% for LLL cancer, and the incidence rate of contralateral metastases from tumours in the RLL in metastatic mediastinal node disease was 7%. Left hilar lymphatics connect to left tracheobronchial nodes or right paratracheal nodes via subcarinal nodes. Therefore, LLL tumours may tend to spread to contralateral mediastinal lymph nodes.

Although Toker *et al.* [16] reported that dissection of the contralateral paratracheal lymph nodes is possible without undertaking more extensive surgical dissection, including cervical dissection techniques, in our NSCLC patient series, we performed systematic mediastinal lymph node dissection, defined as the en-bloc removal of all ipsilateral lymph nodes along with the surrounding fat tissue. Since we did not perform contralateral mediastinal lymph node dissection, we could not accurately evaluate the involvement of contralateral mediastinal lymph nodes in patients with no CT evidence of contralateral lymph nodes. Patients with LLL tumours with lymph node metastasis may include N3 patients who have contralateral mediastinal lymph node metastasis, despite no evidence of contralateral lymphadenopathy on preoperative CT film. In such cases, the majority of first recurrences may be locoregional. In our patient series, however, the first recurrence was more frequently distant recurrence than locoregional recurrence in both LLL and non-LLL tumours, and there were no significant differences in recurrence rates between LLL and non-LLL tumours (data not shown). Distant recurrence is easier to assess clinically and radiographically than locoregional recurrence, and thus the rate of locoregional recurrence can be underreported. Lymph node metastasis promoted a higher incidence of distant recurrence rather than local recurrence [17].

Moreover, tumour size was significantly larger in LLL tumours than in non-LLL tumours ($P = 0.0001$). These patients with LLL tumours had worse survival outcomes, possibly due to the LLL tumours being hidden by the shadow of the left heart, which made them difficult to find.

A summary of studies [5, 8–11, 18–20] showing the association between tumour location and prognosis is shown in Table 4. Regardless of LLL tumours, most studies, except the study of Ou *et al.* [8], indicate that in the advanced stage, tumour location affects the prognosis, Puri *et al.* [5] showed no relationship between tumour location and prognosis in the early stage and Inoue *et al.* [19] reported that tumour location does not affect prognosis in N0 or N1 tumours. Based on our present results, we speculate that tumour location is less likely to affect survival in early-stage tumours, but the prognosis may be affected by tumour location in advanced stage tumours. We, therefore, conclude that LLL tumours have worse outcomes in lymph node-positive NSCLC.

The limitations of this study include its retrospective nature, which evaluated cases from 2000, a small sample size, and the fact that routine adjuvant chemotherapy for N1 or higher patients was started in 2004. These limitations complicated the evaluation of the effects of tumour location on prognosis with respect to adjuvant chemotherapy.

In conclusion, LLL tumours were found to be strongly associated with mortality in NSCLC patients with lymph node metastasis. The location of the primary tumour may aid in determining the optimal management strategy and allow for more accurate prediction of prognosis. This may affect staging criteria and further studies are needed to clarify the underlying reasons why LLL tumours with lymph node metastasis have unfavourable prognoses.

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