NSCLC patients. To overcome the inherent disadvantages of FDG-PET such as poor quality of the anatomical information, new imaging systems using integrated FDG-PET/CT were developed recently [5]. This integrated approach provides higher sensitivity compared with CT alone in MLN staging for NSCLC.

A practical approach adopted in many centers is scheduling patients with negative mediastinal uptake by integrated FDG-PET/CT for resection [6]. However, the incidence of occult MLN metastasis in NSCLC patients showing negative uptake by FDG-PET/CT is 7–16% [6–8]. Several studies therefore investigated factors associated with occult MLN metastasis in NSCLC patients [6–8], since a successful prediction could select candidates for either preoperative cervical mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration. However, these studies were limited in that no histological examination of the involved MLNs was undertaken nor was a source of the negative result by integrated FDG-PET/CT discussed sufficiently.

The aim of the present study was to define risk factors for occult MLN metastasis in patients with NSCLC diagnosed as clinical N0-1 by preoperative integrated FDG-PET/CT and CT. Histopathological examination of the involved MLNs was conducted to examine why these lymph nodes were diagnosed as negative. The patterns of occult MLN metastasis were also analyzed.

2. Patients and methods

2.1. Patient eligibility and staging

The study retrospectively evaluated patients with NSCLC in our hospital who underwent staging by integrated FDG-PET/CT as an adjunct to CT from October 2006 to September 2009. No patient underwent preoperative mediastinoscopy in this period. The following patients were excluded from the present study: those who underwent limited resection (wide-wedge resection or segmentectomy; $n = 144$), patients with diabetes mellitus ($n = 39$), patients who received neo-adjuvant chemotherapy ($n = 11$), and patients with positive mediastinal uptake on integrated PET-CT or enlarged MLNs on CT (i.e., clinical N2/N3; $n = 39$). The remaining 224 patients were staged as clinical N0 or N1 by integrated FDG-PET/CT and CT, and underwent resection with systematic lymph node dissection. The preoperative CT, integrated FDG-PET/CT, and pathological findings were reviewed. Preoperative clinical staging and postoperative pathological staging was based on the 1997 update of the TNM staging system [9]. The study group comprised 122 men and 102 women age from 30 to 83 years (mean age of 65.5 years). Table 1 details the patient characteristics and preoperative tumor evaluations.

2.2. CT imaging

All studies (CT and integrated FDG-PET/CT) were interpreted independently. CT examination was performed using a helical scanner (LightSpeed VCT, General Electric, Waukesha, WI; Aquilion 16, Toshiba, Tokyo, Japan), and all patients had contrast-enhanced CT. Lymph nodes were interpreted as positive if >1 cm across the short-axis diameter. All positive nodes were localized according to the lymph node stations, based on the classification by Naruke et al. [10].

A tumor was deemed central if its center was located in the inner 1/3 of the lung parenchyma (adjacent to the mediastinum) on transverse CT imaging. Non-centrally located tumors were identified as those centered in the outer 2/3 of the lung parenchyma on transverse CT imaging. All CT images were performed within 4 weeks of surgery.

Table 1
Characteristics of patients and tumors ($n = 224$).

Characteristics	Distribution (%)
Sex	
Male	122 (54)
Female	102 (46)
Age (years)	
Mean ± SD	65.5 ± 8.9
Range	30–83
Smoking status	
Smoker	131 (58)
Never smoker	93 (42)
Concurrent lung disease[a]	
Present	40 (18)
Absent	184 (82)
Elevated serum CEA level (>5 ng/ml)	
Yes	68 (30)
No	156 (70)
Lobar distribution of the tumor	
RUL	100 (45)
RML	12 (5)
RLL	38 (17)
LUL	45 (20)
LLL	29 (13)
Location of the tumor	
Central	18 (8)
Non-central	206 (92)
Positive N1 node on PET/CT	
Yes	39 (17)
No	185 (83)
Tumor size (cm)	
Median	3.0
Mean ± SD	3.1 ± 1.5
Range	0.8–9.0
SUV_{max} of primary tumor	
Median	4.0
Mean ± SD	5.6 ± 5.1
Range	0–22.8

[a] Concurrent lung disease includes interstitial lung disease, chronic obstructive pulmonary disorder, bronchial asthma, and tuberculosis.

2.3. Integrated FDG-PET/CT imaging

Patients were asked to fast, except for glucose-free oral hydration, for at least 5 h before the injection of ^{18}F-FDG (3.5 MBq/kg body weight). After injection of the tracer, patients were kept lying comfortably on a bed. No urinary bladder catheterization was performed and no oral muscle relaxants were administered. Whole-body PET/CT fusion scanning was performed 1 h after the injection, using a PET/CT system (Discovery LS, General Electric, Waukesha, WI; Biograph Duo LSD, Siemens-Asahi Medical Technologies, Tokyo, Japan). PET, CT, and integrated PET/CT images were available for review, displayed in axial, coronal, and sagittal planes. The FDG uptake of tumor was visually compared with that of the surrounding tissue in areas devoid of prominent artifacts and overlapping increased FDG uptake organs. A team of experienced radiologists reviewed the integrated FDG-PET/CT images independently from the CT data. Nodal uptake with a standardized uptake value (SUV_{max}) >2.5 were interpreted as positive. All integrated FDG-PET/CT imaging was performed within 4 weeks of surgery.

2.4. Surgical resection

All of the surgical resections and mediastinal nodal dissections were conducted by thoracic surgeons at Osaka Medical Center for Cancer and Cardiovascular Diseases. Systematic lymph node dissection was carried out.

Table 2
Postoperative pathological evaluation of the tumors.

Type of operation	
Lobectomy	213 (95%)
Bilobectomy	10 (4%)
Pneumonectomy	1 (1%)
Histopathological type	
Adenocarcinoma	180 (80%)
Squamous cell carcinoma	37 (17%)
Other types[a]	7 (3%)
Lymph node metastasis	
pN0	168 (75%)
pN1	32 (14%)
pN2	24 (11%)
Pathological stage after surgery[b]	
IA	101 (46%)
IB	64 (29%)
IIA	10 (4%)
IIB	21 (9%)
IIIA	23 (10%)
IIIB	5 (2%)

[a] Other histopathological types of NSCLC included adeno-squamous carcinoma, large cell carcinoma.
[b] Stage of disease was defined according to the 1997 update of TNM criteria established by UICC.

Table 3
Pattern of mediastinal lymph node involvement.

Case	Lobar distribution	pN2 station	Pathological N1 node
1	RUL	1,3	Negative
2	RUL	2	Negative
3	RUL	3	Positive
4	RUL	3	Negative
5	RUL	3,4	Positive
6	RUL	3,4	Positive
7	RUL	3,4	Negative
8	RUL	4	Negative
9	RUL	1,2,3,4	Positive
10	RUL	1,2,4,7	Positive
11	RUL	1,3,4,7	Positive
12	RUL	1,3,4,7	Positive
13	RML	3,7	Negative
14	RLL	7	Negative
15	LUL	4	Positive
16	LUL	4,5	Negative
17	LUL	5	Positive
18	LUL	5	Positive
19	LUL	5	Positive
20	LUL	5	Negative
21	LUL	5	Negative
22	LUL	5,6	Positive
23	LUL	5,6	Positive
24	LLL	7	Positive

LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

2.5. Pathological examination and the size of metastases

All resected tumor specimens were examined by experienced pulmonary pathologists. Histological classification of NSCLC was based on the WHO classification [11]. The dissected lymph nodes were examined histologically following hematoxylin and eosin staining, and the long-axis diameters of the metastatic foci in all involved lymph nodes were measured. The lymph node with the largest metastatic foci was selected as a representative foci of each station containing metastases.

2.6. Statistical analysis

Statistical analysis was performed with Dr.SPSS II software (SPSS Japan, Tokyo, Japan). Univariate data analysis was conducted using Fischer's exact test or Pearson's chi-square test. Multivariate analysis was conducted using the logistic regression (backwards stepwise) method. *P*-values were considered statistically significant if <0.05.

3. Results

3.1. The incidence and pattern of MLN metastasis

The incidence of MLN metastasis in this study was 11% (24 of 224 patients). Table 2 details the postoperative pathological evaluation of the tumors. Of 24 patients with mediastinal node metastasis, multistation MLN metastasis was found in 12 patients (50%), while the other 12 patients showed on a single station (50%). Skip metastasis was found in 10 patients (42%). Forty-four MLN stations in total were involved. Table 3 indicated the patterns of MLN involvement. In patients whose tumors were located in the right upper lobe ($n=12$), 9 had metastasis in the superior lymph nodes (#1, #2, #3, #4) and 3 patients had metastases in both the superior and inferior (#7) lymph nodes. One patient whose tumor was located in the right middle lobe had metastasis in #3 and #7 lymph nodes, while a patient with a tumor in the right lower lobe had metastasis in #7 lymph node. In patients whose tumors were located in left upper lobes ($n=9$), 7 patients had metastasis in the aortic lymph nodes (#5, #6), 1 patient had metastasis in #4 lymph nodes, and 1 patient had metastasis in #4 and #5 lymph nodes. Finally, a patient whose tumor was located in the left lower lobe had metastasis in #7 lymph node.

3.2. Analysis of risk factors associated with MLN metastasis

Table 4 summarizes the results of univariate analysis for factors associated with MLN metastasis. Factors that are significantly associated with MLN metastasis are: never smoked ($P=0.03$), tumor located in the upper or middle lobe ($P=0.01$), tumor >3 cm ($P=0.005$), SUV_{max} of primary tumor >4.0 g/ml ($P=0.0498$), and adenocarcinoma ($P=0.04$). The multivariate risk-factor analysis (Table 5) identified adenocarcinoma ($P=0.04$), tumors located in the upper or middle lobe ($P=0.02$), tumor >3 cm ($P=0.01$), and SUV_{max} of primary tumor >4.0 g/ml ($P=0.04$) as risk factors for MLN metastasis.

3.3. A Pathological examination and the size of metastases

The size of metastatic foci across 44 stations ranged from 0.5 to 9 mm with a mean value of 3.7 ± 2.0 mm (±SD). Thirty of the 44 involved stations (68%) had metastatic foci smaller than 4.0 mm. Table 6 details the size distribution of the metastatic foci.

4. Discussion

The present study defined risk factors for occult metastasis in patients with NSCLC diagnosed as clinical N0-1 by preoperative integrated FDG-PET/CT and CT. The patterns of occult MLN metastasis were also analyzed, and the involved MLNs were examined histologically. The incidence of MLN metastasis in our series of patients was 11%. This finding was concordant with comparable previous studies; Al-Sarraf et al. [6] reported the incidence of occult N2 disease in similar patients as 16%, while Cerfolio et al. [12] reported a 14% incidence, although when they limited the analysis to clinical stage I patients, the incidence decreased to 7% [7]. Risk factors for occult N2 disease reported in these previous studies were as follows: adenocarcinoma [7], tumors located in right upper lobe [6], larger tumor size [7], a high SUV_{max} of the primary tumor [7,12], centrally located tumors [6,7], positive N1 nodes on PET [6],

Table 4
Univariate analysis for factors associated with mediastinal lymph node metastasis.

Variable	Pathological N2 (n=24)	Pathological N0-1 (n=200)	P-value
Sex			
Male	9	113	
Female	15	87	N.S.
Age (years)			
≥65	13	114	
<65	11	86	N.S.
Smoking status			
Smoker	9	122	
Never smoker	15	78	0.03
Concurrent lung disease			
Present	2	38	
Absent	22	162	N.S.
Elevated serum CEA level (>5 ng/ml)			
Yes	7	61	
No	17	139	N.S.
Lobar distribution of the tumor[a]			
Upper or middle lobe	22	135	
Lower lobe	2	65	0.01
Location of the tumor			
Central	2	16	
Non-central	22	184	N.S.
Positive N1 node on PET/CT			
Yes	3	36	
No	21	164	N.S.
Tumor size (cm)			
>3.0	18	90	
≤3.0	6	110	0.005
SUV_{max} of primary tumor			
>4.0	16	91	
≤4.0	8	109	0.0498
Histopathological type			
Adenocarcinoma	23	157	
Non-adenocarcinoma	1	43	0.04

[a] Upper or middle lobe includes right upper lobe, right middle lobe, and left upper lobe. Lower lobe includes right lower lobe, left lower lobe.

Table 5
Multivariate analysis for risk factors for mediastinal lymph node metastasis.

Variable	Odds ratio	Confidence interval	P-value
Adenocarcinoma	9.26	1.13–76.9	0.04
Located in upper or middle lobe	6.29	1.36–29.4	0.02
Tumor size >3 cm	4.18	1.48–11.76	0.01
SUV_{max} of primary tumor >4.0	2.79	1.04–7.52	0.04

and poorly differentiated histology [12]. A limitation of these studies was the lack of histological examination of the involved MLNs and insufficient consideration of why the involved lymph nodes showed as negative by integrated FDG-PET/CT.

Adenocarcinoma was also identified as a risk factor for occult MLN metastasis in the present patient cohort. Interestingly, Lee et al. [7] reported similar data in that all of their 16 patients with pathological N2 disease showed adenocarcinoma as the primary tumor cell type. On the contrary, in the Al-Sarraf and co-workers' series [6], the primary tumor cell type did not affect the incidence of occult MLN metastasis. A major difference between their series and ours is the inclusion of patients with enlarged lymph nodes (>1 cm) on CT in our analysis. In the comparative study [6], 8 of 25 patients with pathological N2 disease in their series had enlarged lymph nodes (>1 cm) on CT, and 12 of the 25 had non-adenocarcinoma tumors. It is reported that lymph node metastases from adenocarcinoma were of normal size (1 cm ≤ across the short-axis diameter) more frequently than those from squamous cell carcinoma [13,14]. Therefore, we speculate that patients with MLN metastasis from squamous cell carcinoma tended to be excluded in our series and included in the series of patients reported on by Al-Sarraf and co-workers [6].

Tumor location in the upper or middle lobe also proved to be a risk factor for occult MLN metastasis in the present study. A predisposition of lobar distribution was also observed in the previous study by Al-Sarraf and co-workers, with the right upper lobe dominating in their series. The other risk factors for occult MLN metastasis were identified as tumor size >3 cm, SUV_{max} of primary tumor >4.0 g/ml. It is well known that the incidence of MLN metastasis increased as the tumor size increased [15]. The relationship between SUV_{max} of the primary tumor and incidence of lymph node metastasis has also been investigated previously. Downey and colleagues [16] reported higher SUV_{max} of the primary tumors in patients with pathological nodal involvement than in patients without nodal involvement, while Cerfolio and colleagues [8] showed that SUV_{max} of lung tumors increased as the cancer progressed from N0 to N3.

In contrast to the report of Al-Sarraf et al. [6], positive N1 nodes on PET was not a risk factor for MLN metastasis in the present study. This difference might be attributable to the relatively high incidence of skip metastasis in the present series (42%).

To overcome a limitation of similar previous studies, we conducted histological examination of the involved MLNs. This additional analysis demonstrated that metastatic foci of occult MLN metastases were small; of 44 stations, the size of foci ranged from 0.5 to 9 mm with a mean value of 3.7 ± 2.0 mm, and 30 of the 44 involved stations (68%) contained foci of <4.0 mm diameter. This finding is supported by previous studies wherein the metastatic foci of false-negative lymph nodes by PET were small. Takamochi et al. [17] reported such foci to be 1–7.5 mm (mean, 3.4 mm; n = 12), while Nomori et al. [18] found that false-negative (n = 8) and true-positive (n = 28) lymph nodes on PET contained foci ranging from 0.5 to 9 mm (mean, 3 mm) and 4–18 mm (mean, 10 mm), respectively. No metastatic foci smaller than 4 mm were detected with PET.

The pattern of occult MLN metastasis shown in the present study was identical to the typical distribution in NSCLC patients reported by Naruke et al. [19] These authors reviewed 1815 patients who underwent systematic lymph node dissection, and examined which nodes had the highest likelihood of metastasis. Distribution of MLN metastasis from each lobe in their series was as follows: right upper lobe tumor, #3 (12.3%) and/or #4 (8%); right middle lobe tumor, #3 and/or #7 (16.4%); right lower lobe tumor, #7 (13.7%); left upper lobe tumor, #5 (12.3%) and/or #6 (6.7%); and left lower lobe tumor, #7 (11.9%). Based on our data, patients with tumors in the right upper or middle lobe are potential candidates for cervical mediastinoscopy because their possible metastatic mediastinal lymph nodes (#3, #4, #1, #2, #7) are easily accessible by cervical mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration. Skip metastasis was found in 10 patients (42%) in

Table 6
Distribution of size of metastatic foci.

	Size (mm)											
	<1.0	<2.0	<3.0	<4.0	<5.0	<6.0	<7.0	<8.0	<9.0	<10.0	≥10.0	Total
No.	1	5	12	12	5	3	2	1	0	3	0	44

the present series, which is a relatively high incidence compared to other reports for NSCLC patients (25–29%) [15]. In these 10 patients, it is speculated that metastatic MLNs were negative for integrated FDG-PET/CT and CT because they are the first nodal target of lymph from a primary tumor site and metastatic foci were still small.

Because of the small size of the metastatic foci, occult MLNs are considered difficult to be detected by endobronchial ultrasound-guided transbronchial needle aspiration. Therefore, we recommend cervical mediastinoscopy for the patients with tumors in the right upper or middle lobe who have risk factors for occult MLN metastasis.

5. Conclusions

The present study demonstrated that adenocarcinoma, tumors located in the upper or middle lobe, tumor size >3 cm, and SUV_{max} of primary tumor >4.0 g/ml are risk factors for occult MLN metastasis in patients with NSCLC diagnosed as clinical N0-1 by preoperative integrated FDG-PET/CT and CT. The metastatic foci of involved stations were small, with 68% of foci measuring <4.0 mm. The pattern of occult MLN metastasis discerned in the present study was typical for reported distribution of metastatic foci in NSCLC patients. Patients with tumors in the right upper or middle lobe are considered candidates for cervical mediastinoscopy because their metastatic mediastinal lymph nodes (#3, #4, #1, #2, #7) are easily accessible by these modalities.

Conflict of interest statement

None of the authors has any financial or other potential conflict of interest.

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This study was based on wedge bronchoplasty alone; therefore, the anastomosis region was elevated to maintain the surgical field. This would also be the case with sleeve bronchoplasty, with only stay sutures.

5. Conclusion

The key feature of our method is that the surgeon observes the operative field directly through the working wound, while the surgical team observes via a monitor. One advantage is that the surgeon is able to use the same instruments in VATS as used in conventional thoracotomy, and the same suturing techniques can be applied to vascular reconstruction, especially of the pulmonary artery.

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eComment: Bronchial anastomosis: to wrap or not to wrap?

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We read with interest the electronic manuscript of Kamiyoshihara et al. [1] about an original technique of video-assisted thoracic surgery lobectomy with bronchoplasty for lung cancer. In their surgical technique, the authors affirm that they applied an absorbable sealing material (fibrin glue sealant) after completion of the anastomosis and sealing test, to prevent postoperative anastomosis insufficiency, without any wrapping techniques.

It is known that certain risk factors, such as chronic obstructive pulmonary disease, preoperative pleuro-pulmonary infection, prolonged steroid therapy, and hyperglycaemia may contribute to broncho-pleural fistulas (BPF) or broncho-vascular fistulas (BVF) [2]. Protection of the bronchial stump with well-vascularized tissue results in reinforcement of the bronchial stump. While the benefit of anastomosis wrapping is recognized as a means of lowering the risk of BPF or BVF, controversy remains concerning which tissue should be used [3]. A pedicled pericardial fat pad fulfils the criteria of ease of harvesting, minimal operative trauma, does not require reconstruction, and can also be used in minimally-invasive techniques.

In conclusion, although no prospective randomized trials evaluating different wrapping techniques compared to no-wrapping techniques are available, we recommend wrapping for all bronchial anastomoses with or without risk factors.

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eComment: Indications and clinical benefits of mini-invasive parenchymal-sparing bronchoplastic procedures

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We read with great interest the article by Kamiyoshihara and colleagues [1] reporting their results after seven cases of hybrid video-assisted thoracic surgery (VATS) lobectomy with bronchoplasty. The most suitable surgical approach for treating malignancies of the lung is a matter of controversy and continuous discussion. 'Complete' VATS that is performed using only the vision of a monitor is generally limited to lung resections of minimal difficulty [2]. Indeed this method results in more or less sacrificing the completeness of oncological resection, and therefore cannot be applied to all cancer operations, including bronchoplasty. Therefore, the technical addition of a minithoracotomy ('working wound') seems to be particularly relevant in bronchoplastic procedures where the use of special instrumentation and a direct view of the surgical field are mandatory. Furthermore, we would briefly discuss the clinical benefits of this surgical approach. Parenchymal-sparing bronchoplastic procedures are absolutely indicated in those patients with poor respiratory reserve in order to preserve more functional lung; in these patients this type of procedure becomes a necessity rather than a choice. Being frail patients in terms of respiratory function, they probably benefit even more than others from a minimally-invasive strategy of care [3]. In fact VATS lobectomy, despite controversial results, seems to be a less invasive and safer procedure with a lower morbidity rate compared with lobectomy by thoracotomy technique, with acceptable functional and oncologic outcome [4, 5]. Therefore, the combination of mini-invasive technique and parenchyma-sparing resection is the best treatment in these critical cases. On the basis of these clinical considerations, we warmly advocate further investigations of the minimally-invasive techniques in order to improve the performance of VATS resections with bronchoplasty.

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ORIGINAL ARTICLE

Differences in chemosensitivity between primary and paired metastatic lung cancer tissues: In vitro analysis based on the collagen gel droplet embedded culture drug test (CD-DST)

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ABSTRACT

Background: To elucidate the differences in chemosensitivity to anticancer drugs between primary and metastatic lesions in non-small cell lung cancer (NSCLC) patients, we examined the *in vitro* chemosensitivities of surgically resected NSCLC tissues.

Methods: A total of 32 specimens were enrolled: 26 specimens of primary lesions paired with metastases in the lymph node, 3 specimens of primary lesions paired with metastases in the adrenal gland, and 3 specimens of primary lesions paired with metastases in the lung. The collagen gel droplet embedded culture drug test (CD-DST) was applied to examine the sensitivity of the tissues to anticancer drugs, including cisplatin, gemcitabine, vinorelbine, docetaxel and 5-fluorouracil.

Results: The degree of *in vitro* sensitivity to each anticancer drug varied between the primary and metastatic lesions. The sensitivity of the paired metastatic lesions was significantly lower than that of the primary lesions only for gemcitabine (P=0.029), vinorelbine (P=0.012), and docetaxel (P=0.009). The incidence of cases diagnosed as CD-DST-sensitive among the paired metastatic lesions was significantly lower than that for the primary lesions for vinorelbine (P=0.035) or docetaxel (P=0.022). The difference in the sensitivity to gemcitabine between the primary and paired non-lymphatic metastases was clearer than that between the primary lesion and paired lymph node metastases.

Conclusions: The sensitivities of the paired metastatic lesions to some anticancer drugs were significantly lower than those of the primary lesions. When performing chemotherapy based on CD-DST data using primary tumors from patients with postoperative recurrence, an appropriate regimen can be selected by carefully considering these differences.

KEYWORDS Non-small cell lung cancer (NSCLC); chemosensitivity test; collagen gel droplet embedded culture drug test (CD-DST); metastatic tissue; chemotherapy

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Introduction

Lung cancer is a major cause of death worldwide. More than 70% of lung cancer patients die of systemic metastasis. Although chemotherapy modalities to fight this disease have been aggressively developed, they have failed to achieve satisfactory therapeutic effects and prognoses. Indeed, many advanced lung cancers are finally resistant to anticancer drugs, and the response rates of systemic metastatic disease are worse than those associated with induction chemotherapy (1-3). Also, primary lesions and their corresponding metastases frequently show significant differences in their sensitivity to chemotherapy, and similar differences are also seen among metastatic sites (4). Considering these observations together, it was suggested that the chemosensitivity of some tumors is strongly affected by the biological aggressiveness of the tumor, such as the metastatic potential of the tumor cells themselves, the metastatic route, and site-specific circumstances associated with the metastatic process (5-9). Thus, it is clinically important to analyze the heterogeneity of chemosensitivity to anticancer drugs within tumor tissue. In

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fact, such tumor heterogeneities of potential drug sensitivity was recently indicated in the patient-derived xenograft specimen treated experimentally with anticancer drugs (10), but the heterogeneity of tumor chemosensitivity in individual patients has been not sufficiently examined.

Recently, in vitro anticancer drug sensitivity tests using clinical specimens have been used to provide data for designing individualized chemotherapies. Several in vitro anticancer drug sensitivity tests have been developed for various types of malignant tumors, and these tests have been applied experimentally as well as clinically (11-14). The collagen gel droplet embedded culture drug test (CD-DST) is an in vitro anticancer drug sensitivity test (15-17) that has been used at our institute in chemotherapy for patients with non-small cell lung cancer (NSCLC) (18-20) as well as those with other thoracic tumors (21,22). So far, this test has been used to assess surgically resected specimens from NSCLC primary lesions and to provide data regarding their sensitivity to anticancer drugs and has also been clinically applied to aid the development of individualized chemotherapies for NSCLC patients who have suffered postoperative recurrence (18,20). In fact, good predictability was obtained when the test was used to aid the treatment of recurrent disease, and the accuracy of treatment response predictions based on the CD-DST data was as high as 70%, but this was still not satisfactory because these chemosensitivity data were obtained from primary NSCLC tissues, not systemic metastatic tissues (20).

In the present study, in order to elucidate the differences in the chemosensitivity to anticancer drugs between primary and metastatic lesions in individual NSCLC patients, we examined the *in vitro* chemosensitivities of surgically resected NSCLC tissues to representative anticancer drugs. In addition, the in vitro chemosensitivities of tumors at different metastatic sites was examined.

Patients and methods

Patients, tissue specimens, and CD-DST data acquisition

The primary lesions and paired metastatic NSCLC tissues used in the present study were collected in the following manner: between 2001 and 2009, 1790 patients underwent surgical treatment for lung cancer, and of them, the CD-DST was selectively performed in 597 NSCLC patients after they had provided informed consent. The tested specimens were primary lung cancer tissues, and in cases in which the tumor was locally advanced, 37 metastatic tissues, including 32 nodal and 5 pulmonary metastatic lesions were also tested at the same time. The paired specimens used for the test were obtained by surgical resection for postoperative recurrence, such as adrenal and pulmonary metastasis. In addition, the following specimens were excluded from the present analysis: patients undergoing neoadjuvant chemotherapy before primary surgery or chemotherapy before metastasectomy for recurrent disease, and patients whose CD-DST data were not obtained due to a technical issue. As a result, a total of 32 CD-DST datasets for primary and metastatic NSCLC lesions were enrolled: 26 CD-DST datasets for primary tumors paired with nodal metastatic lesions, 3 for primary tumors paired with adrenal gland metastatic lesions, and 3 for primary tumors paired with pulmonary metastatic lesions (2 displaying synchronism and 1 displaying asynchronism).

The clinicopathological data of the patients enrolled in the present study are summarized in Table 1. The pathological stage (p-stage) of the disease was based on the general guidelines of the Japan Lung Cancer Society (23). As described above, the patients were divided into two groups, those (n=26) with CD-DST data for primary and nodal metastatic lesions and those (n=6) with CD-DST data for primary and distant metastatic lesions. The former group consisted of 8 squamous cell carcinomas, 14 adenocarcinomas, 3 large cell carcinomas, and one adenosquamous cell carcinoma. The nodal specimens used for the test were obtained from dissected mediastinal or hilar lymph nodes while the metastases were histologically confirmed during surgery. The latter group consisted of 1 squamous cell carcinoma, 4 adenocarcinomas, and 1 large cell carcinoma. The metastatic lesions were diagnosed using intraoperative and postoperative histological examinations.

CD-DST was performed as described previously by Kobayashi *et al.* (15-17). In brief, each surgically obtained specimen was finely minced using a scalpel and digested in cell dispersion enzyme solution (EZ, Nitta Gelatin Inc., Osaka, Japan) for 2 hr. The dispersed cancer cells were then washed twice, collected by centrifugation at 250 g for 3 min, filtered through an 80 um nylon mesh, and then incubated in a collagen gel coated flask (CG-flask, Nitta Gelatin Inc.,) in a CO_2 incubator at 37

Table 1. Clinicopathological characteristics of the patients

		No. of patients (%)
Patients with paired primary and nodal metastatic lesions (n=26)		
Age	mean	66 years-old
Gender	male / female	18 (69%) / 8 (31%)
p-stage (23)	IIB / IIIA /IIIB / IV	2 (8%) / 18 (69%) / 5(19%) / 1(4%)
Histology (23)	squamous / adeno / large / adenosquamous *	8 (31%) /14 (54%) /3 (12%) /1 (4%)
Patients with paired primary and distant metastatic lesions (n=6)		
Age	mean	62 years-old
Gender	male / female	5 (83%) / 1 (17%)
Distant site	lung / adrenal gland	3 (50%) / 3 (50%)
Histology*	squamous / adeno / large	1 (17%) / 4 (67%) / 1 (17%)

*** adeno: adenocarcinoma; squamous: squamous cell carcinoma; large: large cell carcinoma; adenosquamous: adenosquamous cell carcinoma**

concentration of 50 ug/ml, and the colonies in the collagen gel droplets were stained for three hr. The collagen droplets in the 60 mm dish were stained just before exposure (day 1). Thereafter, each collagen droplet was fixed with 10% neutral formalin buffer, washed in water, air dried, and quantified by image analysis. The growth rate of the controls was calculated as the total volume of the control group on day 7/total volume on day 1. The in vitro sensitivity was expressed as the T/C ratio (%), where T was the total volume of the treated group and C was the total volume of the control group. A T/C (%) of 50% or less to an anticancer drug was regarded demonstrating in vitro-sensitivity.

Anticancer drugs

The anticancer drugs tested in the CD-DST were 0.2 ug/ml cisplatin (CDDP), 0.1 ug/ml docetaxel (TXT), 0.05 ug/ml vinorelbine (VNR), 8.0 ug/ml gemcitabine (GEM), and 1.0 ug/ml 5-furuolouracil (5-Fu). The culture time was 1 hr for GEM, while it was 24 hr for the other drugs (15-18,20).

Statistical analyses

Statistical analyses were performed using the paired T test or Fisher's exact probability test. The level of significance was set at 5%.

Results

Chemosensitivity of the primary tissues and paired metastatic lesions to each anticancer drug

In vitro sensitivity data for the primary and paired metastatic tissues were obtained in all 32 patients for CDDP, but were only obtained in 29 patients for 5-FU, and in 28 patients for GEM, VNR, and TXT, because of technical problems or material deficiencies. Table 2 shows a summary of the chemosensitivity data of the primary (P) and paired metastatic lesions (M) for each anticancer drug. With regard to the T/C ratio (%) of each anticancer drug, the mean ratio in the primary tissue was generally lower than that in the paired metastatic lesion, especially for GEM (P=0.029), VNR (P=0.012), and TXT (P=0.009), in which the difference was significant, indicating that the paired metastatic lesions showed significantly less sensitivity to these drugs than the primary lesions. Fig 1 shows a comparison of the CD-DST data for the primary lesions and their paired metastatic lesions for each anticancer drug. For GEM, VNR, and TXT, although a minority of cases showed T/C ratios that were lower in the paired metastatic lesions than those in the primary tissues, the T/C ratios of the metastatic lesions were generally higher than those of the primary lesions. In contrast, for CDDP and 5-FU (Figure 1), no such observation was seen, as described in Table 2.

Regarding the diagnosis of CD-DST, whether the lesion was in vitro-sensitive or –resistant based on this chemosensitivity test, the frequency of in vitro-sensitive cases was generally lower for the metastatic lesions than the primary tissues, especially for VNR (P=0.035) and TXT (P=0.022), and the difference was significant according to Fisher's exact probability test (Table 2).

Chemosensitivity analysis based on the metastatic route

As described in Patients and Methods, 6 metastatic specimens were obtained from non-nodal metastases (3 from the adrenal gland and 3 from the lung). Then, the difference in chemosensitivity between the primary lesions and their paired metastatic lesions was analyzed according to the metastatic route, namely lymphatic (n=26) versus non-lymphatic (n=6). Figure 2 shows waterfall plots of each anticancer drug reflecting the differences in the T/C ratio (%) between the primary and metastatic lesions. The cases associated with a non-lymphatic route (white column) were widely distributed in these plots, and in the GEM group, 4 cases

Table 2. Comparison of in vitro sensitivity data produced by the CD-DST between primary and paired metastatic lesions in patients with NSCLC

	CDDP (P)	CDDP (M)	GEM (P)	GEM (M)	VNR (P)	VNR (M)	TXT (P)	TXT (M)	5-FU (P)	5-FU (M)
Number	32	32	28	28	28	28	28	28	29	29
T/C ratio (%)										
Mean	64.3	72.0	61.3	75.2	58.7	72.8	59.6	74.1	73.1	79.0
S.D.	20.7	21.0	26.9	24.8	25.9	22.9	24.5	24.3	21.4	24.6
Median	62	74	58	79	56	74	55	79	73	77
p value (P vs M)*	0.13		0.029		0.012		0.009		0.33	
Mean										
Number of sensitive cases (%)	7 (22%)	4 (13%)	9 (32%)	5 (18%)	11 (39%)	4 (14%)	13 (46%)	5 (18%)	4 (14%)	2 (7%)
P value (P vs M)**	0.32		0.21		0.035		0.022		0.39	

(P): Primary lesions, (M): Paired metastatic lesions; *: Paired T test; **: Fisher's exact probability test.

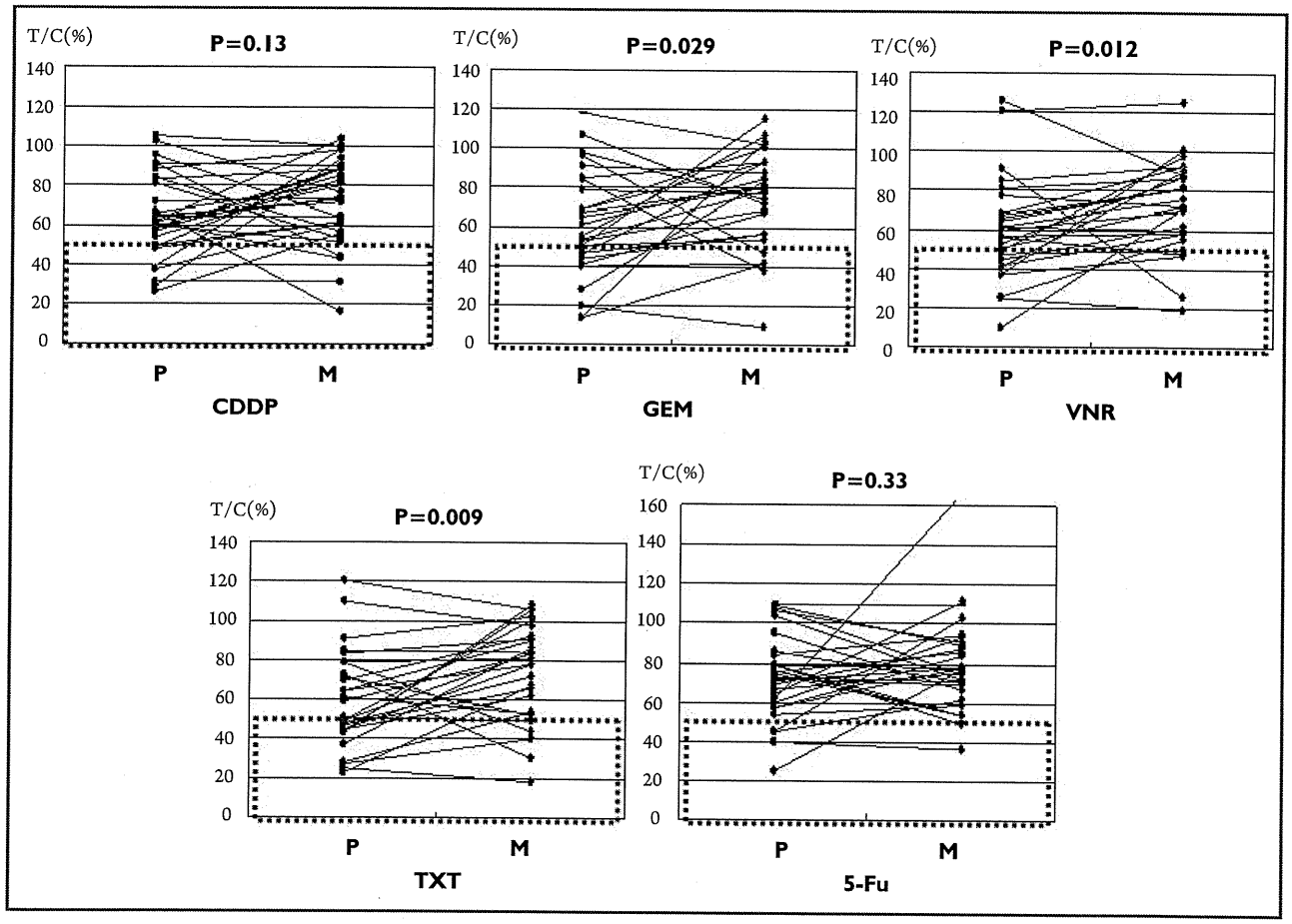

Figure 1. Comparison of the in vitro chemosensitivities (T/C ratio, %) of primary lesions and their paired metastatic NSCLC lesions. P: primary lesions, M: paired metastatic lesions. The cases surrounded with dotted-line frames were diagnosed as being in vitro-sensitive. The P value for each anticancer drug was calculated using the Paired T test. Fig 1. shows a comparison of CD-DST data between each primary lesion and its paired metastatic lesion for each anticancer drug. For GEM, VNR, and TXT, the T/C ratio of the metastatic lesions was significantly higher than that of the primary lesions. In contrast, for CDDP and 5-FU, no significant differences in chemosensitivity were observed.

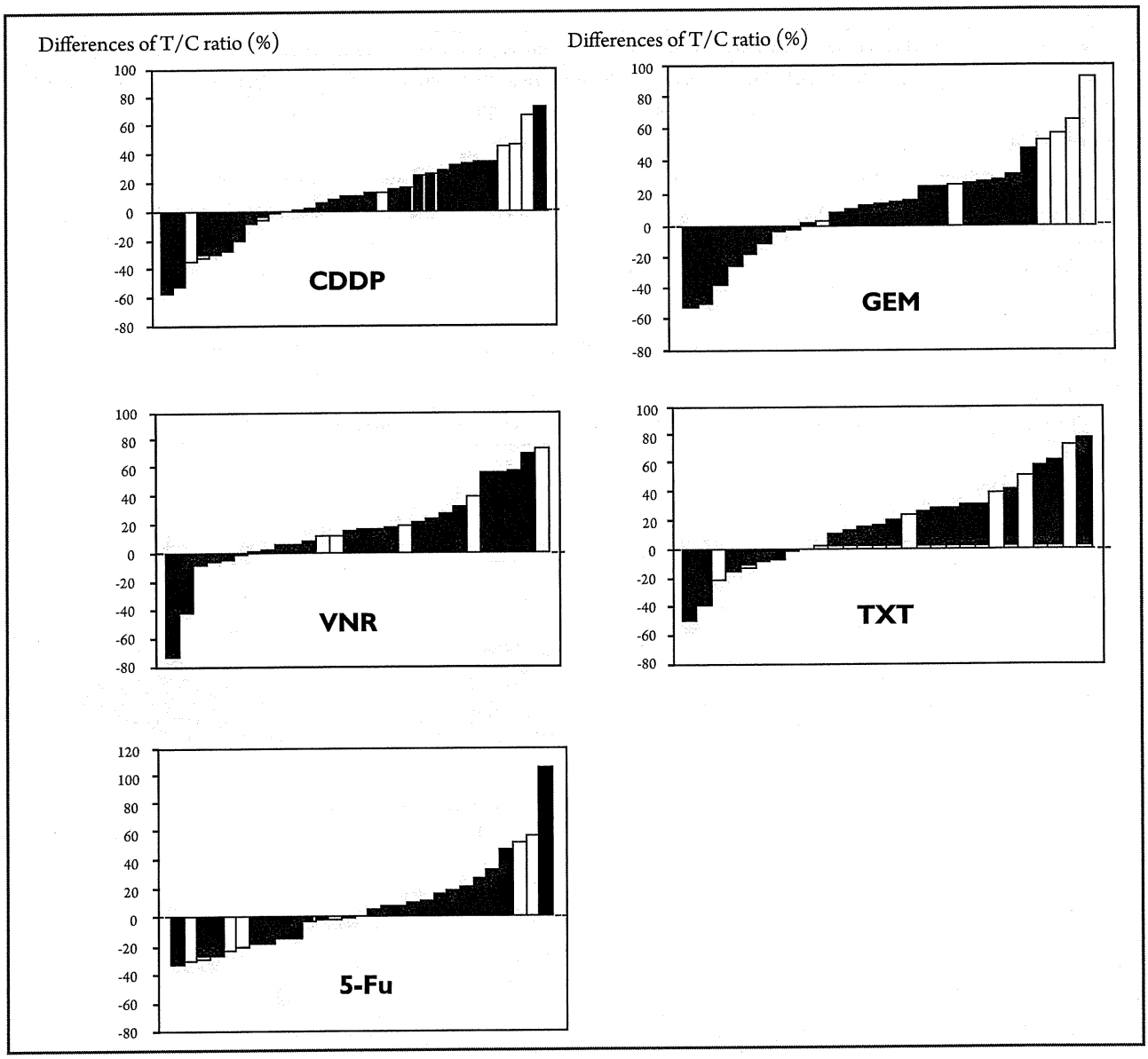

Figure 2. Differences in the T/C ratio (%) between the primary lesions and their paired metastatic lesions. Differences in the T/C ratio (%) between the primary lesions and their paired metastatic lesions are shown by waterfall plots. The black columns show the difference between primary lesions and their paired lymph node lesion. The white columns show the difference between primary lesions and their paired non-lymphatic lesions. Although the cases involving a non-lymphatic route (white column) were widely distributed, 4 cases (67%) treated with GEM showed a 30% or greater increase in in vitro resistance in the paired metastatic lesions compared with the primary tissue. Three cases (50%) showed similar results for CDDP.

(67%) showed at least a 30% greater number of in vitro resistant metastatic lesions than primary tumors. Also, three cases (50%) showed similar observations for CDDP.

Discussion

For the past 20 years, we have investigated the technical development of the CD-DST and have presented experimental and clinical results that aid the selection of individualized chemotherapy for patients, especially for those with lung cancer (15-17). For example, we reported that the CD-DST displayed clinical significance for some "old generation" anticancer drugs in NSCLC patients (18). In this report, the chemotherapeutic effects of treatment for postoperative recurrence were analyzed in comparison with the CD-DST data obtained by surgery. CDDP-based combined chemotherapy yielded a good response

more frequently with *in vitro*-sensitive regimens than with *non-in vitro*-sensitive regimens; and consequently, the CD-DST results for CDDP and CBDCA, a key drug for chemotherapy, correlated with the clinical response. Next, we showed the similar results for some "new generation" anticancer drugs, which were thought to have stronger therapeutic effects than the "old generation" drugs. In fact, so good responses to the recurrent tumors were obtained by chemotherapy even with a single agent regimen such as GEM, TXT, and VNR, when diagnosed as in vitro- sensitive (20).

In addition to our series (18,20), there have been several reports regarding the clinical application of *in vitro* sensitivity tests for the treatment of lung cancer patients. Kawamura *et al.* (19) described the survival benefit of CD-DST-based chemotherapy for patients with stage IV lung cancer. Yoshimasu *et al.* (24) also reported the usefulness of another in vitro chemosensitivity test, the histoculture drug response assay (HDRA), for treating postoperative recurrence in lung cancer patients. Recently, Tanahashi *et al.* (25) reported the clinical application of the HDRA for postoperative adjuvant chemotherapy in lung cancer patients and demonstrated that overall survival was prolonged by treatment using an HDRA-sensitive regimen. In addition, there have also been some promising reports regarding other novel chemosensitivity tests for the treatment of patients with NSCLC (10,26). In particular, such an in vivo test system as patient-derived xenograft model described by Dong *et al.* (10) was newly promising for predicting drug sensitivities. Thus, it is considered that these chemosensitivity tests may be clinically applicable for sensitivity test-guided, individualized treatment of cancer patients. However, it has been well recognized that there are some limitations to apply these in vitro tests in clinical practice enough. In fact, there are still some technical problems of primary culture failure, anticancer drug level, bacterial contamination, measurement only for cancer cells, and so on. Anyway, these tests including CD-DST (15-17) have been developed while overcoming such technical problems step by step.

Interestingly, we must also pay particular attention to the fact that most of these analyses are based on sensitivity data obtained from primary, not metastatic, lesions. In other words, it is possible that these data do not reflect the characteristics of all tumor tissues in a particular patient. Since chemosensitivity data could not be obtained for all sites, chemotherapy was performed based on the data of the most representative primary site in patients with NSCLC (18,20,24). However, the prediction of chemotherapeutic effects using sensitivity tests was not always satisfactory in our series (18,20) or those of others (19,24). Unfortunately, the reason for these problems is unclear. From this standpoint, this study is extremely important for elucidating the cause of predictive failure.

According to the present study, although a minority of patients had metastatic lesions that were more in vitro-sensitive than the primary lesion, some anticancer drugs, for example, TXT, VNR, and GEM, showed significantly less in vitro-sensitivity in metastatic lesions than in primary lesions, and then, these differences resulted in a lower incidence of in vitro-sensitive cases for TXT and VNR. In contrast, only small differences in sensitivity were detected between the primary and metastatic lesions for CDDP and 5-Fu. Furukawa *et al.* (27) reported similar results for various anticancer drugs using specimens from primary breast cancer lesions and their paired nodal metastatic tumors by the HDRA. Interestingly, they also showed that the sensitivity of the metastatic nodal lesions to CDDP was not different from that of the primary lesions. Therefore, when performing individualized chemotherapy based on CD-DST data using primary tumor specimens, false-sensitive regimens, including some anticancer drugs that display in vitro-sensitivity, e.g., TXT and VNR, might be selected.

Surprisingly, the effectiveness of some anticancer drugs depended on the metastatic route or site. GEM and CDDP showed a trend towards reduced sensitivity in non-lymphatic metastatic lesions compared with lymph node metastases, although the observation was not subjected to statistical analysis because of the small number of samples. This trend might be closely associated with our previously reported result (20); i.e., in CD-DST-based chemotherapy for recurrent disease, the predictive accuracy of CD-DST data was highest for lymph node recurrence. In contrast, among patients with pleural or bone metastasis, few such associations between CD-DST data and response were observed, despite the fact that we performed chemotherapy with an in vitro- sensitive regimen (20). In addition, a similar tendency was also found in a recent report: Tanahashi *et al.* (25) described that the incidence of postoperative lymph node recurrence was low in lung cancer patients undergoing adjuvant chemotherapy involving an in vitro-sensitive regimen. Thus, for some anticancer drugs, the metastatic route or site may also influence the predictive performance of CD-DST.

A few reports have demonstrated clear differences in the in vitro or in vivo chemosensitivity of primary lesions and their paired metastatic lesions using human tumor tissues (10). Also, several biomarkers associated with chemosensitivity have been aggressively developed (28,29), but although the chemosensitivity heterogeneity of tumor tissues has been studied (10), no studies comparing tumors according to the site of the lesion have been performed. Besides, there are few studies comparing these tests. Inaba *et al.* (30) previously reported an in vitro-in vivo correlation of CD-DST, and such comparison studies may be also necessary in the future. Anyway, in this study, the sensitivity of tumors to anticancer drugs showed surprisingly variation among the tumor tissues in individual patients. In particular, it was interesting that these differences were closely related to the type of anticancer drug used and the metastatic

route/site. Based on these observations, when performing CD-DST-based chemotherapy for NSCLC patients, especially those with postoperative recurrent disease, an appropriate regimen should be selected after carefully considering these differences. Further analysis is required to establish a promising strategy for CD-DST-guided chemotherapy for patients with NSCLC.

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Clinical Science

Outcome of surgical resection for recurrent pulmonary metastasis from colorectal carcinoma

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Repeat thoracotomy

Abstract

BACKGROUND: The outcomes after repeat pulmonary resection for colorectal cancer (CRC) and the factors associated with the prognosis of these patients remain uncharacterized.

METHODS: Data on 156 patients who underwent curative resection of pulmonary metastasis from CRC were reviewed. Repeat pulmonary resection was performed in 25 patients; the present study examined the outcomes and factors associated with prognosis after repeat pulmonary resection.

RESULTS: The 5-year survival rate after the first pulmonary resection was 56.2%. A multivariate analysis identified a histological type other than well-differentiated adenocarcinoma, a high prethoracotomy serum carcinoembryonic antigen (CEA) level, and the presence of hilar or mediastinal lymph node metastasis as poor prognostic factors for the first pulmonary resection. The 5-year survival rate after repeat pulmonary resection was 42.1%. Hilar or mediastinal lymph node metastasis at the time of the repeat resection was significantly associated with poor survival.

CONCLUSIONS: Repeat pulmonary resection for metastatic CRC provides satisfactory outcomes. Hilar or mediastinal lymph node involvement is consistently associated with a poor prognosis after the first and repeat pulmonary resections.

Colorectal cancer (CRC) remains one of the leading causes of cancer death in Western countries. More than two thirds of these patients undergo primary curative resection; however, more than half of the resected patients eventually succumb to the disease.[1] The most common sites of recurrence after resection of primary CRC are liver and lung. Patients with untreated metastatic CRCs have a median survival time of less than 10 months and a 5-year survival frequency of less than 5%.[2] Recently, antiangiogenic therapy with bevacizumab combined with oxaliplatin-based chemotherapy was reported to improve the survival time of patients with CRC.[3] However, few patients achieved complete remission using these new treatments, and most patients therefore exhibit disease progression.

Therefore, surgery remains the best treatment for patients with pulmonary metastases from CRC if potentially curative

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resection is expected and is an established treatment modality in patients with metastatic CRCs. The reported 5-year survival rates after pulmonary metastasectomy for CRC are 24% to 71.2%.[2–15]

Repeat pulmonary resection is also effective for recurrent pulmonary metastasis.[16] Several authors[5,9,11,13–15,17] have advocated this treatment for patients with metastatic CRCs; however, the outcomes after repeat pulmonary resection for CRC and the factors associated with the prognosis of these patients remain uncharacterized. The present study examined the outcome of surgical resection for recurrent pulmonary metastasis from CRCs and determined the prognostic factors compared with those of the first pulmonary resection.

Patients and Methods

Patient selection

From January 1980 to December 2008, a total of 156 patients with previous CRCs underwent curative pulmonary resection at the Osaka Medical Center for Cancer and Cardiovascular Diseases. Curative resection was defined as follows: no additional extrapulmonary sites of metastatic disease or already resected if present, no locoregional recurrence, and no residual macroscopic tumor tissue after the resection. Histopathological evaluations of the resected lung specimens confirmed CRC metastases in all patients.

Patients were selected for resection of pulmonary metastases after meeting the following criteria: (1) pulmonary metastases were deemed to be completely resectable by preoperative radiological examination, (2) absence of apparent hilar or mediastinal lymph node metastases determined by preoperative radiologic examination, (3) metastatic disease limited to the lungs or extrapulmonary distant metastasis(es) that was controlled or controllable if present, (4) locoregional control of the primary CRC was achieved or achievable, and (5) good general condition and adequate respiratory function to tolerate lung resection.

Before 2006, lymph node involvement was generally assessed by computed tomography (CT) scanning, with lymph nodes diagnosed as positive if they extended more than 10 mm across the short-axis diameter. Since 2006, lymph node involvement is generally assessed by F18-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) in our hospital.

Patient characteristics

Clinical information was obtained from the medical records in our hospital. The median time interval between resection of primary CRC and first pulmonary resection was 27 months (range, 0–109 months). The mean age at the time of first pulmonary resection was 62 years (range, 39–83 years of age). Thirty-eight patients had previously undergone resection for extrapulmonary metastases or local recurrences before the pulmonary resection. Of these, 29 patients underwent liver metastasectomy, 6 patients underwent resection of a local recurrence of the primary tumor, 2 patients underwent inguinal lymph node metastasectomy, and 1 patient underwent resection of a para-aortic lymph node metastasis. Three patients underwent simultaneous resection of metastatic CRCs to the lung and either to an extrathoracic site or local recurrence: thyroid metastasis in 1 patient, brain metastasis in 1 patient, and local recurrence of primary tumor in 1 patient. Perioperative chemotherapy at thoracotomy, including preoperative and/or postoperative adjuvant therapy, was performed in 76 patients as follows: 5-fluorouracil or its derivatives were administered in 61 patients; tegafur in 23 patients; doxifluridine in 21 patients; fluorouracil in 4 patients; carmofur in 3 patients; UFT in 9 patients; and S-1 in 1 patient. Cisplatin-, irinotecan-, and oxaliplatin-based chemotherapy were administered to 6, 4, and 5 patients, respectively. Table 1 summarizes the patient characteristics.

Repeat pulmonary resection

If new nodules had evolved after the first pulmonary resection, a second resection was defined as a repeat pulmonary resection. Planned staged thoracotomy for bilateral metastases was counted as a single operation and was therefore excluded from this study definition. In the survival analysis of patients who underwent a planned staged thoracotomy, the date when the earlier surgery was performed was recognized as the starting point. Repeat pulmonary metastasectomies were also performed if the patient met the criteria for the first pulmonary resection as described earlier. Repeat pulmonary resections were performed in 25 patients; 24 of these patients underwent second pulmonary resections, and 1 patient underwent a third pulmonary resection.

Follow-up schedule

Follow-up generally involved a chest x-ray or a chest and abdominal CT scan, a physical examination, and blood chemistry performed every 6 to 12 months after the first pulmonary resection. Follow-up information was obtained from the medical records in our hospital, letters from the patient's general practitioner, or from the death certificates of the Osaka Cancer Registry. Patients or their families were contacted by phone or by letter if necessary.

Statistical analysis

The statistical analyses were performed using the StatView 5.0 software program (SAS Institute, Berkley, CA). The overall survival after the first and repeat pulmonary resections was analyzed by the Kaplan-Meier method using the dates of the first and second pulmonary resections, respectively, as the starting points. Significance of differ-

Table 1 Patient characteristics and details of the first pulmonary resection

Characteristics	n
Sex	
Male	91
Female	65
Age at the first pulmonary resection (y)	
Mean	62
Range	39–83
Stage of primary tumor	
Dukes A	2
Dukes B	37
Dukes C	85
Dukes D	21
Unknown	11
Location of primary tumor	
Colon	74
Rectum	82
Histology of primary tumor	
Well-differentiated adenocarcinoma	65
Moderately differentiated adenocarcinoma	77
Others*	11
Unknown	3
Interval between primary resection and first pulmonary resection (months)	
Median	27
Range	0–109
Prethoracotomy serum CEA level (ng/mL)	
<5	90
≥5	66
History of surgical treatment of extrathoracic recurrence	
Yes	41
No	115
Repeat pulmonary resection	
Yes	25
No	131
Number of resected metastases	
1	100
2	32
≥3	24
Site of metastasis	
Unilateral	130
Bilateral	26
Maximum tumor size (mm)	
≤30	115
>30	41
Type of resection	
Sublobar resection	99
Lobectomy or pneumonectomy	57
Hilar or mediastinal lymph node metastasis	
Yes	15
No	141

*Others include poorly differentiated adenocarcinoma and mucinous adenocarcinoma.

ences between subgroups was calculated using the log-rank test. The multivariate analysis of prognostic factors was performed using the Cox multivariate proportional hazard model. A P value of less than .05 was considered statistically significant. Data are expressed as the mean ± standard deviation or median values.

Results

Details of first pulmonary resection

There was no operative major morbidity or mortality. Sublobar resection (wide-wedge resection or segmentectomy) was performed in 99 patients, lobectomy in 56, and pneumonectomy in 1 patient. One hundred patients had a solitary metastasis, and 56 patients had multiple metastases. The details of the first pulmonary resections are shown in Table 1. The median time interval between the first pulmonary resection and death or the latest follow-up examination in the present series was 43 months (range, 4–270 months).

Clinical course after the first pulmonary resection

Ninety-three patients developed recurrence after the first pulmonary resection (Fig. 1). The initial pattern of recurrence after lung resection was pulmonary metastasis in 39 patients, including 7 patients with radiologically apparent mediastinal involvement, surgical margin relapse in 5 patients including 1 patient with radiologically apparent mediastinal involvement, pleuritis carcinomatosa in 2 patients, pulmonary metastasis and extrathoracic recurrence in 7 patients, and extrathoracic recurrence in 40 patients. Twenty-five patients underwent a second pulmonary resection; 13 of these subsequently experienced recurrent disease as pulmonary metastasis in 10 patients and extrathoracic recurrence in 3 patients. Only 1 patient underwent a third pulmonary resection. Currently, 69 patients are alive with no evidence of disease, 14 patients are alive with disease, 8 patients died of another disease, and 65 patients succumbed to the disease.

Overall survival of patients after the first pulmonary resection

The cumulative 3-, 5-, and 10-year survival rates after the first pulmonary resection were found to be 71.4%, 56.2%, and 44.0%, respectively (Fig. 2).

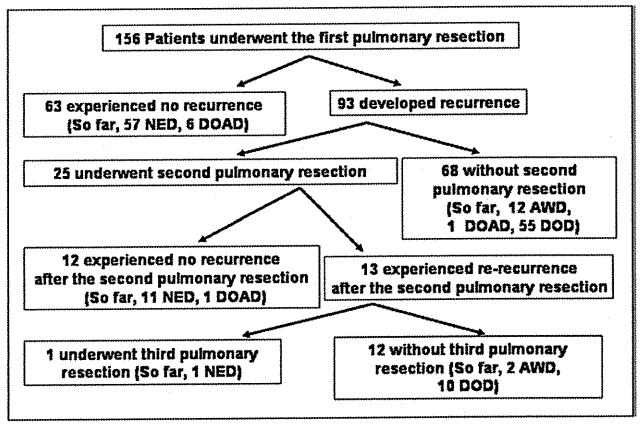

Figure 1 Clinical course after the first pulmonary resection. AWD, alive with disease; DOAD, died of another disease; DOD, died of disease; NED: no evidence of disease.

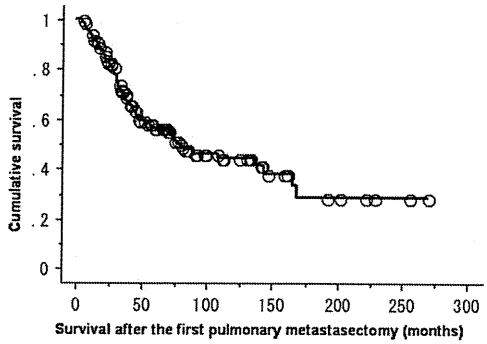

Figure 2 Overall survival of patients after the first pulmonary resection. The cumulative 3-year, 5-year, and 10-year survival rates after the first pulmonary resection were 71.4%, 56.2%, and 44.0%, respectively.

Analysis of prognostic factors for the first pulmonary resection

The following factors were selected for the univariate analysis of survival: sex, age, pathological stage of the primary CRC according to the Dukes classification, the location of the primary tumor, the histology of the primary tumor (well-differentiated adenocarcinoma/moderately differentiated adenocarcinoma or other/unknown), the interval between primary resection and first pulmonary resection (<24 or ≥24 months), the prethoracotomy serum carcinoembryonic antigen (CEA) level (<5 or ≥5 ng/mL), a history of surgical treatment for extrathoracic recurrence, repeat pulmonary resection (yes/no), the number of resected metastases, the site of metastasis (unilateral/bilateral), the maximum tumor size (≤3 or >30 mm), the hilar or mediastinal lymph node metastasis (yes/no), and the type of resection (sublobar resection/lobectomy/pneumonectomy). Table 2 shows the results of the univariate analysis. Significant relationships ($P < .05$) were found between survival and the following factors: histology of the primary tumor, prethoracotomy serum CEA levels, the maximum tumor size, the type of resection (sublobar resection, lobectomy, or pneumonectomy), and hilar or mediastinal lymph node metastasis. The significant factors identified by the univariate analysis were then subjected to a multivariate analysis (Table 3). A moderately differentiated carcinoma or other histological type, an elevated prethoracotomy serum CEA level (≥5 ng/mL), and hilar or mediastinal lymph node metastasis were found to be independent and significant determinants of a poor prognosis.

Table 3 Multivariate analysis of prognosis after the first pulmonary resection

Variable	*P* value	Risk ratio	95% confidence interval
Histology of primary tumor: moderately differentiated adenocarcinoma or others	.03	1.75	1.06–2.89
Prethoracotomy serum CEA level: ≥5 ng/mL	.01	1.87	1.16–3.03
Maximum tumor size: >30 mm	.1	1.53	.92–2.52
Hilar or mediastinal lymph node metastasis: yes	.04	2.12	1.05–4.29

Details of repeat pulmonary resections

Twenty-one patients who had pulmonary metastasis and 4 patients who had surgical margin relapse after the first pulmonary resection underwent repeat pulmonary resections. There was no operative major morbidity or

Table 2 Univariate analysis of the prognosis after the first pulmonary resection

Factors	n	5-year survival	*P* value
Sex (male/female)	91/65	49.7/65.2	NS
Age at first pulmonary resection (<63/≥63 y)	76/80	61.2/50.5	NS
Stage of primary tumor (Dukes ABC/D/unknown*)	124/21/11	55.3/49.6	NS
Location of primary tumor (colon/rectum)	74/82	56.6/55.5	NS
Histology of primary tumor (Well/moderately differentiated adenocarcinoma or others/unknown*)	65/88/3	61.9/51.6	.04
Interval between primary resection and first pulmonary resection (<24/≥24 months)	64/92	53.3/58.1	NS
Prethoracotomy serum CEA level (<5/≥5 ng/mL)	90/66	65.2/43.1	.006
History of surgical treatment of extrathoracic recurrence (yes/no)	41/115	46.3/59.2	NS
Repeat pulmonary resection (yes/no)	25/131	64.0/54.5	NS
Number of resected metastases (solitary/multiple)	100/56	60.0/49.9	NS
Site of metastasis (unilateral/bilateral)	130/26	61.3/33.5	NS
Maximum tumor size (≤30/>30 mm)	115/41	59.9/46.1	.01
Type of resection (sublobar resection/lobectomy or pneumonectomy)	99/57	57.7/53.7	NS
Hilar or mediastinal lymph node metastasis (yes/no)	15/141	28.1/59.4	.006

NS = not significant.
*Excluding unknown cases.

Table 4 Patient characteristics and details of repeat pulmonary resections

Characteristics	n
Sex (male/female)	
Male	17
Female	8
Age at second pulmonary resection (y)	
Mean	61
Range	47–79
Stage of primary tumor	
Dukes B	6
Dukes C	11
Dukes D	5
Unknown	3
Location of primary tumor	
Colon	8
Rectum	17
Histology of primary tumor	
Well-differentiated adenocarcinoma	11
Moderately differentiated adenocarcinoma	11
Others	2
Unknown	1
Interval between first and second pulmonary resection (months)	
Median	20
Range	5–57
Serum CEA level (ng/mL) before second pulmonary resection	
<5	18
≥5	7
Number of resected metastases at second pulmonary resection	
1	16
2	4
≥3	5
Site of metastasis	
Unilateral	23
Bilateral	2
Site of recurrence	
Pulmonary metastasis	21
Surgical margin relapse	4
Maximum tumor size (mm) at second pulmonary resection	
≤30	20
>30	5
Type of resection at second pulmonary resection	
Sublobar resection	16
Lobectomy or pneumonectomy	9
Hilar or mediastinal lymph node metastasis at second pulmonary resection	
Yes	23
No	2

mortality in the present patients. The surgical mode of second pulmonary resection was a wedge resection in 8 patients, segmentectomy in 8 patients, completion lobectomy in 4 patients, lobectomy in 3 patients, and completion pneumonectomy in 2 patients. All repeat pulmonary metastasectomies were curative resections. The median time interval between the first and repeat pulmonary resection was 20 months (range, 5–57 months). The mean patient age at the time of second pulmonary resection was 61 years (range, 47–79 years of age). Table 4 summarizes the patient characteristics and details of repeat pulmonary resections. The median time interval between second pulmonary resection and either death or the latest follow-up in the present series was 20 months (range, 1–238 months).

Overall survival of the patients after second pulmonary resection

The cumulative 3- and 5-year survival rates after the second pulmonary resection were 54.1% and 42.1%, respectively (Fig. 3).

Analysis of the prognostic factors for repeat pulmonary resection

The following factors were selected for a univariate analysis of survival for repeat pulmonary resection: sex, age at second pulmonary resection, pathological stage of the primary CRC according to the Dukes classification, location of primary tumor, histology of primary tumor, interval between first and second pulmonary resection (<20 or ≥20 months), serum CEA level before second pulmonary resection (<5 or ≥5 ng/mL), the number and site of resected metastases at the second pulmonary resection, site of recurrence (pulmonary metastasis/surgical margin relapse), maximum tumor size at second pulmonary resection (≤30 or >30 mm), type of resection at second pulmonary resection (sublobar resection, lobectomy, or pneumonectomy), and hilar or mediastinal lymph node metastasis at the time of the second pulmonary resection (Table 5). Significant relationships were identified only between hilar or mediastinal lymph node metastasis at the second pulmonary resection and survival after the repeat pulmonary resection.

Comments

In our hospital, pulmonary metastasectomies have been performed for various diseases including CRC, soft-tissue

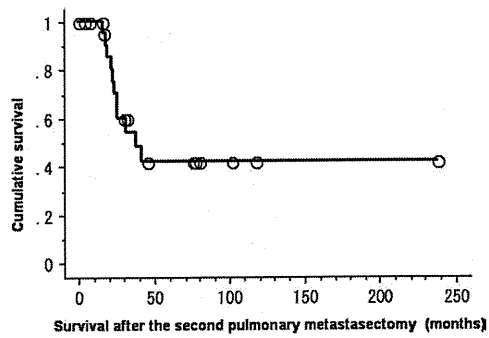

Figure 3 Overall survival rates of patients after the second pulmonary resection. The cumulative 3- and 5-year survival rates after the second pulmonary resection were 54.1% and 42.1%, respectively.

Table 5 Univariate analysis of the prognosis for repeat pulmonary resections

Factors	N	5-year survival	*P* value
Sex (male/female)	17/8	46.2/33.3	NS
Age at second pulmonary resection (<61 y/≥61 y)	13/12	45.7/40.0	NS
Stage of primary tumor (dukes BC/D/unknown*)	17/5/3	41.7/25.0	NS
Location of primary tumor (Colon/rectum)	8/17	42.9/41.0	NS
Histology of primary tumor (well/moderately differentiated adenocarcinoma or others/unknown*)	11/13/1	44.4/41.6	NS
Interval between first and second pulmonary resection (<20/≥20 months)	12/13	55.6/25.0	NS
Serum CEA level before second pulmonary resection (<5/≥5 ng/mL)	18/7	36.1/53.6	NS
Number of resected metastases at second pulmonary resection (solitary/multiple)	16/9	47.6/33.3	NS
Site of metastasis at second pulmonary resection (unilateral/bilateral)	23/2	44.3/0	NS
Site of recurrence (pulmonary metastasis/surgical margin relapse)	21/4	54.9/0	NS
Maximum tumor size at second pulmonary resection (≤30/>30 mm)	20/5	43.0/40.0	NS
Type of resection at second pulmonary resection (sublobar resection/lobectomy or pneumonectomy)	16/9	55.9/25.0	NS
Hilar or mediastinal lymph node metastasis at second pulmonary resection (yes/no)	2/23	0/46.8	.048

NS = not significant.
*Excluding unknown cases.

sarcoma, transitional cell carcinoma, and hepatocellular carcinoma according to the general eligibility criteria described in the Patients and Methods section and with good surgical outcomes.[18–23] The present study analyzed the outcomes in patients undergoing pulmonary metastasectomy from CRCs. The overall 5-year survival rate was 56.2%, which was consistent with the 24% to 71.2% range previously reported.[4–15]

Twenty-five patients who met the criteria described for this study underwent a second pulmonary metastasectomy and had a 5-year survival rate after the second resection of 42.1%. Table 6 compares the outcomes in studies involving more than 10 patients undergoing repeat pulmonary resection of metastatic CRCs.[5,9,11,13–15,17] The overall 5-year survival rates after the second pulmonary resection in these previous reports ranged from 23% to 52.1%. Considering the results of the current study, good surgical outcomes were achieved by repeat pulmonary resections of metastatic CRCs.

Many studies[5,8,9,14,24] showed no association between repeat pulmonary resection and poor survival by a multivariate analysis for survival after the first pulmonary resection. In addition, previous studies[5,13] of repeat pulmonary resection patients identified no increase in the risk of morbidity or mortality with a repeat pulmonary resection compared with the initial resection. In the present study, there was no major operative morbidity or mortality for patients undergoing repeat pulmonary resection even in 2 patients who had undergone completion pneumonectomies. These findings indicated that repeat pulmonary resection for metastatic CRC patients is a safe procedure that provides satisfactory patient outcomes.

In the present study, the poor prognostic factors for the first pulmonary resection of metastatic CRC included a moderately differentiated carcinoma or other histological type, an elevated prethoracotomy serum CEA level (≥5 ng/mL), and hilar or mediastinal lymph node metastasis according to a multivariate analysis. The prethoracotomy serum CEA levels were the most consistently reported prognostic factor for pulmonary metastasectomy from CRC.[4–6,9,12,19,24–28] We previously reported that the prethoracotomy CEA level was the most useful prognostic factor, and an elevated serum CEA level is associated with extrathoracic metastasis after pulmonary metastasectomy from CRCs. A number of reports[4,5,25,29] associated the presence of hilar or mediastinal lymph node metastases with a poor patient prognosis. Several authors[7,25] have shown results consistent with the present study, showing that a histological diagnosis for the primary CRC of well-differentiated adenocarcinoma is an independent significant prognostic factor after the first pulmonary resection of CRC.

Although prognostic factors for the first pulmonary resection of metastatic CRC have been well studied, the predictive factors for repeat pulmonary resection have not been sufficiently investigated. Ogata et al[13] reported that patients with extrathoracic recurrence before a second pulmonary metastasectomy or with mediastinal lymph node metastasis had a poorer prognosis. Welter et al[14] identified an increasing number of metastases as a poor prognostic factor for repeat pulmonary resection for metastatic CRC patients by a multivariate analysis, whereas Park et al[15] showed an association between elevated serum preoperative CEA levels and a poor prognosis by a univariate analysis.

Interestingly, the present study showed that the prognostic factors for the first and repeat pulmonary resection are different. Hilar or mediastinal lymph node involvement is consistently associated with a poor prognosis for both the first and repeat pulmonary resections, whereas the histological type of the primary CRC and the prethoracotomy serum CEA level does not significantly affect patient survival after second pulmonary resection. The differences in the prognostic factors for the first and repeat pulmonary resections depend on the differences between the characteristics of these 2 cohorts. The characteristics between these 2 cohorts