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ORIGINAL SCIENTIFIC REPORT

Prognostic Impact of Tumor Doubling Time in Patients with Metachronous Lung Cancer

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Abstract

Background Good prognosis following surgery for metachronous lung cancer has been reported. However, prognostic factors have not been fully investigated. The purpose of this study was to identify the preoperative predictor of survival in metachronous lung cancer.

Methods Patients who underwent a second pulmonary resection for metachronous lung cancer at our institution between 2000 and 2014 were analyzed.

Results A retrospective chart review identified 86 eligible patients (of 6213; 1.4%). The 5-year overall survival was 77%. All 86 cancers met Martini and Melamed's criteria for second primary cancer. However, on pathological examination based on morphological concordance between the initial and metachronous cancer, 73 (85%) cases were diagnosed as second primary cancer and 13 (15%) as a possible recurrent tumor. The 5-year overall survivals were 82% for second primary cancers and 52% for possible recurrent tumors. Tumor doubling time > 180 days ($p < 0.001$), pathological diagnosis of second primary cancer ($p = 0.013$), pathological stage IA ($p = 0.016$), interval between resections > 2 years ($p = 0.040$), and consolidation/tumor diameter ratio ≤ 0.5 ($p = 0.045$) were associated with superior overall survival. Multivariate Cox regression analysis identified tumor doubling time > 180 days as the only independent predictor of overall survival (hazard ratio 3.600, 95% confidence interval 1.226–10.338; $p = 0.0196$).

Conclusions Surgical resection for metachronous lung cancer is effective and feasible. Particularly, a tumor doubling time > 180 days is associated with superior survival in patients with metachronous lung cancer.

Introduction

The incidence of metachronous lung cancer has increased in recent years as a result of longer survival after resection of primary lung cancers, with a reported incidence of 2% to 6% per patient per year of follow-up [1, 2]. Although good prognosis after second resection for metachronous lung cancer has been reported, with a 5-year overall survival of 33% to 66% [1, 3–6], prognostic factors have not been fully investigated.

In patients who present with second pulmonary nodules, distinguishing initial cancer recurrence from second primary cancer is a challenging task. The classic criteria for a

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metachronous second primary cancer were defined by Martini and Melamed [7]. A tumor is considered metachronous second primary cancer if the histologic type is discordant or if the disease-free interval is at least 2 years for tumors with a cell type similar to that of the primary cancer. Patients are also considered to have a metachronous second primary cancer if the tumor is associated with carcinoma in situ or arises in a different lobe without common lymphatics. However, we propose that, in the current era of rising incidence of early-stage adenocarcinoma, the validity of Martini and Melamed's criteria, established more than 40 years ago, should be reassessed.

The purpose of this study was to clarify the prognosis of metachronous lung cancer and identify the preoperative factors that predict survival in metachronous lung cancer.

Methods

Patients

Between 2000 and 2014, all patients who underwent surgical resection for lung cancer at the National Cancer Center Hospital were identified from a prospectively maintained surgical database. Information on patients who underwent multiple resections for metachronous lung cancer at the National Cancer Center Hospital was reviewed. In this study, metachronous lung cancer was defined as any lung cancer occurring after the initial resection, regardless of interval, tumor location, or histologic type. Patients who underwent either the initial resection or the second resection at other institutions were excluded. Patients having tumors that were retrospectively detectable on CT scans before the first resection were also excluded, because their tumors were not metachronous lung cancers but were synchronous lung cancers. Patients who underwent multiple resections for synchronous lung cancers were also excluded. Patient age, sex, smoking history, comorbidities (hypertension, coronary artery disease, diabetes mellitus, tuberculosis, gastrointestinal disease, pulmonary disease, renal disease, hepatic disease, and cerebrovascular disease were included in our surgical database), pulmonary function, serum carcinoembryonic antigen (CEA) level, tumor size, tumor histology, degrees of differentiation, tumor node metastasis (TNM) stage, surgical procedure, survival, and cause of death were extracted from medical records and the surgical database. Consolidation/tumor diameter ratios (CTRs) of metachronous lung cancer were calculated from preoperative thin-sliced computed tomography (CT) scans according to previously reported methods [8]. Tumor doubling time (TDT) ([the elapsed time (days) $\times$ log 2]/[3 $\times$ log (tumor diameter at the final measurement; mm)/tumor diameter at the initial measurement; mm)]) of the metachronous lung cancer was calculated from preoperative thin-sliced CT scans at two different time points, according to previously reported methods [9]. We used a TDT of 180 days as the threshold to divide tumors into fast- and slow-growth groups, according to a previous study [10]. Tumor histology was described according to the 2015 World Health Organization classification [11]. All patients were staged using the malignant tumor staging system as per the Union for International Cancer Control TNM Classification (7th edition, 2009) [12]. Pathologists reviewed the pathology slides from the initial cancer and designated the metachronous cancer as a second primary cancer or possible recurrent tumor by comparing tumor morphology, histologic features, and degrees of differentiation.

The timing of surveillance for patients who underwent surgical resection of lung cancer in our institution was 3–4-month intervals until 2 years after surgery, 6-month intervals until 5 years, and then 12-month intervals until 8–10 years. Follow-up CT scans were performed at least annually. In follow-up CT, thin-sliced, in addition to the routinely acquired 1-cm thick images of the entire lung and mediastinum, high-resolution images ($\leq$2 mm thickness) of the emerging pulmonary lesion were obtained to characterize the CT appearance.

The National Cancer Center Ethical Committee approved the study and waived the need for individual patients to provide consent because of the retrospective nature of the study, because consent could not be obtained from all of the patients, and because individual patients were not identified in the study.

Statistical analysis and data calculations

Fisher's exact test or Mann–Whitney *U* test was used to evaluate differences in patient/tumor characteristics between groups. Survival time was defined as the time between the date of second resection and the last follow-up date. Overall survival was defined as the time between second resection and death from any cause. Survival curves were estimated by the Kaplan–Meier method, and differences in survival were assessed by the log-rank test. Significance was defined as a p value < 0.05.

Results

Patient and tumor characteristics

Between January 2000 and December 2014, 6213 consecutive patients underwent surgical resection for lung cancer at the National Cancer Center Hospital. Of these, 86 patients (1.4%) underwent multiple resections for

metachronous lung cancer at the National Cancer Center Hospital. Patient and tumor characteristics of metachronous lung cancer are shown in Table 1. The mean age at the second resection was 70 years, and 53 out of 86 patients (62%) were men. The most frequent comorbidity was hypertension (34%), followed by diabetes mellitus (17%) and coronary artery disease (8%). The median interval between first and second resection was 1540 days (range 366–4218 days). The mean forced expiratory volume in 1 s/forced expiratory volume at the second resection was 76 ± 17%. The median interval between the first resection and emergence of metachronous lung cancer was 520 days (range 181–4175 days). The TDT of the metachronous lung cancer was calculated from the preoperative CT in 80 of 86 patients (93%). The mean TDT was 316 ± 305 days. In 6 out of 86 patients (7%), the TDT could not be calculated because the metachronous lung cancer was undetectable on the second-latest CT scan.

All 86 metachronous lung cancers (100%) met Martini and Melamed's criteria for metachronous second primary cancer [7]. However, comparative investigation of histology revealed that the pathological diagnosis of metachronous lung cancer was second primary cancer in 73 patients (85%), and a possible recurrent tumor in 13 patients (15%).

Histology and pathological stage of the initial and metachronous cancer

The histologic concordance of the initial and metachronous cancer is shown in Table 2. Seventy-one of 86 patients (83%) had concordant histologic types. Both the initial and metachronous cancers were adenocarcinomatous in 61 of 86 patients (71%). The pathological stages of the initial and second primary cancer are shown in Table 3. The proportion of pathological stage IA was significantly higher in the second primary cancer than in the initial cancer (78% vs.

Table 1 Patient characteristics and tumor characteristics of metachronous lung cancer

Characteristics	n = 86
Age (years, mean ± SD)	70 ± 9
Sex, male	53 (62%)
Smoking history (+)	59 (69%)
Interval between resections (days, median, range)	1540 (366–4218)
Preoperative pulmonary function	
Forced expiratory volume in 1 s/forced vital capacity	76 ± 17%
Forced expiratory volume in 1 s (%predicted)	79 ± 17%
Forced vital capacity (%predicted)	95 ± 21%
Adjuvant therapy for the initial cancer (+)	4 (5%)
Serum CEA level (ng/mL, mean ± SD)	3.2 ± 2.3
Histological type of metachronous lung cancer	
Adenocarcinoma	66 (77%)
Squamous cell carcinoma	17 (20%)
Others	3 (3%)
Degrees of differentiation of metachronous lung cancer	
Well-differentiated	38 (44%)
Moderately/poorly differentiated	48 (56%)
Tumor diameter (mm, mean ± SD)	19 ± 8
Consolidation/tumor diameter ratio (mean)	0.79
Tumors with consolidation/tumor diameter ratio > 0.5	69 (80%)
Tumor doubling time (days, mean ± SD)	316 ± 305
Interval between first resection and emergence of metachronous lung cancer	520
(days, median, range)	(38–4175)
Metachronous cancer met Martini and Melamed's criteria	86 (100%)
Pathological diagnosis of metachronous lung cancer	
Second primary cancer	73 (85%)
Possible recurrent tumor	13 (15%)

SD standard deviation, *CEA* carcinoembryonic antigen

Table 2 Histologic type of the initial and metachronous cancer

The initial cancer	The metachronous cancer	$n = 86$
Concordant histology		71 (83%)
Adenocarcinoma	Adenocarcinoma	61 (71%)
Squamous cell carcinoma	Squamous cell carcinoma	10 (12%)
Discordant histology		15 (17%)
Adenocarcinoma	Squamous cell carcinoma	3 (3%)
Squamous cell carcinoma	Adenocarcinoma	3 (3%)
Other combinations		9 (10%)

52%, $p = 0.0009$). Pathological stage of the initial cancer stratified by pathological diagnosis of the metachronous lung cancer (second primary cancer or possible recurrent tumor) was also analyzed. The proportion of pathological stage I initial cancer was significantly higher in patients who developed second primary cancer than in those who developed a possible recurrent tumor (54/73 = 74% vs. 5/13 = 38%, $p = 0.002$).

Operative side, type of surgical procedure, and perioperative outcome

The operative side and type of surgical procedure are shown in Table 4. Sixty-nine of 86 patients (80%) underwent the second resection on the contralateral side. The proportion of sublobar resections (wedge resection or segmentectomy) was significantly higher in the second resection than in the initial resection (83% vs. 12%, $p < 0.001$). The median duration of postoperative hospital stay was 4 days (range 2–335 days). Seventy-nine of 86 patients (92%) were discharged within 7 postoperative days, and the 90-day mortality rate was 0%. In-hospital death occurred due to pneumonia on the 335th postoperative day in one patient (1%) with severe chronic obstructive pulmonary disease.

Survival

The median follow-up period from the second resection was 52 months (range 3–171 months). Overall survival at

Table 4 Operated side and type of surgical procedure performed

The initial cancer	The metachronous cancer	$n = 86$
Ipsilateral side		17 (20%)
Lobectomy	Wedge resection	10 (12%)
	Segmentectomy	2 (2%)
	Completion pneumonectomy	2 (2%)
Wedge resection	Wedge resection	2 (2%)
	Lobectomy	1 (1%)
Contralateral side		69 (80%)
Lobectomy	Wedge resection	31 (36%)
	Segmentectomy	20 (23%)
	Lobectomy	12 (14%)
Segmentectomy	Segmentectomy	3 (3%)
	Wedge resection	1 (1%)
Pneumonectomy	Wedge resection	2 (2%)

5 years from the second resection was 77% (Fig. 1a). Six of 86 patients (7%) died from diseases other than lung cancer. The 5-year overall survival was 82% in patients with second primary cancers and 52% in patients with possible recurrent tumors (Fig. 1b). In univariate analysis, a TDT > 180 days ($p < 0.001$), pathological diagnosis of a second primary cancer ($p = 0.013$), pathological stage IA ($p = 0.016$), interval between resections > 2 years ($p = 0.040$), and CTR ≤ 0.5 ($p = 0.045$) were significantly associated with superior overall survival (Fig. 1c–f). On the other hand, histological concordance ($p = 0.376$), operative side (ipsilateral vs. contralateral) ($p = 0.541$), tumor size (greater than 2 cm) ($p = 0.202$), sex ($p = 0.093$), smoking history ($p = 0.083$), pulmonary function (forced expiratory volume in 1 s/forced vital capacity < 70%) ($p = 0.368$), and surgical procedure (lobectomy or more vs. sublobar resection)($p = 0.310$) were not associated with overall survival.

Multivariate analysis

TDT > 180 days ($p < 0.001$), pathological stage IA ($p = 0.016$), interval between resections > 2 years

Table 3 Pathological stage of the initial and metachronous second primary cancer

Pathological stage (ver. 7)	The initial cancer ($n = 86$)	The second primary cancer ($n = 73$)
Stage IA	45 (52%)	57 (78%)
Stage IB	14 (16%)	9 (12%)
Stage IIA	13 (15%)	2 (3%)
Stage IIB	3 (3%)	2 (3%)
Stage IIIA	8 (9%)	2 (3%)
Stage IIIB	2 (2%)	1 (1%)
Stage IV	1 (1%)	0 (0%)

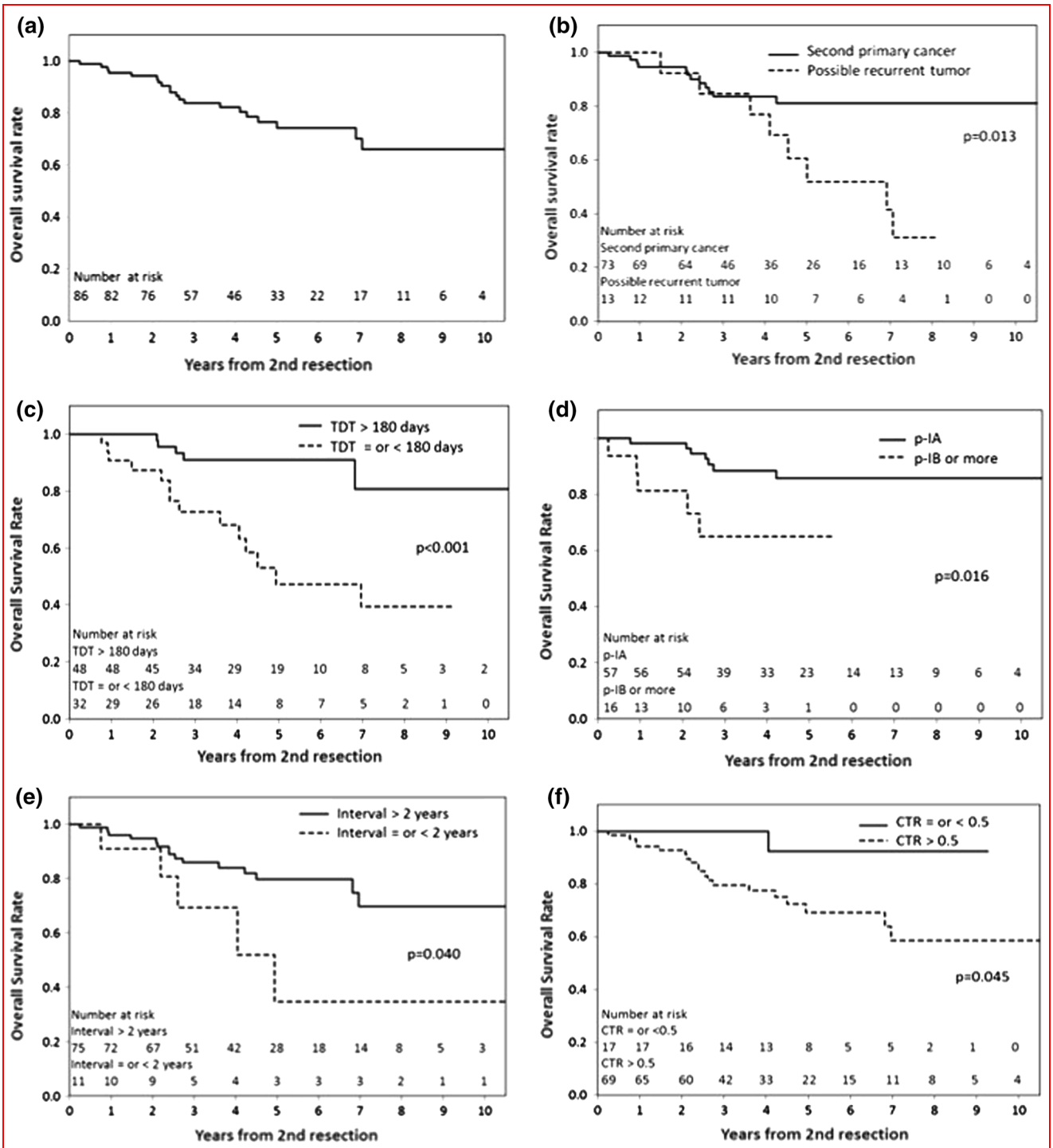

Fig. 1 Kaplan–Meier estimates of overall survival after resection of metachronous lung cancer. **a** All patients, **b** pathological diagnosis (second primary cancer vs. possible recurrent tumor), **c** tumor doubling time, **d** pathological stage, **e** interval between resections, and **f** consolidation/tumor diameter ratio (CTR)

($p = 0.040$), and CTR ≤ 0.5 ($p = 0.045$) were significant favorable prognostic factors in univariate analysis. Pathological stage was excluded from multivariate analysis, because it could not be applied to possible recurrent tumors. The remaining three factors were selected for multivariate Cox regression analysis; this analysis identified TDT > 180 days as the only independent predictor of overall survival (hazard ratio 3.600, 95% confidence interval 1.226–10.338; $p = 0.0196$). Interval between resections > 2 years (hazard ratio 2.954, 95% confidence

Table 5 Patient and tumor characteristics of metachronous lung cancer stratified by tumor doubling time

Characteristics	TDT > 180 days (n = 48)	TDT ≤ 180 days (n = 32)	p value
Age (years, mean ± SD)	71 ± 8	67 ± 10	0.09
Sex, male	29 (54%)	24 (75%)	0.2
Smoking history (+)	28 (58%)	26 (81%)	0.05
Interval between resections (days, median, range)	1713 (667–3369)	988 (366–4119)	0.0001
Serum CEA level (ng/mL, mean ± SD)	3.3 ± 2.5	3.0 ± 2.2	0.8
Tumor diameter (mm, mean ± SD)	18 ± 8	18 ± 6	1
Consolidation/tumor diameter ratio (mean)	0.73	0.84	0.2
Pathological diagnosis of metachronous lung cancer			
Second primary cancer	47 (98%)	20 (63%)	<0.0001
Possible recurrent tumor	1 (2%)	12 (38%)	
Pathological stage of second primary cancer			
I	42 (88%)	17 (85%)	1
II or more	6 (13%)	3 (15%)	
Histological type of metachronous lung cancer			
Adenocarcinoma	43 (90%)	20 (63%)	0.005
Others	5 (10%)	12 (37%)	
Degrees of differentiation of metachronous lung cancer			
Well-differentiated	27 (56%)	9 (28%)	0.02
Moderately/poorly differentiated	21 (44%)	23 (72%)	

TDT tumor doubling time, *SD* standard deviation, *CEA* carcinoembryonic antigen

interval 0.986–8.853; $p = 0.0531$) and CTR ≤ 0.5 ((hazard ratio 5.103, 95% confidence interval 0.673–38.722; $p = 0.1150$) was not significant.

Clinical implication of tumor doubling time in metachronous lung cancers

Patient characteristics and tumor characteristics of metachronous lung cancer stratified by tumor doubling time are shown in Table 5. A TDT > 180 days was a significant predictor of pathological diagnosis of second primary cancer (98% of tumors with a TDT > 180 days vs. 63% with a TDT ≤ 180 days, $p < 0.0001$). The proportion of adenocarcinoma was significantly higher in metachronous lung cancers with a TDT > 180 days than in those with a TDT ≤ 180 days (90% vs. 63%, $p = 0.005$). The proportion of well-differentiated tumors was significantly higher in metachronous lung cancers with a TDT > 180 days than in those with a TDT ≤ 180 days (56% vs. 28%, $p = 0.02$).

Comment

The purpose of this study was to determine the prognosis and prognostic factors pertaining to surgical resection of metachronous lung cancers. The 5-year overall survival rate after surgical resection of metachronous lung cancers was high (77%), and univariate analyses showed that the following were significant favorable prognostic factors: a TDT > 180 days, an interval of more than 2 years between resections, a pathological diagnosis of second primary cancer, a CTR ≤ 0.5, and a pathological stage of IA.

We observed highly favorable patient outcomes in this study: 0% mortality rate at day 90; 1.2% in-hospital mortality rate; median postoperative hospital stay of 4 days; and a 5-year survival of 77%. The 5-year survival rate achieved in this study is superior to that achieved in previous similar studies (33–66%) [1, 3–6]. The reason for this may be related to patient population characteristics. We studied patients who underwent lung cancer resection twice at our hospital, and most metachronous lung cancers were consequently found during a yearly CT follow-up. Therefore, the percentage of pathological stage IA lung cancers in our study was higher (78%) than in previously reported studies (49–68%) [3–5].

TDT is known to reflect the biological malignancy of tumor cells in various types of cancers, and is also known to be a prognostic factor in patients undergoing resection of primary lung cancer [9]. However, TDT can rarely be calculated in primary lung cancer patients, because most primary lung cancer is resected immediately after diagnosis. In contrast, TDT could be calculated in 93% of patients with metachronous lung cancer in this study, because most metachronous lung cancer was retrospectively

detectable on the second-latest computed tomography scan. Furthermore, a TDT > 180 days was the strongest prognostic factor in patients who underwent resection of metachronous lung cancer ($p < 0.001$). Thus far, a relationship between TDT and prognosis in patients with metachronous lung cancer resection has not been reported. Therefore, we believe that demonstrating the availability of tumor doubling time in metachronous lung cancer is a valuable insight.

It has been reported that the disease-free interval and the interval between resections are not associated with prognosis following surgery for metachronous lung cancer [1, 3, 5]. However, in our study, an interval of more than 2 years between surgical procedures was also a significant prognostic factor for patients who underwent metachronous lung cancer resection ($p = 0.040$). Lesions that grow rapidly are detected by CT earlier than those that grow slowly. This observation may explain our finding that prognosis was unfavorable in cases with a short interval between surgical procedures. Pathological stage IA and CTR ≤ 0.5 were also revealed as significant favorable prognostic factors in this study. Many studies have shown that pathological stage is linked with prognosis [1, 5]. The CTR is a known prognostic factor in patients who undergo resection of a primary lung cancer [8], and we found that CTR was a prognostic factor in metachronous lung cancers as well. Most metachronous lung cancer patients had small tumors, with an average diameter of 19 ± 8 mm, and sublobar resection had been performed in 83% of cases. Consistent with recent reports, surgical procedure (lobectomy or sublobar resection) did not correlate significantly with prognosis [1, 3, 4, 6]. Sublobar resection is therefore an acceptable option for the treatment of metachronous lung cancers.

In this study, all 86 metachronous cancers met Martini and Melamed's criteria for metachronous second primary cancer. However, based on the comparison of pathological findings, the 86 metachronous lung cancers were classified into two categories, namely: (1) second primary cancers ($n = 73$) and (2) possible recurrent tumors ($n = 13$). Second primary cancers had a more favorable prognosis than did possible recurrent tumors (5-year survival rates: 83% and 52%, respectively, $p = 0.013$). In metachronous lung cancers, second primary cancers and recurrences of the initial cancer are extremely difficult to differentiate before surgery, but a TDT $\geq$ 180 days correlated significantly with the pathological diagnosis of second primary cancer in the resected specimens (98% of tumors with a TDT > 180 days vs. 63% with a TDT $\leq$ 180 days, $p < 0.0001$). In general, second primary cancers have a lesser malignant potential than do recurrent tumors; hence, the tumor growth rate of second primary cancers may have also been low, and a number of patients with second primary cancers may have been included among those with a TDT > 180 days.

This study has three major limitations. The first is selection bias due to the retrospective design based on the surgical database. Stereotactic body radiotherapy is one of the important treatment options for patients with poor pulmonary function. However, this study included only surgical cases with relatively good pulmonary function. Moreover, in most of the cases examined in this study, metachronous lung cancer was discovered during a regular follow-up CT carried out after initial cancer resection, and, as a result, many of the selected cases may have consisted of early-stage lung cancer with favorable prognosis. However, we placed special emphasis on accuracy of information and comparison of pathological findings between initial lung cancers and metachronous lung cancers; therefore, patients whose initial surgery had been performed at other hospitals were excluded from the study. The second limitation was the small sample size leading to an increased probability of type 2 error. However, the number of cases in our study (86) was comparable to those of recent reports (33–69) [1, 4–6]. The third limitation was the absence of the use of molecular techniques to distinguish second primary cancer from possible recurrent tumor. Many molecular techniques have been reported to be effective for this purpose [13], and the addition of molecular techniques may have enhanced this study. However, comprehensive histological assessment of surgical specimens has also been reported to be a reliable method to differentiate second primary cancer and recurrent tumor and has shown good reproducibility among lung pathologists [14, 15]. The usefulness of molecular testing should be validated in future studies.

In conclusion, surgical resection of metachronous lung cancer matched to Martini and Melamed's criteria confers a high 5-year survival rate of 77%. Especially, in this study, metachronous lung cancers with a TDT > 180 days had a significantly superior prognosis. Measuring TDT is a useful and convenient method to predict prognosis in patients with metachronous lung cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent The Institutional Ethical Committee approved the study and waived the need for individual patients to provide consent because of the retrospective nature of the study, because consent could not be obtained from all of the patients, and because individual patients were not identified in the study.

References

1. Lee BE, Port JL, Stiles BM et al (2009) TNM stage is the most important determinant of survival in metachronous lung cancer. Ann Thorac Surg 88:1100–1105
2. Lou F, Huang J, Sima CS et al (2013) Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg 145:75–81
3. Hamaji M, Allen MS, Cassivi SD et al (2013) Surgical treatment of metachronous second primary lung cancer after complete resection of non-small cell lung cancer. J Thorac Cardiovasc Surg 145:683–690
4. Haraguchi S, Koizumi K, Hirata T et al (2010) Surgical treatment of metachronous nonsmall cell lung cancer. Ann Thorac Cardiovasc Surg 16:319–325
5. Battafarano RJ, Force SD, Meyers BF et al (2004) Benefits of resection for metachronous lung cancer. J Thorac Cardiovasc Surg 127:836–842
6. Bae MK, Byun CS, Lee CY et al (2011) The role of surgical treatment in second primary lung cancer. Ann Thorac Surg 92:256–262
7. Martini N, Melamed MR (1975) Multiple primary lung cancers. J Thorac Cardiovasc Surg 70:606–612
8. Sakurai H, Nakagawa K, Watanabe S et al (2015) Clinicopathologic features of resected subcentimeter lung cancer. Ann Thorac Surg 99:1731–1738
9. Usuda K, Saito Y, Sagawa M et al (1994) Tumor doubling time and prognostic assessment of patients with primary lung cancer. Cancer 74:2239–2244
10. Wang J, Mahasittiwat P, Wong KK et al (2012) Natural growth and disease progression of non-small cell lung cancer evaluated with 18F-fluorodeoxyglucose PET/CT. Lung Cancer 78:51–56
11. Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E (2012) Histological typing of lung and pleural tumours, World Health Organization International Histological Classification of Tumors. Springer, Berlin
12. Sobin LHGM, Wittekind C (2009) International Union Against Cancer (UICC) TNM classification of malignant tumours. Wiley-Liss, New York
13. Vignot S, Frampton GM, Soria JC et al (2013) Next-generation sequencing reveals high concordance of recurrent somatic alterations between primary tumor and metastases from patients with non-small-cell lung cancer. J Clin Oncol 31:2167–2172
14. Girard N, Deshpande C, Lau C et al (2009) Comprehensive histologic assessment helps to differentiate multiple lung primary nonsmall cell carcinomas from metastases. Am J Surg Pathol 33:1752–1764
15. Nicholson AG, Torkko K, Viola P et al (2018) Interobserver variation among pathologists and refinement of criteria in distinguishing separate primary tumors from intrapulmonary metastases in lung. J Thorac Oncol 13:205–217