Original Article

Surgical Treatment of Metachronous Nonsmall Cell Lung Cancer

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Purpose: We report surgical results of metachronous nonsmall cell lung cancer (NSCLC).
Methods: We report mortality and analyze prognostic factors for overall survival in patients with metachronous NSCLC at Nippon Medical School from July 1982 to July 2008.
Results: Thirty-three out of 1726 patients (1.9%) who underwent lung resection had metachronous NSCLC. Mortality rate was 10%. On univariate analyses, the different histologies at the first and second operations were the only significant poor prognostic factor. Twenty-two patients (73%) had the same histology at the first and second operations: adenocarcinoma in 18 (60%) and squamous cell carcinoma in 4 (13%). Their actuarial 5- and 10-year overall survivals were both 71%, compared to 47% and 16% for patients with different histology (p = 0.0174). Sex (p = 0.1742), locations of the first and second cancers (p = 0.3957), operative procedures in patients with p-stage I at the second operation (p = 0.2782), pathological stage at the first operation (p = 0.5958), and pathological stage at the second operation (p = 0.0609) were not prognostic factors. Different histology at the first and second operations was significant based on a multivariate analysis (Hazard ratio: 3.918; p value: 0.0269; 95% confidence interval: 1.169–13.131). The actuarial 5- and 10-year overall survivals for the first cancer was 86% and 64%, compared to 65% and 45% for the second (p = 0.0609).
Conclusions: Our study shows that a surgical approach is beneficial for patients with metachronous NSCLC. Good prognosis in patients with the same histology may support the current criteria of metachronous NSCLC mainly based on the histology. (Ann Thorac Cardiovasc Surg 2010; 16: 319–325)

Key words: nonsmall cell lung cancer, metachronous carcinoma, mortality, prognosis

Introduction

The frequency of metachronous nonsmall cell lung cancer (NSCLC) has increased from 0.5% to 4.5%, probably because of early detection and curative resection of the first cancer, and recently many articles have been reported in this regard.[1–13] Metachronous NSCLC still has controversial problems, especially in the criteria for diagnosis and treatment. Occasionally, differentiating it from local recurrence or pulmonary metastasis is very difficult if the first and second cancers have the same histology. Surgery in the bilateral thoraces or completion pneumonectomy is quite risky in compromised hosts. In the present study, we report mortality and analyze prognostic factors for overall survival in patients with metachronous NSCLC in our institution.

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Material and Methods

From July 1982 to July 2008, a total of 1726 patients with lung cancer underwent lung resection at the Division of Thoracic Surgery, Department of Surgery, Nippon Medical School, and the Department of Surgery, Nippon Medical School Musashikosugi Hospital. The definition of metachronous lung cancer was according to Martini and Melamed[1] and described as follows: (A) different histology, and (B) same histology if (1) the free interval between cancers was at least 2 years, or (2) if the origin was from carcinoma in situ, or (3) if the second cancer was in a different lobe or lung without carcinoma in lymphatics common to both and extrapulmonary metastases at the time of diagnosis. Of the 1726 patients, 33 (1.9%) had metachronous NSCLC in their medical records. Two were excluded from the present study because of the lack of a detailed clinical background, and one was excluded because of radiotherapy for the second cancer. Therefore 30 patients, including 18 males and 12 females, were analyzed in the present study. One patient had three primary lung cancers. The first and second lung cancers in all patients were staged pathologically according to the staging system of UICC (International Union Against Cancer).[14]

The postoperative pulmonary functions were predicted according to a simplified system, which we developed using plain chest roentgenograms of patients with primary lung cancer.[15] The predicted postoperative percent of forced expiratory volume in one second (ppo % FEV1.0) or percent of vital capacity (ppo % VC) is (42-R)/(42-T)×preoperative % FEV1.0 or % VC, where R is the number of subsegments scheduled for lung resection, and T is the number of tumor-related subsegments. The T is determined as follows: (a) if a tumor is located in the periphery of the lung, the T factor is equal to 1 in a tumor 3 cm or less in its largest dimension and equal to 2 in one more than 3 cm in its largest dimension; (b) if a tumor obstructs large airways, the T factor is equal to the number of subsegments showing atelectasis or postobstructive pneumonia. We determined the operability and the permissible extent of lung resection to achieve a ppo % VC of more than 60% and/or a ppo % FEV1.0 of more than 44%.[15]

All patients were seen quarterly in our outpatient clinic for chest X-rays and/or tumor markers and semiannually for computed tomography (CT) of the head, chest, and abdomen and a whole body ^{99m}Tc bone scintigraphy for the first three years, thereafter annually for the next two years, after each resection. Operative mortality was defined as death from all causes occurring during the hospitalization period following surgery.

To accomplish statistical analyses of prognostic factors for the overall survival of patients, we grouped the patients by sex, locations of the first and second cancers (ipsilateral vs. contralateral thorax), histology of lung cancer (the same histology vs. different histology at the first and second operations), operative procedures in patients with p-stage I at the second operation (limited resections vs. lobectomy), pathological stage at the first operation (p-stage I vs. p-stage II or III), and pathological stage at the second operation (p-stage I vs. p-stage II or III). For univariate analyses, the overall survival for subgroups described above was statistically analyzed using Kaplan-Meier estimated survival curves, and the significance of the difference was analyzed by the log-rank test. For multivariate analysis, the Cox proportional hazards model was used to examine the effect of significant risk factors based on the univariate analyses on survival. The statistical analysis was performed using the SPSS 10.0 software package (SPSS, Inc., Chicago, IL, USA) and the StatView 5.0J software package (SAS Institute, Inc., Cary, NC, USA). $P < 0.05$ was considered significant.

Results

The clinicopathological features of the patients are shown in Table 1. The median age of patients with the first cancer was 64 (range, 34–82). The mean periods between operations for the first and second lung cancers were 4.6 years (range, 0.8–13.5).

Three patients (10%) died during hospitalization. Of these, 1 died of massive bleeding from the aorta during completion pneumonectomy, 1 died of pneumonia 232 days after segmentectomy, and 1 died of lung cancer 27 days after lobectomy. During the follow-up period, 6 patients (4 males and 2 females) of the 30 died of lung cancer, and 3 (all males) died of other diseases. Seventeen patients (9 males and 8 females) were alive, and further information about 1 female patient is unknown.

Thirty patients, including 18 males and 12 females, had metachronous NSCLC. The actuarial 5- and 10-year overall survivals after the second operation for male patients were 58% and 36%, compared to 73% and 73% for female patients ($p = 0.1742$) (Fig. 1). Ten patients (33%) had the first and second cancers in the ipsilateral thorax: in the right upper and lower lobes in 6 (20%), in the left upper and lower lobes in 3 (10%), and in segments 6 and 8 of the right lower lobe in 1 (3%). Twenty patients (67%) had the first and second cancers in the contralateral tho-

Table 1. Clinicopathological features of metachronous lung cancer cases

Case	Age Sex	Pack-years	INT(Y)	HIS1	HIS2	LO	P1	P2	S1	S2	Survival (Y) Prognosis
1	78M	44	1.5	AdSq	Ad	Ipsi	LLL	CP	IA	IA	0.0D
2	65F	0	12.1	Ad	Ad	Ipsi	LLL	CP	IA	IB	1.8A
3	65F	0	5.0	Ad	Ad	Ipsi	RLL	PRRUL	IA	IA	5.0A
4	62F	0	4.6	Ad	Ad	Ipsi	RUL	PRRLL	IA	IA	1.2U
5	64F	95	7.7	Sq	Sq	Ipsi	LLL	CP	IA	IIB	1.3A
6	57M	20	10.3	Ad	Ad	Ipsi	RUL	RS6	IIB	IA	4.8A
7	45M	0	5.9	Ad	Ad	Ipsi	RUL	CP	IB	IIB	2.4D
8	57M	80	8.5	Ad	AdSq	Ipsi	RLL	CP	IIB	IA	10.0A
9	34M	15	13.5	Ad	Ad	Ipsi	RUML	PRRLL	IA	IA	5.0A
10	82M	59	2.4	Ad	Ad	Ipsi	RS6	CPRLL	IA	IA	4.8A
11	67M	0	2.1	Sq	Pd	Cont	LUL	RLL	IIIA	IIIA	0.1D
12	65M	75	2.2	Sq	Sq	Cont	LLL	RUL	IB	IIB	6.4A
13	66M	125	4.5	Ad	Sq	Cont	LUL	RUL	IA	IIIB	1.6D
14	46F	0	3.2	Ad	Ad	Cont	LLL	RS6	IA	IA	6.8A
15	64M	44	2.5	Ad	Ad	Cont	LUL	PRRUL	IB	IA	7.5A
16	78M	0	1.9	Sq	Ad	Cont	LUL	RS10	IB	IB	0.6D
17	65F	0	4.3	Ad	Ad	Cont	LUL	RS6	IA	IA	5.7A
18	51F	0	5.0	Ad	Ad	Cont	LUL	RUL	IIA	IIIA	5.0A
19	50M	45	2.2	Sq	Ad	Cont	LUL	RUL	IB	IA	7.5D
20	51F	0	3.6	Ad	Ad	Cont	LLL	RUL	IIIA	IB	2.3D
21	54F	0	2.2	Ad	Ad	Cont	RML	LS1+2	IA	IA	10.0A
22	76M	120	5.2	Sq	Ad	Cont	RLL	PRLUL	IA	IA	5.9D
23	73M	28	5.4	Ad	Ad	Cont	LUL	PRRLL	IA	IA	8.1A
24	67F	0	3.7	Ad	Ad	Cont	RLL	PRLLL	IB	IA	3.6D
25	67M	50	6.5	Sq	Sq	Cont	LUL	PRRUL	IIA	IA	2.8D
26	78M	33	4.0	Ad	Ad	Cont	LUL	PRRLL	IB	IA	1.0A
27	80M	60	1.3	Ad	Sq	Cont	PRLUL	PRRLL	IA	IA	0.9A
28	67F	21	2.1	Ad	Ad	Cont	RML	LS6	IA	IA	0.4A
29	78M	115	2.0	Sq	Sq	Cont	LLL	RUL	IA	IIIB	0.0D
30	62F	0	2.1	Ad	Ad	Cont	LLL	RUL	IA	IB	3.5A

M, male; F, female; INT, interval between the first and second operations; HIS, histology; Ad, adenocarcinoma; AdSq, adenosquamous carcinoma; Sq, squamous cell carcinoma; LO, location of the lesion; Ipsi, ipsilateral; cont, contralateral; P, operative procedure; LLL, left lower lobectomy; LUL, left upper lobectomy; RLL, right lower lobectomy; RML, right middle lobectomy; RUL, right upper lobectomy; RUML, right upper and middle lobectomy; CP, completion pneumonectomy; CPRLL, completion lobectomy of right lower lobe; PRRLL, partial resection of right lower lobe; PRRUL, partial resection of right upper lobe; PRLLL, partial resection of left lower lobe; PRLUL, partial resection of left upper lobe; RS6, resection of right S6; RS10, resection of right S10; LS1+2, resection of left S1+2; LS6, resection of left S6; S, pathological stage; D, dead; A, alive; U, unknown.

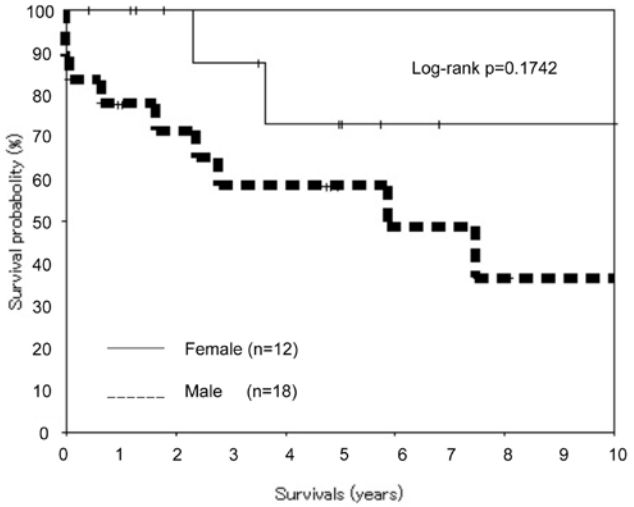

Fig. 1. Actuarial overall survival after the second operation for male or female patients with metachronous nonsmall cell lung cancer.

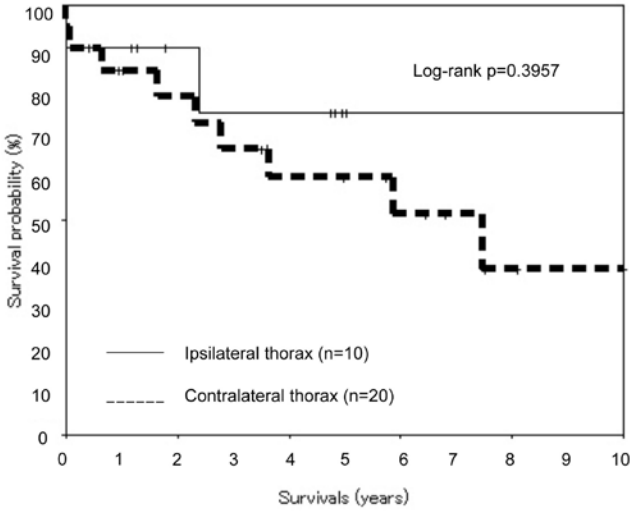

Fig. 2. Actuarial overall survival after the second operation for patients who had the first and second cancers in the ipsilateral and contralateral thoraces.

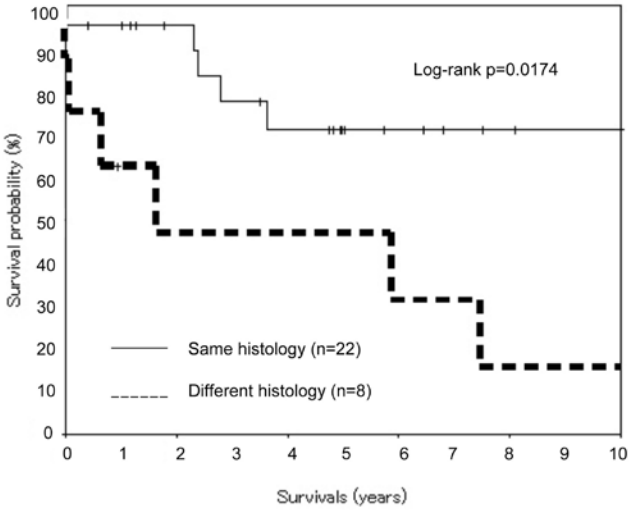

Fig. 3. Actuarial overall survival after the second operation for patients with the same and different histologies at the first and second operations.

rax: in the right lower and left upper lobes in 7 (23%), in the right and left upper lobes in 5 (17%), in the right and left lower lobes in 3 (10%), in the right upper and left lower lobes in 3 (10%), and in the right middle and left upper lobes and the right middle and left lower lobes each in 1 (3%). The actuarial 5- and 10-year overall survivals after the second operation for patients who had the first and second cancers in the ipsilateral thorax were both 75%, compared to 60% and 39% for patients who had the first and second cancers in the contralateral thorax ($p = 0.3957$) (Fig. 2). Twenty-two patients (73%) shared the same histology at the first and second operations: adenocarcinoma in 18 (60%) and squamous cell carcinoma in 4 (13%). Eight patients had different histology at the first and second operations: adenocarcinoma and squamous carcinoma in 5 (17%), adenocarcinoma and adenosquamous carcinoma in 2 (7%), and squamous cell carcinoma and poorly differentiated carcinoma in 1 (3%). The actuarial 5- and 10-year overall survivals after the second operation for patients with the same histology at the first and second operations were both 71%, compared to 47% and 16% for patients who had different histology ($p = 0.0174$) (Fig. 3). Twenty-eight patients (93%) underwent lobectomies, and 2 (7%) underwent wedge resections at the first operation. Ten patients (32%) underwent wedge resections, 7 (23%) underwent lobectomies, 6 (20%) underwent segmentectomies, 5 (17%) underwent completion pneumonectomies, and 2 (7%) who underwent wedge resections at the first operation also underwent the same at the second operation. Of 23 patients with p-stage I at the second operation, 10 underwent wedge resections, 7 underwent segmentectomies, and 6 underwent lobectomies. The actuarial 5- and 10-year overall survivals after the second operation for patients with p-stage I who had undergone limited resections at the second operation were 78% and 63%, compared to 63% and 31% for patients with p-stage I who had undergone lobectomies ($p = 0.2782$) (Fig. 4). Eighty percent and 77% of patients at the first and second operations were stage I if pt1nxm0 is included in stage I (Table 1). The actuarial 5- and 10-year overall survivals after the second operation for patients with p-stage I at the first operation were 70% and 45%, compared to 50% and 50% for patients with p-stages II and III ($p = 0.5958$) (Fig. 5). The actuarial 5- and 10-year overall survivals after the second operation for patients with p-stage I at the second operation were 74% and 50%, compared to 36% and 0% for patients with p-stages II and III ($p = 0.0610$) (Fig. 6). The actuarial 5- and 10-year overall survivals for the first cancer were 86% and 64%, compared to 65% and 45% for the second cancer ($p = 0.0609$) (Fig. 7).

On univariate analyses, different histology at the first and second operations was the only significant poor prognostic factor. Moreover, different histology at the first and second operations remained as a significant factor based on a multivariate analysis (hazard ratio: 3.918; p value: 0.0269; 95% confidence interval: 1.169–13.131).

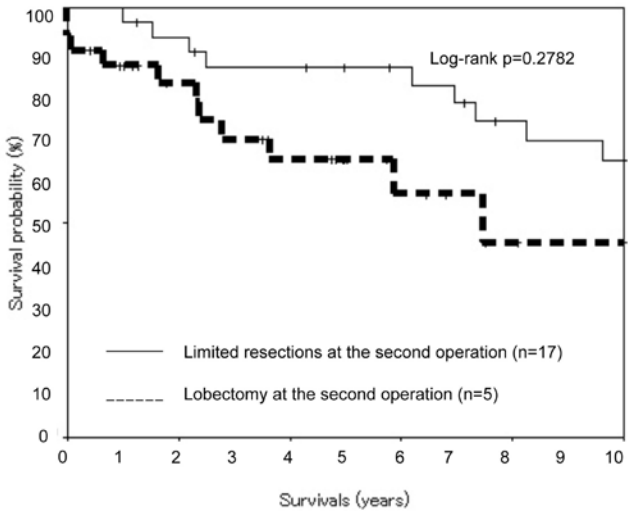

Fig. 4. Actuarial overall survival after the second operation for p-stage I patients with limited resections and lobectomies.

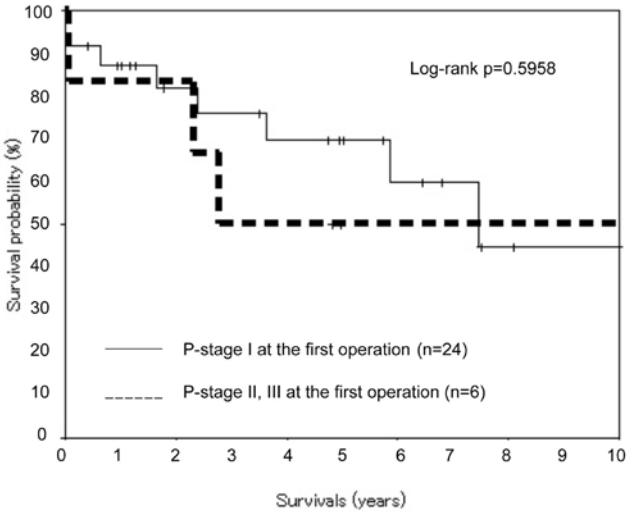

Fig. 5. Actuarial overall survival after the second operation for patients with p-stage I and p-stages II and III at the first operation.

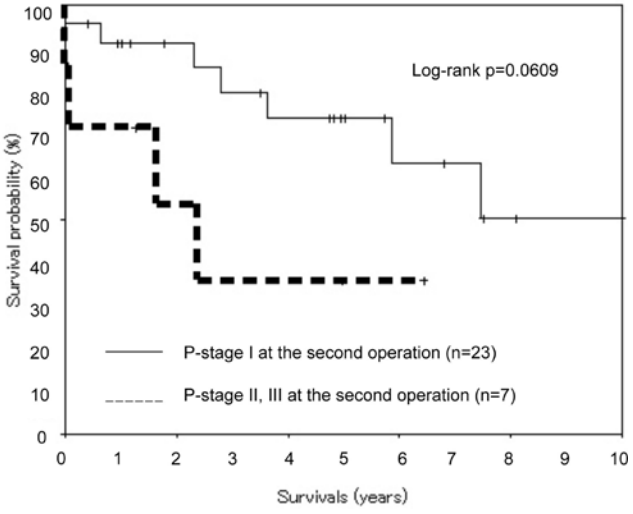

Fig. 6. Actuarial overall survival after the second operation for patients with p-stage I and p-stages II and III at the second operation.

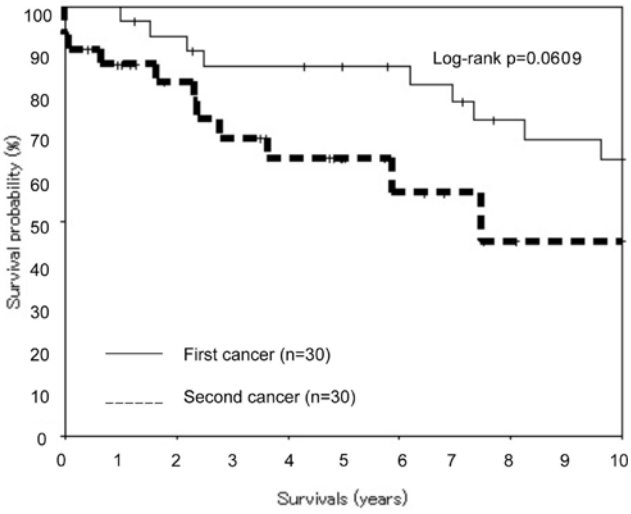

Fig. 7. Actuarial overall survival for the first and second lung cancers.

Discussion

Various criteria for the diagnosis of metachronous NSCLC have been used.[1–13] However, histology is the most important criterion, and prolonged free interval, origin, or location of the second cancer is necessary if the first and second cancers have the same histology.[1,2,7,8] Including the present study, the 5-year survival rates in the same and different histology groups are reported in only 7 articles (Table 2). Our study shows that the 5-year survival rate in the same histology group is 71%, significantly better than in the different histology group. This is probably because some cases with different histology had poorly differentiated second carcinomas. The same histology group and different histology group had no significant difference in the pathological stage in the first and second cancers ($p = 0.6389$ and $p = 0.9517$, respectively). Thirty percent of the same histology group and 25% of the different histology group received chemotherapy after the first operation. Aziz et al. reported a contrary result.[11] Riquet

Table 2. Reported clinical data on metachronous lung cancer

Author (year)	Criteria of MPLC	Frequency (%)	Proportion of stage I in the FC and SC (%)	Treatment for the FC (%)	Treatment for the SC (%)	Mortality (%)	5-year survival for the SH and DH (p value)	5-year survival for the FC and SC (%)
Mathisen (1984)	Machisen	3.9	ND, ND	ND	ND	ND	28, 18 (ND)	60, 33
Deschamps (1990)	Martini	0.5	93, 77	P2, L89, LR9	P16, L41, LR43	4.5	40, 36 (ND)	55, 34
Adebonojo (1997)	Martini, Antakli	2.8	73, 78	L95, LR3, RT3	P16, L59, LR22, RT3	5.6	37, 37 (ND)	75, 37
Aziz (2002)	Martini	4.5	60, 48	P2, L78, LR20	CP27, L63, LR5	7.5	31, 51 (p=0.03)	ND, 44
Battafarano (2004)	Martini	3.2	64, 73	P4, L83, LR13	P6, L45, LR49	5.8	35, 40 (NS)	ND, 33
Riquet (2008)	Martini	3.4	ND, ND	ND	P+CP31, L39, LR30	ND	45, 25 (NS)	ND, 32
Haraguchi (present)	Martini	1.9	80, 77	L93, LR7	CP17, L26, LR57	10	71, 47 (p=0.0174)	86, 65

MPLC, multiple primary lung cancer; FC, first cancer; SC, second cancer; SH, same histology; DH, different histology; ND, not described; P, pneumonectomy; L, lobectomy; LR, limited resection; RT, irradiation; CP, completion pneumonectomy; NS, not significant.

et al.[13] showed that the prognosis in the same histology group is better than in the different histology group, and Battafarano et al. showed an opposing result; the difference, however, did not reach statistical significance in either article. Three articles showed that the prognosis in the same histology is similar to or better than in different histology, but statistical significance wasn't described.[2,5,8] Therefore the prognosis in the same histology seems to be better than in pulmonary metastases. It is suggested that these results may support the current criteria of metachronous NSCLC mainly based on histologies like those of Martini and Melamed.

The other feature about histology in the present study is that adenocarcinoma is dominant in metachronous NSCLC with the same histology, though squamous cell carcinoma has been usually dominant.[1,3–6,9,10] Recently, Battafarano et al.[12] and Adebonojo et al.[8] also reported adenocarcinoma to be dominant in the same histology. The change in the same histology seems to reflect an increase of adenocarcinoma in all races worldwide.

Operative procedures for the second metachronous carcinoma usually depend on the extent and location of the disease, the initial surgical procedure, and the patient's pulmonary reserve.[8,11] We performed lobectomies and mediastinal lymph node dissections in 93% of the patients for the first cancer, and we performed limited resections in 57% for the second cancer to preserve pulmonary function. The survival rate was improved, but the mortality rate was 10%. However, limited resections are favored, even in the first operation in some series, because a previous limited resection allows various options for the second cancer.[2,7,11,12] A limited resection is thought to increase local recurrence slightly, but it does not predispose to higher rates of second primary lung cancer compared with routine lobectomy.[7,11] However, even these series had a high mortality rate of 5.8%–7.5%.[11,12] Surgery in the bilateral thoraces or completion pneumonectomy is very risky in compromised hosts or elderly patients. Therefore it is suggested that the operability and the permissible extent of lung resection in patients with metachronous NSCLC should be determined by stricter criteria.

In conclusion, our study showed that a surgical approach is beneficial for patients with metachronous NSCLC, and good prognosis in patients with the same histology may support the current criteria of metachronous NSCLC, which is mainly based on the histology.

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