Clinical outcomes and prognostic factors for surgically resected second primary lung cancer

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Clinical outcomes and prognostic factors for surgically resected second primary lung cancer

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ABSTRACT

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This study was designed to analyze the predictive factors for survival in second primary lung cancer patients following operation.

A total of 1,852 patients who underwent resection for primary lung cancer between January 1990 and December 2008 were reviewed, retrospectively. Of those patients, the 42 who underwent operation for second primary lung cancer were analyzed in this report.

Nineteen patients were treated for synchronous second primary lung cancer and 23 patients were treated for metachronous second primary lung cancer. The overall five year survival rate for patients with synchronous second primary lung cancer was comparable to that of patients with single lung cancer (51.4% versus 48.7%, p= 0.755). The overall five year survival rate after the first tumor resection in patients with metachronous second primary lung cancer was significantly better than that of patients with single lung cancer (85.4% versus 48.7%, p= 0.003), but was not significantly different after the second tumor resection (77.0% versus 48.7%, p= 0.057). According

to the univariate analysis, histologic concordance and the stage of both the first and second tumors were significant predictors of survival rate of synchronous tumor patients, while histologic concordance and second tumor stage were important for metachronous tumor survival rates.

Surgically resected second primary lung cancer had a survival rate comparable with single lung cancer. Histologic concordance between the first and second tumors, and the pathological stage of the second tumor were important prognostic factors both in synchronous second primary lung cancer and metachronous second primary lung cancer. In addition, the pathological stage of the first tumor had a significant influence on the prognosis for synchronous second primary lung cancer.

Key words : second primary lung cancer, surgery, prognosis

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I. INTRODUCTION

The number of reports of second primary lung cancer (SPLC) has increased since it was first reported by Beyreuther in 1924 [1]. The reported incidence rates of synchronous SPLC range from 0.2% to 20% [2, 3], with the development rate for metachronous SPLC between 1 and 2% per patient per year. Despite these increases in the number of reports, the outcome and prognosis for patients who have undergone resection of SPLC are still unclear. Although SPLC has been considered to be associated with a poor prognosis, with a five-year survival of approximately 20% [4], the reported survival rates range from 0 to 70% in synchronous [2, 5] and from 4 to 66% in metachronous SPLC [6, 7]. Several prognostic factors for survival in SPLC patients have been identified, such as age and gender of the patient, tumor size, and the stage of the second tumor [7-12]. Most recently, Finley et al. reported that only female gender was a significant predictor of better survival, in the largest study of synchronous primary lung cancers [9]. Lee et al. suggested that stage was the only significant determinant of survival after surgical treatment of metachronous lung cancer [7]. However, these

results were not consistent.

Therefore, we have reviewed our past experience regarding the clinical features of resected SPLC, to assess patient outcomes after resection and to identify predictive factors associated with survival.

II. MATERIALS AND METHODS

1. Patients and definition

A total of 1,852 patients underwent surgery with curative intent for primary lung cancer between January 1990 and December 2008 at Severance Hospital, Yonsei University Health System. All patients undergoing surgery were registered in our prospective lung cancer database and received close follow up treatment.

Preoperative evaluation included medical history, physical examination, chest radiography, and blood tests. Chest CT scan, abdominal sonography, and bone scintigraphy were performed routinely. These imaging studies were eventually replaced by PET-CT with its introduction. Cervical mediastinoscopy was performed in patients with suspected N2 or N3 disease.

Patients were followed up at the outpatient clinic at three month intervals for the first two years, and every six months for three years after that. After five years, follow-up data were obtained by direct telephone contact or a single, yearly visit. Follow up was complete up to June 2010. Physical examination, chest radiography and measurement of tumor markers were carried out at the

outpatient clinic. In addition, chest CT scan, abdominal sonography and bone scintigraphy were performed at six month interval for the first two years and at one year interval for subsequent three years. Imaging studies were replaced by PET-CT since its introduction.

Forty-two patients, who had undergone an operation for SPLC by December 2009, were retrospectively selected for this study.

The diagnosis of synchronous SPLC was made if there was radiographic evidence of a second tumor before operation, or if a second tumor was discovered incidentally during operation or in the resected specimen. In this study, the cases in which the second tumor was detected during the follow-up period after resection of the first tumor were included if the second tumor was ascertained to have been present at the time of the first tumor resection upon reviewing the imaging files, despite it not being evident at the time of the first resection. Metachronous SPLC was defined as a single lung lesion occurring after a prior resection. Patients with two or more lesions and patients with pure bronchioloalveolar carcinoma in all lesions were excluded. Patients with tumors other than non-small cell carcinoma were included if one of the tumors was a non-small cell carcinoma. In synchronous SPLC, the larger of the two tumors was reported as the first tumor and the remaining tumor as the second. In metachronous SPLC, the initial primary tumor was defined as the first tumor and latter as the second tumor. The definition of SPLC was based on Martini and Melamed's criteria (Table 1) [13].

Table 1. Martini and Melamed criteria for diagnosis of second primary lung cancer.

Synchronous tumors

A. Tumor physically distinct and separate
B. Histology
    1. Different
    2. Same, but different segment, lobe or lung, and
        a. Origin from carcinoma in situ
        b. No carcinoma in lymphatics common to both
        c. No extrapulmonary metastasis at time of diagnosis

Metachronous tumors

A. Different histology
B. Same histology if;
    1. Intervals between cancers at least 2 years or
    2. Origin from carcinoma in situ or
    3. Second cancer in different lobe or lung, but;
        a. No carcinoma in lymphatics common to both
        b. No extrapulmonary metastasis at time of diagnosis

2. Data collection

The Institutional Review Board of Yonsei University College of Medicine approved this retrospective study. The need for consent from each patient whose records were evaluated was waived because the individuals were not identified within the study. Information was collected regarding patient demographics and tumor factors that could be associated with overall survival. All patients were staged at the time of diagnosis of the first tumor according to the sixth edition of the TNM classification [14]. The patients were then restaged by the seventh edition of the TNM classification of malignant tumors introduced in 2009 [15].

The interval between metachronous tumors was calculated from the date of resection of the first tumor to the date of radiographic presentation of the second

tumor. The survival interval after the first tumor resection was calculated from the date of first tumor resection to the date of last follow-up or death. The survival interval after the second tumor detection was from the date of second tumor presentation to the date of last follow up or death. Operative mortality included deaths from all causes occurring within 30 days of surgery or anytime during the same hospitalization period.

3. Statistical analysis

We conducted descriptive analyses of patient characteristics, clinical features and outcomes. Comparative analyses to identify differences between patients and tumor characteristics were performed using a chi square or Fisher exact test on categorical variables, and student's t-tests on continuous variables. Survival analysis was conducted using survival curves generated by the Kaplan-Meier method. Overall survival differences were assessed for statistical significance using the log-rank test. Cox proportional hazards model was used for multivariate analyses of prognostic factors, using variables that were significant in the univariate analysis and pneumonectomy, since cases with different histology tended to undergo pneumonectomy. A *p*-value of less than 0.05 was considered statistically significant. All statistical analysis was performed using SPSS version 18.0 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago, Illinois, USA).

III. RESULTS

1. Patient and tumor characteristics

Among the 1,852 patients, there were 19 with surgically resected synchronous SPLC (1.0%). During the follow-up period, 40 patients developed metachronous MPLC (2.2%) of which 23 underwent resection for the second tumor (1.2%). The median follow-up time after first tumor resection was 51.2 months (range: 12.2 to 161.1 months). The median age of the synchronous SPLC patients was 62 (range: 46 to 72 years old). Twelve patients (63.2%) were diagnosed in preoperative radiographic studies, three patients (15.8%) were diagnosed incidentally in the resected specimen, and four patients (21.0%) had a second tumor ascertained retrospectively to be present at the time of the first tumor resection upon reviewing the imaging files. The median age, at presentation of the second tumor, of the metachronous SPLC patients was 64 (range: 52 to 74 years). The median interval between the first tumor resection and detection of the metachronous second tumor was 31.5 months (15.1~97.1). No patients developed third primary lung cancer during the follow-up period. There were no differences, with respect to age, sex, smoking history, forced expiratory volume for 1 second (FEV_1%), histologic concordance, tumor location and the pathological stage of the second tumor, between the patients with synchronous SPLC and those with metachronous SPLC. However, the stage of the first tumor in the metachronous SPLC patients was significantly lower than that in the synchronous SPLC patients (p= 0.031) (Table 2).

Table 2. Clinicopathological Characteristics of patients with Synchronous and Metachronous tumors

Variables	Synchronous (n=19)	Metachronous (n=23)	*p value*
Age, mean ± SD	60.8 ± 7.69	64.1 ± 6.73[a]	0.146
Sex			0.429
male	13	13	
female	6	10	
Smoking history			0.976
yes	9	11	
no	10	12	
FEV_1%, mean ± SD	86.6 ± 28.54	92.1 ± 19.06[b]	0.435
Histology			0.073
similar	8	16	
different	11	7	
First/second tumor location			0.320
ipsilateral	12	11	
contralateral	7	12	
pStage of first tumor			0.031
I	10	17	
II	3	6	
III	6	0	
pStage of second tumor			0.391
IA	17	18 [c]	
IB	1	2	
IIA	1	0	
IIIA	0	3	

[a] Age at resection of second tumor. [b] FEV_1% at the resection of second tumor.
[c] Five patients only underwent a wedge resection without lymph node dissection or sampling.
FEV_1 = forced expiratory volume for 1 second; SD = standard deviation.

2. Histological classification

Eight (42.1%) of the patients with synchronous SPLC presented with similar histologies between the two tumors. One patient had squamous cell carcinoma and seven patients had adenocarcinoma; none of them exhibited lymph node metastasis. Four of these patients had tumors in the ipsilateral lung and four patients had tumors in the contralateral lung.

Of those with metachronous SPLC, histologic concordance was observed in 16 patients (69.6%). Eleven patients had adenocarcinoma and five had squamous cell carcinoma. Of these, seven patients had tumors in the ipsilateral lung and nine had tumors in the contralateral lung (Table 3).

3. Pathological staging

In the synchronous SPLC group, the pathological stage of the first tumor was stage I in 10 (52.6%), stage II in three (15.8%) and stage IIIA in six patients (31.6%). The pathological stage of the second tumor was stage IA in 17 patients, IB in one patient and IIA in one patient.

In the metachronous SPLC group, the pathological stage of the first tumor was stage I in 17 (73.9%) and stage II in six patients (26.1%). The pathological stages of the five patients who only underwent wedge resection for the second tumor, without lymph node dissection or sampling, were regarded as stage I despite an unconfirmed nodal status. The stage of the second tumor was IA in 18 patients, IB in two patients and IIIA in three patients (Table 3).

Table 3. Histological Classification and Pathological Stage of the First and Second tumors

Histology (*first tumor* / second tumor)	Synchronous (n=19)	Metachronous (n=23)
Squamous cell carcinoma /		
Squamous cell carcinoma	1	5
Adenocarcinoma	5	2
Adenocarcinoma /		
Squamous cell carcinoma	2	3
Adenocarcinoma	7	11
Adenosquamous carcinoma	1	
Carcinoid tumor	1	1
Adenosquamous cell carcinoma /		
Adenocarcinoma	1	1
Large cell carcinoma /		
Squamous cell carcinoma	1	
pStage (*first tumor* / second tumor*)*	Synchronous (n=19)	Metachronous (n=23)
Stage I /		
IA	10	15
IIIA		2
Stage II /		
IA	3	3
IB		2
IIIA		1
Stage IIIA /		
IA	4	
IB	1	
IIA	1	

4. Tumor location and resection type

In the synchronous SPLC group, the second tumor was in the ipsilateral lung in 12 patients (63%) and in the contralateral lung in seven patients (37%). Out of the 12 patients with ipsilateral tumors: six received pneumonectomies, one received a bilobectomy and three received lobectomies with added sublobar resections. In two patients, a second tumor was detected in the same lobe of the resected specimen after the lobectomy; both of them had tumors with different histologies. All seven patients with contralateral lesions underwent sequential resections (time interval, 1~26 months). In the sequential resection for the second tumor, a contralateral lobectomy was performed in three patients and a sublobar resection was performed in four patients.

In the metachronous SPLC group, ipsilateral tumors were diagnosed in 11 (48%) and contralateral tumors in 12 patients (52%). All patients underwent a lobectomy for the first tumor. In the resection for the second tumor, completion pneumonectomies were performed in nine, ipsilateral sublobar resections in two, contralateral lobectomies in seven and contralateral sublobar resections in five patients (Table 4).

Table 4. Location and Type of Resection for the First / Second tumor

Synchronous	n=19
Ipsilateral	*12 (63%)*
pneumonectomy	6
bilobectomy	1
lobectomy / sublobar resection	3
lobectomy	2
Contralateral	*7 (37%)*
lobectomy / lobectomy	3
pneumonectomy / sublobar resection	1
lobectomy / sublobar resection	3
Metachronous	n=23
Ipsilateral	*11 (48%)*
lobectomy / completion pneumonectomy	9
lobectomy / sublobar resection	2
Contralateral	*12 (52%)*
lobectomy / lobectomy	7
lobectomy / sublobar resection	5

5. Outcome and survival

In the synchronous SPLC group, there were two operative mortalities (10.5%). Both of them underwent a pneumonectomy for tumors with different histologies in ipsilateral different lobes. One patient died from esophageal perforation four months after their operation, but during the same hospitalization period. The other patient expired due to acute respiratory distress syndrome on postoperative day 7.

In the metachronous SPLC group, two operative mortalities occurred (8.6%). One patient died of postoperative bleeding after a completion pneumonectomy; the other died of pneumonia after a contralateral lobectomy with lobectomy

status for the first tumor.

The median follow-up time after the first tumor resection was 60.8 months (12.2~161.1). The overall five year survival rate for patients with synchronous SPLC was comparable that for patients who had single lung cancer (51.4% versus 48.7%, p= 0.755) (Figure 1).

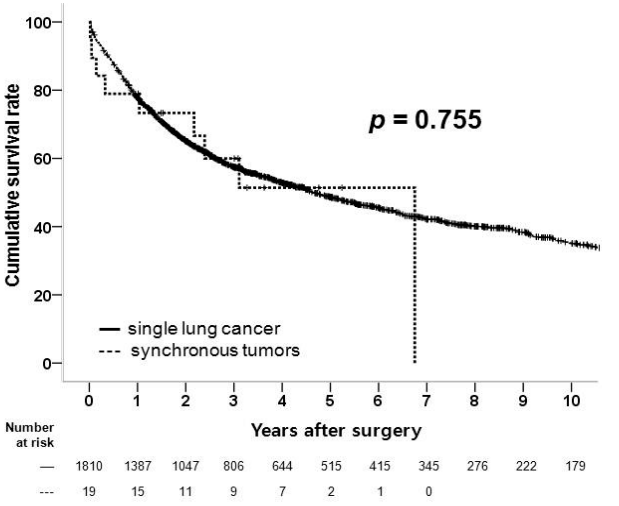

Figure 1. Overall survival difference between synchronous second primary lung cancer patients and single lung cancer patients.

In patients with metachronous SPLC, when measured from time of the first tumor resection, the overall five year survival was significantly higher than in

patients who had single lung cancer (85.4% versus 48.7%, *p*= 0.003). However, when measured from the resection of the second tumor, there was no significant difference between metachronous SPLC and single lung cancer survival rates (77.0% versus 48.7%, *p*= 0.057) (Figure 2).

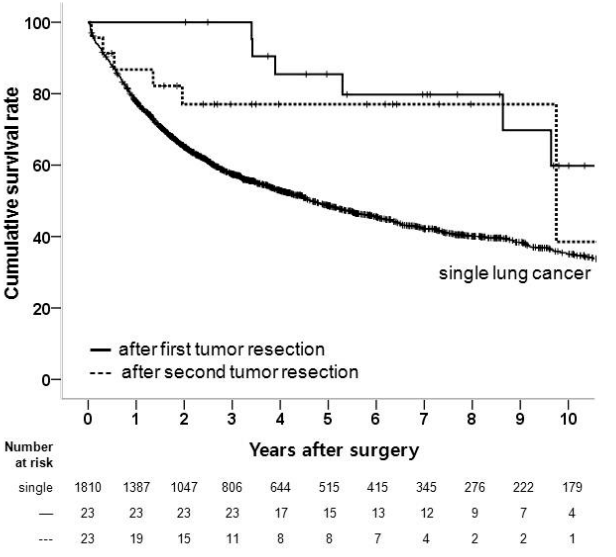

Figure 2. Overall survival difference between metachronous second primary lung cancer and single lung cancer patients.

6. Prognosis on survival

The prognostic significance of factors in relation to survival rate, obtained by univariate analysis, is outlined in Table 5.

Table 5. Univariate Analysis of Prognostic Factors Related to Survival

Variables	Synchronous			Metachronous		
	n	5YSR	*p*	n	5YSR	*p*
Age			0.588			0.699
<63	10	35.0		7	85.7	
≥63	9	51.9		16	74.5	
Sex			0.062			0.238
male	13	18.7		13	66.1	
female	6	83.3		10	90.0	
Smoking history			0.127			0.114
yes	9	20.7		11	60.6	
no	10	60.0		12	91.7	
FEV_1%			0.415			0.174
<80	7	35.7		5	50.0	
≥80	12	48.1		18	83.0	
Time interval			-			0.336
<2year	-	-		9	85.7	
≥2year	-	-		14	71.4	
Histology			0.024			0.004
similar	8	75.0		16	93.3	
different	11	20.8		7	38.1	
First / second tumor location			0.733			0.544
ipsilateral	12	64.3		11	72.7	
contralateral	7	22.2		12	82.5	
Pneumonectomy			0.237			0.269
yes	6	50.0		9	66.7	
no	13	47.9		14	85.1	
Resection of second tumor			0.520			0.084
anatomical resection	13	50.8		15	65.2	
sublobar resection	6	27.8		8	100.0	
pStage of first tumor			0.042			0.485
I	10	71.1		17	81.6	
II,III	9	33.3		6	66.7	
pStage of second tumor			0.023			<0.0001
IA	17	49.4		18	94.4	
IB,II,III	2	0.0		5	20.0	
Adjuvant therapy			0.223			0.227
yes	8	71.4		4	50.0	
no	11	31.2		19	53.0	

FEV_1 = forced expiratory volume for 1 second; 5YSR = overall five year survival rate (%); 5YSR = overall five year survival rate.

In the synchronous SPLC group, histologic concordance between the first and second tumors, and the stages of the first and second tumors were significant prognostic factors. Regarding the stage of the first tumor, patients with stage I had a better five year survival rate than patients with a stage higher than I (71.1% versus 33.3%, p= 0.042). These results were similar in patients with single lung cancer (68.3% versus 33.0%, p< 0.0001). There was no difference in survival rate between patients with stage I synchronous SPLC and those with stage I single lung cancer (71.1% versus 68.3%, p= 0.769). Likewise, there was no difference in survival rate, in patients with tumor stages higher than I, between these two groups (33.3% versus 33.0%, p= 0.325) (Figure 3).

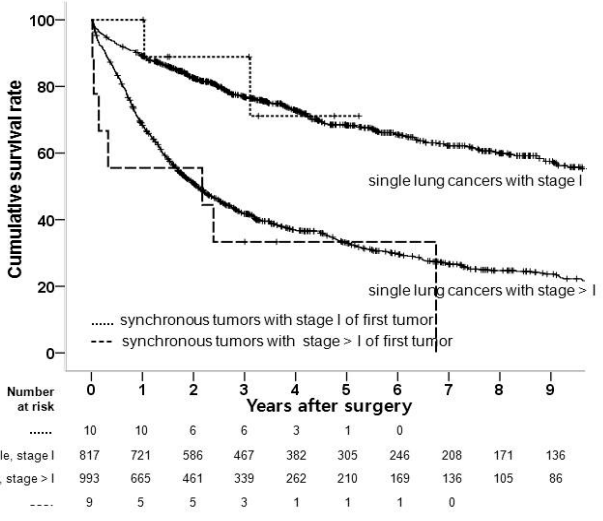

Figure 3. Survival rates according to the pathological stage of the first tumor in synchronous second primary lung cancer patients.

In the metachronous SPLC group, histologic concordance and the stage of second tumor were found to be significant prognostic factors of survival in the univariate analysis (Table 4). Regarding the stage of the second tumor, patients with stage IA had a better five year survival rate than patients with stages higher than stage IA (94.4% versus 20.0%, $p< 0.0001$); these results were similar in patients with single lung (81.6% versus 42.7%, $p< 0.0001$). There was no difference in survival rates between patients with stage IA metachronous SPLC and those with stage IA single lung cancer (94.4% versus 81.6%, $p= 0.449$). Likewise, there was no difference in survival rate, in patients with tumor stages higher than I, between these two groups (20.0% versus 42.7%, $p= 0.194$) (Figure 4).

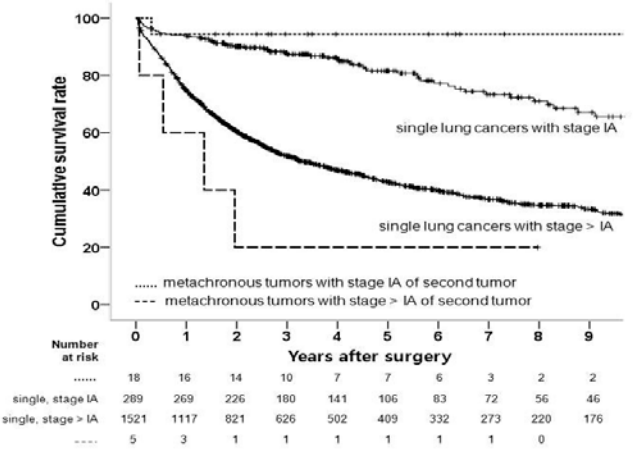

Figure 4. Survival rates according to the pathological stage of second tumor in metachronous second primary lung cancer patients.

IV. DISCUSSION

In our study, the survival rate for patients with SPLC was not as poor as in previous reports [16, 17]. The overall five-year survival rate was 51.4% for patients with synchronous SPLC and 77.0% for metachronous SPLC. In patients with synchronous SPLC, histologic concordance and the stage of both the first and second tumors were significant prognostic factors. In the metachronous SPLC group, histologic concordance and the stage of the second tumor significantly influenced survival likelihood.

Several studies have compared the survival rates between synchronous SPLC and metachronous SPLC patients [16, 18, 19]. They reported that survival rates of synchronous SPLC tended to be lower than that of metachronous SPLC, but the difference was not important in terms of clinical practice. However, comparisons between SPLC and single lung cancer could provide more practical information on whether or not the presence of a second tumor has an influence on prognosis. Therefore, we have compared SPLC with single lung cancer in survival analysis.

van Rens et al. also compared the survival rates between patients with synchronous SPLC and with single lung cancer [3]. According to their results, the overall five year survival rate after resection among 73 patients with synchronous SPLC was significantly lower than in 2,644 patients with primary single lung cancer (19% versus 41%, $p< 0.0001$). However, in our study, the overall survival rate of the patients with synchronous SPLC was similar to

patients who underwent resection for single lung cancer (51.4% versus 48.7%, p= 0.755); survival rates according to tumor stage were also similar between the two groups (stage I: 71.1% versus 68.3%, p= 0.769; stage > I: 33.3% versus 33.0%, p= 0.325). In the univariate analysis, the prognosis of patients with SPLC was influenced not only by the stage of the first tumor but also by that of the second. However, two of the patients with second tumors more advanced than stage I had first tumors of stage III; therefore, their poor prognosis might not have been due to the second tumor stage but to the advanced first tumor stage. Based on these results, we can infer that, even in the presence of synchronous SPLC, prognosis depends strongly on the stage of the first tumor. Regarding surgical outcome, patients with synchronous SPLC seemed to have poorer results than those with single lung cancer, but the difference was not statistically significant (operative mortality; 10.5% versus 3.0%, p= 0.116). Thus, we concluded that resection for synchronous SPLC had a comparatively favourable prognosis and presented an acceptable surgical risk.

van Res et al. also compared survival rates between 121 patients with metachronous SPLC and 2,263 patients with single lung cancer [12]. According to their results, the overall five year survival rate after the first resection was better than that of single lung cancer (70% versus 41%); which was similar to ours (85.4% versus 48.7%, p= 0.003). We could, therefore, infer that long term survivors after resection of their first tumor have a high probability of developing second primary lung cancer.

However, according to their results, overall five year survival rates after the second resection was lower than that for patients with primary single lung cancer (26% versus 41%) [12, 20]. Additionally, they suggested that, due to the reduction in survival rate between the two resections, survival rate after the second resection was influenced by the first tumor; and therefore, the stage of the first tumor and the interval between resections were variables of interest. However, according to their multivariate analysis, stage of the second tumor and age of the patient were significant predictors of survival, whereas stage of the first tumor and the interval between resections were not.

Contrarily to their results, in our study, where survival was measured from the second tumor resection, survival rates for patients with metachronous SPLC tended to be higher than for single lung cancer; although the difference was not statistical significance (77.0% versus 48.7%, p= 0.057). The increased survival rate could have been due to the lower stage tumors in patients with metachronous SPLC; correspondingly, stage I tumors made up 45% of single lung cancer cases and 87% of cases of metachronous SPLC. Because of this, we compared survival rates according to stage of second tumor, survival rate for patients with metachronous SPLC was not inferior to that of single lung cancer patients; as shown in Figure 4 (stage IA; 94.4% versus 81.6%, p= 0.449; stage > IA; 20.0% versus 42.7%, p= 0.194). Our data also suggested that the time interval between resections had no impact on survival rate, whether adopting the two year definition of the Martini and Melamed's criteria (85.7% versus

71.4%, p= 0.336) [13], or the four year one of the American College of Chest Physicians (86.2% versus 80.0%, p= 0.621) [21].

Similarly, Meerbeeck et al. compared metachronous SPLC 23 patients with solitary lung cancer 511 patients [22]. They also reported that the survival rate of metachronous SPLC patients was comparable to that for the solitary lung cancer patients,where the difference between the patient groups was of borderline significance (p= 0.08).

Regarding surgical outcome, there were two operative mortalities in our cohort. The difference between surgical mortality in the metachronous SPLC and single lung cancer groups was not statistically significant (8.7% versus 3.0%, p= 0.120). Thus, we have concluded that resection for metachronous SPLC had a comparatively favourable prognosis and presented an acceptable surgical risk.

Contrarily to other studies [7, 9, 11], histologic concordance had a significant impact on survival rates for both synchronous SPLC and metachronous SPLC patients in our study.; i.e.tumors with different histologies adversely affected overall survival. This could have been due to the high proportion of pneumectomies in patients with different histologies (44.4% for different histology versus 29.2% for similar histology, p= 0.307); as, because there was no doubt that the second tumor was second primary lung cancer and not a metastatic nodule, a more aggressive resection tended to be performed. Additionally, although undergoing a pneumonectomy did not significantly affect survival in patients with SPLC in the univariate analysis, it was clear that it adversely affected overall survival in

the 1,810 patients with single lung cancer (31.7% versus 56.7%, $p< 0.0001$). Accordingly, we may infer that the poor prognosis, for patients with tumors of different histology, was caused by the need for a pneumonectomy rather than histology itself. Thus, we conducted a multivariate analysis, including pneumonectomy, in addition to the variables that were significant in the univariate analysis. However, we could not find any independent predictors of survival rate; this may have been due to the small number of patients in this study.

There were several limitations in our study. First, this study was a retrospective study in a single center, thus the results were based on highly selected patients with inherent biases. Second, because our data were from patients who underwent resections for SPLC, we did not include any information on those patients with SPLC who were medically inoperable; for instance, patients who needed surgical resection but whose pulmonary function was inadequate for surgery or those who had a serious comorbidity. Third, our study included a small number of patients. Thus, we could not find any statistical differences between some of the variables, even though they presented clearly different patterns, and were unable to find any independent predictors of survival in the multivariate analysis.

V. CONCLUSION

In summary, resected SPLC patients had a considerably positive prognosis, with five year survival rate of 50% or greater both in the synchronous SPLC and metachronous SPLC groups. These results were comparable to single lung cancer patients. Histologic concordance between the first and second tumors, and the pathological stage of the second tumor were important prognostic factors in both synchronous SPLC and metachronous SPLC patients. In addition, the pathological stage of the first tumor had a significant influence on prognosis in the synchronous SPLC group.

REFERENCES

1. Beyreuther H. Multiplicität von Carcinomen bei einem Fall von sog. "Schneeberger" Lungenkrebs mit Tuberkulose. Virchows Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin 1924;250:230-43.

2. Adebonojo SA, Moritz DM, Danby CA. The results of modern surgical therapy for multiple primary lung cancers. Chest 1997;112:693-701.

3. van Rens MT, Zanen P, Brutel de La Riviere A, Elbers HR, van Swieten HA, van Den Bosch JM. Survival in synchronous vs. single lung cancer: upstaging better reflects prognosis. Chest 2000;118:952-8.

4. Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. J Natl Cancer Inst 1998;90:1335-45.

5. Okada M, Tsubota N, Yoshimura M, Miyamoto Y. Operative approach for multiple primary lung carcinomas. J Thorac Cardiovasc Surg 1998;115:836-40.

6. Razzuk MA, Pockey M, Urschel HC, Jr., Paulson DL. Dual primary bronchogenic carcinoma. Ann Thorac Surg 1974;17:425-33.

7. Lee BE, Port JL, Stiles BM, Saunders J, Paul S, Lee PC, et al. TNM stage is the most important determinant of survival in metachronous lung cancer. Ann Thorac Surg 2009;88:1100-5.

8. Tanvetyanon T, Robinson L, Sommers KE, Haura E, Kim J, Altiok S, et al. Relationship between tumor size and survival among patients with resection of multiple synchronous lung cancers. J Thorac Oncol 2010;5:1018-24.

9. Finley DJ, Yoshizawa A, Travis W, Zhou Q, Seshan VE, Bains MS, et al. Predictors of outcomes after surgical treatment of synchronous primary lung cancers. J Thorac Oncol 2010;5:197-205.

10. van Bodegom PC, Wagenaar SS, Corrin B, Baak JP, Berkel J, Vanderschueren RG. Second primary lung cancer: importance of long term follow up. Thorax 1989;44:788-93.

11. Riquet M, Cazes A, Pfeuty K, Ngabou UD, Foucault C, Dujon A, et al. Multiple lung cancers prognosis: what about histology? Ann Thorac Surg 2008;86:921-6.

12. van Rens MT, Zanen P, de la Riviere AB, Elbers HR, van Swieten HA, van den Bosch JM. Survival after resection of metachronous non-small cell lung cancer in 127 patients. Ann Thorac Surg 2001;71:309-13.

13. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-12.

14. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710-7.

15. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest 2009;136:260-71.

16. Antakli T, Schaefer RF, Rutherford JE, Read RC. Second primary lung cancer. Ann Thorac Surg 1995;59:863-6; discussion 867.

17. Ribet M, Dambron P. Multiple primary lung cancers. Eur J Cardiothorac Surg 1995;9:231-6.

18. Aziz TM, Saad RA, Glasser J, Jilaihawi AN, Prakash D. The management of second primary lung cancers. A single centre experience in 15 years. Eur J Cardiothorac Surg 2002;21:527-33.

19. Rea F, Zuin A, Callegaro D, Bortolotti L, Guanella G, Sartori F. Surgical results for multiple primary lung cancers. Eur J Cardiothorac Surg 2001;20:489-95.

20. van Rens MT, de la Riviere AB, Elbers HR, van Den Bosch JM. Prognostic assessment of 2,361 patients who underwent pulmonary resection for non-small cell lung cancer, stage I, II, and IIIA. Chest 2000;117:374-9.

21. Shen KR, Meyers BF, Larner JM, Jones DR. Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:290S-305S.

22. Van Meerbeeck J, Weyler J, Thibaut A, Vansteenkiste J, Aumann J, Deneffe G, et al. Second primary lung cancer in Flanders: frequency,

clinical presentation, treatment and prognosis. Lung Cancer 1996;15:281-95.

ABSTRACT(IN KOREAN)

이차성 원발성 폐암의 수술 후 임상적 결과 및 예후인자

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배 미 경

이차성 원발성 폐암의 보고는 증가하고 있으나 수술적 절제 후의 치료 성적 및 예후에 관해서는 아직 일관된 바가 없다. 이에 이차성 원발성 폐암의 수술 후 임상적 결과를 살펴보고 예후인자를 규명하고자 하였다.

1990년 1월부터 2008년 12월까지 원발성 폐암으로 수술 받은 1852명의 환자 가운데 이차성 원발성 폐암으로 수술 받은 42명의 환자들을 대상으로 하였다.

19명은 동시성 이차폐암이었고 23명은 이시성 이차폐암이었다. 동시성 이차폐암환자의 5년 생존율은 51.4% 로 단일 폐암환자의 48.7% 에 비교할 만 하였다 (p= 0.755). 이시성 이차폐암환자의 첫 번째 종양 절제로부터의 5년 생존율은 85.4%로 단일 폐암환자에 비해 좋았으나 (p= 0.003) 두 번째 종양 절제로부터의 생존율은 77.0%로 차이가 없었다 (p= 0.057). 단변량 분석 시 동시성 이차폐암의 경우, 두 종양의 조직학적 일치도와 먼저 발생한 종양 및 나중에 발생한 종양의 병기가 의미 있는 예후인자였고, 이시성 이차폐암의 경우, 조직학적 일치도와 나중에 발생한 종양의 병기가 중요하였다.

결론적으로 이차성 원발성 폐암 환자의 수술적 절제 후 생존율은 단일 폐암 환자의 생존율보다 낮지 않았고, 두 종양의 조직학적 일치도 및 병기가 예후에 중요하였다.

핵심되는 말 : 이차성 원발성 폐암, 폐절제술, 예후인자

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