ORIGINAL ARTICLE

Multiple primary cancers involving lung cancer at a single tertiary hospital: Clinical features and prognosis

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Abstract

Background: The development of other primary cancers in patients with lung cancer is unfortunate and uncommon, although the frequency is increasing. The aim of this study was to determine the clinical features and prognosis in patients with multiple primary cancers (MPC) involving lung cancer.

Methods: After a retrospective review of 1644 patients who were newly diagnosed with primary lung cancer between 1998 and August 2012 at a tertiary hospital, 105 patients were included.

Results: The median age at the time of lung cancer diagnosis was 67 years, and 68 patients were male. Synchronous primary cancers occurred in 47% of the study population (49/105). Among those with metachronous cancer (56/105), the median interval between the diagnosis of lung cancer and another malignancy was 47.1 months; 21 patients were diagnosed with lung cancer as the first primary tumor. The most frequent type of other malignancy was urogenital (30%), followed by gastrointestinal (30%) and thyroid malignancies (16%). Advanced stage of lung cancer (hazard ratio (HR), 3.2; 95% confidence interval (CI), 1.8–5.7; $P < 0.001$), supportive care only as treatment for lung cancer (HR, 2.8; 95% CI, 1.3–6.0; $P = 0.006$), and head and neck cancer as another malignancy (HR, 3.9; 95% CI, 1.4–10.8; $P = 0.010$) were independent predictors of shorter survival from the time of diagnosis of the second primary cancer.

Conclusion: Advanced lung cancer stage, symptomatic supportive care only without antitumor therapy for lung cancer, and head and neck cancer as another primary malignancy were poor prognostic factors in patients with MPC involving primary lung cancer.

Introduction

Lung cancer remains the leading cause of cancer mortality,[1,2] and its incidence is expected to increase. Screening for lung cancer was recently introduced to allow early diagnosis and treatment, as in other cancers.[3] The development of medical technology has facilitated diagnosis at an earlier stage and better treatment of lung cancer, in addition to increasing the average life expectancy. After the diagnosis of lung cancer, various forms of antitumor therapy have been performed for curative and palliative care.[4,5] These treatments have increased overall survival time, such that the chance of finding another cancer in a patient with a single primary cancer has increased. Moreover, the development of radiologic evaluation and advanced diagnostic tools has further increased the chance of discovering another independent primary cancer that is distinguished from metastasis during follow-up after treatment for the initial primary cancer.[6]

Multiple primary cancer (MPC) was defined by Warren and Gates as two or more tumors occurring at different locations that are histologically malignant and distinct such that one tumor is not a metastasis of the other.[7] MPC was classified into two groups according to time of occurrence; the synchronous group was defined as MPC diagnosed within six months of the primary cancer diagnosis; and the metachronous group as MPC diagnosed more than six months after primary cancer diagnosis. The incidence of MPC is approximately 9% according to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER).[8] In Korea, the frequency of MPC was reported as

1.24% by Koo *et al*. in 1999,[9] and 12.8% in patients with non-small cell lung cancer (NSCLC) with curative resection by Son *et al*. in 2013.[10] Several studies have attempted to identify clinical features and outcomes in patients with MPC, but the predictive factors associated with mortality in MPC patients with lung cancer are not well defined. This retrospective study was undertaken to identify the clinical features, prevalence, and location of MPC, and the prognostic factors contributing to mortality in lung cancer patients with MPC.

Methods

Patients

Among patients with a diagnosis of primary lung cancer between January 1998 and August 2012 who were admitted to the Ewha Womans University Medical Center, we selected those who were confirmed by histologic evaluation to have primary lung cancer accompanied by at least one other tumor in another organ during this period. According to the definition of MPC,[7] patients with tumors at other organs that were confirmed metastases of the primary lung cancer were excluded from the study. In addition, we only included patients with MPC diagnosed by histopathological evaluation in our hospital. Following a review of the medical records, data on age at the time of diagnosis of primary lung cancer, other malignancy, gender, smoking history, location of MPC, histopathologic findings, treatment modalities for lung cancer, and final clinical outcome were obtained. Lung cancer was classified as NSCLC and small cell lung cancer (SCLC) by histologic type. Histologic analysis of lung cancer was based on the World Health Organization classification,[11] and the stage of lung cancer was according to the clinical tumor node metastasis (TNM) classification.[12] NSCLC with stage IIIB and IV and SCLC with extensive stage were classified as advanced lung cancers. For another primary tumor, the involved organ and histologic type were recorded. The involved organ was classified on the basis of location as follows: head and neck, thyroid, breast, lung, gastrointestinal tract, hepatobiliary, urogenital, and blood. We excluded patients who were not followed up after diagnosis and those who were confirmed to have precancerous lesions, such as carcinoma *in situ*, or early gastric cancer on histopathologic findings.

Data collection

All lung cancer patients underwent chest X-ray, chest computed tomography (CT), and evaluation of percutaneous needle aspiration samples, sputum cytology, and/or bronchoscopic biopsies. For diagnostic confirmation of metastasis to other sites, patients underwent bone scans, positron emission tomography (PET), and brain magnetic resonance imaging (MRI) or CT. MPC of enrolled patients was confirmed by radiologic and histologic evaluation. Until 1 March 2013, survival and causes of death were identified from medical records, by interviews with the patients' families/doctors, or by accessing the national death registry data. Survival time was calculated from the diagnosis of the first and second cancer to the patient's death or last follow-up. The retrospective review of medical records and radiographic findings was approved by the Institutional Review Board of Ewha Medical Center (IRB Number: 13-41-05).

Statistical analysis

For statistical analysis, SPSS 21.0 software (SPSS Inc., Chicago, IL) was used throughout the study, and $P < 0.05$ was taken to indicate statistical significance. Continuous variables were analyzed by calculating the mean, standard deviation, median, and interquartile range (IQR). Cumulative survival probabilities were estimated using the Kaplan-Meier method, and the log-rank test was applied to compare survival curves according to patient characteristics. Cox proportional hazard multivariate analysis was performed to identify independent factors associated with death, and time zero was determined as the date of diagnosis of the second primary cancer. Hazard ratios (HR) with 95% confidence intervals (CI) were used to report the results.

Results

Between January 1998 and August 2012, 1644 patients were newly diagnosed with primary lung cancer at this hospital. Among them, a total of 106 patients (6.4%) were diagnosed with MPC involving lung cancer, and five of the 106 patients had three primary tumors. One of the five patients belonged in both the synchronous and metachronous group based on diagnosis of primary lung cancers, and was, therefore, excluded from the analysis. Finally, 49 (47%) of the total 105 patients were included in the synchronous group and 56 patients were included in the metachronous group. Of the metachronous group, 21 (37.5%) had lung cancer as the first primary tumor and 35 had another malignancy as the first primary tumor preceding lung cancer.

The clinical characteristics of all patients are listed in Table 1. The median age of all patients at the time of diagnosis of lung cancer was 67 years (IQR, 61–72 years). There was no significant difference in the age at diagnosis of lung cancer between the groups. Among all patients, 55 (54%) were non-smokers. Regarding the histologic distribution of lung cancer, adenocarcinoma (46%) was the most frequent type, followed by squamous cell carcinoma (32%) and SCLC (14%). The prevalence of adenocarcinoma, squamous cell, and small cell carcinoma was the same in both groups. In terms of the stage of lung cancer, 47% (42/90) of NSCLCs were diagnosed at

Table 1 Clinical characteristics

Variable	Synchronous	Metachronous		Total (*n*)
		LCF	OCF	
Patients (number)	49	21	35	105
Age at diagnosis of lung cancer (years)	66 (61–72)	65 (60–71)	70 (61–76)	67 (61–73)
Age at diagnosis of other cancer (years)		69 (64–73)	66 (59–72)	
Male: female	36 : 13	12 : 9	20 : 15	68 : 37
Smoking	(*n* = 48)	(*n* = 20)	(*n* = 34)	(*n* = 102)
Never smoker	23	10	22	55 (54%)
Ex-smoker	9	6	7	22 (22%)
Current smoker	16	4	5	25 (25%)
Pack-years	21.1 ± 23.7	20.6 ± 26.4	17.4 ± 27.2	19.8 ± 25.2
Histologic type of lung cancer				
Adenocarcinoma	24	7	17	48 (46%)
Squamous cell carcinoma	15	8	9	32 (31%)
Non-small cell carcinoma	1	1	1	3 (3%)
Small cell carcinoma	8	3	4	15 (14%)
Others	1	2	4	7 (7%)
Stage of lung cancer				
Non-small cell lung cancer				90
Stage I	13	7	8	28 (28%)
Stage II	4	4	3	11 (10%)
Stage IIIA	7	1	1	9 (9%)
Stage IIIB	2	2	1	5 (5%)
Stage IV	15	4	18	37 (35%)
Small cell lung cancer				15
Limited	2	1	0	3 (3%)
Extensive	6	2	4	12 (11%)
Lung cancer treatment				
Best supportive care only	14	0	10	24 (23%)
Operation	17	14	10	41 (39%)
Chemotherapy	23	13	18	54 (51%)
Radiation therapy	12	4	8	24 (23%)

Data are median (interquartile range), mean ± standard deviation, or frequency (%). LCF, lung cancer first; MPC, multiple primary cancer; OCF, other cancer first.

stage IIIB/IV and 80% (12/15) of SCLC at extensive stage. Regarding the treatment of lung cancer, 23% of all patients (24/105) were managed with only supportive care for symptoms, but all patients of the lung cancer first (LCF) group received antitumor therapy (Table 1).

The other malignancies were most frequently located in the urogenital region, followed by the gastrointestinal tract, thyroid, hepatobiliary, and head and neck regions (Table 2). Two patients of the metachronous group had second primary lung tumors confirmed as SCLC, demonstrating a different

Table 2 Location of other malignancies preceding or following the lung cancer

Cancer location	Synchronous	Metachronous		Total (*n* = 105)
		LCF	OCF	
Urogenital cancer	13	3	17	32 (30%)
Gastrointestinal cancer	16	7	8	31 (30%)
Thyroid cancer	9	4	4	17 (16%)
Hepatobiliary cancer	7	2	2	11 (11%)
Head and neck cancer	3	2	3	8 (8%)
Breast cancer	2	0	2	4 (4%)
Lung cancer†	0	2	0	2 (2%)
Hematologic malignancy‡	0	1	0	1 (1%)

†The secondary lung cancer was diagnosed on the other side from the first lung cancer and was a confirmed different pathologic type. ‡CML (chronic myeloblast leukemia). LCF, lung cancer first; OCF, other cancer first.

Table 3 Clinical outcomes and mortality

Variable	Total (n = 105)
Overall mortality	75 (71%)
Survival duration	
Synchronous (months)†	10.6 (IOR3.2–18.1)
Metachronous (months)†	
LCF	56.3 (IOR29.5–92.8)
OCF	67.8 (IOR31.6–107.1)
From the first cancer	
1 year survival rate	70.8%
5 year survival rate	41.8%
From the second cancer	
1 year survival rate	45.1%
5 year survival rate	13.8%
Cause of death	
Lung cancer progression	51 (68%)
Infection	11 (15%)
Other cancer progression	8 (11%)
Acute myocardiac infarction	3 (4%)
Cerebrovascular accident	2 (3%)

Data are medians (IQR) or frequency (%). †Median survival was calculated from first cancer diagnosed date. LCF, lung cancer as the first tumor; OCF, other cancer as the first tumor.

histologic type in a different lobe compared with the first primary lung cancer. In the metachronous group, the median time interval between diagnosis of the first and second primary cancers was 47.1 months. The time interval between the two malignancies was 47.2 months (IQR, 22.6–62.1 months) in the LCF group and 47.1 months (IQR, 24.3–74.1 months) in the other cancer first (OCF) group ($P = 0.767$).

The overall clinical outcomes are summarized in Table 3. Among the 105 patients, 75 (71%) had died as of March 2013 with a median follow-up period of 12.2 months from the diagnosis of lung cancer. The median survival time of the synchronous group was 10.6 months (IQR, 3.2–18.1 months). The synchronous group showed a shorter survival time than the metachronous group (10.6 months vs. 58.8 months, $P \leq 0.001$). There was no difference in the median survival time from diagnosis of the first primary cancer between the LCF and OCF groups, with 56.3 (IQR, 29.5–92.8 months) and 67.8 months (IQR, 31.6–107.1 months), respectively ($P = 0.558$). The median survival time calculated from the time of diagnosis of the second primary cancer was 8.7 months in the LCF and 8.9 months in the OCF, and there was no statistical significance ($P = 0.722$). There was a difference between the survival rate from the diagnosis of the first primary cancer and from the diagnosis of second primary cancer; the one-year survival rates were 71% and 45%, respectively, and the five-year survival rates were 42% and 14%, respectively. The most common cause of death was lung cancer progression (Table 3).

Regarding the survival time from the date of diagnosis of the second primary cancer, four factors were associated with mortality in the univariate analysis ($P < 0.05$): smoking status, lung cancer stage, treatment for lung cancer, and the organ site of the other primary tumor. After adjusting for age, gender, the synchronous or LCF and OCF groups, these four factors were introduced into the Cox regression hazard model, which revealed that advanced lung cancer stage (HR, 3.2; 95% CI, 1.8–5.7; $P < 0.001$), best supportive care only as lung cancer treatment (HR, 2.8; 95% CI, 1.3–6.0; $P = 0.006$), and head and neck cancer as the other primary malignancy (HR, 3.9; 95% CI, 1.4–10.8; $P = 0.010$), were the independent predictive factors for shorter survival time (Table 4).

In the subgroup analysis of synchronous and metachronous groups, advanced lung cancer stage was an independent poor prognostic factor in both groups (HR 4.2, $P = 0.004$ vs. HR 3.9, $P = 0.005$) in analysis based on the Cox regression hazard model (Table 4). In the metachronous group, head and neck cancer as another malignancy was associated with a shorter survival (HR 6.8, $P = 0.012$). The variable of lung cancer treatment was excluded in this subgroup analysis because all patients in the LCF group had antitumor therapy.

Discussion

The results of the present study showed that advanced lung cancer stage, symptomatic supportive care only without antitumor therapy for lung cancer, and head and neck cancer as another primary malignancy were poor prognostic factors in patients with MPC involving primary lung cancer. In addition, approximately 6% of patients had MPC involving lung cancer among all patients newly diagnosed with primary lung cancer over 15 years.

The prevalence of MPC has increased over the past decades. According to the National Cancer Institute's SEER data, the incidence of MPC is approximately 9% among all cancer patients.[8] In addition, Kurishima *et al.* reported a prevalence of 8.2% among patients with lung cancer,[13] and Son *et al.*[10] reported 12.8% among patients with operable NSCLC. However, in our study, the percentage of patients with MPC among patients newly diagnosed with primary lung cancer was 6.4% over 15 years. The difference in the incidence of MPC among studies is thought to reflect variable methodologies of studies and differences in recruitment source and study size. This study only included patients who were followed up and treated after diagnosis of another cancer in our hospital. Generally, the incidence of cancer increases after the age of 60 years, and lung cancer is the most common cancer in males over the age of 65 in Korea.[2] In our study, the median age at diagnosis of lung cancer was similar in synchronous and metachronous groups, and the time interval between the two primary malignancies in the LCF and OCF groups showed no significant difference. Liu *et al.*[14] and Duchateau and Stokkel[15] reported that the time interval

Table 4 Multivariate analysis of prognostic factors contributing to mortality

	Total		Synchronous		Metachronous	
Variable	HR (95% CI)†	*P*	HR (95% CI)†	*P*	HR (95% CI)†	*P*
Age	1.020 (0.983–1.058)	0.300	1.066 (0.994–1.144)	0.074	1.020 (0.963–1.080)	0.503
Gender		0.946		0.119		0.249
Female‡	1		1		1	
Male	1.034 (0.394–2.710)		3.885 (0.704–21.45)		0.475 (0.134–1.686)	
Advanced lung cancer stage	3.177 (1.780–5.672)	<0.001	4.164 (1.587–10.93)	0.004	3.940 (1.528–10.16)	0.005
Best supportive care only	2.843 (1.340–6.029)	0.006	1.401 (0.478–4.106)	0.539	¶	
Non-adenocarcinoma lung cancer	1.413 (0.741–2.694)	0.293	1.039 (0.368–2.928)	0.943	0.978 (0.299–3.194)	0.970
Smoking history		0.848		0.747		0.513
Never smoker‡	1		1		1	
Ex-smoker	1.085 (0.437–2.695)	0.861	1.464 (0.518–4.138)	0.789	2.242 (0.570–8.825)	0.248
Current smoker	1.228 (0.596–2.527)	0.577	1.012 (0.268–3.827)	0.986	1.480 (0.398–5.497)	0.559
Presented with		0.092		0.384		0.275
Urogenital cancer§	1		1		1	
Head and neck cancer	3.880 (1.391–10.819)	0.010	1.905 (0.283–12.83)	0.508	6.765 (1.530–29.91)	0.012
Thyroid cancer	0.775 (0.254–2.363)	0.653	0.612 (0.132–2.848)	0.531	0.884 (0.144–5.422)	0.894
Hepatobiliary cancer	1.906 (0.798–4.551)	0.146	1.425 (0.365–3.488)	0.610	2.585 (0.645–10.36)	0.180
Gastrointestinal cancer	1.115 (0.500–2.484)	0.790	1.128 (0.385–3.488)	0.835	2.077 (0.651–6.622)	0.217
Hematologic cancer	0.500 (0.050–4.989)	0.555			0.654 (0.048–8.882)	0.750
Breast cancer	3.520 (0.896–13.831)	0.071	7.508 (0.949–59.39)	0.056	2.577 (0.211–31.50)	0.459
Second lung cancer	1.439 (0.165–12.534)	0.742			1.056 (0.264–11.344)	0.948
Combined group with lung cancer		0.117				
Synchronous‡	1					
Metachronous						
LCF	1.085 (0.487–2.414)	0.842			1‡	
OCF	0.543 (0.290–1.016)	0.056			1.541 (0.628–3.786)	0.345

†Cox proportional hazards model was used with forced inclusion of variables significant in the univariate analysis. ‡Reference category. §Urogenital malignancies were used as the reference category because they were the most frequent type of cancer. ¶The variable of lung cancer treatment was excluded. CI, confidence interval; HR, hazard ratio; LCF, lung cancer first; OCF, other cancer first.

between the two malignancies in patients with NSCLC was shorter in the OCF group than in the LCF group. They suggested that treatment of another primary cancer might induce the development of lung cancer, and that different mechanisms influenced cancer progression in the two subgroups. However, those studies performed analyses only for types of MPC, and not for specific treatments of MPC. In contrast, our study showed no difference in the time interval between malignancies in these two groups. Although the cause of discrepancy between our study and previous studies is difficult to explain, we assume that racial differences in the study population, the type of other malignancies, and differences in the start time of the study may influence the results.

Aguilo *et al.*[16] reported that MPC does not adversely affect the survival of patients with lung cancer, and that patients with MPC even had a slightly better survival than patients with lung cancer as a unique primary. However, this survival analysis was performed from the date of diagnosis of lung cancer in both groups of LCF and OCF. As the LCF group is not at risk of death in the period prior to the diagnosis of another primary malignancy, the survival of the LCF group would be overestimated compared with that of OCF when the zero time point of survival analysis is based on the date of lung cancer diagnosis. In addition, it is difficult to fairly compare the survival time between both groups from the date of diagnosis of the first primary cancer, because both groups are not "true MPCs" until the development of the second cancer, and the period between the diagnosis of two primary cancers might be not considered in analyses of the risk of death used in the previous study. Therefore, in our study, Cox proportional hazard analysis was performed from the date of diagnosis of the second primary cancer.

The most common histologic type of NSCLC in Korea is adenocarcinoma;[17] this was also demonstrated in Japan[13] and Taiwan,[14] and confirmed in this study. However, the histologic type of lung cancer is not associated with the prognosis of MPC involving lung cancer. Similar to previous studies,[14,16] our study showed that the urogenital regions and the gastrointestinal tracts were the most frequent sites of other primary malignancies. Because smoking is considered to be a carcinogenic agent at these sites, as for lung cancer, the incidence of these cancers is related. The 16% prevalence of thyroid cancer as another malignancy observed in our study is relatively high. Previous studies in Europe[14–16] reported that the preva-

lence of thyroid cancer in patients with lung cancer was approximately 2%. The incidence of thyroid malignancies as another primary cancer was relatively high compared with that of Western populations. This discrepancy might be related to geographic and racial differences. According to Korean cancer statistics, the incidence of thyroid cancer is the most rapidly increasing among malignancies in both genders, and thyroid cancer is the most common malignancy at the present time.[2] Because the period of our research is similar to that of a Korean survey performed over 11 years since 1999, we consider that our results reflect the frequency of malignancies of the general Korean population. Second primary lung cancer was diagnosed in two patients in the LCF group and the histologic type of the second primary lung cancer was SCLC in both cases. Some studies have suggested that adenocarcinoma in NSCLC undergoes transformation to SCLC after antitumor therapy;[18,19] therefore, further evaluation of this possibility is necessary.

Previous studies have suggested smoking, lung cancer stage, and temporal relationship of other malignancies as prognostic factors in patients with lung cancer with MPC.[13–16] Our study also showed that advanced lung cancer stage, best supportive care only without active antitumor therapy for lung cancer, and head and neck cancer as another primary malignancy were poor prognostic factors, despite the difference in time zero for survival analysis between those studies and our study. Patients with advanced lung cancer stage are known to have a shorter life expectancy than those with early stage disease. Therefore, they might not survive until the development of a second primary cancer, or might have a shorter survival because they did not receive proper treatment, irrespective of another malignancy. According to Rheingold *et al*.,[20] the development of a second primary cancer depends on surviving a first primary cancer, thus, lung cancer stage would itself affect the survival of lung cancer patients with MPC.

Some studies of other malignancies have suggested that chemotherapy or radiation therapy influence the development of a second primary cancer.[21–24] Our study showed that supportive care only for lung cancer was a poor prognostic factor. Although additional studies of the influence of antitumor therapy for primary lung cancer in the development of a second primary malignancy are required, because antitumor therapy itself is considered to affect survival, proper antitumor therapy must be suggested for lung cancer patients with MPC. Compared with previous studies, patients with head and neck cancer were a relatively small series, but had poorer rates of survival.[14–16] Jayaprakash *et al*. reported that patients with head and neck cancer followed by lung cancer had poorer overall survival than the overall population of patients with lung cancer.[25] Because head and neck cancer and lung cancer have common carcinogenic factors, such as smoking and environmental effects, these factors are assumed to affect survival.[25,26] However, the number of patients that presented with head and neck cancer might be too small to conclude that it is a prognostic factor related to survival.

Our study has several limitations related to its retrospective nature and the inclusion of a relatively small number of cases from only one tertiary hospital. Because we did not compare survival between patients with MPC involving lung cancer and those with only primary lung cancer, it is hard to draw any conclusion that MPC in lung cancer patients has a clear impact on prognosis. Further large-scale studies of MPC involving lung cancer are warranted. Nevertheless, this study has significant value in identifying prognostic factors of survival in patients with MPC involving lung cancer.

Conclusion

In conclusion, patients who had an advanced stage of lung cancer and those who did not receive active antitumor therapy had a poor prognosis, as in previous studies of lung cancer only without MPC. In addition, head and neck cancer as another primary malignancy might be a poor prognostic factor.

Disclosure

No authors report any conflict of interest.

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