Characteristics of additional primary malignancies in Korean patients with non-small cell lung cancer

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ABSTRACT

Background: Long-term cancer survival results in increasing numbers of multiple primary malignancies in one person, which represents growing clinical challenge in patients with lung cancer. This study was intended to assess the incidence rate, temporal relationship, and characteristics of additional primary malignancies (APM) in Korean patients with non-small cell lung cancer (NSCLC).

Materials and methods: We reviewed all 632 NSCLCs (313 adenocarcinomas, 276 squamous cell carcinomas, and 43 other NSCLCs) patients who underwent curative resection of NSCLC at the Dong-A University Medical Center from January 1991 to December 2009. We used the hospital information system and medical record to collect data about these patients and their tumors. In the data base, the following parameters were recorded: patient's demographics (age, gender and smoking habit), time interval between the diagnosis of the NSCLC and APM, NSCLC characteristics (date of diagnosis, histology, TNM staging, operative details, and survival) and characteristics of APM (site of tumor, date of diagnosis, histology, TNM staging, operative details, and survival).

Results: Eighty-one (12.8%) of the 632 patients with NSCLC had APMs. Thirty-three patients (40.8%) had APM in their history [occurring earlier than six months or more before NSCLC diagnosis; prior (P) group], 18 patients (22.2%) were diagnosed with an APM synchronously [diagnosed within six months before or after NSCLC; synchronous (S) group], and the remaining 30 patients (37.0%) were diagnosed with an APM during the follow-up period [occurring six months or more after NSCLC diagnosis; metachronous (M) group]. The second primary malignancy occurred most often two to five years in both P group (39.4%) and M group (36.7%). The most frequent APM was stomach cancer (25.0%), followed by colorectal cancer (19.0%), and thyroid cancer (10.7%). Interestingly, we found difference in the incidence of APM between different NSCLC histotypes. In the adenocarcinoma group, colorectal cancer was the most frequently discovered [12 of 46 events (26.1%)], followed by thyroid cancer [9 of 46 events (19.6%)]. In the squamous cell carcinoma group, stomach cancer occurred most frequently [12 of 36 events (33.3%)].

Conclusions: APMs are commonly seen in patients with NSCLC, either preceding or following its occurrence. Therefore, it is important to recognize the characteristic of NSCLC patients with APM in order to detect the second primary malignancy as early as possible and to achieve a possible cure of disease.

KEYWORDS Multiple primary malignancies; non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide. Lung cancer is the fourth most common cancer and is the first leading cause of cancer deaths in Korea (1). Recently, the use of the advanced diagnostic tools for detecting a malignancy in an earlier stage as well as the development of potentially curative treatment modalities and supportive care has contributed to continuous though slow improvement in lung cancer patient survival. Long-term survival results in increasing numbers of multiple primary malignancies in one person (2,3), which represents growing clinical challenge in patients with lung cancer.

However, the increased risk of developing an additional primary malignancy (APM) in patients with a diagnosis of lung

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cancer has received less attention and few studies have examined this association (4-11). Studies in several countries have found risk of multiple primary malignancies ranging from 0.9% to 26.3%. The methodology of studies varied considerably and there were notable differences in the sample size and source. Therefore, the overall results reported in these literatures (4-11) have only limited generalizability to the Korean population, because of geographic and cultural variability that underlies the epidemiological conditions and risk factors of lung cancer.

To our knowledge, no recent studies focused on the association between APMs of other organs and non-small cell lung cancer (NSCLC) in Korea. Therefore, we attempt to assess the incidence rate, temporal relationship, and relevant characteristics of APMs in Korean patients with NSCLC.

Materials and methods

Study subjects

We first conducted a retrospective review of the database for NSCLC patients who underwent curative resection of NSCLC at the Dong-A University Medical Center between January 1991 and December 2009, and we uncovered 669 registered patients. The clinicopathologic information was collected through an exhaustive revision of the medical records, pathology reports, and minutes of cancer committees, even if the patients had been diagnosed or treated in another center. Of them, complete clinicopathologic data were available for 632 NSCLCs patients, who were then included in the study (94.5% of the initial sample). We reviewed all 632 NSCLCs (313 adenocarcinomas, 276 squamous cell carcinomas, and 43 other NSCLCs) patients who were 458 men and 174 women with ages ranging from 25 to 84 years (median 64 years).

We used the hospital information system and medical record to collect data about these patients and their tumors. In the data base, the following parameters were recorded: patient's demographics (age, gender and smoking habit), time interval between the diagnosis of the NSCLC and APM, NSCLC characteristics (date of diagnosis, histology, TNM staging, operative details, and survival) and characteristics of APM (site of tumor, date of diagnosis, histology, TNM staging, operative details, and survival). TNM stages of NSCLC and APM were defined according to the criteria of the American Joint Committee on Cancer (12).

The criteria for multiple primary malignancies that we used were those proposed by Warren and Gates (13): each of the tumors must present a definite histologic picture of malignancy; each must be distinct; and the probability that one was a metastatic lesion from the other must be excluded. Immunohistochemical staining was performed using cancer-site specific antibodies if necessary (14). If the lung tumor has no histological verification, there is a possibility of cancer process in both the lung cancer and the new cancer of other organs instead of independent entities, and thus the patient may not be coded as having multiple malignancies. In addition, the criteria for second primary lung cancer that we used were those proposed by Martini and Melamed (15). If tumors are present at the same time, they must be separated and the histology must be different. If both tumors have the same histology, they are located in different lungs, lobes, or segments, they have no common lymphatics, and there are no distant metastases, they are considered to be two independent primary tumors. If these criteria are not met, the two tumors are considered to be a primary tumor with a metastasis. Any epithelial or mesenchymal malignant neoplasms detected during the period of clinical investigation was enrolled, but non-melanoma skin cancers (i.e., squamous cell carcinoma and basal cell carcinoma) were not included as APM as it was assumed that these cancers did not influence prognosis or survival.

The time interval between the onset of the NSCLC and APM was investigated. Consistent with previous studies (3,16-18), the APM was considered 'synchronous' if diagnosed within 6 months before or after NSCLC (S group), and 'prior' if it occurred earlier than 6 months (P group). APM occurring 6 months or more after NSCLC diagnosis was classified as 'metachronous' (M group).

According to the definition of the International Agency for Research on Cancer (19), we classified malignancies involving the oral cavity, pharynx, larynx, esophagus, lung, pancreas, stomach, bladder, kidney, liver and cervix as 'smoking-related' group. In the other way, malignancies from the stomach, colorectum, pancreas, thyroid, breast, ovary, endometrium, and prostate were considered as 'adenocarcinoma' group, because a majority of cancers at these sites are various types of adenocarcinoma.

The follow-up of the patients started from the month following NSCLC operation or diagnosis of the first cancer and ended at death or completion of follow-up (30 April 2013).

Statistical analysis

Data are shown as mean (or median) ± standard deviation (or range) for continuous variables and as absolute and relative frequencies for categorical variables. To compare the different patients groups, the Student's *t* test was used for continuous variables and the Fisher's exact test (when the numbers were small) or chi-square test was used for categorical variables. Survival curves were calculated by the Kaplan-Meier method, and differences between groups were compared using the log-rank test. Null hypotheses of no difference were rejected if P values were less than 0.05. All statistical tests were performed

Table 1. Clinicopathologic characteristics of 81 non-small cell lung cancer patients with additional primary malignancies according to group of time interval.

Clinicopathologic characteristics	Group			Total (n=81, %)	P value
	P (n=33, %)	S (n=18, %)	M (n=30, %)		
Age (years)* (mean±SD)	66.2±9.7	64.9±7.9	59.8±8.4		0.015
Age (years)† (mean±SD)	61.5±11.0	64.9±7.9	59.8±8.4		0.198
Gender					0.183
Male	22 (66.7)	11 (61.1)	25 (83.3)	58 (71.6)	
Female	11 (33.3)	7 (38.9)	5 (16.7)	23 (28.4)	
Smoking					0.089
Never	18 (54.5)	10 (55.6)	7 (23.3)	35 (43.2)	
Former	7 (21.2)	4 (22.2)	13 (43.4)	24 (29.6)	
Current	8 (24.3)	4 (22.2)	10 (33.3)	22 (27.2)	
Histology					<0.001
AD	26 (78.8)	10 (55.6)	8 (26.7)	44 (54.3)	
SQ	6 (18.2)	8 (44.4)	21 (70.0)	35 (43.2)	
Other	1 (3.0)	0 (0)	1 (3.3)	2 (2.5)	
Stage					0.191
IA	18 (54.6)	10 (55.5)	12 (40.0)	40 (49.4)	
IB	4 (12.1)	3 (16.7)	10 (33.3)	17 (21.0)	
IIA	7 (21.2)	2 (11.1)	5 (16.7)	14 (17.3)	
IIB	1 (3.0)	3 (16.7)	3 (10.0)	7 (8.6)	
IIIA	3 (9.1)	0 (0)	0 (0)	3 (3.7)	

*, At diagnosis of non-small cell lung cancer, †, At diagnosis of first malignancy. Abbreviations: P, prior; S, synchronous; M, metachronous; SD, standard deviation; AD, adenocarcinoma; SQ, squamous cell carcinoma; Other, other non-small cell lung cancer including 1 lymphoepithelioma-like carcinoma and 1 pleomorphic carcinoma.

with SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Ethics statement

The study protocol was approved by the Institutional Review Border of Dong-A University Medical Center (IRB No. 12-138). Written informed consent was obtained from all the patients before surgery to permit the use of their clinical and pathological data for research.

Results

Eighty-one (12.8%) of the 632 patients with NSCLC had a history of other malignancy or developed a secondary primary malignancy in the follow-up period. Because two APMs were found in three patients, a total 84 events were occurred. When the patients were divided into three groups according to the time interval between the onset of the NSCLC and APM, 33 patients (40.8%) had APM in their history (P group), 18 patients (22.2%) were diagnosed with an APM synchronously (S group), and the remaining 30 patients (37.0%) were diagnosed with an APM during the follow-up period (M group).

Clinicopathologic characteristics of study subjects

Table 1 lists the demographic and clinicopathologic characteristics of NSCLC patients with APM by the time interval. Of course, the age was younger in the M group than that in the P or S group at diagnosis of the NSCLC. However, there was no age difference at diagnosis of first malignancy among three groups of patients. The sex distribution revealed no remarkable differences among three groups. Although no statistical difference was found, the frequency of smoking history (former and current) tended to be higher in M group that in P and S groups. Regarding the NSCLC histotypes, more adenocarcinomas (78.8%) were found in P group compared with the other groups (M group, 26.7%, S group, 55.6%), while more squamous cell carcinomas (70.0%) and fewer adenocarcinomas (26.7%) were seen in M group and the prevalence of

Table 2. Time interval between appearance of non-small cell lung cancer and additional primary malignancy in 81 patients.

Time interval	Group			Total (n=81, %)	P value
	P (n=33, %)	S (n=18, %)	M (n=30, %)		
<1 month	–	13 (72.2)	–	13 (16.1)	–
1-6 months	–	5 (27.8)	–	5 (6.2)	–
6 months-1 year	3 (9.1)	–	7 (23.3)	10 (12.3)	0.260*
1-2 years	6 (18.2)	–	1 (3.3)	7 (8.6)	–
2-5 years	13 (39.4)	–	11 (36.7)	24 (29.6)	–
5-10 years	8 (24.2)	–	9 (30.0)	17 (21.0)	–
>10 years	3 (9.1)	–	2 (6.7)	5 (6.2)	–

*, P value, difference between P and M group. Abbreviations: P, prior; S, synchronous; M, metachronous.

adenocarcinoma and squamous cell carcinoma was mostly equal in S group. Comparing the NSCLC tumor stage, no significant difference was found. The patients in this study subject were more likely to be diagnosed with early-stage of their NSCLC with 70.4% in stage I.

Time interval between appearance of NSCLC and APM

Among 81 patients, 33 patients (40.8%) had APM in their history (P group), 18 patients (22.2%) were diagnosed APM synchronously (S group), and the remaining 30 patients (37.0%) were diagnosed APM during the follow-up period (M group). The mean time interval was 56.7 months (range, 8-229 months) in P group and 58.6 months (range, 7-360 months) in M group, essentially the same. The second primary malignancy occurred within five years after the diagnosis of first malignancy in about two-thirds of patients (P group, 66.7% and M group, 63.3%). The second primary malignancy occurred most often two to five years in both P group (39.4%) and M group (36.7%). Of 18 patients in S group, nine (50.0%) had APM diagnosed at the same time as their NSCLC, three (16.7%) had a prior malignancy and six (33.3%) had a subsequent malignancy (Table 2). Among three patients who had two APMs, two patients had two each prior APMs and one patient had two synchronously occurred APMs. The time interval for these three patients revealed in Table 2 depicted their interval between NSCLC and first APM.

Site distribution of the APM in patients with NSCLC

The most frequent APM in patients with NSCLC was stomach cancer [21 of 84 events (25.0%)], followed by colorectal cancer [16 of 84 events (19.0%) and thyroid cancer (9 of 84 events (10.7%)]. Malignancies in these three major sites accounted for 54.7% of all the detected APM. Stomach cancer was the most frequent APM in both P and M groups, but stomach cancer tended to be diagnosed prior to the diagnosis of NSCLC (11 out of 21 events, 52.4%). Thyroid cancer also tended to be diagnosed prior to the diagnosis of NSCLC (5 out of 9 events, 55.6%). Interestingly, the majority of colorectal cancers [9 out of 16 events (56.3%)] were synchronously discovered at the diagnosis of NSCLC. Liver cancers tended to be diagnosed after the diagnosis of NSCLC [5 out of 6 events (83.3%)]. However, the numbers of the remaining other sites were too small for statistical evaluation to determine specific disposition to time interval (Table 3 and Figure 1). Three of the patients had developed two APMs: one of these patients had stomach and prostate cancer, the other patient had colon and bladder cancer and another patient, thyroid and liver cancer.

Associations between NSCLC histotypes and APM

Among 84 events, 46 adenocarcinomas, 36 squamous cell carcinomas and two other NSCLCs (one lymphoepithelioma-like carcinoma and one pleomorphic carcinoma) had a history of APM. We found difference in the incidence of APM between different NSCLC histotypes. In the group of adenocarcinoma, colorectal cancer was the most frequently discovered (12 of 46 events (26.1%), followed by thyroid cancer [9 of 46 events (19.6%)]. Interestingly, 12 out of 16 colorectal adenocarcinomas (75.0%) and all thyroid cancers developed in adenocarcinoma patients. Malignancies considered 'adenocarcinomas' group such as the colorectum and thyroid carcinomas were more frequently seen in adenocarcinoma group. Furthermore, cholangiocarcinomas of the liver developed in adenocarcinoma patients, whereas 3 of 4 hepatocellular carcinomas were developed in non-adenocarcinomas patients. In the squamous cell carcinoma group, stomach cancer occurred most frequently [12 of 36 events (33.3%)]. Interestingly, 12 out of 21 stomach cancers (57.1%) developed in squamous cell carcinoma patients. There was significantly increased frequency of bladder and kidney pelvis [both are urothelial carcinoma, 5 out of 7 (71.4%)], head and neck [3 out of 4 (75.0%)], and esophagus [3 out of 4 (75.0%)] cancers, considered smoking-related cancers (Table 4). Of six metachronous lung cancer, histology of first and second

Table 3. Site distribution of additional primary malignancy in 84 events preceding or following non-small cell lung cancer.

Site	Group			Total (n=84, %)
	P (n=35, %)	S (n=19, %)	M (n=30, %)	
Stomach	11 (31.4)	3 (15.7)	7 (23.4)	21 (25.0)
Colorectum	5 (14.3)	9 (47.4)	2 (6.7)	16 (19.0)
Thyroid	5 (14.3)	3 (15.7)	1 (3.3)	9 (10.7)
Lung	0 (0)	0 (0)	6 (20.0)	6 (7.1)
Liver	0 (0)	1 (5.3)	5 (16.7)	6 (7.1)
Bladder	2 (5.7)	1 (5.3)	2 (6.7)	5 (5.9)
Esophagus	1 (2.9)	0 (0)	3 (10.0)	4 (4.8)
H&N	2 (5.7) (1 larynx, 1 hypopharynx)	1 (5.3) (1 larynx)	1 (3.3) (1 nasopharynx)	4 (4.8)
GYN	2 (5.7) (1 cervix, 1 endometirum)	0 (0)	1 (3.3) (1 ovary)	3 (3.6)
Prostate	2 (5.7)	0 (0)	0 (0)	2 (2.4)
Kidney (pelvis)	1 (2.9)	0 (0)	1 (3.3)	2 (2.4)
Breast	2 (5.7)	0 (0)	0 (0)	2 (2.4)
Sarcoma	2 (5.7)	0 (0)	0 (0)	2 (2.4)
GIST	0 (0)	1 (5.3)	0 (0)	1 (1.2)
AML	0 (0)	0 (0)	1 (3.3)	1 (1.2)

Abbreviations: P, prior; S, synchronous; M, metachronous; H&N, head and neck malignancy including 1 hypopharynx, 1 nasopharynx and 2 larynx; GYN, gynecologic malignancy including 1 ovary, 1 endometirum and 1 cervix; Sarcoma, 1 liposarcoma at buttock and 1 hemangiopericytoma at retroperitoneum; GIST, low-risk group of gastrointestinal tumor at stomach; AML, acute myeloid leukemia.

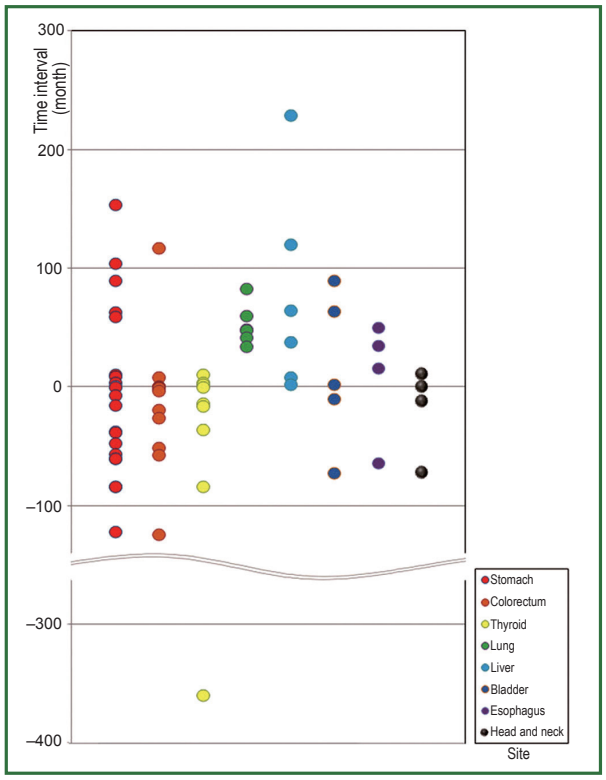

Figure 1. Time interval between the date of diagnosis of non-small cell cancer and that of additional primary malignancies according to site distribution of additional malignancy in 84 events.

NSCLC was both adenocarcinoma in two patients, both squamous cell carcinoma in two patients, first squamous cell carcinoma and second adenocarcinoma in one patient and first adenocarcinoma and second adenosquamous carcinoma in one patient.

Survival analysis

Figure 2 shows the Kaplan-Meier curves for survival after the diagnosis of NSCLC in the three different groups. All in S group were censored. The 5-year survival rate calculated from diagnosis of the NSCLC showed no significant difference between M group and P group (P=0.602), whereas the 5-year survival rate calculated from diagnosis of the first cancer tended to show a longer survival in P group than in M group, although it was marginally significant (P=0.054).

Discussion

Eighty-one (12.8%) of the 632 patients with NSCLC had a history of another malignancy or developed a secondary primary malignancy in the follow-up period at our institute through about two decades. This is one of the few works to analyze the clinical relevance of APM linked to NSCLC based on a broad sample of patients and using well-defined diagnostic criteria, moreover, is the first to be performed in Korea.

Table 4. Site distribution of additional primary malignancy according to histotype of non-small cell lung cancer in 84 events.

Site	Histotype of NSCLC			Total (n=84, %)
	AD (n=46, %)	SQ (n=36, %)	Other (n=2, %)	
Stomach	8 (17.4)	12 (33.3)	1 (50.0)	21 (25.0)
Colorectum	12 (26.1)	4 (11.1)	0 (0)	16 (19.0)
Thyroid	9 (19.6)	0 (0)	0 (0)	9 (10.7)
Lung	3 (6.5)	3 (8.3)	0 (0)	6 (7.1)
Liver (4 HCC, 2 cholangio)	3 (6.5) (2 cholangio, 1 HCC)	2 (5.6) (2 HCC)	1 (50.0) (1 HCC)	6 (7.1)
Bladder	2 (4.3)	3 (8.3)	0 (0)	5 (5.9)
Esophagus (3 SQ, 1 AD)	1 (2.2) (1 SQ)	3 (8.3) (2 SQ, 1AD)	0 (0)	4 (4.8)
H&N	1 (2.2) (1 larynx)	3 (8.3) (1 larynx, 1 hypopharynx, 1 nasopharynx)	0 (0)	4 (4.8)
GYN	2 (4.3) (1 cervix, 1 endometrium)	1 (2.8) (1 ovary)	0 (0)	3 (3.6)
Prostate	1 (2.2)	1 (2.8)	0 (0)	2 (2.4)
Kidney (pelvis)	0 (0)	2 (5.6)	0 (0)	2 (2.4)
Breast	2 (4.3)	0 (0)	0 (0)	2 (2.4)
Sarcoma	1 (2.2) (1 liposarcoma)	1 (2.8) (1 hemangiopericytoma)	0 (0)	2 (2.4)
GIST	1 (2.2)	0 (0)	0 (0)	1 (1.2)
AML	0 (0)	1 (2.8)	0 (0)	1 (1.2)

Abbreviations: NSCLC, non-small cell lung cancer; AD, adenocarcinoma; SQ, squamous cell carcinoma; Other, other non-small cell lung cancer including 1 lymphoepithelioma-like carcinoma and 1 pleomorphic carcinoma; HCC, hepatocellular carcinoma; Cholangio, cholangiocarcinom; H&N, head and neck malignancy including 1 hypopharynx, 1 nasopharynx and 2 larynx; GYN, gynecologic malignancy including 1 ovary, 1 endometirum and 1 cervix; Sarcoma, 1 liposarcoma at buttock and 1 hemangiopericytoma at retroperitoneum; GIST, low-risk group of gastrointestinal tumor at stomach; AML, acute myeloid leukemia.

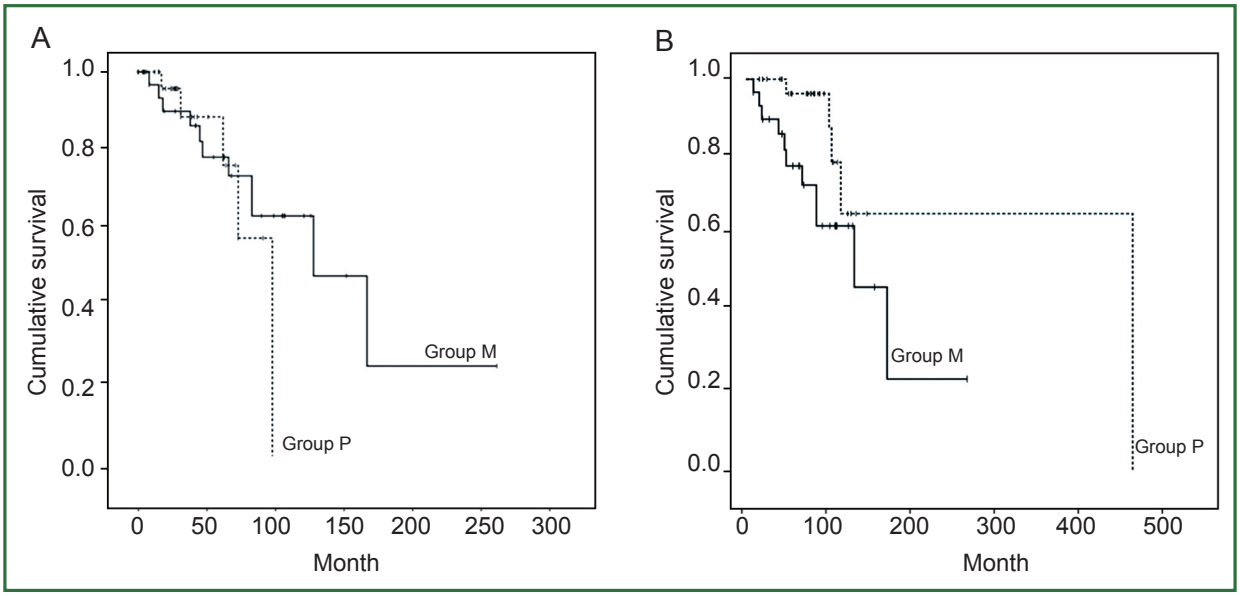

Figure 2. Kaplan-Meier survival curves for patients with non-small cell lung cancer (NSCLC) and additional primary malignancy (APM) in their history (P group), and patients with an APM found in follow-up period after NSCLC (M group), measured from the date of the diagnosis of NSCLC. (A) The 5-year survival rate calculated from diagnosis of the NSCLC showed no significant difference between M group and P group (P=0.602); (B) The 5-year survival rate calculated from diagnosis of the first cancer tended to show a longer survival in P group than in M group, although it was marginally significant (P=0.054).

In the literature, only a few studies have been published on lung cancer patients with APM (4-10). The estimated prevalence for APM varied between 0.9% and 26.3% among the various series, because of methodological differences observed in their definition and scope of study. With respect to the prevalence of APM, the relatively high prevalence of APM in the present study can be explained by the fact that the present study was performed most recently and therefore patients with NSCLC are living longer and have more opportunity for the development of a subsequent cancer.

The prevalent sites of APM in relation to the NSCLC are clinically important in order to facilitate effective follow-up and to stay alert for second malignancies in the patients suffering from NSCLC. In this study, the most frequent sites of the APM were the stomach, colorectum, thyroid and lung in order of frequency. The finding that gastrointestinal and thyroid cancers frequently developed as the second malignancy in NSCLC patients led the authors to suggest that the major organ distribution of APM in subjects with NSCLC does not differ from that of the general Korean population. Interestingly, the incidence of esophageal cancer and head and neck cancer was higher in present study population (4.8% each) than in general Korean population (1.1% and less than 1%, respectively) (1).

However, this is not the case in the Western studies. One Western group (the Netherland group) reported that the most frequently diagnosed double malignancies were located in the lungs, the head and neck region, and the urinary tract (5). On the other hand, one Asian group (Taiwan group) reported that upper aerodigestive tract tumors were the most frequent malignancies accompanying lung cancer, followed by colorectal and cervical cancer (7), similar to our result. It is important to recognize that the site of the APM varied according to the geographical setting of the series and racial difference has important role in the susceptibility to APM. Therefore, the characteristic of APM in Korean patients with NSCLC could be applicable to other areas with similar epidemiological conditions.

Knowledge of the period of risk as well as the site of second malignancies could help physicians design care plans for survivors of cancer patients. In the present study, about two-thirds of the second primary tumor occurred within 5 years after the diagnosis of first malignancy. In other research, the majority of patients with NSCLC as the first malignancy had their secondary malignancy within 1-2 years after the diagnosis of lung cancer (median 10 months), while the majority of patients with other cancer as the first malignancy had to be followed longer in order to detect the second primary lung cancer (median 46 months) (7). A different group reported that more than 80% of second primary tumors were diagnosed within one year after the diagnosis of NSCLC (5). The discrepancy of our findings compared to previous literatures should be interpreted in light of the recent progress in diagnosis and treatment of NSCLC, which significantly modified its natural history. The most recent study reported that the cumulative relative risk for colon, esophagus, and stomach cancers is higher in NSCLC patients than that of the rest of the general population and the increased risk differs from chance variation only in the first 3 to 5 years after initial diagnosis (4).

Individuals with a personal history of first malignancy are at risk of other malignancies because of genetic and environmental factors such as smoking. This study showed that malignancies considered as 'adenocarcinoma' group from the colorectum and thyroid were more frequently seen in adenocarcinoma histotype of NSCLC which are less frequently associated with a history of smoking than squamous cell carcinoma. Other study also reported that the risk of contracting adenocarcinomas at sites where the majority of tumors are adenocarcinomas is increased only among patients with adenocarcinoma of the lung, but not among squamous cell carcinoma patients (8). These findings suggested that genetic factors might be shared between the two malignancies and raise risk of APM in patients with adenocarcinoma of the lung. Conversely, in the group of squamous cell carcinomas, stomach cancer was occurred most frequently. Although stomach cancers are histologically considered an 'adenocarcinoma' group, it is well-known as a smoking-related cancer. Furthermore, there was significantly increased frequency of smoking-related cancer such as bladder and kidney pelvis, head and neck, and esophagus. Therefore, it appears that the exposure to tobacco smoking is the main underlying factor for smoking-related cancer risks. Interestingly, regarding the histologic type and time interval, 59.1% of patients with adenocarcinomas of the lung were diagnosed with an APM in their history (P group), whereas 60.0% of patients with squamous cell carcinomas of the lung were diagnosed with an APM during the follow-up period (M group). With respect to the risk of new primary tumors following first cancer, the excess risks might be determined according to complicated relations with etiologic factors such as environmental carcinogens, exposure duration, genetic problems, and organ specificity. Therefore, further investigation will be necessary in order to explain the apparent carcinogenetic associations between histotype of NSCLC and APM.

The 5-year survival rate calculated from diagnosis of the NSCLC showed no significant difference between M group and P group, which is the same as the results reported by others (5,10). Interestingly, the 5-year survival rate calculated from diagnosis of the first cancer tended to show a longer survival in P group than in M group, although it was marginally significant. This is consistent with the findings of Liu *et al.* (7) and Koppe *et al.* (11). This circumstance suggests that the prognosis of NSCLC patient with APM is more conditioned by the natural history of NSCLC than by APM, because NSCLC is the first leading cause of cancer deaths.

There are several limitations in our analysis, as the one hospital database may not be a true representation of the Korean population sample. Results should be confirmed by large, multicenter studies. Another limitation of the present study is absolute numbers were relatively small for several tumor sites, therefore limiting the statistical power of the study. The third limitation is that the present study cannot provide the complementary evidence for survival analysis, because all patients in S group are right-censored and the case numbers of study subgroups are relatively small. The fourth limitation is that an intensive risk analysis was not performed in our study. Further assessment of the relative risk is necessary to elucidate a useful target for screening studies and strategies in larger group of patients with NSCLC. Finally, it is difficult to sort out the hereditary and acquired basis of multiple tumors, because these factors often interact closely and risk factors such as smoking, alcohol intake, and cardiovascular disease were not consistently recorded or available, due to its retrospective character.

In conclusion, APMs are commonly seen in patients with NSCLC, either preceding or following its occurrence. Therefore, it is important to recognize the characteristics of these patients with APM in order to detect the second primary malignancy as early as possible and to prolong survival and achieve a possible cure of disease.

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