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Characteristics of metachronous second primary lung cancers

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Abstract:

AIM: In this study, we aimed to investigate the characteristics of metachronous second primary lung cancer (MSPLC) and the differences between primary lung cancer (PLC) and metachronous lung cancer.

MATERIALS AND METHODS: Patients diagnosed with lung cancer between January 2014 and December 2016 were retrospectively studied. MSPLC tumor cases and a new diagnosis of PLC were evaluated. Clinical, radiological, and demographic findings of the two groups, previous histopathologic diagnosis of MSPLC, histopathologic diagnosis of lung cancer in both groups, stages of treatment, and treatment history were recorded. All data were analyzed using the Chi-square, *t*-test, Kaplan–Meier, and Log-rank method. In all tests, $P < 0.05$ was considered statistically significant.

RESULTS: There were 53 (16.1%) cases in MSPLC group and 277 (83.9%) cases in the PLC group. There were no statistically significant differences between clinical, radiological, and demographic findings, cancer histopathologies, tumor stages, oncological, and surgical treatment characteristics of the cases ($P > 0.05$). The most frequent primary cancers were laryngeal carcinoma (11 cases) in the MSPLC group, with higher age (64 and 61, $P = 0.01$, respectively). Tumor size was smaller (44 mm and 52 mm, respectively) than the PLC group ($P = 0.03$). All other characteristics of both groups ($P > 0.05$) and survival were similar (15 months and 17 months, $P = 0.87$, respectively).

CONCLUSION: Among the lung cancers diagnosed in our clinic, 16% were detected as MSPLC. MSPLC group were older than the PLC group and tumor size is lower than the PLC group. There was no significant difference in treatment options and survival between the two groups.

Keywords:

Lung cancer, metachronous tumor, second primary cancer

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Introduction

Survival in cancer patients is increased due to advances in cancer diagnosis and treatment, advances in imaging technologies, developments in cancer screening programs, as well as increased awareness of cancer, and the patient's access to physicians easily. Especially increased survival with curative treatments in some cancers such as Hodgkin's lymphoma and breast cancer, caused increase in number of second primary cancers as a result.[1,2]

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There are two generally accepted concepts in multiple organ cancers: These are metachronous and synchronous tumor concepts. The diagnosis of a secondary tumor of different histological type in the same organ or other organ at the same time or within a very short period of the diagnosis of primary organ cancer is defined as synchronous tumor, while the same or different histological type cancer diagnosed 2 years or more after the diagnosis of primary organ cancer is called metachronous tumor.[3,4] Metachron cancers are the most common cause of death in patients with primary cancer in any system or organ and who survive after first cancer.[5] The incidence of metachronous second primary lung cancer (MSPLC) varies between 0.9% and 26.3%.[6]

In this study, we planned to investigate the clinical-radiological, demographic, and survival characteristics of MSPLC compared to primary lung cancer (PLC).

Materials and Methods

The records of patients diagnosed with lung cancer between January 2014 and December 2016 in chest diseases department of our hospital were reviewed retrospectively. The medical history of these cases was examined to rule out whether they had been diagnosed with cancer before. The patients who were previously diagnosed with lung cancer or other organ cancer and newly diagnosed as lung cancer convenient with the definition of the metachronous tumor were considered as MSPLC group, while those diagnosed with lung cancer with no previous diagnosis of lung or other organ cancer were considered as the PLC group. Patients with uncertain histopathological diagnosis, synchronous tumor cases, and patients with third or fourth PLC were excluded from the study.

The clinical, radiological, demographic findings of both groups, the duration between the second and first primary cancer diagnosis in the MSPLC group, the histopathological diagnoses of the first primary cancers in the MSPLC group, the anatomic localizations, histopathological diagnosis, stages of the lung cancers, history of surgical and oncological treatment of the lung cancers in both groups, also with death time of the deceased patients according to the national death notification system, and follow-up periods of the surviving patients were recorded. The data of both groups were compared with each other. Lung cancer staging was performed according to the 7th TNM staging.[7] The study was planned in accordance with the international Helsinki Declaration. Written informed consent forms were obtained for all diagnostic procedures. Local ethics committee approval was obtained for the study.

Statistical analysis

Statistical analysis was performed using the SPSS 17.0 (IBM Inc., Released 2008 SPSS Statistic for Windows Chicago, IL, USA) program. In descriptive statistics, continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as percentage. The Kolmogorov–Smirnov test was used for normal distribution tests. The data of the groups were analyzed with the Chi-square, independent samples *t*-test, and Mann–Whitney U-tests. Survival analyzes were calculated using the Kaplan–Meier method and comparisons were made using the Log-rank method. $P < 0.05$ was considered statistically significant in all tests.

Results

Of the 341 patients with lung cancer, 13 were excluded out of the study (8 were synchronous tumors and 3 were as PLC). The mean age of the 330 included patients was 61.7 ± 9.8 and 61 (18.5%) were female, whereas 269 (81.5%) were male. The number of cases in the MSPLC group was 53 (16.1%), whereas there were 277 (83.9%) cases in the PLC group. In the MSPLC group, 10 (18.9%) of the patients were female and 43 (81.1%) were male, and the mean age was 64.7 ± 10.9 years. In the PLC group, 51 (18.4%) were female, 226 (81.6%) were male, and the mean age was 61.1 ± 9.4. Considering all of the cases, the mean smoking history was 39.7 ± 16.5 pack-year. In the MSPLC group, 43 cases (81.1%) smoked, 3 cases (5.7%) never smoked, and 7 cases (13.2%) had no history of smoking, whereas the mean smoking history was 40 ± 14.9 pack-years. In the PLC group, these rates were 205 (74%), 18 (6.5%), 54 (19.5%), and 39.6 ± 16.8, respectively. There was no statistically significant difference in smoking history between the two groups ($P = 0.86$). When the demographic characteristics and radiology of the two groups were compared, in the MSPLC group, the age of the patients was more advanced (64.7 and 61.1 years, $P = 0.01$) and the tumor size was smaller (44.7 and 52.9 mm, $P = 0.03$). In the radiological examination, the rate of localized lung cancer in the left lower lobe was higher in the PLC group when compared with the MSPLC group (22.6% and 38.7%, respectively, $P = 0.02$). There was no statistically significant difference between the two groups regarding other characteristics ($P > 0.05$) [Table 1].

The mean duration between the diagnosis of first cancer and the new lung cancer was 64.1 ± 47.5 (24–288) months. When the distribution of primary tumors was examined, laryngeal cancer was found to be most frequent ($n = 11$, 20.7%), followed by colon cancer ($n = 8$, 15%) [Table 2]. When the histopathological distribution of lung cancer was examined, 44 patients (83%) had non-small cell lung cancer (NSCLC) in MSPLC group

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Table 1: Clinical, radiological, and demographic findings of the patients

	MSPLC (*n*=53)	PLC (*n*=277)	*P*
Age (mean±SD)	64.7±10.9	61.1±9.4	0.01
Gender (female/male), *n* (%)	10/43	51/226	0.93
Smoking (pack-years)	40±14.9	39.6±16.8	0.86
Symptom, *n* (%)			
Weight loss	27 (50.9)	108 (38.9)	0.10
Weakness	20 (37)	119 (42.9)	0.48
Cough	17 (32)	96 (34.6)	0.71
Loss of appetite	14 (26.4)	103 (37.1)	0.13
Bloody sputum	12 (22.6)	59 (21.2)	0.82
Other	7 (13.2)	26 (9.3)	0.39
Tumor localization, *n* (%)			
Upper right lobe	9 (16.9)	39 (14)	0.58
Upper left lobe	8 (15.1)	42 (15.2)	0.99
Right middle lobe	11 (20.7)	28 (10.2)	0.06
Lower right lobe	13 (24.6)	60 (21.7)	0.87
Lower left lobe	12 (22.7)	108 (38.9)	0.02
Tumor size (mean/mm)	44.7±22.2	52.9±25.7	0.03

MSPLC: Metachronous second primary lung cancer, PLC: Primary lung cancer, SD: Standard deviation

Table 2: Distribution of primary cancers of metachronous second primary lung cancer cases

	n (%)
Larynx cancer	11 (20.7)
Colon cancer	8 (15)
Lung cancer	6 (11.3)
Lymphoma	4 (7.6)
Gastric cancer	4 (7.6)
Prostate cancer	4 (7.6)
Gynecologic cancers	4 (7.6)
Breast cancer	3 (5.7)
Bladder cancer	3 (5.7)
Renal cancer	2 (3.7)
Other (skin-thyroid cancer…)	4 (7.5)
Total	53 (100)

and 218 patients (78.8%) had NSCLC in the PLC group, there was no statistical difference between the two groups (P = 0.47) [Table 3]. When stages of the NSCLC cases were examined, in the MSPLC group, the number of stage 1A-3A cases was 25 (56.8%), the number of Stage 3B-4 cases was 19 (43.2%) and in the PLC group, these numbers were 94 (43.2%) and 124 (56.8%), respectively, where the difference was not statistically significant (P = 0.09). When the subgroups were examined, the rate of stage 3A patients was significantly higher in MSPLC cases compared to PLC cases (27.2% and 14.3%, respectively, P = 0.03) [Table 4].

In this study, the most common cancer seen in patients with MSPLC was found to be laryngeal cancer (n = 11, 20.7%) followed by colon cancer (n = 8, 15%). Cancers of the oral cavity, pharynx, larynx, esophagus, lung, pancreas, stomach, kidney, liver, and cervix

Table 3: Distribution of histological diagnosis

	MSPLC (*n*=53)	PLC (*n*=277)	*P*
NSCLC	44 (83)	218 (78.8)	0.47
NSCLC with no subtype	10 (18.8)	67 (24.1)	0.40
Squamous cell carcinoma	24 (45.2)	98 (35.3)	0.17
Adenocarcinoma	10 (18.8)	53 (19.1)	0.96
SCLC	6 (11.3)	47 (19.9)	0.33
Other lung cancers (carcinoid neuroendocrine carcinoma…)	3 (5.6)	12 (4.3)	0.67

MSPLC: Metachronous second primary lung cancer, NSCLC: Non-small cell lung cancer, PLC: Primary lung cancer, SCLC: Small cell lung cancer

Table 4: Stages of non-small cell lung cancer cases

	MSPLC (*n*=44), *n* (%)	PLC (*n*=218), *n* (%)	*P*
Stage 1A	4 (9.1)	20 (9.2)	0.98
Stage 1B	4 (9.1)	14 (6.4)	0.52
Stage 2A	2 (4.5)	20 (9.2)	0.31
Stage 2B	3 (6.9)	9 (4.1)	0.43
Stage 3A	12 (27.2)	31 (14.3)	0.03
Stage 3B	5 (11.3)	26 (11.9)	0.91
Stage 4	14 (31.9)	98 (44.9)	0.10
Stage 1A-3A	25 (56.8)	94 (43.2)	0.09
Stage 3B-4	19 (43.2)	124 (56.8)	0.09

MSPLC: Metachronous second primary lung cancer, PLC: Primary lung cancer

are cigarette-related cancers.[8] In this study, smoking history of MSPLC group and PLC group was similar. Regarding this subject, Lu *et al*.[6] reported laryngeal cancer as the most frequently seen second primary cancer (20 of 99 cases) followed by colon cancer (16 of 99 cases) in patients with MSPLC. Liu *et al*.[9] found colorectal cancers as the third-ranking in frequency following after upper aerodigestive tract and cervical cancers. The literature as well as the results of our study support that lung cancer may be seen as the second primary disease, especially in patients who have previously diagnosed other cancer and a history of smoking. Familial colorectal cancer is more common in patients with lung adenocarcinoma. The fact that most tumors of the colorectal region have adenocarcinoma histology and although uncertain, DNA replication error seen in some lung adenocarcinoma cases is similar with colorectal tumor carcinogenesis mechanisms may explain the coexistence of lung adenocarcinoma and colorectal tumor.[10-12] In addition, the Turkish Cancer Statistics in 2014[13] showed that colorectal cancer is the third-most common tumor in both women and men, so this condition should be kept in mind.

Regarding surgical treatment history of the cases, 9 (16.9%) patients were operated in the MSPLC group, and 60 (21.6%) patients were operated in the PLC group. The difference between the two groups was not statistically significant (P = 0.43). When oncologic treatment history was examined, oncological treatment data of 57 (17.2%) cases could not be reached. As 274 cases

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had been followed up by the oncology outpatient clinic of our hospital, oncological treatment data for these patients were analyzed. Considering these patients, in the MSPLC group, 30 (65.2%) patients received standard oncologic treatment, while 16 (34.8%) patients did not. In the PLC group, these rates for treated and untreated cases were 161 (70.9%) and 66 (29.1%), respectively, where the difference between two groups was not statistically significant ($P = 0.41$).

When the survival analysis was performed using the Kaplan–Meier method, 30 (56.6%) deaths occurred in the MSPLC group and 158 (57%) deaths occurred in the PLC group throughout the study period. The mean survival was 15.7 ± 1.9 months in the MSPLC group, whereas it was 17.1 ± 1 months in the PLC group and the difference between two groups was not statistically significant ($P = 0.87$) [Figure 1].

Discussion

In this study, we investigated the characteristics of metachronous lung cancer cases and examined 330 lung cancer cases in a 3-year period. Fifty-three (16.1%) of these cases had MSPLC characteristics. The most common primary tumor was laryngeal cancer (20.7%). In our study, we determined that patients with MSPLC were diagnosed with lung cancer at a later age, and tumor sizes were smaller at the time of diagnosis. Smoking history, tumor stage, treatment options, and survival time of the two groups were similar.

In our study, we found the age of diagnosis (64.7 years) of MSPLC group to be significantly higher compared to the PLC group (61.1 years). When the literature was investigated, it was found that the age groups of the second primary cancers were similar in most of the studies,[14] and even Levi *et al*.[15] reported that the patients

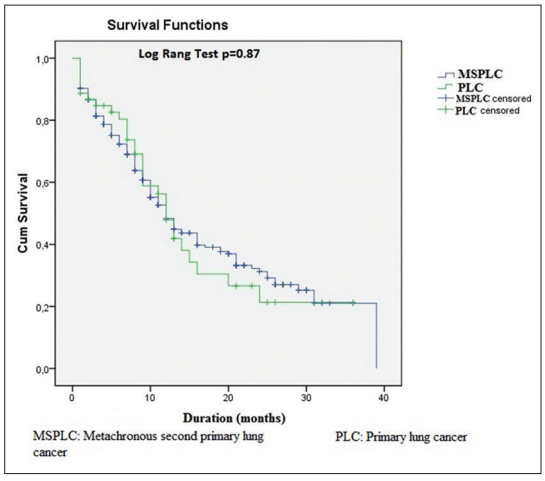

Figure 1: Graph showing the difference between overall survival of primary lung cancers and metachronous second primary lung cancers

diagnosed with MSPLC were at a relatively younger age. Pagès *et al*.[16] found the mean age to be 63 in 1147 MSPLC cases and 61 in PLC cases ($P < 0.001$). They argued that this difference may be related to the cancerogenesis of multiple primary cancers or to individual predisposition or both factors. It is expected that the diagnosis of MSPLC should be made earlier in cases with a previous history of cancer and followed up in a health institution.

In most of the studies, it has been reported that survival is better in patients with MSPLC. Reinmuth *et al*.[17] compared 2698 patients with PLC and 444 patients with MSPLC, and reported that median survival was 904 days in patients with MSPLC and 543 days in patients with PLC ($P < 0.0001$). They also reported that the diagnosis of malignancy was a good prognostic factor. The authors explained this with two different hypotheses. The first of these hypotheses is that early diagnosis and surgical treatment in early stages during metastasis screening, and second, various genetic and epigenetic changes associated with primary cancers may affect the risk and development of lung cancer.[18,19] In their study, Duchateau and Stokkel[20] compared 634 patients with PLC and 148 patients with MSPLC who had no other malignancy history and reported that the survival rates of the MSPLC group were better and that the tumor might have a different growth habit in patients with MSPLC. In contrast, Liu *et al*.[9] found the mean survival as 65 months in patients with PLC and 81 months in the MSPLC group, and reported that the difference was not statistically significant ($P = 0.55$). Similarly, Son *et al*.[21] also found no significant difference in survival between the two groups. Similarly, in our study, no significant difference was found in survival in both groups (MSPLC: 15.7 months, PLC: 17.1 months, $P = 0.87$). Since there was no difference between the two groups in terms of stage, smoking history, oncologic, and surgical treatment, we think that survival characteristics were also similar.

In patients with MSPLC, the time elapsed after the first diagnosis of cancer has been reported with different numbers in different studies. When the literature is examined, it is seen that this period varies between 40 and 83 months.[6,9,20] In our study, the time between the first cancer diagnosis and the second PLC was 58.8 months. This long period suggests that chemotherapy (CT) or radiotherapy (RT) for the first tumor may have an effect. Studies on this subject have reported that increase in MSPLC may occur 1–4 years after CT and 5 years after RT, in which CT and RT treatments increase the risk of MSPLC.[22,23]

The mean tumor size was 44.7 mm in the MSPLC group and 52.9 mm in the PLC group ($P = 0.03$). When the literature was examined, we could not find a study that

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gave tumor size in MSPLC cases. Therefore, although we cannot make definitive judgments about tumor size in MSPLCs, at least based on the data of this study, we think that the tumor was diagnosed when it was relatively small in size.

Since our study is a retrospective and single-center experience, there are some limitations. As it is a single-center experience, the number of cases is small, and therefore, the results cannot be generalized. As also it is a retrospective study, there are significant data losses such as performance status, comorbidity characteristics, and treatment characteristics of primary cancer.

Conclusion

Among the patients with lung cancer diagnosed in our clinic, we detected a significant proportion of metachronous lung cancer (16%). Laryngeal cancer was primary cancer in 20.7% of these cases, and colon cancer was present in 15% as primary cancer. We found that MSPLCs appeared in more advanced ages than PLCs as expected, and since these patients were under oncologic follow-up for their primary cancers, we found that tumor size is relatively smaller at the time of diagnoses when compared to PLCs. However, we did not find any significant difference between the two groups in terms of treatment options and survival. We concluded that especially patients with larynx and colon cancer who have smoking history should be followed up more closely for MSPLC.

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Conflicts of interest
There are no conflicts of interest.

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