

Overview of Patients with Multiple Primary Tumors During Eighty-four Months Follow-up: A Single Center Experience

Seksen-dört Aylık İzlemde Çoklu Primer Tümör Tanılı Hastalarımıza Bakış: Tek Merkez Deneyimi

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ABSTRACT

Introduction: Advances in oncological diagnosis and treatment increase survival and remission of the disease. However, prolonged survival also increases the likelihood of developing second primary malignancies. The aim of this article was to evaluate whether the second primary tumor is associated with the first primary tumor and to determine the survival time in patients diagnosed with cancer, treated, and followed-up, and to make recommendations about the follow-up of these patients.

Methods: Patients who were admitted to the İstanbul Training and Research Hospital, Clinic of Radiation Oncology and Medical Oncology, between January 2011 and December 2017, and who had a follow-up of more than 6 months were retrospectively reviewed. Of 9892 patients, multiple primary tumors (MPT) were detected in 121 patients. The origin of tumor, occurrence time, gender, age, metastasis and survival rates of the patients were investigated. Data were collected using Excel and transferred to SPSS 22.0 program.

Results: There were 56 (46%) female and 65 (54%) male patients. The mean age of the female patients was 58 years and the mean age of the male patients were 64 years. The median age for both sexes was 63 (range: 37-82). The second primary tumor was found to be metachronous in 89 patients (74%) and synchronous in 32 patients (26%). The incidence of MPT was 1.22%. Breast-breast cancer pair in women and larynx-lung cancer pair in men were in the foreground. Eighty-one patients (67%) had a history of smoking and 18 patients (15%) had a history of alcohol use. In synchronous and metachronous tumors, the most common metastasis was observed in the skeletal system. Median overall survival was 51 months in synchronous tumors and 72 months in metachronous tumors.

Conclusion: The development of a second primary cancer in a patient diagnosed with cancer is higher than in those who have not been diagnosed with cancer. Early diagnosis of patients and prolongation of survival may increase the incidence of second primary tumors. For this reason, new complaints emerging

ÖZ

Amaç: Onkolojik tanı ve tedavilerdeki gelişmeler sağkalımı artırmakta ve hastalığın remisyonunu sağlamaktadır. Bununla birlikte uzamış sağkalım ikincil primer malignitelerin gelişmesi olasılığını da artırmaktadır. Bu makalenin amacı kanser tanısı konulmuş, tedavi almış ve takip edilen hastalarda ikinci tümörün birinci tümörle ilişkili olup olmadığını ve sağkalım sürelerini değerlendirmek, bu hastaların takibinde neler yapılabileceği konusunda önerilerde bulunmaktır.

Yöntemler: Ocak 2011 ile Aralık 2017 tarihleri arasında, İstanbul Eğitim ve Araştırma Hastanesi Radyasyon Onkolojisi ve Tıbbi Onkoloji polikliniklerine başvuran, 6 aydan uzun süreli takipleri olan, 9892 hasta dosyası retrospektif olarak incelendi. Yüz yirmi bir hastada multiple primer tümör (MPT) olduğu saptandı. Tümörün hangi organlarda olduğu, ne zaman geliştiği, hastaların cinsiyeti, yaşı, metastaz, sağkalım oranları araştırıldı. Veriler Excel'de toplanarak SPSS 22.0 programına aktarıldı.

Bulgular: 56 (%46) kadın, 65 (%54) erkek hasta vardı. Kadın hastaların yaş ortalaması 58, erkek hastaların ise 64 olarak bulundu. Her iki cins için ortalama yaş 63 (37-82) olarak tespit edildi. Hastaların 89'unda (%74) ikinci tümör metakron, 32'sinde (%26) senkron olarak saptandı. Çoklu MPT görülme oranımız %1,22 idi. Kadınlarda meme-meme kanseri; erkeklerde larenks-akciğer kanseri çiftleri ön planda gözlemlendi. 81 (%67) hastada sigara içme öyküsü; 18 (%15) hastada alkol kullanma alışkanlığı öyküsü vardı. Senkron ve metakron tümörlerde en sık metastaz iskelet sisteminde gözlemlendi. Senkron tümörlerde medyan genel sağkalım 51 ay, metakron tümörlerde 72 ay olarak saptandı.

Sonuç: Kanser tanısı almış bir hastada ikinci bir kanser gelişimi, kanser tanısı almamış kimselere göre daha fazladır. Hastaların erken teşhis edilmesi ve sağkalımın uzaması ile ikincil tümöre yakalanma sıklığı artabilmektedir. Bu nedenle kanser tanısı almış hastaların takipleri sırasında ortaya çıkan



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during the follow-up of patients diagnosed with cancer should be considered and second primary tumors should be suspected. We think that long-term follow-up, especially for detecting early metachronous tumors, will contribute to survival in patients with cancer.

Keywords: Multiple primary tumors, synchronous, metachronous

yeni yakınmalar önemsenmeli ve ikincil tümörler göz önünde bulundurulmalıdır. Özellikle metakron tümörleri erken saptamak için kanserli hastalarda uzun süreli takibin sağkalıma katkısı olacağını düşünüyoruz.

Anahtar Kelimeler: Çoklu primer tümör, senkron, metakron

Introduction

Advances in oncologic diagnosis and treatment increase survival and remission of the disease. However, prolonged survival increases the likelihood of developing second primary malignancies. The term “multiple primary malignant tumors” was first used by Billroth in 1889, and the first paper describing multiple primary tumors (MPT) was published by Warren and Gates in 1932 (1,2). According to today’s definition, the features that should be available in MTPs are: 1) Each tumor should be diagnosed as malignant histopathologically, 2) each tumor should be histopathologically different tumors, and 3) each tumor should not be recurrence or metastasis of other tumor. While synchronous tumors are defined as tumors seen within 6 months after primary tumor diagnosis, metachronous tumors are tumors diagnosed after 6 months of primary tumor diagnosis (2). Although the mechanism of occurrence cannot be determined exactly, genetic mutations, chemotherapy and/or radiotherapy applications and prolonged survival of cancer patients are known to increase the risk of second primary tumor development (3-6).

The aim of this article was to evaluate whether the second primary tumor is associated with the primary tumor in patients who were treated and followed-up with cancer diagnosis, to evaluate the survival time and to make recommendations about the follow-up of these patients.

Methods

The files of 9892 patients who were followed for more than 6 months in Radiation Oncology and Medical Oncology clinics between January 2011 and December 2017 were examined. One hundred and twenty-one patients with primary tumors diagnosed as having synchronous or metachronous tumors were included in the study. The incidence of MPT was 1.22%. Patients with $\geq$ primary tumors and those who had been diagnosed with cancer for the first time in more than 7 years were excluded from the study. Overall survival (OS) was defined as the time from diagnosis to last follow-up or death. The data about whether the patients were alive or not were obtained from the computer system of our hospital. Patient case report forms and consent are included in each patient’s file. Approval was obtained from the İstanbul Training and Research Ethics Committee of our hospital (decision no: 1628, date: 04.01.2019).

Statistical Analysis

Data were collected in Excel and transferred to SPSS 22.0 program. Mean, standard deviation, median, minimum, maximum, frequency and percentage values were used in statistical analysis. The definition of the variables was measured by the Kolmogorov Smirnov test. The

chi-square test was used for the analysis of qualitative independent data, and Fisher’s Exact test was used when the chi-square conditions were not met. Independent sample t-test was used for the analysis of quantitative independent data. Kaplan-Meier log-rank test was used for survival analysis.

Results

Of 121 patients, 56 (46%) were female and 65 (54%) were male. The mean age of the female patients was 58 ± 10.37 years and the mean age of the male patients was 64 ± 8.62 years. The median age for both sexes was 63 (37-82) years. The second primary tumor was found to be metachronous in 89 patients (74%) and synchronous in 32 patients (26%). The time between the detection of the first and second primary tumors was 1.1 months (range: 0-6) in synchronous tumors and 30.8 months (range: 7-78) in metachronous tumors. Eighty-one patients (67%) had a history of smoking and 18 patients (15%) had a history of alcohol use.

In 32 patients with synchronous tumors, breast cancer/breast cancer pair was the most common tumor pair (38%), followed by breast cancer/colorectal cancer pair (13%). Among 89 patients with metachronous tumor, laryngeal cancer/lung cancer was the most common tumor pair (13%), followed by prostate cancer/lung cancer (8%). When MPTs were evaluated histopathologically, invasive ductal carcinoma/invasive lobular carcinoma was most common in synchronous tumors, whereas adenocarcinoma was the most common carcinoma in metachronous tumors, followed by epidermoid carcinoma.

The metastasis was observed after a mean period of 15 (4.78 ± 11.29) months in synchronous tumors and 29 (9.07 ± 18.24) months in metachronous tumors. The most common site of metastasis was observed as skeletal system in four (40%) patients with synchronous tumor and in nine (36%) patients with metachronous tumor ($p=0.126$). Demographic characteristics of patients with synchronous and metachronous tumors are shown in Table 1.

In our study, the most common tumor in women was found to be breast cancer (64%) and the second most common tumor was colorectal cancer (14%). In men, laryngeal cancer (25%) was the most common cancer, followed by prostate cancer (17%). Tumor pairs were breast-breast and breast-colorectal in women, and larynx-lung and prostate-lung in men. The distribution of tumors by gender is shown in Table 2.

In our study, surgery for synchronous tumors was performed in 25 patients (78%). Then, the curative treatment of the patients was determined starting from the tumor, whichever of the diseases would determine the survey. The curative treatment was performed to primary tumor in 82 patients (92%) with metachronous tumors. Median OS was 51 (95% confidence interval (CI): 43.69-58.30) months for synchronous

tumors and 72 (95% CI: 59.44-84.55) months for metachronous tumors (log rank: 0.145). General survival graphs of synchronous and metachronous tumors are shown in Figure 1.

Table 1. Demographic distribution of synchronous and metachronous tumors

	Synchronous tumor, n=32 (26%)	Metachronous tumor, n=89 (74%)	p
Gender			
Female	24 (75)	32 (36)	<0.001
Male	8 (25)	57 (64)	
Smoking			
Smoker	19 (59)	62 (70)	0.289
Non-smoker	13 (41)	27 (30)	
Alcohol use			
Yes	1 (3)	17 (19)	0.029
No	31 (97)	72 (81)	
Metastasis			
Present	10 (31)	26 (29)	0.829
Absent	22 (69)	63 (71)	
1. Primary			
Localization ¹			
Breast	18 (56)	21 (24)	0.002
Colorectal	5 (16)	12 (14)	
Larynx	-	16 (18)	
Other	9 (28)	40 (45)	
Histopathology ¹			
Adenocarcinoma	11 (34)	29 (33)	0.003
IDC/ILC	17 (53)	21 (24)	
SCC	1 (3)	24 (27)	
Other	3 (9)	15 (17)	
Stage ¹			
Stage 1-2	21 (66)	61 (69)	0.762
Stage 3-4	11 (34)	28 (31)	
2. Primer			
Localization ²			
Breast	16 (50)	15 (17)	0.001
Lung	2 (6)	29 (33)	
Colorectal	3 (9)	7 (8)	
Other	11 (34)	38 (43)	
Histopathology ²			
Adenocarcinoma	8 (25)	27 (30)	0.001
IDC/ILC	16 (50)	15 (27)	
SCC	2 (6)	24 (27)	
Other	6 (19)	23 (26)	
Stage ²			
Stage 1-2	21 (66)	54 (61)	0.621
Stage 3-4	11 (34)	35 (39)	
¹ first primary tumor, ² Second primary tumor, IDC/ILC: invasive ductal carcinoma/ invasive lobular carcinoma, SCC: squamous cell carcinoma			

¹first primary tumor, ²second primary tumor, IDC/ILC: invasive ductal carcinoma/ invasive lobular carcinoma, SCC: squamous cell carcinoma

Table 2. Gender distribution of most common tumor, histopathology and stage

	Female, n=56 (46%)	Male, n=65 (54%)	p
Localization ¹			
Breast	36 (64)	3 (5)	<0.001
Colorectal	8 (14)	9 (14)	
Larynx	-	16 (25)	
Gynecological	4 (7)	-	
Prostate/bladder	0/2 (0/4)	11/6 (17/9)	
Other	6 (11)	20 (30)	
Histopathology ¹			
Adenocarcinoma	14 (25)	26 (40)	0.004
IDC/ILC	34 (60)	4 (6)	
SCC	2 (4)	23 (35)	
Other	6 (11)	12 (19)	
Stage ¹			
Stage 1-2	40 (71)	42 (65)	0.426
Stage 3-4	16 (29)	23 (35)	
Localization ²			
Breast	30 (54)	1 (2)	<0.001
Lung	4 (7)	27 (42)	
Colorectal	5 (9)	5 (8)	
Prostate/bladder	-	8/2 (12/3)	
Other	17 (30)	22 (33)	
Histopathology ²			
Adenocarcinoma	13 (23)	22 (34)	0.065
IDC/ILC	30 (54)	1 (2)	
SCC	3 (5)	23 (35)	
Other	10 (18)	19 (29)	
Stage ²			
Stage 1-2	39 (70)	36 (55)	0.109
Stage 3-4	17 (30)	29 (45)	

¹first primary tumor, ²second primary tumor, IDC/ILC: invasive ductal carcinoma/ invasive lobular carcinoma, SCC: squamous cell carcinoma

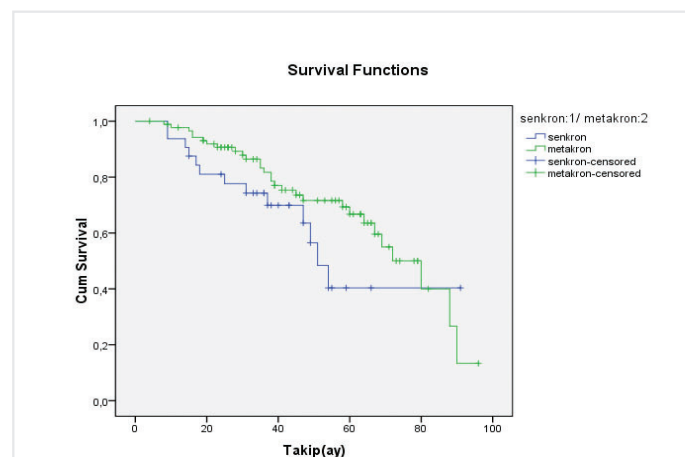


Figure 1. Overall survival in synchronous and metachronous tumors

Discussion

We see that the number of patients diagnosed with cancer at an early stage has increased with the increased use of screening programs and that the survival of patients has been prolonged with new treatments developed. With long survival times, the probability of developing a second primary tumor increases. Metachronous tumors often develop as a result of previous cancer treatments such as chemotherapy and radiotherapy, whereas synchronous tumors are associated with organ-specific carcinogens such as cigarettes and alcohol (3). The development of a second cancer in a patient diagnosed with cancer is 1.29 times higher than in patients with no diagnosed cancer (4). This is due to cancer development in different organs as a result of exposure to the same carcinogens in the primary tumor site (such as smoking, alcohol use) or genetic changes (7,8). Smoking and alcohol use can also trigger a second cancer in the lung, esophagus, pancreas, cervix and bladder. This condition is called “field cancerization effect” (9-11). Thirty-three patients (27.2%) in our study had the first tumor diagnosis in these organs.

MPTs can occur at any age, but they are reported to be more common after the age of 50 (12-14). The median age of our patients was 63 (37-82) and was consistent with the literature. We can attribute the incidence of MPT in advanced age to weakening of immunity with aging, prolongation of exposure to carcinogens, and sensitization to carcinogens with aging.

According to surveillance, epidemiology, end results program data, in which annual cancer statistics are published, prostate-respiratory system cancer is the most common tumor pair in men, followed by prostate-colon cancer (primary tumor-second tumor). Breast cancer-breast cancer pair is the most common and breast cancer-colorectal cancer pair is the second most common pair in women (15). In this study, similar to the above data, the most common MPT pair in female patients was breast-breast and breast-colorectal cancer pairs. However, the situation was slightly different in male patients. In men, larynx-lung and prostate-lung cancer were the most common cancer pairs. We think that the difference in male patients is mainly due to the fact that we have more head and neck cancer patients and small number of cases diagnosed with lung cancer. This difference can be explained by the high smoking and alcohol use in male patients.

The male/female ratio in patients with MPTs varies between 0.9 and 3.5 in various publications (15,16). The male/female ratio was 1.1 in our patients and this was consistent with the literature. MPTs are mostly seen as metachronous (16,17). Eighty-nine patients (73.6%) in our study had metachronous tumors.

In the literature, the incidence of MPT in genitourinary tumors is reported as 13.5% (17). In our study, there were 17 patients with genitourinary cancer and this rate was found to be 14%. In a study evaluating the success of Positron-emission tomography/ Computed Tomography (PET/CT) in the detection of synchronous primary tumor, 9.5% of patients had synchronous primary tumor, PET/CT detected 84% of them and treatment changed in 80% of patients (18). Similar to the other studies, metachronous tumors (76%) were observed more in our study. However, in contrast to the above study, the incidence of synchronous tumors was higher (36%). In our study, the contribution of PET/CT in detecting

synchronous and metachronous tumors, in the initial staging and in follow-up was significant. Almost all cases were diagnosed in this way.

In terms of prognosis, it is seen that there is a worse survival time in MPT cases especially in synchronous tumors. The reason for this is to fight two cancers in the same period in the synchronous tumor group, whereas the primary tumor is treated in metachronous tumors and the time to development of a second cancer was shown to be longer (19). In our study, the median OS was 51 months in synchronous tumors and 72 months in metachronous tumors.

In the literature, the incidence of MPT varies between 0.4% and 21% (19,20). This rate was 1.22% in our patients. Adenocarcinoma was the most common histological type in one series (21). Similar to the literature, the histology of adenocarcinoma was prominent in 37 patients (31%) in our study.

While synchronous tumors are caused by exposure to similar carcinogens, the negative effects of the treatments for first tumor can be mentioned on the development of metachronous tumors. The etiology may include the causes of the primary tumor or treatments applied to the primary tumor (22). In our study, 81 patients (67%) had a history of smoking and 18 (15%) had a history of alcohol use. Regarding the relationship between synchronous and metachronous tumors with alcohol use and smoking in our study, no difference was found between smoking and development of both tumors, while alcohol use was higher in metachronous tumors. As mentioned above, we could expect more cigarette and alcohol use in synchronous tumors, but this was not observed in this group because synchronous tumor pairs had more breast meme breast carcinomas. We know that smoking and alcohol use are not as intensely related to the etiology of breast tumors, as in head and neck and lung cancers. Laryngeal-lung carcinoma pair was more common in metachronous tumors. The association of this tumor pair is generally associated with smoking and alcohol use. As a result, alcohol use in metachronous tumors was statistically higher in our study.

Conclusion

Early detection of cancer and prolonged survival may increase the incidence of second primary tumors. For this reason, new complaints emerging during the follow-up of patients diagnosed with cancer should be considered and second primary tumors should be suspected. When metachronous tumor is diagnosed, multidisciplinary approaches may prolong survival in these patients. In addition, patients should be given increased awareness by giving up smoking and alcohol, paying attention to their weight, doing sports, and participating in screening test programs (fecal occult blood test, smear examination, mammography etc.). We think that long-term follow-up will contribute to the survival of patients who have survived more than 5 years, especially for cancers that may develop metachronously.

Ethics Committee Approval: Approval was obtained from the Istanbul Training and Research Ethics Committee of our hospital (decision no: 1628, date: 04.01.2019).

Informed Consent: Patient case report forms and consent are included in each patient's file.

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