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Mehmet Esat Duymus[1], Tolga Koseci[2], Mehmet Serindere[3], Meral Ceylan[2], Abdullah Bulgurcu[4], Ozlem Ipci[5], Cemile Karadeniz[2], Yusuf Murat Bag[6], Dilsa Mizrak Kaya[2]

[1]Department of Surgical Oncology, Hatay Education and Research Hospital, Hatay, Turkey
[2]Department of Medical Oncology, Hatay Education and Research Hospital, Hatay, Turkey
[3]Department of Radiology, Hatay Education and Research Hospital, Hatay, Turkey
[4]Department of General Surgery, Hatay Education and Research Hospital, Hatay, Turkey
[5]Department of Pathology, Hatay Education and Research Hospital, Hatay, Turkey
[6]Department Gastrointestinal Surgery, Van Training and Researcher Hospital, Van, Turkey

Patterns of multiple primaries in fortyfour cancer patients: a single-center clinical experience

Address for correspondence:
Mehmet Esat Duymus, M.D
Department of Surgical Oncology, Hatay Education and Research Hospital, Hatay, Turkey
e-mail: esatduymus@hotmail.com

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ABSTRACT

Introduction. Multiple primaries are defined as the existence of more than one synchronous or metachronous cancer type in the same individual. Due to a longer follow-up time after a primary cancer diagnosis, the likelihood of detection of a second primary is also increased. We report on patterns of multiple primaries in a cohort of cancer patients from a single institution.

Material and methods. We identified 44 patients with multiple primaries that were diagnosed, treated, and followed up between March 2011 and January 2022 from our prospectively maintained database at the Hatay Education and Research Hospital Cancer Unit.

Results. The median follow-up time was 60 months (range; 3–103). The median time between the diagnosis of the first primary and the second primary was 29 months (range; 0–94). The median OS was 76 months (95% CI 26.6–125.4) from the first diagnosis and 27 months (95% CI 0.65–53.4) from the diagnosis of the second primary for the entire cohort. The first diagnosed tumor was localized in the gastrointestinal system in 43.2% of patients and 65.9% of all tumors were adenocarcinoma. The first diagnosed cancer was at an early stage (Stages I and II) in 63.6% of patients. At the staging evaluation of the second primary, 54.5% of patients were found to be in the early stage (Stages I and II) and 45.5% were found to be in the late stage (Stages III and IV).

Conclusions. Our study is important as this is the largest cohort study about practical implications of managing multiple primaries. The risk of second and further primaries should be kept in mind in the active follow-up Introduction and surveillance of cancer patients .

Key words: carcinoma, invasive cancer, multiple primaries, pattern, survival

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Introduction

Cancer remains a global health problem with over 18 million new cases and 9.6 million deaths in 2018 [1]. It is the second major cause of death in the United States [2]. The lifetime probability of being diagnosed with an invasive cancer is about 40% [2]. Cancer survival has improved in the last decades, and the 5-year relative survival rate is approximately 67% for all cancers [2]

Multiple primaries are defined as the existence of is the second major cause of death in the United States more than one synchronous or metachronous cancer [2].

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The lifetime probability of being diagnosed with an type in the same individual. Synchronous refers to the time interval of fewer than 6 months between the two diagnoses, whereas metachronous refers to the time interval of more than 6 months. Due to a longer follow-up time after a primary cancer diagnosis, the likelihood of detection of a second primary has also increased. Moreover, persisting genetic and environmental risk factors and toxic effects of therapies can lead to second and further primaries in cancer patients. The reported frequency of multiple primary cancers is in the range of 2–17% [3–7].

Although there are many epidemiological studies and multi-institutional reports on the frequency of multiple primaries from different countries, there is no study about how to manage multiple primaries in daily clinical practice.

In the present study, we aimed to evaluate the patterns of multiple primaries in a cohort of cancer patients from a single institution. To the best of our knowledge, this is the largest cohort that includes all types of cancers, and all pathological specimens were evaluated in the same clinic.

Material and methods

Patients

A total of 44 cancer patients with multiple primaries that were diagnosed, treated, and followed up between March 2011 and January 2022 were identified in our prospectively maintained database at the Hatay Education and Research Hospital Cancer Unit. The study was carried out with the local ethics committee's approval (meeting number: 10, decision number: 09, date: 03/09/2020).

Diagnosis, staging, and follow-up

All patients had an imaging study, such as computer tomography (CT) or positron emission tomography (PET)/CT scan, as a staging workup. Overall survival (OS) was calculated as the time interval from the date of the first cancer diagnosis to death or loss to follow-up. Patients who were lost to follow-up were censored on that date. After the completion of therapy, patients were followed up at 3- to 6-month intervals in the first 2 years and then less frequently until the completion of 5 years or a patient's death.

Statistical analysis

The IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analyses. The Kolmogorov-Smirnov test was performed for assessing the normality of the distribution of numerical variables. The normally distributed numerical variables were expressed as mean ± standard deviation (SD). The non-normally distributed numerical variables were expressed as median (minimum-maximum). The categorical variables were expressed as frequency (percentages). The Kaplan-Meier analysis and the log-rank test were used to analyze and compare OS. A two-sided p-value < 0.05 was considered significant.

Results

The demographic, clinical, and pathological characteristics of 44 patients are summarized in Table 1. Most of the patients were male (54.5%), and the median age at diagnosis was 61.5 years (range; 18–86). Most of the patients were older than 60 years (61.4%).

The median follow-up time was 60 months (range; 3–103). The median time between the diagnosis of the first primary and the second primary was 29 months (range; 0–94). At the last analysis, 23 patients died. Median OS was 76 months (95% Cl 26.6–125.4) from the first diagnosis and 27 months (95% Cl 0.65–53.4) from the diagnosis of the second primary for the entire cohort. The 2- and 5-year OS rates were 75% [20.4 months (95% CI 18.3–22.4)] and 54.5% [42.4 months (95% CI 36.1–48.8)] (Fig. 1), respectively.

Table 2 shows the 5-year overall survival analysis according to age and sex. Median OS was longer in female patients compared to male patients but did not reach a significant value [49.5 months (95% CI 43.2–55.7) *vs.* 36.6 months (95% CI 26.7–46.4), p = 0.26] (Fig. 2). Median OS was also non-significantly longer for patients younger than 60 years compared to patients older than 60 years [47.3 months (95% CI 38.3–56.3) *vs.* 39.4 months (95% CI 30.9–47.9), p = 0.26] (Fig. 3).

Patterns of primarily diagnosed cancer

The first diagnosed tumor was localized in the gastrointestinal system in 43.2% of patients, and 65.9% of all tumors were adenocarcinomas. The first diagnosed cancer was at an early stage (Stages I and II) in 63.6% of patients.

Patterns of secondarily diagnosed cancer

A complete restaging evaluation with CT or PET/CT scan and with biopsies was performed in all patients at the diagnosis of the second primary. The localization of the second primary was the gastrointestinal system, lung, and prostate in 25.1%, 18.2%, and 13.6% of patients, respectively. The histology of the second primary was adenocarcinoma in 54.6% of patients. At the staging evaluation of the second primary, 54.5% of patients were found to be in the early stage (Stages I and II), and 45.5% were found to be in the late stage (Stages III and IV).

Table 1. Demographic, clinical and pathological characteristics of patients

Age (mean ± SD)	61.30 ± 16.02		
Age			
< 60	17 (38.6%)		
≥ 60	27 (61.4%)		
Sex			
Male	24 (54.5%)		
Female	20 (45.5%)		
Location of first primary tumor	n (%)	**Location of second primary tumor**	n (%)
Colon	8 (18.2%)	Lung	8 (18.2%)
Rectum	5 (11.4%)	Prostate	6 (13.6%)
Skin	5 (11.4%)	Colon	5 (11.4%)
Breast	4 (9.1%)	Skin	4 (9.1%)
Gastric	3 (6.8%)	Breast	4 (9.1%)
Prostate	3 (6.8%)	Rectum	4 (9.1%)
Lip	2 (4.5%)	Lymph	3 (6.8%)
Bladder	2 (4.5%)	Kidney	2 (4.5%)
Brain	2 (4.5%)	Thyroid	2 (4.5%)
Ovary	1 (2.3%)	Ureter	1 (2.3%)
Endometrium	1 (2.3%)	Appendix	1 (2.3%)
Kidney	1 (2.3%)	Bladder	1 (2.3%)
Lymph	1 (2.3%)	Ovary	1 (2.3%)
Pancreas	2 (4.5%)	Gastric	1 (2.3%)
Esophagus	1 (2.3%)	Endometrium	1 (2.3%)
Thyroid	1 (2.3%)		
Nasopharynx	1 (2.3%)		
Cervix	1 (2.3%)		
Pathology of first primary tumor	**n (%)**	**Pathology of second primary tumor**	**n (%)**
Adeno carcinoma	25 (56.8%)	Adeno carcinoma	20 (45.5%)
Invasive ductal carcinoma	4 (9.1%)	Invasive ductal carcinoma	4 (9.1%)
SCC	3 (6.8%)	NHL	3 (6.8%)
BCC	3 (6.8%)	BCC	2 (4.5%)
Urothelial carcinoma	3 (6.8%)	Urothelial carcinoma	2 (4.5%)
Glioblastoma	2 (4.5%)	SCC	2 (4.5%)
Serous carcinoma	1 (2.3%)	RCC	2 (4.5%)
RCC	1 (2.3%)	Papillary carcinoma	2 (4.5%)
NHL	1 (2.3%)	Small cell carcinoma	2 (4.5%)
Papillary carcinoma	1 (2.3%)	NET	2 (4.5%)
		Non-small cell carcinoma	2 (4.5%)
		Serous carcinoma	1 (2.3%)
Stage of first primary tumor	**n (%)**	**Stage of second primary tumor**	**n (%)**
Stage I–II	28 (63.6%)	Stage I–II	24 (54.5%)
Stage II–IV	16 (36.4%)	Stage III–IV	20 (45.5%)
Median follow-up time from the first primary tumor (min–max)	60 (3–103)	**Median follow-up time from the secondary primary tumor (min–max)**	24 (2–97)
Died		23 (52.3%)	

SD — standard deviation; BCC — basal cell carcinoma; SCC — squamous cell carcinoma; RCC — renal cell carcinoma; NHL — non-hodgkin lenfoma; NET — neuroendocrine tumor

Discussion

In the present study, we showed that even in cancer patients who are in active follow-up second primary cancers are mostly detected in the late stages. This can be related to an increased focus on the first primary.

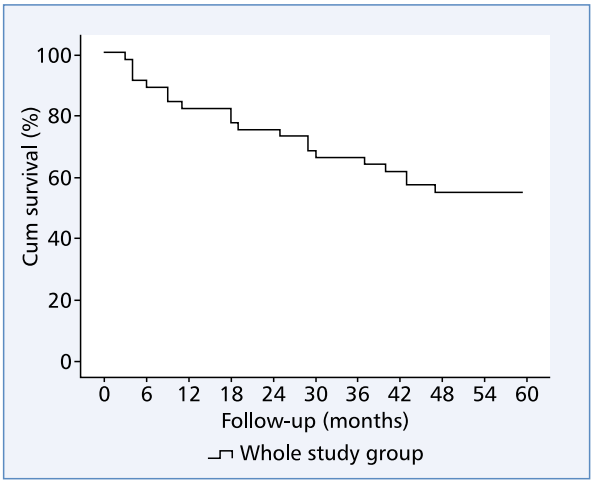

Figure 1. Kaplan-Meier curves for 2-year and 5-year overall survival

Multiple primaries were defined differently by the SEER (Surveillance, Epidemiology, and End Results) Program and the IACR/IARC (International Association of Cancer Registries and International Agency for Research on Cancer) [6, 7]. There are two main differences between these definitions. First, the time to distinguish between synchronous and metachronous multiple primaries, the IACR/IARC recommends 6 months while the SEER database suggests 2 months. Second, the tumors located in the different part of an organ, while the SEER database considers tumors located in different parts of the same organ as different tumors, the IACR/IARC evaluates the organ as a whole without segmenting it. Persisting genetic and environmental risk factors and toxic effects of therapies can lead to second and further primaries in cancer patients.

In a recent pilot study, Saegobin et al. [8] assessed the implications of cancer-related therapy in the development of a new primary. They found that 24 of a total of 602 patients had a second cancer within 5 years from the diagnosis of the first primary. In conclusion, they reported no increased risk of the second primary after exposure to different kinds of cancer therapies. Likewise, in our cohort, the development of the second

Table 2. 5-year overall survival analysis according to age and sex

	5-year OS rate	Survival time (month)	95% CI		Log-rank	
			Upper	Lower	Chi-square	P-value
Age < 60	64.7%	47.3 ± 4.6	38.3	56.3	1.277	0.258
Age ≥ 60	48.1%	39.4 ± 4.4	30.9	47.9		
Male	50%	36.6 ±5.1	26.7	46.4	1.283	0.257
Female	60%	49.5 ± 3.2	43.2	55.7		

OS — overall survival; CI — confidence interval

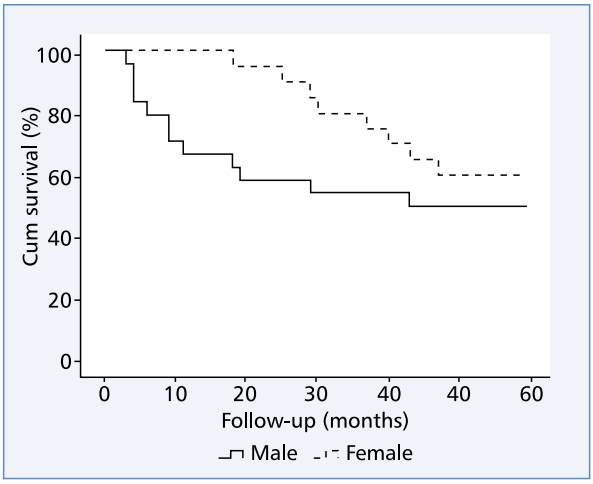

Figure 2. Kaplan-Meier curves for 5-year overall survival according to sex

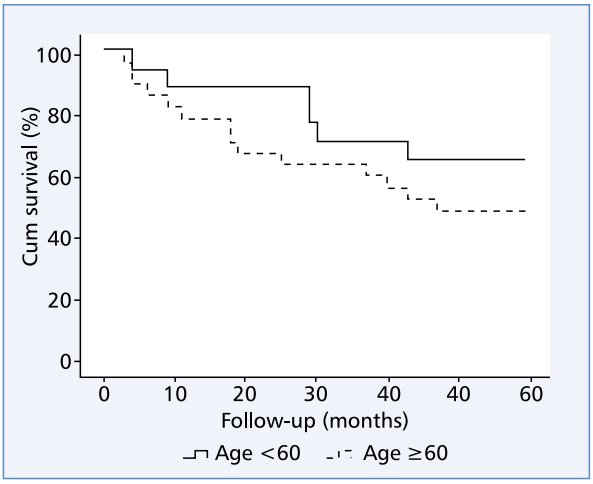

Figure 3. Kaplan-Meier curves for 5-year overall survival according to age

primaries did not seem to be related to the therapy of the first primaries.

The median time between the diagnosis of the first and second primary in our study was fewer than 3 years. It is less than the previously reported 5–10 years [8]. This can be related to the increased median age in our cohort.

Some population-based studies evaluated the incidence of second primaries in different parts of the world [3, 9, 10]. These population-based studies can identify genetic and environmental risk factors that can cause multiple primaries. However, none of these reports showed a specific risk factor that can be the cause for multiple primaries. Some other studies are designed to assess the frequency of multiple primaries in a specific body part such as gynecologic malignancies, and the colorectal or aerodigestive tracts [11–17]. The reports evaluating the effect of cancer treatment on the development of second primaries demonstrated that both chemotherapy and radiotherapy can cause secondary primaries [18–23].

The present analysis has some limitations such as being a retrospective and single-center study. The retrospective nature of the study made it impossible to elucidate the exact relation between different primaries. Well-designed, prospective studies will help to identify causes and optimum follow-ups of multiple primaries.

Conclusions

Our study is important as this is the largest cohort study about practical implications of managing multiple primaries. The risk of second and further primaries should be kept in mind in the active follow-up and surveillance of cancer patients.

Informed consent

Since the current investigation focused on retrospective data collection, no informed consent was required. Nonetheless, we acquired legal authorization from the Hospital Managers, laboratories, local and state Health Secretariats to access databases, laboratory, and medical records.

Conflict of interest

The authors have no conflicts of interest to declare for this study.

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None.

Authors contribution

The authors confirm contribution to the paper as follows: Conceptualization: MED; Formal Analysis: TK, MS, OI; Investigation: MC, AB, YMB; Methodology: MED, DMK, MS; Project Administration: OI, CK; Writing — Original Draft: MED, DMK, YMB, CK; Writing — Review & Editing: All authors.

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