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ORIGINAL ARTICLE

Multiple primary malignant neoplasms: Multi-center results from Turkey

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Summary

Purpose: *Multiple primary malignant neoplasms (MPMNs) are defined as a diagnosis of two or more independent primary malignancies of different histologies/origins in an individual. The frequency of MPMN is being increasing. In this study we aimed to determine the frequency and clinical features of second primary cancers (SPCs).*

Methods: *From January 1990 to December 2010, patients with MPMNs were screened in 5 centers. Data were obtained retrospectively from hospital charts.*

Results: *Three hundred seventy-seven patients with MPMNs were evaluated. The median age at initial cancer diagnosis was 61 years (range 18-88). The median age at second cancer was 64 years (range 20-89). The median time between two cancer diagnoses was 15 months (range 0-504). Male to female ratio was 1.44 (M/F 223/154). The most frequent initial cancer types were head and neck (54 patients, 14.3%), breast (54 patients, 14.3%), and colorectal (43 patients, 11.4%). The most frequent second cancer types were lung (76 patients, 20.2%), colorectal (39 patients, 10.3%) and breast (33 patients, 8.8%). The most common cancer pairs in females were breast-gynecologic cancers (15 patients, 9.7%), colorectal-breast cancers (9 patients, 5.8%) and breast-colorectal cancers (7 patients, 4.5%). The most common cancer pairs in males were head and neck-lung cancers (29 patients, 13%), bladder-lung cancers (9 patients, 4%), and bladder-prostate cancers (7 patients, 3%). The median follow up was 36 months (range 1-595).*

Conclusion: *Physicians should be aware of SPCs probabilities. Newly developed suspicious lesions should be evaluated rigorously. Histopathologic evaluations of suspicious lesions for second tumors should be used extensively if needed. In our series, the most common pairs were breast-gynecologic cancers in females and head and neck-lung cancers in males.*

Key words: cancer, chemotherapy, multiple primary malignancies, second primary

Introduction

The number of cancer survivors is increasing worldwide. Among all cancer patients the 5-year survival rate is now almost 66% [1]. One of the most serious problems experienced by cancer survivors is the development of new cancers. The term MPMNs, was first used by Billroth in 1889 and the first literature report about MPMNs was published by Warren and Gates in 1932 [2]. According to Warren and Gates description, both the primary and secondary tumors should be malignant, with histologic confirmation, there should be at least 2 cm of normal tissue between the two tumors (if the tumors are in the same region), they should be separated in time by at least 5 years and metastatic tumor should be excluded.

MPMNs may be synchronous or metachronous. The term "synchronous" is used when the second primary malignancy is diagnosed within 6 months of the primary tumor and "metachronous" is used when the second primary malignancy is diagnosed more than 6 months after the diagnosis of the primary tumor [3].

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MPMNs prevalence ranged from 0.7 to 11.7% in various publications [4-8]. According to SEER (Surveillance, Epidemiology, and End Results) data, the risk of developing subsequent MPMN varies from 1% for an initial liver primary diagnosis to 16% for bladder cancer primaries [9]. Ishimaro et al. published that at least 1.2% of patients referred to PET/CT with cancer diagnosis have a second cancer [10].

In this study we aimed to evaluate the demographic and clinical features and the most common cancer pairs of MPMN in our centers.

Methods

Five centers from Turkey participated in this study. The hospital charts of cancer patients from 1990 to 2010 were reviewed in these centers. Three hundred and seventy- seven adult patients with SPCs data were retrospectively evaluated. All patients had histopathologic diagnosis of the first and second cancer. If the second tumor was diagnosed within the first 6 months from the diagnosis of the first tumor it was accepted as synchronous tumor, and if after 6 months it was accepted as metachronous tumor. Second tumors developing in the same organ/system (e.g. synchronous or metachronous colon tumors, contralateral breast cancer) and skin tumors (except malignant melanoma) were not included in the study. Demographic, clinical, and pathological characteristics of patients were analyzed.

Statistical analysis

Descriptive analysis was performed for demographic and clinical characteristics of the patients. Student's t-test or Mann-Whitney U test were used for comparison of numeric variables between the two groups. Chi-square test was used for comparison of ratios between groups. For all data analysis, the Statistical Package for Social Sciences (SPSS v 15.0, SPSS Inc., Chicago, IL, USA) was used. Significance was put at $p<0.05$.

Results

Two hundred and twenty three patients (59.2%) were male and 154 (40.8%) female (male/female ratio 1.44). Patients' median age at diagnosis of the first cancer was 61 years (range 18-88), and at second cancer diagnosis it was 64 years (range 20-89). Three hundred and twenty four (83.3%) of the patients had their second cancer diagnosis after the age of 50.

Ninety-five percent of patients (358 patients) had 2 cancers, 4% (18 patients) had 3 cancers and 0.2% (1 patient) had 4 cancer diagnoses. The median period between 2 cancer diagnoses was 15 months (range 0-504). One hundred and forty three (38%) patients were diagnosed as synchronous MPMN and 234 (62%) as metachronous MPMN. Ninety-one (24%) of the patients who were diagnosed with synchronous MPMN had their MPMN diagnosis within 1 month after the first diagnosis, and 52 (14%) 1-6 months after the first diagnosis. Thirty-eight (10%) of the patients with metachronous MPMN had their diagnosis within 6-12 months after the first diagnosis, and 196 (52%) within 1 year after the first diagnosis. Eighty patients (21%) had their second cancer diagnosis after their first diagnosis within at least 5 years.

The most frequently detected synchronous tumors were lung cancer (26 patients, 18.2%) and head-neck tumors (21 patients, 14.7%); most frequent metachronous tumors were lung cancer (50 patients, 21.4%) and breast cancer (33 patients, 14.1%).

Taking into consideration the first cancer diagnosis, the first 5 most frequent cancer types were head-neck cancer (54 patients, 14.3%), breast cancer (54 patients, 14.3%), colorectal cancer (43 patients, 11.4%), bladder cancer (33 patients, 8.8%) and gastric cancer (30 patients, 8%).

Taking into consideration only the second cancer diagnosis, the first 5 most frequent cancer types were lung cancer (76 patients, 20.2%), colorectal cancer (39 patients, 10.3%), breast cancer (33 patients, 8.8%) and gynecologic cancers (28 patients, 7.4%).

Among third cancers, most frequently observed were colorectal cancer (6 patients, 1.6%), intracranial tumors (3 patients, 0.8%) and gynecologic cancers (2 patients, 0.5%). In one case, 4 primary tumors (colon, breast, renal cell carcinoma/RCC and lung cancer) were observed.

In women, the most frequent 5 primary tumor types were breast cancer (51 patients, 33%), gynecologic tumors (21 patients, 13.6%), colorectal cancers (20 patients, 13%), thyroid cancer (11 patients, 7.1%) and gastric cancer (10 patients, 6.5%). Most frequently observed secondary tumors were breast cancer (29 patients, 19%), gynecological tumors (26 patients, 16.9%) colorectal cancer (15 patient 9.7%), lung cancer (13 patients, 8.4%) and RCC (12 patients, 7.8%). Finally, most frequently observed third cancers in women were RCC (2 patients, 1.3%), intracranial tumors (2 patients, 1.3%), colorectal cancer (2 patients, 1.3%) and gynecologic tumors (2 patients, 1.3%) (Table 1).

Most frequently observed tumor pairs (primary tumor- second tumor) in women were breast cancer-gynecologic cancer (15 patients, 9.7%), colorectal cancer-breast cancer (9 patients, 5.8%), breast cancer - colorectal cancer (7 patients, 4.5%), gynecologic cancer- breast cancer (6 patients, 3.8%) and malignant mesenchymal tumor combinations (5 patients, 3.2%) (Table 2).

In men, the most frequent 5 primary tumor types were head-neck tumors (47 patients, 19.7%), bladder cancer (31 patients, 13.9%), prostate cancer (26 pa-

Table 1. The most common tumor types in women

Most common primary tumors	*N (%)*
Breast cancer	51 (33.1)
Gynecologic tumors	21 (13.6)
Colorectal tumors	20 (13)
Thyroid carcinoma	11 (7.1)
Gastric cancer	10 (6.5)
Most common second tumors	
Breast cancer	29 (19)
Gynecologic tumors	26 (16.9)
Colorectal tumors	15 (9.7)
Renal cell carcinoma	12 (7.8)
Most common third tumors	
Colorectal tumors	2 (1.3)
Intracranial tumors	2 (1.3)
Renal cell carcinomas	2 (1.3)
Gynecologic tumors	2 (1.3)

Table 2. The most common cancer pairs in women

Primary cancer	*Second cancer*	*N (%)*
Breast cancer	Gynecologic tumors	15 (9.7)
Colorectal tumors	Breast cancer	9 (5.8)
Breast cancer	Colorectal tumors	7 (4.5)
Gynecologic tumors	Breast cancer	6 (3.8)
Breast cancer	Malignant mesenchymal tumors	5 (3.2)

Table 3. The most common tumor types in men

Most common primary tumors	*N (%)*
Head and neck tumors	47 (19.7)
Bladder cancer	31 (13.9)
Prostate cancer	26 (11.7)
Colorectal tumors	23 (10.3)
Gastric cancer	20 (9)
Most common second tumors	
Lung cancer	63 (28.3)
Colorectal tumors	24 (10.8)
Renal cell carcinoma	18 (8.1)
Prostate cancer	14 (6.3)
Head and neck tumors	13 (5.8)
Gastric cancer	13 (5.8)
Most common third tumors	
Colorectal tumors	4 (1.8)
Intracranial tumors	1 (0.4)
Prostate cancer	1 (0.4)

Table 4. The most common cancer pairs in men

Primary cancer	*Second cancer*	*N (%)*
Head and neck tumors	Lung cancer	29 (13)
Bladder cancer	Lung cancer	9 (4)
Bladder cancer	Prostate cancer	7 (3)
Gastric cancer	Lung cancer	7 (3)
Prostate cancer	Lung cancer	5 (2.2)

tients 11.7%), colorectal cancer (23 patients, 10.3%) and gastric cancer (20 patients, 9%). Most frequently observed secondary tumors were lung cancer (63 patients, 28.3%), colorectal cancer (24 patients, 10.8%), RCC (18 patients 8.1%), and prostate cancer (14 patients, 6.3%). Most frequently observed third tumors in men were colorectal cancer (4 patients, 1.8%), intracranial tumor (1 patient, 0.4%) and prostate cancer (1 patient, 0.4%) (Table 3).

Most frequently observed tumor pairs (primary tumor-second tumor) in men were head neck-lung cancer (29 patients, 13%), bladder cancer-lung cancer (9 patients, 4%), bladder cancer- prostate cancer (7 patients, 3%), and prostate cancer-lung cancer (5 patients, 2.2%) (Table 4).

Fifty-nine patients (15.6%) had their first tumor diagnosis when the disease was already metastatic, while 218 (84.4%) had non-metastatic disease. When considering the second tumor cases, 79 patients (21%) had metastatic disease at diagnosis, and 298 (79%) had non-metastatic disease. Four of the patients who had a third cancer (23.5%) had metastatic and 13 patients (76.5%) non-metastatic disease at diagnosis.

Two hundred and thirty eight (63%) patients were smokers (median package-years was 20; range 1-90). The ratio of smokers in female patients was 11.8%, and 88.2% in males (p=0.001). Median body mass index (BMI) of patients during the first diagnosis was 25 (range 16.7- 49.5).

One hundred and thirty eight (36.6%) patients received chemotherapy for the primary tumor and the median number of courses was 4 (range 1-12). Ninety-two (66.7%) of these patients received topoisomerase II inhibitors and/or anthracyclines. Seventy-two (15.1%) of the patients received radiotherapy for their primary tumors. Sixteen patients (4.6%) had second tumors developed in a previous radiotherapy field. Of 225 patients evaluated for recurrences/metastasis 103 developed recurrent/metastatic disease during follow-up. Recurrences/metastasis originated from the first tumor in 37 (17.2%) patients, from the second tumor in 39 (18.1%) and from the third tumor in 3 (1.39). The origin of recurrence/metastasis could not be defined in 14 (6.5%) patients. Median patient follow up was 36 months (range 1-595). During this period 65 patients died.

Discussion

Because of the high effectiveness of certain cancer therapies and the ever expanding older population, the problem of MPMN in the same host has increased.

There are many possible reasons for developing second cancers, such as cancer treatments themselves (radiotherapy, chemotherapeutics such as alkylating agents, topoisomerase II inhibitors), genetic and environmental factors.

Ionizing radiation is the possible cause of a big number of second cancers [14]. The risks of lung cancer, meningioma, glioma and sarcoma have also been found to rise with increasing radiation doses above 5 Gy [15-17]. Especially after 10 or more years from the initial cancer diagnosis, secondary solid tumor risk is significant [18]. In our study 16 (4.6%) patients had second tumors developing in a previous radiotherapy field.

Second primary malignancy development after chemotherapy was reported in 1970 by Kyle et al. who described a case of acute myeloid leukemia (AML) developing after treatment for multiple myeloma [19]. Nowadays, it is known that topoisomerase II inhibitors, anthracyclines and alkylating agents can cause AML [20-29]. However, our knowledge over chemotherapy-induced solid tumors is limited. Bladder cancer may develop after cyclophosphamide use. Moreover, elevated risk of sarcomas, bone and lung cancer have also been observed after alkylating agent chemotherapy [17,30].

The primary factors among environmental causes are smoking and the use of alcohol. Tobacco smoking appears related with cancers of the head and neck, esophagus, respiratory system, pancreas, urinary system and cervix [11-13]. The "Field cancerization" theory supposes that the same carcinogenic effects of tobacco and alcohol that give rise to the primary tumor also promote the growth of secondary tumors located in the same "condemned mucosa" of the aerodigestive tract and bladder [31]. It is a known fact that continued smoking increases the second cancer frequency and quitting decreases the risk [32-34]. In addition, it is also argued that genetic factors and lifestyle are important factors for the development of second cancers [35,36].

Hormonal and nutritional factors have reciprocal associations between cancers of colon, breast and female genital organs. However, the associations are weak and misdiagnosis is possible. Cancers of colon and rectum, biliary tract, ovary, endometrium and prostate may have similar nutritional and dietary components, for example fat intake [37]. However, the main biological mechanism is not clear. Ovary, breast and endometrium are known as hormone-dependent cancers, and it has been suggested that developing colon cancer may also be related to endocrine factors in women [38]. Obesity is associated with breast, colorectal, and endometrial cancers [39-42]. This relationship may be caused by increased production of endogenous estrogens [43].

Genetic abnormalities constitute the other possible etiologic factor for MPMN. Although hereditary susceptibility explains only a small proportion of all second cancers, many hereditary cancer syndromes have been described: Li Fraumeni syndrome, BRCA-related hereditary breast, colon and ovarian cancer, and hereditary nonpolyposis colorectal cancer syndromes (excess risk of gastrointestinal system, ovarian or endometrial cancer) etc [44].

MPMNs can occur at any age. However, from the reviewed series, patients with MPMNs tend to be older than those with a single primary malignant neoplasm. In many autopsy series and clinical reports, the median age of 50-94% of MPMN patients was over 50 years [5,6,8,45,46]. In our study, the median age at second tumor diagnosis was 64 years and 83% of patients with MPMN diagnosis were aged 50 years or over. The ratio of male/female patients with MPMNs in several publications varies between 0.9 and 3.5 with male predominance [7,8,46-48]. Similarly, the male/female ratio was 1.44 in our study. In patients with MPMN diagnosis, the predominance of smokers vs. non smokers was remarkable and varied between 49.1 and 64% in several publications [47-49]. In our patient group, smokers were 63% and this percent was higher in men than in women (88.1 vs. 11.8%, respectively; $p<0.001$). In this study, it is worth noticing that the most common tumors in men were related to smoking (head and neck, lung, and bladder carcinoma). Although the definition of synchronous-metachronous MPMN differs among publications, Aydiner et al. reported 34% of synchronous and 66% of metachronous tumors in their MPMN series [8]. Flannery et al. reported that 20% of MPMNs were diagnosed as synchronous (second tumor diagnosed after 2-3 months) and 80% as metachronous (second tumor diagnosed after 1-2 years) [50]. Synchronous MPMNs are often seen in the genitourinary and gastrointestinal system [51,52]. In our series, 38% of the patients were diagnosed with synchronous and 62% with metachronous MPMNs. Most diagnosed synchronous tumors were lung cancer and head-neck tumors; metachronous tumors were lung cancer and breast cancer.

According to SEER data results (1973-2003), the most common primary tumors in patients with MPMNs are breast carcinoma, prostate carcinoma, respiratory system and lung cancers, colorectal cancer and urinary system cancers [9]. In our study, 5 of the most common tumors were head-neck tumors, breast cancer, colorectal cancer, and bladder and gastric cancer. In the present study, prostate carcinoma was not included in the most common cancers; a reasonable explanation may be that these patients are usually treated and observed in urology clinics and did not apply to our centers. In other Turkish studies, the most common tumors were laryn-

geal carcinoma, lung carcinoma and breast carcinoma in MPMN series [8,46,53].

In the SEER data the most common tumor pairs in males were prostate carcinoma-lung carcinoma and respiratory system cancers, and secondly prostate-carcinoma-colon carcinoma. In women, the first two were breast carcinoma-breast carcinoma and breast carcinoma-colon carcinoma pairs [9]. In our study, head-neck tumors-lung carcinoma, bladder carcinoma-lung carcinoma in males and breast carcinoma-gynecologic cancers, colorectal cancer-breast cancer in females were the most commonly observed cancer pairs.

It is not easy to trace the source of a newly formed tumor in patients with MPMN diagnosis in recurrent/progression cases. For differential diagnosis, a diagnostic biopsy should not be avoided in these cases. In our study, a biopsy was performed in 35 out of 215 patients with relapse/metastasis and differential diagnosis could not be determined despite pathological examination in 9 patients.

MPMN patients are very heterogeneous, and only few reports exist regarding their survival [9]. In our study, 65 (17.2%) of the patients died during follow-up. Our survival data were not mature for further analysis.

It is important that patients treated for cancer should be followed for a long time because of the risk of second cancers. In our study, 21% of the patients were diagnosed with MPMN 5 years after their first cancer. In particular, new lesions should be evaluated carefully and histopathological examination should not be avoided when needed. Nonetheless, cancer patients should be informed about prevention (cessation of smoking and alcohol use, protection from UV light etc.), screening tests (mammography, cervical smear, fecal occult blood test etc.) and should be encouraged to modify their lifestyle.

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