RESEARCH ARTICLE

Multiple Primary Malignancies - A Retrospective Analysis at a Single Center in Turkey

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Abstract

Background: A literature review on 1,104,269 cancer patients concluded that the prevalence of multiple primary malignancies (MPM) is between 0.73% and 11.7%. MPMs seem to have higher incidence than that influenced by hazard only. The purpose of this study was to investigate clinically useful information for effective screening for synchronous and metachronous second primary cancers and to identify a potential surveillance protocol. Materials and Methods: Using statistical and epidemiological indicators we evaluated the patients with MPMs (double locations) admitted to Dr. Abdurrahman Yurtarslan Ankara Oncology Education and Research Hospital between 1981 and 2010. Results: Out of the 130 cases, 24 (18.4%) were synchronous while 106 cases (81.6%) were metachronous tumours. Mean interval time from first to second primary cancers was 4.65 years (0-27 years). The most frequent malignant associations were breast-breast, breast-endometrium and breast-ovary. Both primary and secondary tumors tended to be in an advanced stage explained by the low compliance of the patients to follow-up. Conclusions: The possibility that MPMs exist must always be considered during pretreatment evaluation. Screening procedures are especially useful for the early detection of associated tumors, whereas careful monitoring of patients treated for primary cancer and a good communication between patients and medical care teams should ensure early detection of secondary tumors, and subsequent appropriate management.

Keywords: Multipl primary malignancies - synchronous - metachronous

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Introduction

The entity of multiple primary malignancy (MPM) is not very rare (Kaneko et al., 1999; Aydiner et al., 2000; Morgenfeld and Vaslamatzis, 2003). One of the earliest statistical analyses of MPMs was carried out by Bugher in 1934, who derived an equation for the probability of death from cancer during a given age with a coincidental second malignancy (Bugher, 1934). Improving of survival rates for patients with neoplastic disease due either to early diagnosis or to new therapies allow more patients to survive long enough to develop subsequent primary tumors, whereas the development of more sophisticated diagnostic tools made possible the detection of synchronous occult tumors, for a long time overlooked. The mechanisms involved in the occurrence of MPMs are not yet elucidated. Inherited predisposition could be involved in some of MPMs suggested by the association between hereditary nonpolyposis colorectal cancer and an increased risk of developing ovarian cancer or cancer of the endometrium and small intestine, whereas widespread use of chemotherapeutic agents and radiotherapy might be responsible for associations between specifi c types of primary cancer (Merrouche and Noronha, 2006; Chaturvedi et al., 2007; Erikci et al., 2009).

There is not enough information about a causal relationship between a risk factor and each of the two cancers. The relative risk for the association between the risk factor and each of the two cancers varies from 2-10 and the prevalence of the risk factor in the population varies from 5-50% (Thompson, 1986). These numerical data clearly indicate that the epidemiologic studies of MPMs would provide important information regarding the risk factors of each type of tumor. A literature review on 1,104,269 cancer patients concluded that the prevalence of MPM is between 0.73% and 11.7%. As expected, incidence increases with aging (Demantande et al., 2003).

Multiple primary malignancies can be divided into two categories depending on the interval between tumor diagnosis (Suzuki et al., 2002). Synchronous cancers are second tumors occurring simultaneously or within 6 months after the first malignancy while metachronous multiple malignancies are secondary cancers that developed after more than 6 months from the first

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malignancy.

In this paper we retrospectively analyzed the features of 130 patients with multiple primary tumors admitted to Dr. Abdurrahman Yurtarslan Ankara Oncology Education and Research Hospital.

Materials and Methods

This retrospective study analyzed data from the record sheets of patients with multipl primary tumors admitted between 1981 and 2010 at Dr.Abdurrahman Yurtarslan Ankara Oncology Training and Research Hospital. The inclusion criteria of patients in the study were the presence of at least two neoplastic locations, confirmed by histopathological examination, with distinct histopathology in the two locations. We excluded patients without a clear histopathological confirmation of each tumor and also the patients in whom the second tumour was suspected to be a metastasis of the first location (consequently, cases of suspected brain, lung, liver, bone or ovarian metastases were excluded from the study).

Results

Sixty of 130 patients included in this study were male (44%) and 70 patients (56%) were female. The median age of male and female patients were 54 and 51 respectively. The youngest patient was diagnosed with retinoblastoma at age 1 year old and the oldest patient was diagnosed with breast cancer at age 79. Most of cancers were detected at 40-50 years range (n=32, 24%). Six months (180 days) was considered to be the maximum period for the occurrence of synchronous tumors. Out of the 130 cases, 24 cases (18.4%) were synchronous tumors while 106 cases (81.6%) were metachronous tumors. The median age of synchronous tumors was found 62 years old and of the metachronous tumors was found 55 years old. We detected two patients had three primary tumors and 1 patient had four primary tumours (melanoma, renal cell carcinoma, prostate carcinoma and non-hodgkin lenfoma).

In order of frequency rates of the primary cancers; breast cancer (n=36, 27.7%), head and neck cancers (n=15, 11.5%, of these 12 were larynx cancers, 1 nazopharynx, lower lib and tounge cancer), colorectal cancers (n=12, 9.2%, of these 9 were colon and 3 were rectum). Out of the 36 patients diagnosed first with breast cancer, the tumor histology was commonly invasive ductal carcinoma and mostly at advanced stage. None of the male patients had breast cancer. The second most common cancer seen in our patients that mentioned above was head and neck cancer with a predominancy of male gender (M/F:7/1). Colorectal cancers were found two times frequently in female patients than male patients. Endometrial cancers were the fourth common cancers and mean age was 55.1. For lymphoid malignancies male gender was predominant and Hodgkin Lymphomas were not detected in any female patients. The distribution of gender and age in our patients diagnosed with first cancers is presented in Table 1.

In order of frequency rates of the secondary cancers; lung cancers (n=25, 19.2%), breast cancers (n=20, 15.2%) and colorectal cancers (n=16, 12.3%). Lung cancers were commonly detected at advanced stage (stage 3-4) and almost all lung cancer patients were non-small cell cancer and had epidermoid histology however only two patients were small cell cancer. Median age of 130 patients with second primary cancers was 57.24 (14-82). The youngest patient was diagnosed with Ewing sarcoma at age 14 and the oldest patient was diagnosed with non-melanoma skin cancer at age 82. Many of the second primary cancers were detected at 5-6. decades (n=78, 60%). Within the second primary cancers non-hodgkin lymphomas were the most common malignancies diagnosed over age 65 and median age was 66.8.

When compared first primary cancers with second primary cancers frequency of lung cancers was detected to be increased from eight to first step. Frequency of breast cancer declined from first to second step. Frequency of endometrium cancer was similar (6.9% vs 6.1%) and others frequency of bone-soft tissue tumors, ovary and thyroid tumors were detected to be increased within second primary cancers. Within the second primary cancers frequency of non-melanoma skin cancers were detected to be more increased than the others according to first primary cancers. Table 2 shows the distribution of gender and age in our patients diagnosed with second primary cancers.

Median interval time from first primary cancers to second primary cancers was 4.65 years (0-27 years) for metachronous cancers. Among the first primary breast cancers (n=36), gynecologic cancers (n=14, 38%) were found the most common second primary cancers(8 endometrium, 5 ovary, 1 cervix) to be occurred. Out of these 36 cases, 7 cases suffered from breast cancer. Among the first primary cancers only 12 patients developed hematologic-lymphoid malignancies (n=5 hodgkin lymphoma, n=3 non-hodgkin lymphoma, n=4 had extranodal non-hodgkin lymphoma(tonsil, stomach). Among the second primary cancers only 5 cases developed non-hodgkin lymphoma. Only 1 case suffered from acute

Table 1. The Distribution of Patients with First Primary Cancers According to Gender and Age

	Breast 36(27.7%)	Head-neck 16 (12.3%)	Colorectum 12(9.2%) Colon:9 (6.9%) Rectum:3 (2.3%)	Endometrium 9(6.9%)	Gastric 8(6.1%)
Gender n=130 (%)					
M: 60(44)	0	14	4	0	5
F: 70(56)	36	2	8	9	3
Average age: 52.59	51.39	59.7	63.0	55.1	66.23
M: 54.00	-	61.8	68.0	-	66.8
F: 51.39	51.39	45.0	60.5	55.1	65.3

	Non-hodgkin lymphoma 7(5.3%)	Bladder 7 (5.3%)	Renal 7 (5.3%)	Lung 6 (4.6%)	Hodgkin lymphoma 5(3.8%)	Bone-soft tissue 4(3.04%)
Gender n=130 (%)						
M 60(44)	5	6	4	5	5	3
F 70(56)	2	1	3	1	0	1
Average age: 52.29	55.14	69.05	63.85	66.83	51.4	56.7
M: 54.00	56.6	64.9	65.25	65.2	51.4	50.6
F: 51.39	51.5	94	62	75	-	75

Table 2. The Distribution of Patients with Second Primary Cancers According to Gender and Age

	Lung 25 (19.2%)	Breast 20 (15.2%)	Colorectal 16 (12.3%) Colon:8(6.15%)/ Rectum:8(6.15%)	Bone-soft tissue 11 (8.4%)	Endometrium 8 (6.1%)	Skin 6 (4.6%)	Head-neck 5 (3.8%)	Non-hodgkina lymphom 5 (3.8%)	Ovary 5(3.8%)	Thyroid 5(3.8%)
Gender										
M: 60(44)	16	0	3/5	8	0	1	5	2	0	2
F: 70(56)	9	20	5/3	3	8	5	0	3	5	3
Average										
age:57.19	59.24	58.35	59.43	42.9	56.12	64.0	59.0	66.8	53.0	47.4
M: 55.6	62.6	0	63.75	41.5	-	54	59.0	58.0	0	50.5
F: 56.06	51.5	58.35	55.12	46.6	56.12	66	0	72.6	53.0	45.3

leukemia (myeloid type). This case had primary breast cancer and received antracyclin containing regimen.

For synchronous and metachronous first primary cancers, 61% (n=80) of patients received postsurgery adjuvan chemo-radiotherapy, 22% (n=28) were undergone surgery alone and 17% (n=22) received only chemotherapy or radiotherapy. Among second primary cancers, 18% of patients were undergone surgery and 47% received post surgery chemo-radiotherapy, remain 35% received only chemo-radiotherapy. Patients with first primary breast cancer (n=36), 21 (58%) received adjuvant hormonotherapy (80% tamoxifen and 20% aromatase inhibitors).

During follow-up 14 patients had died (n=6 died from progressive disease, n=non-cancer causes). 22 patients were lost of follow-up, 94 patients are still alive and come to polyclinic controls periodically.

Discussion

In this study if we look at the features of 130 patients that we analyzed, female gender was priority and the most common cancer was breast cancer to be found. Diagnosis of primary tumor was found to be existed earlier in women than in men (mean age 51 vs 54). In our patients most of the tumors were diagnosed at advanced stage (stage 3-4) and at 5-6.decades and were more often metachronous than synchronous. The most frequent first tumor in the subgroup of patients diagnosed before the age of 40 was breast cancer in women and Hodgkin lymphoma in men.

Women with previous breast cancer had an elevated risk of developing a second primary gynecologic cancer compared with the general population. Other authors published similar results (Gülhan et al., 2009). In our study we also found gynecologic cancers the most common cancers among women suffered from breast cancer.

With regard to tumor stage and treatment, there was no difference between first and second malignancies. However, primary and secondary tumors tended to be in an advanced stage and the treatment, depending on the location, involved surgery, radiotherapy and chemotherapy. From our patients, 61% had received radiotherapy or radio/chemotherapy for their first cancer suggesting that this treatment could play an important role in the development of MPM. The advanced stage of secondary malignancies is unusual as compared to other studies. It should be explained either by the low compliance of patients to follow-up or by their tendency to neglect symptoms. The results underscored the importance of a good communication between patients and doctors whereby the doctors should give warnings regarding the risk of developing secondary malignancies after the primary treatment and also about the occurrence of any new symptoms. Due to the poor compliance of our patients to follow-up, a survival analysis was not feasible.

According to the literature, the prognosis of patients with MPM could be determined independently in function of the stage of each cancer. The treatment of choice, depending on the tumor location, involved curative surgical resection of each cancer, radiotherapy and chemotherapy (Passman et al., 1996; Thamura and Van Dalen, 2003) .

Although the mechanisms responsible for the appearance of multiple primary cancers have not been fully explained, among the most frequent factors involved are the genetic susceptibility, the immune system of patients, and the intensive exposure to carcinogens including chemo- and/or radiotherapy used in the treatment of tumors. A secondary malignancy could be defined as a new cancer that occurs as a result of previous treatment with radiation or chemotherapy. Depending on the schedule of treatment, the most common secondary cancers are skin cancer, breast cancer, acute leukemia, colorectal, lung and stomach cancer, the risk of developing any second cancer being 10% at 20 years respectively 26% at 30 years after the treatment of Hodgkin disease, and 3.8 % at 10 years versus 7% at 15 years for patients receiving a doxorubicin-based regimen for breast cancer (Bhatia and Woodward, 2003). The role of hormone therapies must be considered at developing secondary malignancies. We know that using tamoxifen long-time in adjuvant treatment of breast cancer, the risk of developing endometrium cancer is increased. In our study half of(n=8, 50%) 16 patients (total 21 hormone-treated patients) that received tamoxifen were found to be developed endometrium cancer at follow-up.

With regard to tumor stage and treatment, there was no difference between first and second malignancies. However, primary and secondary tumors tended to be in an advanced stage and the treatment, depending on the location, involved surgery, radiotherapy and chemotherapy. From our patients, 45% had received radiotherapy or radio/chemotherapy for their first cancer suggesting that this treatment could play an important role in the development of MPM. The advanced stage of secondary malignancies is unusual as compared to other studies. It should be explained either by the low

compliance of patients to follow-up or by their tendency to neglect symptoms. The results underscored the importance of a good communication between patients and doctors whereby the doctors should give warnings regarding the risk of developing secondary malignancies after the primary treatment and also about the occurrence of any new symptoms.

Genetic susceptibility and the carcinogenic effect of radio/chemotherapy have been largely proposed for the development of secondary malignancies. First, it is known that people with a family history of cancer will inherit genetic cancer susceptibility as a risk factor and moreover, patients treated and survivors of earlier cancers with genetic susceptibility have an increased risk of MPM. In addition, the treatment used for the first malignancy has resulted in some damage of specific regions of DNA with chromosome rearrangement or loss responsible for tumorigenesis (Escobar et al., 2007). Microsatellite instability (MSI) was noticed to occur more frequently in cases of MPM than in sporadic cancers (Horii et al., 1994).

The possibility that MPMs exist must always be considered during pretreatment evaluation. Screening procedures are especially useful for the early detection of associated tumors, preferably before clinical manifestations occur. As observed in our series most patients have been diagnosed in advanced stages. There is some evidence that screening will improve outcomes among patients who may develop second malignancies, although the data are limited. The optimal screening modalities and strategies to reduce mortality from second malignancies remain to be defined for most tumor sites (Vogel, 2006).

In review of the literature regarding MPM, several common points may be concluded (Hu et al., 2009; Angurana et al., 2010). First, the Japanese population appears to have a higher likelihood of developing MPM. Yamamoto et al reported that 15-20% of Japanese patients with colorectal carcinoma developed MPM (Yamamoto et al., 2006). This may be caused by genetic susceptibility, longer average life span or medical advances in chemotherapy and radiotherapy. Second, most patients with MPM are geriatric. Third, smoking-related cancers, prostate cancers and renal cell carcinoma are most commonly associated with MPM (Engeland et al., 1997). Fourth, head and neck cancer survivors are at an increased risk of developing another cancer of the respiratory or digestive tract (Mussari et al., 2000). A 'field cancerization effect' was assumed to explain this phenomenon, with carcinogens to which the organ has been exposed initiating the proliferation of numerous clones of cells (Slaughter et al., 1953). Carcinogenic insults, such as tobacco and alcohol, may increase the likelihood of multiple independent malignant foci developing in the mucosa epithelium. The frequency of MPM depends on the length of the observation period, applied diagnostic and prognostic criteria, exposure to environmental factors, genetically defined individual susceptibility, diagnostic accuracy, follow-up and administered treatment.

The early diagnosis of secondary malignancies should not be neglected in patients treated for a primary malignancy, especially when the long clinical period before the diagnosis of subsequent tumors is taken into consideration. With careful monitoring, secondary tumors can be detected earlier, and, with appropriate intervention, might be better managed, without compromising survival.

Our data should guide oncologists towards a closer follow-up strategy in the management of patients treatedfor common tumors. In our analysis, most multiple primary malignant neoplasms are diagnosed in advanced stages, more often metachronous than synchronous. This result could be explained by the low compliance to follow-up and underscores the importance of communication between patients and medical care team. Each patient must be informed about the risk of developing secondary malignancies after the first treatment and about the importance of reporting any new symptom which might occur. Careful monitoring ensures an early detection for secondary tumors, and, subsequently, an appropriate management.

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