ARAŞTIRMA RESEARCH ARTICLE

MULTIPLE PRIMARY MALIGNANT NEOPLASMS FROM EASTERN BLACK SEA REGION OF TURKEY: SINGLE CENTER EXPERIENCE

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ABSTRACT

Objective: *The incidence of multiple primary malignant neoplasms (MPMN) has been increasing worldwide. MPMN emerging after radiation therapy (RT) change in between the RT-centers and regions. In this study, we aimed to analyze the data on MPMN in a group of patients given RT in our center.*

Material and Method: *We analyzed all patients treated with RT in Karadeniz-Technical-University, Farabi-Hospital, Radiation-Oncology-Center between 1996-2012, retrospectively. MPMN diagnosis was made when each tumor presented a definite picture of malignancy. Demographical features, diagnoses of primary malignancies (PM) and secondary malignancies (SM), time to SM, stages of PM and SM, treatment type, presence of metastasis, and survival status were noted. Factors were analyzed for their relation to the survival.*

Results: *Among a total of 9440 patients, 102 (1.1%) were noted to develop MPMN with male: female ratio-of 4.2. Mean ages at-diagnoses of PM and SM were 58.8±13.9 years, and 64.1±12.8 years, respectively. Time to SM was 83.3±65.8 months. Larynx and lung were the two most frequent sites for primary and secondary tumors, respectively. There were considerable associations of "primary larynx/head&neck cancers with subsequent lung and urogenital cancers" and "primary urogenital cancers with subsequent urogenital and lung cancers".*

Conclusion: *We conclude that patients ≥50 years of age, male patients and larynx cancer survivors need close surveillance for MPMN as lung cancer being the most common subsequent SM. Further analyses by individual centers are needed to construct an effective-surveillance for SM.*

Keywords: *Multiple primary malignant neoplasms, prevalence, radiotherapy, secondary, survival.* ***Nobel Med 2016; 12(2): 13-19***

TÜRKİYE DOĞU KARADENİZ BÖLGESİ'NDE MULTİPL PRİMER MALİGN NEOPLAZİLER: TEK MERKEZ DENEYİMİ

ÖZET

Amaç: Multipl primer malign neoplazi (MPMN) görülme sıklığı dünya genelinde artmaktadır. Radyoterapi (RT) sonrası gelişen MPMN'lerin özellikleri, RT merkezleri ve bölgeler arasında farklı olabilir. Bu çalışmada merkezimizde RT verilen hastalarda MPMN özelliklerini ve sağkalım üzerine etkili faktörleri incelemeyi amaçladık.

Materyal ve Metot: Karadeniz Teknik Üniversitesi, Farabi Hastanesi'nde 1996-2012 yılları arasında RT verilen hastalar retrospektif olarak incelendi. MPMN tanısı için tümörlerin bağımsız olması şartı arandı. Demografik özellikler, primer-malingnite (PM) ve sekonder-malignite (SM) tipi, SM tanısına kadar geçen süre, PM ve SM evreleri, metastaz varlığı ve sağkalım özellikleri incelendi. Sağkalım üzerine etkili faktörler analiz edildi.

Bulgular: 9.440 olgunun 102 (%1,1)'sinde MPMN gelişmişti. Erkek:kadın oranı 4,2 idi. PM ve SM ortalama tanı yaşı sırasıyla 58,8±13,9 ve 64,1±12,8; SM tanısına kadar geçen süre 83,3±65,8 ay idi. En sık PM ve SM bölgeleri sırasıyla larinks ve akciğerdi. Primer larinks/baş-boyun kanserlerinin takipte akciğer ve ürogenital sistem kanserleri gelişimi ile, primer ürogenital kanserlerin ise ürogenital ve akciğer kanserleri gelişimi ile anlamlı ilişkisi vardı.

Sonuç: MPMN gelişimi için ≥50 yaş, erkek cinsiyet ve primer larinks kanseri varlığı risklidir. Bu olgular öncelikle akciğer kanseri olmak üzere SM gelişimi için yakın takip altında tutulmalıdır. Farklı RT merkezlerinin bildireceği MPMN verileri, SM'lerin uygun takibi için gereklidir.

Anahtar kelimeler: Multiple primer malign neoplazi, prevelans, radyoterapi, sekonder, sürvi. **Nobel Med 2016; 12(2): 13-19**

INTRODUCTION

After therapeutic interventions, cancer survivors are at risk of developing a new neoplasm and may even die as a result of a subsequent tumor.[1] This clinical situation is described as multiple primary malignant neoplasm (MPMN). The prevalence of MPMN reported varies from 0.7-11.7%.[2] Currently, the improvements in some cancer therapies and the rapidly aging population have led to an increased incidence of MPMN.[3]

There are many possible reasons for the development of another distinct neoplasm, including the effects of using therapeutic interventions as chemotherapy and radiotherapy. Others include environmental exposures, lifestyle choices, tobacco use, genetics, the theory of a common clonal origin, and the 'screening effect'.[4,5] Regarding the treatment effect, treatment schedules differ in between the individual RT centers due to i.e. differences in the population characteristics, experience of the clinicians and tumor types. Hence, the MPMN emerging after RT may change in between the RT centers and regions. It is important to recognize racial differences in the susceptibility to second cancers.[1] In Denmark, for example, no general susceptibility to second cancers after initial cancer surgery was found.[6] Therefore, center based analysis would help for making long term planning. Improved understanding of the epidemiology and charactheristics of MPMN should help in early diagnosis and improved survival in patients developing subsequent tumors. In this study, we aimed to analyze the data on MPMN in a group of patients given RT for an individual malignancy in our center.

MATERIAL AND METHOD

We analyzed all the patients treated with RT by Karadeniz Technical University, Farabi Hospital, Radiation Oncology Center between 1996-2012-in a 16-year period-, retrospectively. As this is a retrospective study of the already documented findings, ethical approval and informed consent were not applied. This center is the largest RT center in Eastern-Blacksea Area of Turkey serving to the population of approximately 1,000,000. We yearly evaluate 650 patients of whom 99% are scheduled for RT.

Diagnosis of MPMN was made when each of the tumors presents a definite picture of malignancy: Each was distinct and the probability of one being a metastasis of the other was excluded.[7] Both synchronous and metachronous tumors were included in this survey as MPMN but the presences of synchronous tumor and tertiary tumor were specified. Patients with basal cell cancer were excluded from the study. Synchronous tumors were defined as two or more primary tumors that are diagnosed within 6 months of the first primary tumor. Metachronous cancers were defined as those that are detected after an interval of more than 6 months.

Demographical features, the diagnoses of primary and secondary malignancies, time to the diagnosis of secondary malignancies (SM), the stages of primary malignancies (PM) and SM, treatment type (RT versus RT+CT, palliative versus curative), presence of metastasis, and survival status were noted. The factors were analyzed for possible relation to the survival. As this was a retrospective study and noninterventional, no institutional ethics committee approval or patient consent was required.

The statistical analysis was carried out with Statistical Package for Social Sciences for Windows ver. 16.0 (SPSS Inc, Chicago, Ill, USA). Numerical variables were given as mean ± standard deviation. Two groups were compared with paired Student's t-test or Mann Whitney U tests when necessary. Chi-square test with Yates correction and Fisher's exact test were used for 2X2 contingency tables when appropriate for non-numerical data. Cox-Regression survival analysis was used for survival analyses.

RESULTS

Among a total of 9440 patients applied RT between 1996-2012 years, 359 were <18 years of age. None of the patients<18 years of age developed MPMN while among the 9081 adult patients, 102 were noted to develop MPMN with the overall rate of 1.1%. The data of 4 SM patients were unavailable so that 98 SM patients constituted our further study population. 75.5% were ≥50 years of age. Among them, 4 patients had developed three distinct tumors and all remaining patients had two tumors. There were 79 males (80.6%) and 19 females (19.4%) with the male: female ratio of 4.2. Mean ages at diagnoses of the first and second tumors were 58.8±13.9 years and 64.1±12.8 years, respectively. Time to diagnosis of second tumor was 83.3±65.8 months. Comparisons of the first and second malignancies according to the involved systems are given in Table 1. The distributions of SM according to PM groups are given in Table 2. The top 3 sites of SM were lung, bladder and colon.

Twenty-four (24.5%) of the SM were synchronous (19 males, 5 females) and 74 (73.%%) were metachronous (60 males, 14 females). Regarding treatment schedules, 36 patients (36.7%) were given palliative and 57 (58.2%) were given curative treatment. Twenty-three cases (23.5%) had also been given CT in addition to RT. The data of 5 patients were missing. Familial

malignancy history was present in 17 patients (17.3%). There were recurrences in 7 cases (7.1%). Among 84 cases with available data for smoking and alcohol use, 38 were active smoker and 8 were regular alcohol user. There were 24 cases (24.5%) of metastasis in SM cases. The stages of PM and SM are given in Figure. The PM stages were early while SM stages were advanced.

The characteristics of three distinct tumor developer patients were as follows: The first patient was male and had developed skin langerhans cell histiocytosis, lung cancer and NHL at 50, 52 and 54 years of ages. The second patient was also male and had developed bladder cancer, larynx and lung cancer at 61, 68 and 76 years of ages, respectively. The 3rd patient was a male and had developed soft tissue tumor, larynx and, head and neck cancer at 54, 62 and 63 years of age. The 4th patient was the only female TM (tertiary malignancy) patient and and had developed three synchronous tumors as breast cancer, uterus leimyosarcoma and appendix carcinoma at 33 years of age.

When classified according to gender, the most frequent sites for primary tumors in males were the larynx (n=16, 20.2%), followed by the bladder (n=14, 17.7%), prostate (n=12, 15.2%), and colon (n=11, 13.9%) while the most frequent sites for primary tumors in females were the corpus uteri (n=5, 26.3%), breast and skin (each were n=3 and 15.8%), and the colon (n=2, 10.5%). The leading tumor sites for secondary tumors in males were lung (n= 29, 36.7%) and bladder (n=11, 13.9%). In females, the leading sites for secondary tumors were the corpus uteri (n=4, 21.1%), lung (n=3, 15.8%), followed by the breast and head and neck cancer (each were n=2, 10.5%).

The mean ± SD age at first tumor diagnosis was 60.2±13.5 years and 52.9±14.6 years in males and females, respectively (p=0.08). Sixty-seven adult patients (68.4%) were >50 years old. 55% of the male patients and 72.2% of the female patients were treated curatively (p=0.19). 23.5% of the patients had received CT (21.3% of males and 33.3% of females) (p=0.35). Thirty-eigth (38.8%) of the patients were active smokers, with the proportion of male smokers being significantly higher than females (52.2% versus 17.6%; p=0.008). The mean±SD duration between diagnosis of metachronous tumors were 4.7±5.8 years and 7±8.1 years (p=0.07) and the mean ± SD duration between diagnosis of PM and exitus were 72.8±116.4 months and 79.8±97.9 months in males and females, respectively (p=0.93).

In the study population, 12 cases (12.1%) were alive while all other were dead. Mean time to exitus after SM diagnosis was 21.3±24.0 (median: 13 months, min-max: 1-106) months.

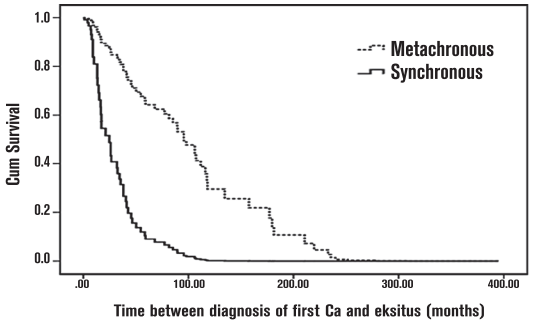

Figure. The cox regression survival graphics of the patients (synchronous vs metachronous MPMN)
MPMN: Multiple primary malignant neoplasms.

Table 1. The comparison of primary and secondary malignancies according to anatomical site (n=98).

Anatomical Site	PM n (%)	SM n (%)
Larynx	17 (17.3%)	5 (5.1%)
Bladder	14 (14.3%)	11 (11.2%)
Colon	13 (13.3%)	8 (8.2%)
Prostate	13 (13.3%)	4 (4.1%)
Skin	10 (10.2%)	1 (1%)
Corpus uteri	6 (6.1%)	5 (5.1%)
Breast	5 (5.1%)	4 (4.1%)
Lung	4 (4.1%)	32 (32.7%)
Lymphoma	3 (3.1%)	4 (4.1%)
Head and neck (other than larynx)	3 (3.1%)	4 (4.1%)
Cervix uteri	2 (2%)	2 (2%)
Soft tissue	2 (2%)	1 (1%)
Kidney	2 (2%)	3 (3.1%)
Brain	2 (2.0%)	5 (5.1%)
Thyroid	1 (1%)	2 (2%)
Seminoma	1 (1%)	None

PM: Primary malignancy, **SM:** secondary malignancy

In the total study population, mean survival was 92.9+89.1 (median: 56.4; min-max: 1-394.5) months. The PMs with the highest mean survival time were brain (201.4+62.3) (95% confidence interval: -358-761), breast (192+137.6) (95% confidence interval: 21-362), lymphoma (174.2+116.7) (95% confidence interval: -115-464). The longest survival was observed in a female patient with primary breast and secondary corpus uteri cancer with 394.5 months of survival. She had died 102 months after the corpus uteri cancer. 90% (n=72) of the male patients and 77.8% (n=14) of the female patients died in the follow-up (p>0.05). Among dead patients, the longest survival was observed in a patient with primary prostate and secondary bladder cancer with 106 months of survival. We performed survival analysis including age at PM, gender, sites of PM and SM, stages of PM and SM, presence of metastasis, charactheristics of SM (synchronous vs metachronous),

Table 2. The distribution of SM according to PM groups.

PM Group	SM Group	n (%)
Urogenital (n=29)	Urogenital	11 (37.9%)
	Lung	8 (27.6%)
	Larynx/Head and Neck	3 (10.3%)
	Gastrointestinal	2 (6.9%)
	Colorectal ca	2 (6.9%)
	Lymphoma	1 (3.4%)
	Soft Tissue	1 (3.4%)
	Cranial	1 (3.4%)
	Total	**29 (100%)**
Larynx/Head&Neck (n=20)	Lung	13 (65%)
	Urogenital	3 (15%)
	Thyroid	1 (5%)
	Cranial	1 (5%)
	Breast	1 (5%)
	Lymphoma	1 (5%)
	Total	**20 (100%)**
Colorectal (n=14)	Lung	5 (35.7%)
	Gynecological	2 (14.3%)
	Urogenital	2 (14.3%)
	Colorectal	2 (14.3%)
	Gastrointestinal	1 (7.1%)
	Thyroid	1 (7.1%)
	Cranial	1 (7.1%)
	Total	**14 (100%)**
Skin (n=10)	Lung	3 (30%)
	Larynx/Head and Neck	2 (20%)
	Lymphoma	2 (20%)
	Rectum	1 (10%)
	Urogenital	1 (10%)
	Gynecological	1 (10%)
	Total	**10 (100%)**
Gynecological (n=8)	Gynecological	3 (37.5%)
	Breast	2 (25%)
	Lung	1 (12.5%)
	Rectum	1 (12.5%)
	Cranial	1 (12.5%)
	Total	**8 (100%)**
Breast (n=5)	Gynecological	3 (60%)
	Lung	1 (20%)
	Gastrointestinal	1 (20%)
	Total	**5 (100%)**
Lung (n=4)	Colorectal	2 (50%)
	Larynx/Head and Neck	1 (25%)
	Urogenital	1 (25%)
	Total	**4 (100%)**
Lymphoma (n=3)	Gynecological	1 (33.3%)
	Cranial	1 (33.3%)
	Skin	1 (33.3%)
	Total	**3 (100%)**
Cranial (n=2)	Larynx/Head and Neck	2 (100%)
	Total	**2 (100%)**
Sarcoma (n=2)	Lung	1 (50%)
	Larynx/Head and Neck	1 (50%)
	Total	**2 (100%)**
Thyroid (n=1)	Breast	1 (100%)

PM: Primary malignancy, **SM:** secondary malignancy

and smoking status as possible factors affecting the survival. The factors related to higher mortality were the higher age at PM (p=0.001, B=0.06), higher stage of PM (p<0.001, B=3.9) and SM (p=0.02, B=2.7), PM from gynecological group (p=0.01, B=3.48), and presence of synchronous tumor (p<0.001, B=2.22) (Figure). On the contrary, SM from urogenital group was associated with lesser mortality (p=0.02, B=-2.06).

DISCUSSION

The overall rate of MPMN was 1.1% within 16 years' time period. The prevalence of MPMN reported varies from 0.7%-11.7%.[2] This wide variation in prevalence of MPMN may be caused by several factors. Different authors may use different criteria to define a case of multiple primaries.[8] The series also differ in age distribution which may have an effect in the MPMN prevalence.[2] Also, obviously, the clinical case series tend to have a lower frequency than autopsy cases series. The highest rates come from the autopsy series as 11.7% from Sweden and 7.5% from Japan.[9,10] On the other hand, the country and the clinic where the study reported from could affect the rate as well. Three studies were reported so far from Turkey.[11-13] All were clinical studies and reported MPMN rates as 0.8%, 1% and 1.2%. Among them, the most recent one was the only one reported from a university RT center.[13] It was from Western Blacksea region and reported paediatric MPMN rate of 0.3% (1 patient among 361 registered pediatric patients) and an adult rate of 1.2%. The adult prevalence found in this study was 1.1% with no pediatric MPMN case which is very comparable with the previous studies reported from different regions of the country.

In our study, there were 80.6% males and 19.4% females with the male: female ratio of 4.2. The male: female ratio reported in the literature ranges from 0.9 to 3.5 but generally reports a male predominance for MPMN.[13] Regarding studies from Turkey, in the

earliest study, the estimated M:F ratio was 1.8 while it was 0.95 in the second study.[11,12] Gursel *et al.* reported male: female ratio of 1.7.[13] Accordingly, the MPMN was much more prevalent among males in our study even when compared to the national data. A reason may be the higher prevalence of smoking- a very well known carcinogen agent, among males (52.2% versus 17.6% in males and females, respectively; p=0.008). There is overall a higher prevalence of smoking in favor of males in Blacksea region of Turkey than the mean national data.[14,15] In this study, the proportion of male smokers was significantly higher than females and Gursel *et al.* also reported high male predominance for smoking. On the other hand, especially Eastern Blacksea region is prominent with its tobacco production. We suggest that the co-effect of smoking and tobacco farming may be one another reason for such high male predominance in this study.

The most frequent sites for primary tumors in males were the larynx, followed by the bladder, prostate, and colon while the most frequent sites for primary tumors in females were the uterus, breast, skin, and the colon. Larynx and bladder cancers are well-associated with smoking while colorectal cancers are also reported to some extend.[16] Thus these results are also in accordance with more prevalent smoking history in the male population. In our study, there were few female MPMN cases. Therefore, it is difficult to draw conclusions on female MPMN. However, among them corpus uteri and breast cancer were more prevalent. This is in accordance with the leading tumor types in the female population. However, the higher incidence of corpus uteri cancer than the breast is somewhat unusual as the breast cancer is the most frequent cancer in the female population. Our center was the unique and only RT center with brachytherapy modality for cervix cancers treating the patients referred from many other regions. We believe that relative lower prevalence of breast cancer conpared to uterus cancer depend on this referral. The leading tumor sites for secondary tumors in males were the lung, followed by the bladder. In females, the leading sites for secondary tumors were the corpus uteri, lung, followed by the breast and head and neck cancer. The association of larynx cancer with subsequent lung cancer is common. The association of gynecological tumors and breast cancer within themselves and in between is also a consistent finding with the literature data.

As noted above, blacksea region is prominent with its tobacco production. The female population actively participates in the tobacco agriculture. The relatively higher prevalences of lung, head and neck as SM in this population may be related to their significant role in the tobacco farming. These data are important because the prevalent sites of second cancers in relation to the site of the index cancer are clinically important in order to facilitate effective follow-up of cancer patients.

In the total study population, larynx and lung were the two most frequent sites for primary and secondary tumors, respectively (Table 1). There were considerable associations of primary larynx/head and neck cancers with subsequent lung and urogenital cancers and primary urogenital cancers with subsequent urogenital and lung cancers (Table 2). Regarding the colorectal cancers which were the 3rd common PM group, subsequent lung cancer was most prevalent with lesser incidences of subsequent gynecological, urogenital and colorectal cancers. Again, the country of the study makes difference in terms of the common tumor site. Different studies from Japan reported the the close combination of gastric cancer and colorectal cancer as the most common sites of multiple primary cancers.[1,17,18] In Western studies, however, different combinations of common sites of multiple cancers are reported.[19] As an example, in the United Kingdom, the small intestine and the female reproductive organs were the most prevalent sites of second cancers after colorectal cancers.[19] Larynx was the most common PM also in the other two Turkish studies.[11,13] Engin reported the second most common cancer as lung cancer while Gursel *et al.* reported bladder, breats and head and neck (other than larynx) as the other frequent PMs.[11,13] In the present study, larynx was followed by also the bladder while head and neck (other than larynx) was not so prevalent among PMs. Instead, there were considerable prevalences of colon and prostate cancers as PM (Table 1). On the other hand, the third Turkish study reported breast cancer and lung cancer as most prevalent.[12] These findings draw attention to differences, not only in between the countries but also in between the regions and centers within also the same country.

The associations of larynx / head and neck cancers with subsequent lung cancer were the constant finding in all Turkish MPMN studies including the present one.[11-13] There were higher incidences of subsequent larynx, lung, and urogenital cancers within each other (Table 2). This is not surprising given the fact that continuous epithelial exposure to alcohol and tobacco increases the risk for the development of malignant cytological changes and independent MPMN.[20,21] Tobacco consumption and/or the so-called "site carcinogenesis" may explain the excess of subsequent larynx, lung, head and neck and urogenital cancers within eachother.[20,22,23] Another possible explanation is that several studies have found that secondary squamous cancers of the head and neck are clonally derived from the primary tumors.[24,25]

It may be possible that MPMNs are derived from similar embryological tissues.[13] In some instances tumors with different aetiologies may simply appear significantly associated because they share similar social class correlates.[26] The associations between cancers may be due to the action of common risk factor exposure, but also to the increased surveillance following a cancer diagnosis.[26]

12.1% were alive while all other were dead. Mean time to exitus after SM diagnosis was 21.3 months. The longest survival was observed in a patient with primary prostate and secondary bladder cancer who had 106 months of survival. There are only a few reports about the survival of patients with MPMNand our study adds an important contribution in this aspect.[13,27] First, mean age at diagnoses of PM was 58.8 years. The MPMN patients were relatively old patients with >75% patients ≥50 years which is a finding in accordance with the previous reports.[2,9,28,29] The higher age at PM diagnosis was also related to higher mortality. This finding draws attention to significance of MPMN in the older age. We found the presence of synchronous tumor and women with gynecological PM have a lower survival from MPMN while SM from urogenital group was associated with lesser mortality. Similarly, Ehrich *et al.* suggested that bladder cancer patients with multiple malignancies have relatively positive outcomes.[30] Not surprisingly, the higher stages of PM and SM were also related to survival. Our findings point the caution that should be directed to aforementioned subgroup of MPMN patients.

In conclusion, our study suggests that about 1% of our patients would develop subsequent SM. Patients ≥50 years of age, male patients, and larynx cancer survivors especially need close surveillance for SM, lung cancer being the most common (~1/3). As the cancer therapies and survival are improving, higher rates of MPMN are expected in the next decades. Further analyses by individual centers are needed to construct an effective surveillance for second cancers.

*The authors declare that there are no conflicts of interest.

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