Second Primary Tumors in Patients with Head and Neck Cancer: A Retrospective Study from a Single Center

Baş Boyun Kanserli Hastalarda İkinci Primer Kanser Gelişimi: Tek Merkezli Retrospektif Çalışma

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ABSTRACT Objective: Patients with squamous cell carcinoma of the head and neck are at risk for developing a second primary cancer. The aim of this study was to determine incidence and localization of second primary tumors. **Material and Methods:** Three hundred twenty-four patients with head and neck cancer diagnosed between 2000 - 2010 were analyzed for the presence of a second malignancy. The data used in this study were obtained retrospectively from a database. **Results:** A total of 324 patients were enrolled in this study, there were 248 males and 76 females ranging between the ages of 18 and 84 years, with a median age of 53 years. Ten patients (3.08%) had metachronous, three patients (0.93%) had synchronous cancers. In our study, 7.12% of the older population (>60 years) had second primary tumors, and 2.46% of the younger population (≤ 60 years) had second primary cancers. There were no statistical differences between two groups (p=0,07). Overall survival of patients with metachronous second primary cancers at 1 and 3 years were 87.5% and 62.5% respectively while these rates were 95.2% and 88.3% respectively in the ones without second primary cancers. **Conclusion:** In our study, 4% of patients had second primary tumors. Screening programs were considered beneficial in high risk patients with head and neck cancers who smoke and use alcohol in order to detect second primary cancers.

Key Words: Carcinoma, squamous cell of head and neck; neoplasms, second primary

ÖZET Amaç: Baş boyun skuamöz hücreli kanser hastaları, ikinci primer gelişimi açısından risklidir. Bu çalışmanın amacı, baş boyun kanserli hastalarda ikinci primer kanser insidansı ve lokalizasyonu araştırmaktır. **Gereç ve Yöntemler:** Çalışmaya 2000 ile 2010 yılları arasında, Gazi Üniversitesi Hastanesi'nde baş boyun kanseri tanısı alan 324 hasta dahil edildi. Çalışmada retrospektif veri tabanı oluşturularak analiz yapıldı. **Bulgular:** Hastaların 248'i erkek, 76'sı kadındı. Ortanca yaş 53 yıl (18-84 yıl) olarak saptandı. Hastaların 10'unda (%3,08) metakron, 3'ünde (%0,83) senkron ikinci primer vardı. Yaşlı hastaların (> 60 yaş) %7,12'sinde, 60 yaş ve daha genç hastaların %2,46'sında ikinci primer kanser geliştiği gözlendi. Bu iki grup arasında istatistiksel fark yoktu (p=0,07). Ortanca sağkalım ikinci primer gelişen grupta 1 yıllık %87,5, 3 yıllık %62,5 iken, gelişmeyen grupta %95,2 ve %88,3 olarak bulundu. **Sonuç:** Bu çalışmada %4 oranında ikinci primer kanser gözlendi. Sigara ve alkol kullanan yüksek riskli baş boyun kanserli hastalarda, görüntüleme takibi ile ikinci primer saptanması faydalı olabilir.

Anahtar Kelimeler: Baş ve boyun skuamöz hücre karsinomu; tümörler, ikinci primer

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The development of a second malignant neoplasm was about 10-40% in patients with head and neck squamous cell carcinoma (HNSCC). Metachronous second cancers most frequently involve the esophagus and lung, whereas synchronous second cancers are more common in head

and neck as occult lesions.[1] Alcohol and tobacco use are the most common risk factors for HNSCC. These agents are also directly responsible for the second cancers of the upper aerodigestive tract and lung.[2,3] The aim of this study was to determine incidence of second primary tumors (SPC) and their localization in patients with HNSCC.

MATERIAL AND METHODS

STUDY POPULATION

Three hundred twenty-four patients with HNSCC diagnosed between 2000-2010 were analyzed for the presence of a second malignancy. The data used in this study were obtained retrospectively from a database. The sites of the primary head and neck tumors were the larynx in 41.97% (n=136), nasopharynx in 27.47% (n=89), oral cavity and lip in %16.97 (n= 55), hypopharynx in 4.32% (n=14), oropharynx in 1.85% (n=6), salivary glands in 4.63% (n=15), other sites in 2.78% (n=9) of the patients (Figure 1). Of 324 patients, 135 (41.67%) were smokers and 45 (13.89%) were nonsmokers. No smoking information was available for 146 patients.

STATISTICAL ANALYSIS

The statistical analyses were performed using SPSS version 21 program (SPSS Inc., Chicago, IL). Descriptive statistics were calculated for baseline demographic and clinicopathological characteristics. We compared presence of a second primary cancer in patients aged above 60 years and below 60 years of age by using Chi-square test. A p value <0.05 was considered as significant. Survival rates were calculated by using life table analysis.

RESULTS

A total of 324 patients were enrolled in this study, 248 males and 76 females between the ages of 18 to 84 years, with a median age of 53 years. The median follow up time was 28 months (range 4-377 months). Ten patients (3.08%) had metachronous and three patients (0.83%) had synchronous cancers (Table 1). The types of the synchronous cancers were non small cell lung cancer, thyroid papillary cancer, and orbital marginal zone lymphoma. Metachronous cancers were determined with the following primary tumor sites: 1.23% (n=4) in the lung as non small cell lung cancer, 0.31% (n=1) in the lung as small cell lung cancer, 0.31% (n=1) in the head and neck, 0.62% (n=2) in thyroid, 0.31% (n=1) in prostate, 0.31% (n=1) in bladder, 0.31% (n=1) in pancreas, 0.31% (n=1) in colon, 0.31% (n=1) in orbit as orbital marginal zone lymphoma (Figure 2). The median time between the the diagnoses of first and the second pri-

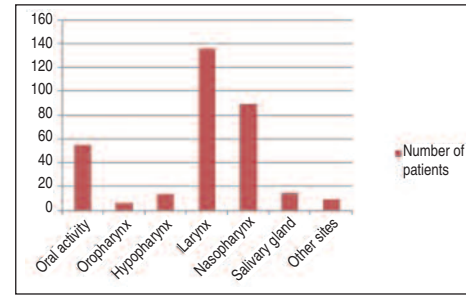

FIGURE 1: The sites of the primary tumors.
(See color figure at Bkz. http://www.turkiyeklinikleri.com/journal/tip-bilimleri-dergisi/1300-0292/)

TABLE 1: Patient demographics and baseline clinical characteristics.

Parameter	Number of patients (%) n=324
Age (min-max)	53 (18-84)
Gender	
Male	248 (76.54%)
Female	76 (23.46%)
Primary site	
Oral cavity	55 (16.97%)
Oropharynx	6 (1.85%)
Hypopharynx	14 (4.32%)
Larynx	136 (41.97%)
Nasopharynx	89 (27.47%)
Salivary gland	15 (4.63%)
Other sites	9 (2.78%)
Second primary	
Synchronous cancer	10 (3.08%)
Metachronous cancer	3 (0.83%)
Tobacco use	
Smoker	135 (41.67%)
Non-smoker	45 (13.89%)
Unknown	144 (44.44%)

Min-max: Minimum-maximum.

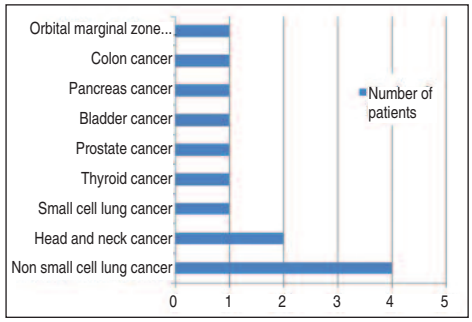

FIGURE 2: The sites of metachonous second primary cancers.
(See color figure at Bkz. http://www.turkiyeklinikleri.com/journal/tip-bilimleri-dergisi/1300-0292/)

mary cancerswas 22 months. Most commonly, SPCs developed in patients with supraglottic tumors (9.80%). In our study, 7.12% of the older population (>60 years) had second primary tumors, and 2.46% of the younger population (≤ 60 years) had SPCs. There were no statistical differences between two groups (p=0.07). Of the patients with SPCs, 69.30% were smokers, and 7.75% were non smokers. Overall survival of patients with metachronous SPC at 1 and 3 years was 87.5% and 62.5% respectively respectively while these rates were 95.2% and 88.3% respectively in the ones without second primary cancers. The difference in median survival between the two groups was not statistically significant. Twenty seven patients (8.3%) died during the follow up: 16 deaths were due to progression of the primary disease, 2 deaths were due to second primary tumor, and 9 deaths were due to causes unrelated with cancer.

DISCUSSION

Head and neck cancer is a heterogeneous disease with differences across the primary tumor sites: such as age, sex, ethnicity, N and M classification, histologic grade, treatment approaches and prognosis. Patients with HNSCC are at risk for developing SPC. The most common sites reported in previous studies after a primary HNSCC were head and neck (35-73%), lung (15-32%), and esophagus (9%) over a 10 year follow up period.[4-7] With improved locoregional control of HNSCC over the last decades due to new surgical techniques and improved in radiotherapy techniques and the use of chemotherapy, second primary tumors have an increasingly negative impact on the survival. Approximately one third of deaths in patients with HNSCC were associated with SPC.[4,6,8]

Most authors assigned the definition of SPC by using Warren and Gates criteria: "(1) Each of the tumors must present a definite picture of malignancy, (2) Each must be distinct, (3) The probability of one being a metastasis of the other must be excluded".[9] Another classification for the type of various lesions was reported by Braakhuis et al: "(1) True SPC, genetically different from the primary tumor, (2) Local recurrence, in which all molecular aberrations are similar, (3) Second field tumor derived from the same genetically altered field as the primary tumor but diverge in a later stage; (4) Metastasis".[10] These classifications are useful, but molecular evaluation is impossible in the majority of centers. Similarly, this classification is also difficult in our center.

In our study, 4% of patients had second primary tumors. These data is not consistent with other studies, that reported higher incidence rates as 10-40%.[1] This could be explained with the short follow up period in our study. The most common second primary malignancy was lung cancer in patients with HNSCC in our study.

Chuang et al. performed a multicenter study on 99,257 patients with HNSCC from 13 cancer registries to assess the risk of SPC.[13] They revealed that lung cancer had a 20-year cumulative risk of 13% with the highest proportion. The proportions of patients who developed a SPC were high after laryngeal cancer. In this study, younger patients had a higher incidence of SPC.[11,12] It was explained with genetic susceptibility and risk factors such as tobacco, alcohol, HPV infection, and treatment modalities. HPV is an important risk factor that may be more important in the younger patients.[13]

Previous studies showed that SPC was observed in tobacco- and alcohol-related cancers. This was explained with the concept of field cancerization. Carcinogenic effects of tobacco and alcohol may effect more than one area in the aerodigestive tract mucosa. All head and neck cancer patients should be advised to avoid these agents.[1]

Morris et al. reported a population-based cohort study on 75,087 patients with head and neck cancer in the Surveillance, Epidemiology, and End Results (SEER) program.[14] Patients with primary hypopharyngeal cancer had the highest risk for development of SPC. The risk of SPC was lowest for the laryngeal cancer. The most common SPC site was head and neck for patients with oral cavity and oropharynx cancer while it was the lung for patients with laryngeal and hypopharyngeal cancer.[14]

A prospective study on 118 patients with HNSCC showed the role of a systematic examination for SPC in high-risk patients treated previously. The authors found undetected SPC in 21 of the 118 patients (18%). They routinely followed up patients with ear nose throat endoscopy (ENT-endo), complete blood counts and a computed tomography (CT) of the head and neck, if there is any suspicion. This study demonstrated that performing ENT-endo was recommended as part of systematic evaluation to detect SPC, with overall detection rate of 2.5%.[15] Petit et al. reported that in 1560 patients with HNSCC the SPC incidence rate was 3.2% when endoscopy was applied twice annually over a period of 10 years.[16]

CT is another method to detect SPC.[16] Wolff et al. showed that CT detected 13 of the 21 histolologically proven diagnosis of SPC with a false-positive rate of 40.7%.[15] In contrast, Swensen et al. reported a 92.4% false positive findings in 1530 individuals aged 50 years or more with a history of smoking at least 20 pack-years who were screened with spiral CT annually.[17] Aberle et al. reported a study on 53,454 patients aged 55-74 years with a smoking history of 30 pack-years, and compared CT with chest radiographs.[18] They showed a significant reduction of 20% in tumor-related mortality due to a lung tumor in CT scanned group.[18]

The first limitation of this study is that, molecular studies were not included. In addition, the possibility of misdiagnosis of a metastasis as second primary tumor. This study also had a short follow up period. Another limitation of this study is its retrospective design, which has the issues of potential selection bias and incomplete data collection. Attempts to address these concerns were made including the use of consecutive patient sampling to reduce patient selection bias. In addition, several efforts were made to obtain complete patient information from medical records, provincial registries and physician offices.

CONCLUSION

In our study, 4% of patients had second primary tumors. The most common second primary malignancy was lung cancer in patients with HNSCC. Screening programs were considered beneficial to detect SPCs in high-risk patients with HNSCC who smoke or use alcohol.

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