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Metachronous second primary malignancy in head and neck cancer patients: is five years of follow-up sufficient?

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Abstract (J Korean Assoc Oral Maxillofac Surg 2018;44:220-224)

Objectives: The aim of this study was to determine the incidence and characteristics of second primary malignancy (SPM) in patients with head and neck squamous cell carcinoma treated at a tertiary care hospital.

Materials and Methods: We retrospectively reviewed the medical records of 221 patients who underwent surgery with or without adjuvant treatment for head and neck cancer from 2000 to 2002. Data of age, sex, risk factors, sites of primary and SPM, TNM stage of primary tumor, incidence of SPM, and survival were collected from medical charts.

Results: Eighteen patients developed SPM during a median follow-up of 67 months, with an overall incidence of 8.14%. In addition, 77.7% of SPMs occurred in the oral cavity, followed by 11% in the lungs. The 5-year overall survival after the diagnosis of SPM in the head or neck was 70%, compared to 30% for SPM in other body regions.

Conclusion: Considering a high incidence of SPM, i.e., 8.14%, in a mean follow-up period of 67 months suggests the need for long-term follow-up. Since treatment of SPM has shown an acceptable survival rate, early detection and curative therapy should be emphasized.

Key words: Second primary malignancy, Survivorship, Survival rate

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I. Introduction

Head and neck cancer patients are declared tumor-free after surgery alone or with adjuvant treatment. Most reputable centers advocate a follow-up plan that emphasizes a monthly visit in the first year, bimonthly in the second year, quarterly in the third year, and every six months in the fifth year of survivorship[1]. After five years of survivor-ship, the patient is considered disease-free. We follow the patients up to five years, and then no follow-ups are recommended unless needed. Recent literature showed that up to 24% of head and neck cancer patients will develop a second primary lesion[2]. The incidence of second primary malignancy (SPM) was mostly found in patients who continued to consume carcinogenic agents and/or smoking[3].

Locoregional control of head and neck cancer has improved in the last couple of decades; however, long-term survival has shown minimal improvement due to distant metastasis and SPM[4,5]. All SPMs have been shown to have a significant impact on survival[6]. In Pakistan, this critical issue has not been addressed in any study to date. We hypothesize based on anecdotal data that incidence of SPM in our population could be higher than in Western populations. Hence, we retrospectively reviewed our patients over a defined period to determine the incidence of SPM and patient outcomes in terms of survival.

II. Materials and Methods

In the present study, the files of 221 newly diagnosed patients with head and neck squamous cell carcinoma (HNSCC) who underwent surgery with or without adjuvant therapy at

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The Aga Khan University Hospital from January 2000 to December 2002 were retrospectively reviewed. Of these, 18 patients developed SPM during the follow-up period and composed our study cohort.

Patients who were inoperable, underwent surgery outside of our hospital, or refused primary surgery were excluded from the study. All patients had a minimum of 10 years of follow-up at the time of data collection. Since this study consisted only of patient chart review, according to institutional policy, exemption was granted by the Ethical Review Committee of The Aga Khan University Hospital (2601-Sur-ERC-13).

SPM was defined using the criteria established by Warren[7] and Hong et al.[8], who stated that the tumors should be histologically malignant and at least 2 cm apart or developed at least 3 years after the original tumor. In addition, any new malignancy of the lung should be considered SPM if it is a single lesion and histologically different, and the possibility of metastatic carcinoma has been excluded, unless the tumor occurred after 3 years, which classifies it a SPM based on the above definition. Tumors were also classified as synchronous or metachronous: a synchronous tumor was defined as occurring within 6 months after the diagnosis of primary tumor, and metachronous malignancy was defined as occurring after 6 months of follow-up.

All patients had a complete medical history taken and head and neck examination performed on every outpatient follow-up. Chest x-rays were performed annually; other complementary examinations were performed based on symptoms and clinical findings.

All patients that fulfilled the inclusion criteria were included in the study. Files were reviewed and Performa were filled. Follow-ups were recorded for all patients, and incidence was determined in terms of frequency/percentage. Survival was calculated using the Kaplan-Meier curve. Data were analyzed using IBM SPSS Statistics (ver. 20; IBM Co., Armonk, NY, USA).

III. Results

The demographic data of patients and primary tumor-related details are shown in Table 1. A total of 18 patients was included in our study. The median age was 53.5±12.0 years. Twelve patients (66.7%) were male and six were female. All patients had some type of addiction such as tobacco or betel nut. Most common site of primary tumor was the oral cavity and was observed in 15 patients (83.3%). We performed pathological staging of the primary tumor using American Joint Committee on Cancer staging system seventh edition[9]; 8 patients (44.4%) had stage IV disease, and stage II disease was observed in 7 individuals (38.9%).

All patients underwent surgery as their primary treatment modality, and eight patients received adjuvant radiotherapy. All patients participated in regular follow-up. Median time to SPM occurrence was 67 months. Sixteen of 18 patients developed SPM in the head and neck, whereas only two patients developed SPM in a non-head and neck site. Of the 16 patients with SPM in the head and neck, 14 were treated surgically, whereas two had treatment with non-surgical modality with curative intent.

The overall incidence of SPM was 8.14%, as shown in Table 2. In patients who developed SPM in the head and neck area, oral cavity was the most common site, observed in 14 patients (77.8%).(Table 3) However, larynx and oral cavity were each also a site of SPM.

Kaplan-Meier curve was used to determine the 5-year and 10-year survival rates (Fig. 1); approximately 70% at 5 years and gradually declined to 38% at 10 years for all head and

Table 1. Characteristics of patients with second primary malignancy

Characteristic	Value
Gender	
Male	12 (66.7)
Female	6 (33.3)
Median age (yr)	53.5±12.0
Addiction	
Tobacco	6 (33.3)
Betel nut	8 (44.4)
More than one	4 (22.2)
Primary tumor site	
Oral cavity	15 (83.3)
Hypopharynx	2 (11.1)
Larynx	1 (5.6)
Primary pathologic T stage	
T1	1 (5.6)
T2	8 (44.4)
T3	2 (11.1)
T4	7 (38.9)
Primary pathologic N stage	
N0	14 (77.8)
N1	2 (11.1)
N2	2 (11.1)
N3	0
Primary pathologic stage	
Stage I	1 (5.6)
Stage II	7 (38.9)
Stage III	2 (11.1)
Stage IV	8 (44.4)

Values are presented as number (%) or mean±standard deviation.
Mohammad Adeel et al: Metachronous second primary malignancy in head and neck cancer patients: is five years of follow-up sufficient? J Korean Assoc Oral Maxillofac Surg 2018

Table 2. Characteristics of second primary tumor

Characteristic	Value
Incidence of SPM (%)	
Overall	8.14
5-year SPM rate	3.6
10-year SPM rate	4.5
Time interval (mo)	67 (0-121)
Site of SPM	
Head and neck	16 (88.9)
Non-head and neck	2 (11.1)
Pathologic stage of SPM (head and neck)	
Stage I	2 (11.1)
Stage II	3 (16.7)
Stage III	7 (38.9)
Stage IV	4 (22.2)
5-year survival rate (%)	
Head and neck	70
Non-head and neck	30

(SPM: second primary malignancy)
Values are presented as %, median (range), or number (%).
Mohammad Adeel et al: Metachronous second primary malignancy in head and neck cancer patients: is five years of follow-up sufficient? J Korean Assoc Oral Maxillofac Surg 2018

Table 3. Second primary malignancy sites

Site	Value
Head and neck	
Oral cavity	14 (77.8)
Oropharynx	1 (5.6)
Hypopharynx	0
Larynx	1 (5.6)
Non-head and neck	
Lung	2 (11.1)
Esophagus	-

Values are presented as number (%).
Mohammad Adeel et al: Metachronous second primary malignancy in head and neck cancer patients: is five years of follow-up sufficient? J Korean Assoc Oral Maxillofac Surg 2018

neck SPMs.

IV. Discussion

Although locoregional control of HNSCC has improved in the last few decades, SPM and distant metastasis are still important aspects that limit survival[10,11]. Vikram et al.[6] reported failure patterns of HNSCC, revealing that SPM and distant metastasis mostly occurred in the first 2 to 3 years of primary treatment, after which the incidence of distant metastasis decreased with time[12]. Conversely, the incidence of SPM remained static over time[13,14]. The data from developing countries have consistently demonstrated a lower frequency of SPMs, which could be attributed to the limited number of studies published; Mehdi et al.[15] reported an incidence of 1.14%, compared to an incidence of 10% to 40% in previous studies[14,16,17]. In the present study, the overall incidence was 8.14%, which was comparable with international data.

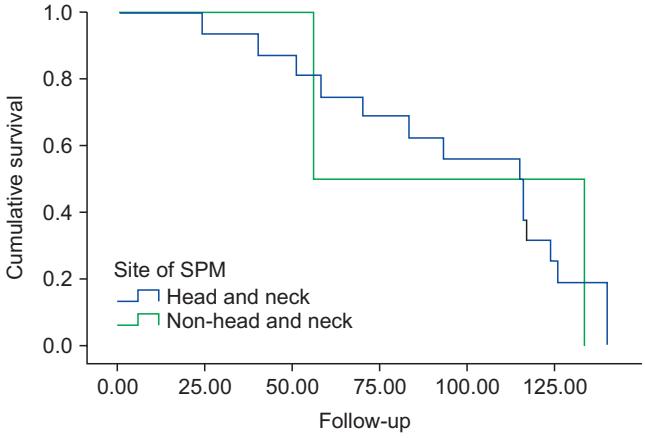

Fig. 1. Survival functions. (SPM: second primary malignancy)
Mohammad Adeel et al: Metachronous second primary malignancy in head and neck cancer patients: is five years of follow-up sufficient? J Korean Assoc Oral Maxillofac Surg 2018

The theory of field cancerization was first introduced by Slaughter and his colleagues in 1953, and refers to continuous exposure of the upper aerodigestive tract to carcinogens that may result in multiple precancerous changes and potentially lead to a malignant change. Patients using alcohol and tobacco have been shown to have the greatest risk for SPMs[11,13]. In Asians, betel quid chewing is also a risk factor for SPM[18]. In the present study, all patients were using tobacco, betel quid, or both. However, none of the patients used alcohol, which could be a limitation due to cultural restraints; the majority of patients may be hesitant to admit consuming alcohol. Because of the retrospective nature of this study, exact details of continued addictions after treatment of the primary malignancy could not be confirmed.

Reportedly, the most common site of SPM is the head and neck, followed by lungs and esophagus[14,19]. Hsu et al.[20] in their study of 18 patients with a SPM showed that 70.2% of SPMs developed in the head and neck, whereas 27.7% occurred in non-head and neck sites. Similarly, in our study, the most frequent location of SPM was head and neck (89%), followed by lungs (11%). The median time interval to develop a SPM in the present study was 67 months, and other studies have reported a median time interval of 48 to 72 months[1,20].

Furthermore, in our study, the 5-year survival in patients with head and neck SPM was 70% and was comparable with other reports[1,21]. Similarly, in a previous study, a 10-year survival of 39% was reported[1], which was nearly in agreement with the results from our study (38%). The decline in

survival observed in long-term follow-up can be attributed to the development of SPM; the median time to develop another tumor was 67 months.

Patients with SPM have a relatively long-term survival, and many patients do well considering it is their second tumor. Therefore, efforts should be made to implement regular follow-ups for early diagnosis[13]. In our study, many patients were diagnosed when they were not monitored because they had completed their 5 years of follow-up. We suggest that treated head and neck cancer patients be followed up throughout their lives to detect early SPMs, which should be treated aggressively to attain maximum benefit. Despite the better outcomes observed in this study, multi-institutional data are required to confirm the results.

In our report, a series of patients was surgically treated for HNSCC in a single tertiary care hospital. This study had several strengths and limitations. The main strength of the study was that all patients with HNSCC in a given period were primarily treated with surgery. Secondly, because patients were primarily treated with surgery, the impact of radiation on development of SPM was minimized. Conversely, study limitations include the retrospective study design, missing records, and small sample size.

V. Conclusion

Based on SPM patterns, we suggest that patients with previously treated HNSCC should receive long-term follow-up for early detection of SPM. Although the 10-year survival decreases by 50% due to development of SPM, an acceptable survival rate can still be achieved by early detection of SPM with regular long-term follow-up and appropriate subsequent curative therapy.

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Authors' Contributions

M.A. collected data, analysed results, wrote manuscript.

M.I.S. gave study idea, designed it and reviewed manuscript.

Ethics Approval and Consent to Participate

Since this study consisted only of patient chart review, according to institutional policy, exemption was granted by the Ethical Review Committee of The Aga Khan University Hospital (2601-Sur-ERC-13).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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