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Second Primary Tumors in Patients with Head and Neck Cancer

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Abstract This is a review on second primary tumors in patients with head and neck cancer. These patients have a high risk of developing other cancers simultaneously or subsequently. The incidence of multiple primary tumors in this population can be as high as 27%. Recurrences are the most common cause of treatment failure within the first 2 years of follow-up. After the third year the diagnosis of a second primary tumor becomes the most important cause of morbimortality in head and neck cancer patients, especially in those treated for cancers early diagnosed. Most second primary tumors occur in the upper aerodigestive tract (40%–59%), lung (31%–37.5%), and esophagus (9%–44%). Patients who develop second primary tumor have a significant reduction of survival expectancy.

Keywords Multiple primary tumors · Second primary tumors · Head neck · Triple endoscopy · Surveillance

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Introduction

Head and neck squamous cell carcinomas represent approximately 3% of all human malignancies and most occur in the upper aerodigestive tract (UADT) [1]. In the United States, the estimated number of newly diagnosed oral cavity, pharynx, and larynx cancers is 49,260 cases and 11,480 deaths in 2010 [1]. The treatment of these patients depends on several factors, including the institutional experience, primary tumor site and clinical stage, and the patients' medical conditions and acceptance [2]. Most recurrences are diagnosed within the first 2 or 3 years after initial treatment, and the majority are local and regional [3, 4]. After the third year, the diagnosis of a second primary tumor (SPT) becomes an important cause of morbimortality [5–8].

Patients with UADT squamous cell carcinomas have a high risk of developing other cancers simultaneously or subsequently. The incidence of multiple primary tumors in these patients can be as high as 27%. Most of these tumors are located in the oral cavity, pharynx, larynx, lungs, or esophagus [9–14, 15•, 16–18]. The main reason for this topographical specificity is the exposure of the squamous epithelium of these organs to the same carcinogenic agents, especially tobacco and alcohol [14, 17, 19, 20].

During the last 20 years, multiple primary tumors in patients with UADT cancer have been considered an important problem because a second cancer has become the major cause of death in patients treated for cancers early diagnosed [7, 8, 21].

Historical Aspects and Basic Considerations

The first description of simultaneous tumors that occurred in one patient was presented by Billroth in 1860, cited by

Warren and Gates [22]. Warren and Gates [22] published in 1932 a comprehensive review of several case series of multiple primary tumors and also reported 1078 autopsies among which 40 new cases (3.7%) of multiple tumors were reported. In this study, the authors proposed and used the following criteria for the diagnosis of multiple primary tumors: confirmation of malignancy in both tumors, each tumor must be distinct, and it is necessary to exclude the possibility that one tumor is a metastasis of the other.

Slaughter et al. [20] in 1953 proposed the "condemned mucosa" theory to explain the high incidence of SPT in patients with carcinomas induced by environmental factors and introduced the concept of "field cancerization" to explain the occurrence of multicentric squamous cell carcinomas in the oral cavity. They showed that the epithelium around the tumor had histologic changes, possibly related to the same carcinogen exposure and then more susceptible to malignant transformation. Other authors have confirmed the existence of multicentric dysplasia foci and in situ carcinoma in patients with squamous cell carcinomas of the larynx [23], pharynx [24], and trachea or bronchi [25]. The existence of premalignant epithelial changes in macroscopic normal epithelium in patients with upper aerodigestive tract carcinomas was also demonstrated [26].

Califano et al. [27] proposed a model of head and neck carcinoma carcinogenesis. Cytogenetic analysis and polymerase chain reaction (PCR) used for the evaluation of microsatellite instability allowed the identification of sequential chromosome losses and possible sites of tumor suppressor genes. These changes are detected cumulatively during tumor progression, while all the tumor genetic alterations identified in situ are present in invasive carcinomas, to which are added progressive additional ones. Different genetic alterations involving the same chromosomes distributed irregularly in the mucous epithelium support the thesis of "field cancerization" and the polyclonal origin of multiple squamous cell carcinomas.

The first tumor diagnosed is arbitrarily defined as the primary or index tumor. Considering the time of diagnosis, multiple tumors can be classified into 1) synchronous (diagnosed simultaneously or within 6 months after the diagnosis of the index tumor); or 2) metachronous (diagnosed after a time interval of 6 months).

Incidence and Localization of Second Primary Tumors

The incidence of SPT varies across several studies, depending mainly on the follow-up time and systematic screening of the cases [9–14, 15•,[16–18]. In three large series of cases, Chuang et al. [15•] with 99,257 patients, Haughey et al. [11] with 40,287, and Panosetti et al. [9] with 9089, the SPT incidence was 10.9%, 14.2%, and 9.4%, respectively.

In patients with UADT primary tumors, the SPT diagnosis occurs at a rate of approximately 3.7% to 6% per year during the follow-up period [5, 16, 17]. The risk of SPT remains high even after 10 years of follow-up and the cumulative risk at 20 years is around 36% [15•]. Most SPT occurs in the UADT (40%–59%), lung (31%–37.5%), and esophagus (9%–44%) [5, 12, 16–18].

Risk Factors and Prevention

Several studies have attempted to identify predictive factors of SPT in patients treated for UADT tumors [10, 12, 14, 15•, 17, 19]. Day and Blot [10] collected data from nine population-based cancer registries in the United States and assessed the risk of SPT in 21,371 patients diagnosed with oral and pharyngeal cancer. They found a relative risk (RR) of SPT development ranging from 4.2 to 23 times (esophagus [RR 23.0], mouth and pharynx [RR 20.0], larynx [RR 6.8], nasal cavity and paranasal sinus [RR 4.9], and lung [RR 4.2]). The elevated risk persisted for over 5 years after the primary tumor diagnosis and was higher in patients aged 60 years or less.

In a case-control study with 85 cases of SPT and 170 controls matched by tumor location, risk factors related to the occurrence of metachronous SPT were smoking (RR 4.9), metal industry work (RR 6.2), clinical stage III and IV tumors (RR 0.1), and follow-up between 6 and 24 months (RR 4.4) or greater than 24 months (RR 11.5) [19].

A study with 1257 patients with oral cavity and larynx primary tumors identified as independent predictors of SPT only tobacco and alcohol consumption (risk five and two times greater, respectively). Five-year disease-free survival after SPT was better in those patients who were nonsmokers or nondrinkers than in the tobacco or alcohol addicts (98% and 90% respectively, $P = 0.01$) [14].

In another study, the risk factors to the diagnosis of SPT were male sex, age less than 60 years, and early primary tumors (T1 and T2) without nodal metastases (N0) located in the larynx or oral cavity. In multivariate analysis only T and N stages were related to the diagnosis of SPT [12]. A positive correlation between SPT and index tumor at clinical stages I and II, age less than 66 years. Early-stage tumors of the larynx or oral cavity were also identified as risk factors by other authors [16].

Leon et al. [17] conducted a case-control study to evaluate the influence of the persistence of tobacco and alcohol use on risk of SPT in patients treated for UADT squamous cell carcinomas. The risk for the development of SPT in patients who continued smoking was 2.9 and for those who continued to consume alcohol was 5.2. The

authors identified a strong association between continuity of tobacco and alcohol consumption with the development of SPT after treatment of primary tumor, being the habit responsible for development of at least 33% of the SPT.

SPT chemoprevention in patients with primary head and neck cancer treated was evaluated in various randomized clinical trials [28–32]. Hong et al. [28] randomized patients to receive high dose of isotretinoin (13-cis-retinoic acid; 50–100 mg per square meter of body-surface area per day) or placebo, to be taken daily for 12 months. After a median follow-up of 32 months, the incidence of second primary tumors was lower in the isotretinoin than in the placebo group (P = 0.005). But 33% of the patients in the isotretinoin group did not complete de treatment because of drug toxicity. In another study, when low-dose isotretinoin was used, it was not demonstrated effective in reducing the rate of second primary tumors [29].

Other substances (alpha-tocopherol [30], retinyl palmitate and/or N-acetylcysteine [31], beta-carotene [32]) were studied, but reduction of SPT incidence was not significant.

Screening and Diagnosis of Second Primary Tumors

A close follow-up, using routine triple endoscopy (laryngoscopy, endoscopy, and bronchoscopy), has been recommended aiming to diagnose precursor lesions and early-stage asymptomatic invasive tumors [33–36]. However, most reports only describe the frequency of diagnoses and not the long-term results of treatment of these patients (Table 1) [11, 33–41]. The efficacy of triple endoscopy was considered better in the earlier reports than in the most recent ones.

On the other hand, there are some doubts on the cost-effectiveness of triple endoscopy used routinely. A study that followed-up 140 patients with UADT primary tumor for 1 to 4 years reported that 18 SPT were diagnosed, and the authors´ conclusion was that in the absence of symptoms endoscopy and bronchoscopy have high cost and minimal benefit [42].

The use of Lugol chromoendoscopy allows identifying areas of suspected mucosal lesions or with premalignant transformation, and can orient the best site for biopsy [3, 34]. More recently, narrow-band imaging combined with magnifying endoscopy have been demonstrated to improve the detection accuracy of a larger number of asymptomatic mucosal premalignant lesions and early cancers of the UADT [43••]. New techniques, like fluorescence spectroscopy and microendoscopy in addition to modern flexible endoscopic techniques, may have an important role in SPT screening in the near future [44].

Positron emission tomography (^{18}F-FDG-PET/CT) seems to be a promising test for early diagnosis of SPT in patients with primary UADT cancer. Haerle et al. [45••] demonstrated that ^{18}F-FDG-PET/CT diagnosed more SPT than triple endoscopy (6.1% and 4.5%, respectively), but with a higher number of false positives. In a series of 589 patients with UADT squamous cell carcinoma submitted to ^{18}F-FDG-PET/CT, Strobel et al. [46] diagnosed 56 SPT in 44 patients, 55% of them at early clinical stage.

Several molecular biology techniques have been used aiming to identify genetic abnormalities associated with the tumor progression and are possible predictors of SPT. Among the genetic alterations, p53 expression [47], and polymorphisms of p21 [48], p73 [49], and glutathione S-transferases [50], were related to the SPT risk in head and neck cancer patients.

Survival and Prognoses

Panosetti et al. [9] identified a better survival in metachronous SPT than in synchronous (55% and 18% in 5 years, respectively). In 49.4% of the synchronic tumors the treatment of the primary tumor had to be modified. The prognosis was worse when a change was needed in the

Table 1 Second primary tumors diagnosis in 100 examinations performed

Study	Cases, *n*	Esophagoscopy[a]	Bronchoscopy[a]	Laryngoscopy[a]
Decade: 1980				
McGuirt et al. [37]	81	7.4	3.7	6.2
Leipzig et al. [38]	384	1.8	3.3	3.6
2000–2005				
Davidson et al. [39]	154	0	1.3	1.3
Guardiola et al. [41]	487	2.9	2.1	0
Hashimoto et al. [34]	326	7.4	Not performed	Not performed
2009				
Kerawala et al. [40]	74	0	0	1.4
Kesting et al. [35, 36]	570	0	2.0	Not performed

[a] Diagnoses per 100 examinations

initial treatment of the primary tumor. When the first treatment was performed according to the standard guidelines the 5-year survival was 28%, and it was only 8% when treatment planning was modified.

Two other studies also showed better survival rates for metachronous tumors. In the study by Di Martino et al. [13], the 5-year post-SPT survival was also significantly higher in the metachronous tumors (26.0%) than in synchronous (11.9%; $P < 0.001$). In the study by Lin et al. [14], the 5-year overall survival for synchronous tumors was 45% and for metachronous it was 70% ($P = 0.003$).

For patients with early glottic tumors (Tis, T1, and T2) treated with radiotherapy alone, Lee et al. [8] showed that the main cause of death in this group was the SPT. In the group of patients with SPT, the 5-year overall survival was 68%, and it was 88% for those without SPT

Franchin et al. [7] also studied patients with early larynx tumors treated with radiotherapy alone and concluded that the development of SPT was the first cause of death in this group, especially in those patients who continued to smoke after primary tumor diagnosis. The 10-year overall survival was 32% for patients who developed SPT and 77% for those who did not.

Rennemo et al. [16] evaluated the impact of SPT on survival rates of patients with head and neck primary cancer. They identified that in patients who developed SPT the overall median survival was 6 years and it was 3 years in those who did not have SPT ($P < 0.05$). In the first 6 years of follow-up, the cancer-specific survival was better in the group who developed SPT (70%) than in the group without SPT (50%). However, after 6 years of follow-up, the group with SPT has worse survival (5-year survival after SPT diagnosis was 16% and 90% of cancer-related deaths were due to SPT).

Jones et al. [12] reported 5-year overall survival was similar in patients with and without SPT (around 49%); however, the overall survival after 15 years of follow-up was 20% in the group that developed SPT and 44% in patients without SPT ($P = 0.029$). In this study, five-year survival after SPT diagnosis was 26% (31% for UADT SPT and 8% for other locations). In Cox regression multivariate analysis the variables related to worse survival were age (older than 60 years), primary tumor T and N stage (T3 and T4 and N positive), and presence of SPT (outside of UADT).

Lin et al. [14] also found better survival in patients with SPT located in UADT than in the lung (66% and 19%, respectively; $P < 0.001$). In the study by Rennemo et al. [16], no patient with lung SPT had survived more than 5 years. Of the 13 patients with esophageal SPT, the highest survival was 14 months. The best survival rates (20% in 5 years) were found in patients with UADT SPT and other locations.

Conclusions

The patients who develop an SPT have a significantly worse prognosis. Thus, the best strategies are prevention and early diagnosis (especially premalignant lesions). It is essential to provide the orientation and psychology support for tobacco and alcohol cessation.

After treatment of the primary tumor, it is necessary to maintain close follow-up of patients and always properly investigate their complaints and any suspicious lesion. The routine use of triple endoscopy (laryngoscopy, bronchoscopy, and endoscopy) allows, in selected cases, the diagnosis of premalignant lesions and invasive tumors. More recently introduced in clinical practice, ^{18}F-FDG-PET/CT is a promising examination in SPT early detection.

Most SPT develops in the UADT mucosa accessible to routine head and neck clinical examination. Patients with metachronous SPT located in UADT have a better prognosis than those with synchronous or located in other sites. The best treatment, offering higher survival expectancy, is the classic set for each tumor site and clinical stage, always respecting the patient's general condition and their choice.

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- • Of importance
- •• Of major importance

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