

Multiple Primary Squamous Cell Carcinomas of the Oral Cavity

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Purpose: There is a subset of patients who develop multiple primary squamous cell carcinomas (SCCs) of the oral cavity. The aim of this study was to better characterize this group of patients and determine whether there are any associated risk factors.

Materials and Methods: This is a retrospective review of all patients treated for oral SCCs at the University of Maryland Department of Oral and Maxillofacial Surgery from November 1989 to February 2013. The inclusion criteria were patients who developed at least 3 primary oral cancers. Lesions were considered separate primaries if they involved different anatomic regions within the oral cavity and were more than 2 cm apart or if they occurred more than 5 years apart.

Results: Of 1,478 patients treated during this time frame, 20 met the inclusion criteria. There were 14 women and 6 men (female-to-male ratio, 2.3:1). Nineteen were Caucasian and 1 was of Indian ethnicity. The average number of primaries per patient was 3.9 (range, 3 to 6 primaries). The mean age at first diagnosis was 63.3 years (44 to 86 yr). The mean interval between the different primaries was 32 months (0 to 228 months). The most common site involved was the gingiva (45% of cases), followed by the tongue, buccal mucosa, retromolar fossa, and soft or hard palate. The mean follow-up was 118 months (22 to 342 months). Eleven patients developed nodal disease. Of those 11 patients, 9 died of the disease (<20% survival). The average time to neck involvement was 66.4 months. The average time from last neck involvement to death was 11.5 months. More than half the patients were nonsmokers or had quit more than 10 years before the first diagnosis. All patients quit smoking during the course of their treatment yet continued to develop multiple primaries. Three patients had proliferative verrucous leukoplakia (PVL), and 4 patients had biopsy-proved lichen planus.

Conclusion: The incidence of multiple primary SCCs within the oral cavity appears to more commonly involve Caucasian women without risk factors, although lichen planus and PVL might play a role. The gingiva appears to be the most commonly involved primary site, and subsequent primaries tend to be restricted to the oral cavity. Close observation and early expectant treatment appear to improve prognosis and survival in these patients. Cervical nodal metastases adversely affected survival ($P = .02$) as did the development of more than 4 primary carcinomas ($P = .04$).

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The incidence of synchronous and metachronous second primary malignancies within the head and neck ranges from 3 to 21%.¹ Theories as to the development of this phenomenon include field cancerization

changes throughout the entire aerodigestive mucosa after exposure to carcinogens such as tobacco. The criteria for multiple primaries as defined by Warren and Gates² are: 1) the 2 neoplasms must be malignant,

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2) the 2 neoplasms must be anatomically separate and not connected by epithelial or submucosal neoplastic changes, and 3) the possibility of the second tumor representing a metastasis from the index tumor must be excluded. The authors have observed a subset of patients who continue to develop new primary oral cancers despite the absence of any obvious risk factors. There are numerous studies in the literature that have looked at the incidence of second primary head and neck malignancies, but there are minimal data that have investigated patients who develop at least 3 oral primary carcinomas.³⁻⁷ The aim of this study was to characterize this group of patients and determine whether there are any associated risk factors. To the authors' knowledge, this is the largest series reported to look specifically at multiple primary squamous cell carcinomas (SCCs) isolated to the oral cavity (≥ 3).

Materials and Methods

This was a retrospective review of all patients treated for oral SCC at the University of Maryland Department of Oral and Maxillofacial Surgery (Baltimore, MD) from November 1989 to February 2013. The following inclusion criteria were used for this study.

1. Patients who developed at least 3 separate oral primary SCCs.
2. Lesions were considered separate primaries if they involved different anatomic regions within the oral cavity and were more than 2 cm apart. Lesions also were considered separate primaries if they occurred more than 5 years apart.
3. Only tumors limited to the oral cavity were included.

Data collected included patient demographics and risk factors. Tumor characteristics, such as stage, oral site involved, nodal involvement, and overall survival, also were analyzed. Applicable data were analyzed using Excel 14.3.9 (Microsoft, Redmond, WA). Probabilities less than .05 were accepted as an indication that the differences did not arise by chance.

This retrospective study was approved by the institutional review board for ethical human research at the University of Maryland.

Results

Twenty of 1,478 patients treated during this time frame met the inclusion criteria (1.4%). There were 14 women and 6 men (female-to-male ratio, 2.3:1). Nineteen patients were Caucasian and 1 was of Indian descent. The mean age at first diagnosis was 63.3 years

(range, 44 to 86 yr). The mean follow-up was 118 months (9 yr 10 months). More than half the patients were nonsmokers or had quit more than 10 years before the initial diagnosis. All patients quit smoking after the first primary yet continued to develop multiple primaries (Fig 1).

The average number of primaries per patient was 3.9 (range, 3 to 6 primaries; Fig 2). The mean interval between the different primaries was 32.2 months (range, 0 to 228 months). These intervals appeared to become progressively shorter as the patients developed multiple primaries (Fig 3). There were 78 primary oral SCCs identified in these 20 patients. The gingiva represented the most commonly involved site, making up 35 of those primaries (45% of cases). This was followed by the tongue (11), buccal mucosa (10), retromolar fossa (8), palate (7), and other (7). The distribution of these sites is shown in Figure 4. The tumor stage at the first primary was equally distributed among the different stages (I to IV). In contrast, early-stage disease (stage I or II) made up more than 75% of the tumors at the second and third primaries (Fig 5).

Interestingly, there were an additional 25 recurrent SCCs (that did not meet the criteria for a separate primary as defined in Materials and Methods) that occurred within this cohort of 20 patients.

Eleven of the 20 patients (55%) went on to develop nodal disease. Of these 11 patients, 82% ($n = 9$) died of the disease. In contrast, 7 of the 9 patients without nodal disease were alive and disease free at the conclusion of this study ($P = .02$). The mean time from the first primary SCC to regional cervical lymph nodal metastasis was 66.4 months (range, 0 to 334 months). The mean time from nodal involvement to death was 41 months. The mean time from the second nodal involvement to death was 11.5 months. Survival was adversely affected in patients who

• Tobacco Use

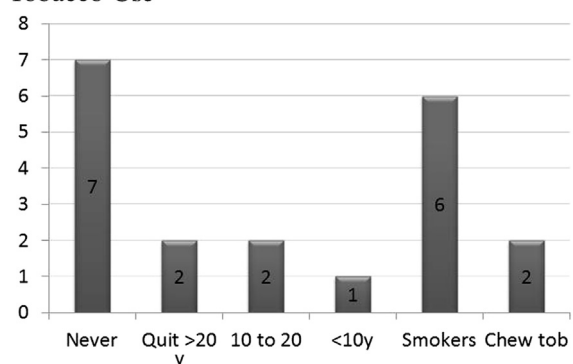


FIGURE 1. Breakdown of patients according to history of tobacco use.

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