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# Clinical analysis of second primary gingival squamous cell carcinoma after radiotherapy

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ABSTRACT

*Introduction:* Clinically, we have observed that some oral cancer patients have a history of radiotherapy for head and neck cancer; we have named this condition radiotherapy-associated cancer (RAC). Gingival cancer, which is usually juxtaposed with other oral cancer subtypes, is seldom reported individually, and there are few reports on the association between the incidence of oral cancer and history of radiation therapy. Therefore, this study aimed to elucidate the clinicopathological features and prognosis of second primary gingival squamous cell carcinoma after head and neck radiotherapy.

*Materials and methods:* The data collected included 450 patients diagnosed with gingival squamous cell carcinoma from 1964 to 2012 at Sun Yat-sen University Cancer, among whom 52 patients had a history of radiotherapy for head and neck cancer. We retrospectively analysed the differences in the clinicopathological characteristics and prognosis between sporadic gingival squamous cell carcinoma and radiation-associated gingival carcinoma, with an emphasis on gingival carcinoma.

*Results:* Sporadic gingival squamous cell carcinoma is less likely to have more advanced T stage, and the second primary tumour is more likely to be located in the molar area of the maxillary gingiva than in the mandibular gingiva (75.6% vs 24.4%, $P < 0.05$). The 5-year overall survival of patients with second primary gingival carcinoma was influenced by age distribution, T classification, N classification, clinical TNM stage, histological grade and radiation history in head and neck. Mandibular gingival carcinoma was more likely to have an increased neck lymph node metastasis than maxillary gingival carcinoma ($P = 0.001$), but there was no significant difference in 5-year overall survival between these two groups ($P = 0.828$). The main therapy for gingiva carcinoma is surgery or comprehensive treatment based on surgery.

*Conclusions:* Second primary gingival squamous cell carcinoma after radiotherapy demonstrated particular clinicopathologic features, such as prominent sites and TNM stage; and there was statistically significant difference in 5-year overall survival and prognosis between second primary gingival carcinoma after radiotherapy and sporadic gingival carcinoma.

## Introduction

Oral cancer has become the sixth most common cancer in the world [1]. In 2015, approximately 45,780 new cases of cancer in the oral cavity and pharynx were reported in the United States. Of these, 8650 died due to cancer-related death [2]. Tobacco abuse and alcohol abuse have been identified as the most important risk factors for oral cancers, especially squamous cell carcinoma [3], as well as DNA oncogenic viruses and habits, such as chewing betel nut [4]. Among those patients with oral squamous cell carcinoma, a fraction was observed to have a history of radiotherapy in head and neck region. Radiotherapy is one of the most important treatments of malignant tumours in the head and neck region but is known to cause deleterious side effects such as radionecrosis and oncogenesis [5]. Many studies have reported an association between an increased risk of tongue cancer and radiation treatment for head and neck malignancies such as nasopharyngeal

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carcinoma (NPC) [6–8].

Gingival cancer is a relatively rare malignant neoplasm and represents less than 10% of all oral cancers in Europe and the United States [9–11]. However, the incidence of gingival cancer is higher in China than in Europe and the United States, ranked only second to tongue cancer among oral cancers. Reports on gingival carcinoma are seldom and often grouped with other subsites of oral cancer. There is also no systematic study about the development of second primary gingival squamous cell carcinoma (SPGSCC) after radiotherapy. This study is aimed to elaborate the clinicopathological characteristics and prognosis of SPGSCC after radiotherapy for head and neck cancer.

## Materials and methods

### *Patient data*

Consecutive patients with an initial diagnosis of oral squamous cell carcinoma and who received primary treatment at Sun Yat-sen University Cancer between January 1964 to December 2012 were enrolled in this retrospective study. In all, 3377 patients were initially included in this study, among whom 174 had a history of radiotherapy for head and neck cancer. Gingival carcinoma as a subgroup ranked only second to tongue carcinoma among all oral cancers. Of the 450 patients with this subtype in our study, 52 accepted radiation therapy a number of years ago. All 174 patients conformed to the diagnostic criteria of second primary oral squamous cell carcinoma (SPOSCC) after radiotherapy based on descriptions by Cahan, et al. and Arlen, et al. [12–14]. First, the patients should have a previous history of irradiation for head and neck carcinoma; second, a new cancer of the oral mucosa developed and was not the result of a metastasis from or a recurrence of the previous cancer; and third, the period from the end of the radiation treatment to the diagnosis of SPOSCC is at least 6 months.

In our study, the main radiation mode for head and neck cancer was a conventional radiotherapy method using either Cobalt-60 or 6-MV X-rays during the earlier stages of the study period and 3D conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) in recent years. Among the 174 patients with a history of definitive radiotherapy for their first primary cancer, the median radiation dose for the primary tumour region was 70 Gy (range from 45 Gy to 92 Gy), the median radiation dose for the neck region was 59.5 Gy (range from 24 Gy to 76 Gy), and the second primary cancer manifested in the radiation field (Table 1).

### *Clinical data*

We analysed the clinical and pathological data and therapeutic regimens of the patients. The disease sites of the second primary oral cancers were mostly located in the tongue followed by the gingiva, hard palate, and buccal mucosa. The period from radiotherapy for the first primary cancer to the appearance of the second primary cancer ranged from 12 months to 468 months with a median time of 96 months. The median age at diagnosis of the second primary oral cancer was 53 years with a range from 30 to 84 years. We used the 7th criteria of the American Joint Committee on Cancer (AJCC, 2010) to reclassify the stages of the oral cancer.

### *Follow-up and statistical analysis*

The patients were followed up until December 2016. SPSS software (version 20.0, Chicago, IL, USA) was used to analyse all these data. Survival curves were generated using the Kaplan–Meier method, and the log-rank test was used for univariate analysis. To improve research efficiency and credibility, propensity score matching (PSM) was also used to analysed this data. In addition, a *P*-value less than 0.05 was considered statistically significant.

**Table 1**
Demographic and clinical characteristics in SPOSCC and sporadic oral squamous cell carcinoma.

| | SPOSCC | | Sporadic oral squamous cell cancer |
|---|---|---|---|
| | NPC survivors | Non-NPC survivors | |
| *Location:* | | | |
| Tongue | 75 | 11 | 1844 |
| Gingiva | 47 | 5 | 398 |
| Hard Palate | 20 | 3 | 245 |
| Buccal Mucosa | 7 | 1 | 264 |
| Floor of the Mouth | 2 | 0 | 267 |
| Lips | 0 | 1 | 162 |
| Retromolar Area | 0 | 2 | 23 |
| *Sex:* | | | |
| Male | 138 | | 2134 |
| Female | 36 | | 1069 |
| Age: | | | |
| < 50 | 90 | | 1681 |
| ≥50 | 84 | | 1522 |
| *Year of radiotherapy diagnosis:* | | | |
| Before1990 | 80 | | |
| 1990–2000 | 68 | | |
| After(≥)2000 | 26 | | |
| *Radiation technique:* | | | |
| Conventional radiotherapy | 165 | | |
| 3DCRT/IMRT | 9 | | |
| *Radiation dose: (median, range, Gy)* | | | |
| Primary tumour region | 70 (45–92) | | |
| Neck region | 59.5 (24–76) | | |
| Age at first primary cancer diagnosis, median (range, yr): | 43 (19–74) | | |
| Age at SPOSCC cancer diagnosis, median (range, yr) | 53 (30–84) | | |
| Latency from FPC to SPOC, median (range, mon) | 96.0 (12–468) | | |

SPOSCC, second primary oral squamous cell carcinoma; NPC, nasopharyngeal carcinoma; 3DCRT, 3-dimensionalconformal radiotherapy; IMRT, intensity-modulated radiotherapy; FPC, first primary cancer; SPOC, second primary oral cancer.

## Results

### *Clinical characteristics*

There were 3377 patients diagnosed with oral squamous cell carcinoma during the defined study period, and tongue carcinoma represented the majority of cancer locations (57.2%) among these patients, followed by gingiva (13.3%), buccal mucosa (8.1%), floor of the mouth (8.0%), hard palate (7.9%), lips (4.8%), and retromolar area (0.7%). Interestingly, there were 174 patients diagnosed with SPOSCC, and the locations were a little different than those observed in patients with sporadic oral squamous cell carcinoma (SOSCC), the three most common being the tongue (49.4%), gingiva (29.9%), and hard palate (13.2%). Among the 174 SPOC patients, 151 patients were NPC survivors, and 23 patients were non-NPC survivors, but their first primary cancer was located in head and neck area that was subjected to radiotherapy. The clinical features of the second primary tumours are shown in Table 1. The ratio between men and women was different in SPOSCC and SOSC (male:female = 3.83:1 in SPOSCC; male:female = 1.996:1 in SOSC).

Among oral cancer patients, there were 450 diagnosed with gingival squamous cell carcinoma, 52 with a history of radiotherapy for head and neck carcinoma, 47 who were NPC survivors, and 5 who were non-NPC survivors. Within this last subset of 5 patients, 4 accepted definitive radiotherapy for tongue cancer, and 1 accepted definitive