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# Osteoradionecrosis in patients with salivary gland malignancies

J. Rhet Tucker [a,c], Li Xu [a], Erich M. Sturgis [a], Abdallah S.R. Mohamed [b,e], Theresa M. Hofstede [a,c], Mark S. Chambers [a,c], Stephen Y. Lai [a], Clifton David Fuller [b], Beth Beadle [b], G. Brandon Gunn [b], Katherine A. Hutcheson [a,d,*]

[a] Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[b] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[c] Section of Oral Oncology and Maxillofacial Prosthodontics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[d] Section of Speech Pathology and Audiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[e] Department of Clinical Oncology and Nuclear Medicine, Alexandria University, Alexandria, Egypt

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SUMMARY

*Purpose:* The present study was undertaken to evaluate osteoradionecrosis (ORN) in patients with salivary gland malignancies (SGM) after treatment with radiation therapy.

*Materials and methods:* The medical records of 172 patients treated with radiation therapy for SGM during a 12-year period (August 2001 to November 2013) were reviewed. Incidence, time to event, staging and management of ORN were analyzed.

*Results:* Of the 172 patients, 7 patients (4%) developed ORN (median latency: 19 months, range: 4–72 months). Of those 7 patients, 4 required major surgery, 1 required hyperbaric oxygen therapy (HBO), one required minor debridement, and one required conservative management. Total prescribed radiation dose varied from 50 Gy (1 case) to 70 Gy (1 case) among those patients who developed ORN, and radiotherapy was delivered postoperatively after osseous resection in 4 of 7 cases. Three of the 7 cases of ORN occurred after traumatic injury to the bone. Of the 7 patients who developed ORN, 3 had SGM of the major glands, 3 had other sites of the oral cavity, and 1 had a sinonasal location.

*Conclusion:* While the rate of ORN after radiotherapy for SGM was somewhat lower (4%) than previously published data on patients with squamous cell carcinomas of the head and neck treated with radiation therapy (8–14%), ORN necessitating major surgery remains a clinically significant, possible late effect of radiotherapy in SGM survivors. Location of SGM is very important, with cases that developed ORN disproportionally having primary disease arising in the oral cavity.



## Introduction

Salivary gland malignancies (SGM) are relatively rare but are rising in incidence [1]. SGM account for 3–5% of all head and neck cancers and can occur in major glands (parotid, submandibular, and sublingual) or minor glands within the mucosal lining of the oral cavity, oropharynx, and nasal cavity. The most common histological subtypes of SGM are adenoid cystic carcinoma, mucoepidermoid carcinoma, and acinic cell carcinoma [2]. Radiation therapy has been shown to be effective at increasing the survival of high-risk patients who have close or positive margins, lymph node metastasis, locally advanced disease, bone or nerve involvement, and/or recurrent disease [3], and therefore it is delivered in nearly 40% of SGM patients treated at our institution in the last decade.

Advancements have been made in radiation delivery and optimization of dose distribution, but many complications still cannot be avoided due to critical normal structures in close proximity to the radiation target volume. Among the most serious of these complications is osteoradionecrosis (ORN). ORN is linked to radiation-induced hypoxia, hypocellularity, hypovascularity and decreased wound healing [4]. Although most commonly a delayed complication, the onset of ORN has been shown to begin as early as 2 weeks after radiation concludes, with an irreversible and potentially progressive course [5,6]. ORN has been well characterized after radiotherapy in mixed cohorts of patients with more common cancers of the head and neck, typically SCC, but not specifically for SGM patients whose radiation plans differ considerably from those for SCC patients [6,7]. The present study was undertaken to

* Corresponding author at: The University of Texas MD Anderson Cancer Center, P.O. Box 301402, Department of Head and Neck Surgery Unit 1445, Houston, TX 77030, USA. Tel.: +1 713 792 6513; fax: +1 713 794 4662.
*E-mail address:* karnold@mdanderson.org (K.A. Hutcheson).

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evaluate the incidence, time to event, staging, and management of ORN after radiation therapy treatment for SGM.

## Materials and methods

Patients with newly diagnosed SGM and no prior history of cancer (with the exception of non-melanoma skin cancer) were prospectively recruited to an epidemiologic cohort at the University of Texas MD Anderson Cancer Center between 2001 and 2013. A total of 325 SGM patients were recruited for the study. A retrospective analysis was undertaken to evaluate ORN among the 181 patients who received radiation for malignant salivary gland tumors. Nine patients who did not complete the prescribed course of radiation or whose outside radiation records were incomplete were also excluded. Thus, 172 patients were included in this study (Fig. 1).

The medical records of the patients were reviewed. Age at diagnosis, sex, primary tumor site, histopathology, surgical history, and total radiation dosages were recorded. Mandible and maxillary specific dose-volume histograms (DVH) were reconstructed from radiation plans when available. Additionally, ORN subsite was contoured on post-ORN diagnostic CT and contours were propagated to original planning CT when available to calculate dose given to the respective subsite. The presence of ORN, site of ORN (mandibular or maxillary), time to occurrence, as well as grade was also recorded. ORN was graded according to the criteria in Table 1 [6]. The primary tumor location was identified and categorized as: major gland, oral cavity, sinonasal tract, and oro-hypopharynx/larynx. SGMs were also grouped according to their pathology; adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma/salivary duct carcinoma, acinic cell carcinoma were the major pathologic categories. Pre-radiotherapy dental prophylaxis was routinely applied and has been detailed elsewhere along with surveillance schedules [6]. Descriptive statistics were calculated and graphically summarized. Cumulative incidence was estimated per the Kaplan Meier method. Statistical analyses were performed using Stata Data Analysis Software version 10.0 (College Station, TX, USA).

**Table 1**
Classification of ORN.

| | |
|---|---|
| Grade 1 | Minimal bone exposure (conservative management only) |
| Grade 2 | Minor debridement needed |
| Grade 3 | Hyperbaric oxygen needed |
| Grade 4 | Major surgery required |

**Table 2**
Patient cohort.

| Patient information | All patients [%] | Patients with ORN |
|---|---|---|
| Median age (years) | 54 | 53 |
| *Gender* | | |
| Male | 87 [51] | 1 |
| Female | 85 [49] | 6 |
| *Radiation dose (Gy)* | | |
| 50–59 | 7 [4] | 1 |
| 60–64 | 103 [60] | 4 |
| 65+ | 41 [24] | 1 |
| Outside | 21 [12] | 1 |
| *Radiation technique* | | |
| IMRT | 143 [83] | 5 |
| Proton | 15 [9] | 1 |
| Unknown | 14 [8] | 1 |
| *Tumor site* | | |
| Parotid/submandibular/sublingual | 74 [43] | 3 |
| Oral cavity | 41 [24] | 3 |
| Oro-hypopharynx/larynx | 19 [11] | |
| Sinonasal tract | 23 [13] | 1 |
| Other | 15 [10] | |
| *Histological type* | | |
| Adenoid cystic carcinoma | 93 [54] | 4 |
| Mucoepidermoid carcinoma | 16 [9] | 1 |
| Adenocarcinoma/salivary duct carcinoma | 27 [16] | 1 |
| Acinic cell carcinoma | 10 [6] | |
| Other | 26 [15] | 1 |
| *Smoking (at diagnosis)* | | |
| Never | 92 [53] | 3 |
| Former | 56 [33] | 2 |
| Current | 24 [14] | 2 |

## Results

### SGM cohort

Demographic information of the 172 included patients is tabulated in Table 2. The mean age of the patients at diagnosis was 54, and 51% of the patients were male. 67% of SGM were in the major salivary glands or in the oral cavity. 92 (53%) were current smokers at diagnosis. Radiotherapy was delivered postoperatively in 156 (91%) of cases, 29 of whom received chemotherapy. 96% of the patients received a total dose of more than 60 Gy of radiation, and IMRT technique was used in 143 (83%) of patients.

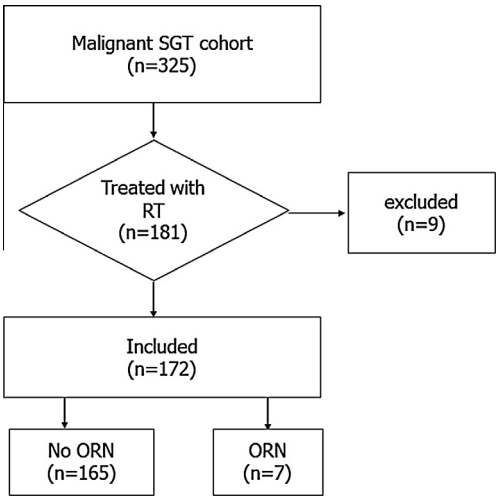


**Fig. 1.** Patient screening.

### Osteoradionecrosis

At a median follow-up of 29 months, ORN developed in 7 of the 172 patients (4%), with a median latency of 19 months (range: 4–72 months). Case details are summarized in Table 3 and incidence plot of ORN is shown in Fig. 2. Three patients developed maxillary ORN, 3 developed mandibular ORN, and one developed ORN of the maxilla, mandibular condyle, and temporomandibular joint. All 7 ORN cases had pre-treatment dental evaluation and prophylaxis including 1 planned dental extraction prior to cancer treatment. Three of the 7 cases of ORN developed following a traumatic insult to the bone after initial healing (two had dental extractions and one a motor vehicle accident). Among these ORN cases, 4 required major surgery, 1 required hyperbaric oxygen (HBO) therapy, 1 required minor debridement, and the final case was managed conservatively over a period of 48 months. Total radiation dose among ORN cases ranged from 50 Gy to 70 Gy.