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Symptom burden and dysphagia associated with osteoradionecrosis in long-term oropharynx cancer survivors: A cohort analysis

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ABSTRACT

Objective: The purpose is to examine the relationship between mandibular osteoradionecrosis (ORN) and chronic dysphagia in long-term oropharynx cancer (OPC) survivors, and to determine the perceived symptom burden associated with ORN.

Materials and methods: Medical records of 349 OPC patients treated with bilateral IMRT and systemic therapy were reviewed. ORN was graded using a published 4-point classification schema. Patients were considered to have chronic dysphagia if they had aspiration pneumonia, stricture or aspiration detected by fluoroscopy or endoscopy, and/or feeding tube dependence in long-term follow-up $\geqslant$1 year following radiotherapy. MD Anderson Symptom Inventory – Head and Neck Module (MDASI-HN) scores were analyzed in a nested cross-sectional survey sample of 118 patients.

Results: 34 (9.7%, 95% CI: 6.8–13.3%) patients developed ORN and 45 (12.9%, 95% CI: 9.6–16.9%) patients developed chronic dysphagia. Prevalence of chronic dysphagia was significantly higher in ORN cases (12/34, 35%) compared to those who did not develop ORN (33/315, 11%, $p < 0.001$). ORN grade was also significantly associated with prevalence of dysphagia ($p < 0.001$); the majority of patients with grade 4 ORN requiring major surgery (6 patients, 75%) were found to have chronic dysphagia. Summary MDASI-HN symptom scores did not significantly differ by ORN grade. Significantly higher symptom burden was reported, however, among ORN cases compared to those without ORN for MDASI-HN swallowing ($p = 0.033$), problems with teeth and/or gums ($p = 0.016$) and change in activity ($p = 0.015$) item scores.

Conclusions: ORN is associated with excess burden of chronic dysphagia and higher symptom severity related to swallowing, dentition and activity limitations.

Introduction

The annual estimated incidence of oropharynx cancer is approximately 130,300 cases per year worldwide with an estimated 15,000 new cases diagnosed annually in the United States [1,2]. Over the last few decades, the incidence of oropharynx cancer has been increasing dramatically in developed countries such as the United States, Canada, Australia, the United Kingdom, Denmark, the Netherlands, Norway and Sweden [3]. This rise in the incidence of oropharynx cancer is attributed to human papillomavirus (HPV). HPV-positive oropharyngeal squamous cell carcinomas (OPSCC) that have better response to treatment and lower overall recurrence rates when compared to HPV negative OPSCC [3–5].

Treatment of OPSCC primarily involves radiotherapy and chemotherapy with the goal of preservation of anatomy and function [6]. While highly effective at curing OPSCC, radiation therapy can induce normal tissue changes that can cause a myriad of acute and chronic complications [2]. These complications can include oral mucositis, increased risk of infections, xerostomia, neuropathic pain, osteoradionecrosis (ORN) and dysphagia which can lead to significant morbidity and decreased quality of life in oropharynx cancer survivors [2,6].

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One of the most common late complications of treatment affecting quality of life is dysphagia. It is estimated that 12–38.5% of patients treated with primary radiotherapy or chemoradiotherapy for locoregionally advanced stage head and neck cancer develop chronic dysphagia, when defined by chronic aspiration, stricture and/or gastrostomy dependence [6–8]. Radiation dose distributions to swallowing-critical muscle regions including the pharyngeal constrictors, suprahyoid muscles, and the larynx primarily correlate with chronic dysphagia [9–11].

ORN is a potentially severe late complication of radiation treatment for head and neck cancer. ORN is diagnosed based on clinical features and symptoms. The most accepted definition of ORN is an area of exposed bone that fails to heal after a period of 3 months, after exclusion of all other diagnoses [12,13]. Fortunately, ORN is becoming a less common complication with increased use of intensity-modulated radiation therapy (IMRT). Despite a declining rate of ORN, the rate is still significant with an estimated incidence of 6.4% in head and neck cancer patients [13]. Among the risk factors for ORN, the most significant are high osseous radiation dose distributions, extraction of teeth within the field of radiation, smoking and alcohol consumption [13–15]. ORN can manifest as an asymptomatic condition to severely debilitating presentation with related pain, disfigurement and functional impairment [12]. However, the functional burden of ORN is not well characterized. Chronic dysphagia has been reported in severe cases of ORN, particularly with advanced cases requiring mandibulectomy with removal of the symphysis, but group level associations between dysphagia and ORN are limited [16]. The purpose of this retrospective study is to examine the relationship between ORN and chronic dysphagia in long-term oropharynx cancer survivors and to characterize perceived symptom burden associated with ORN. We hypothesized to detect a higher prevalence of dysphagia and higher perceived symptom burden among ORN patients.

Materials and methods

Study design and eligibility criteria

A retrospective cohort study with nested cross-sectional survey analysis was performed to characterize the functional burden of ORN. Eligibility criteria were: (1) adults greater than 18 years of age diagnosed with OPSCC; (2) treatment with definitive intensity-modulated radiation therapy (IMRT) and systemic therapy (induction and/or concurrent chemotherapy or targeted therapy); and (3) a minimum of 1-year disease free follow-up. This study comprised the same patient population as described by Hutcheson et al. (2016), with final inclusion of 349 patients [8]. All eligible patients were sampled from a prospective epidemiologic registry. The Institutional Review Board at the University of Texas MD Anderson Cancer Center approved the chart review, and a waiver of informed consent was obtained.

Study variables and data source

A review of the electronic medical record was used to collect demographic data, medical comorbidities, tumor and treatment variables, ORN and dysphagia endpoints.

Osteoradionecrosis measures

ORN was graded according to treatment based severity classification system first published by Tsai et al. [14]. Grade 1 ORN is defined as minimal bone exposure requiring conservative treatment only, grade 2 ORN receiving minor debridement, grade 3 ORN requiring hyperbaric oxygen treatment and grade 4 ORN necessitating major surgery [14]. Time to event, initial staging, evolution of staging, and treatments for ORN were coded. ORN was the primary stratification variable for this analysis.

Dysphagia measures

Chronic dysphagia present for $\geqslant$1 year was the primary endpoint measure and was defined in accordance with Caudell et al. as (1) dependent on a feeding tube; (2) aspiration seen on a modified barium swallow (MBS) or fiberoptic endoscopic evaluation of swallow (FEES); (3) pharyngoesophageal stricture determined by an MBS or endoscopy; or (4) aspiration pneumonia with radiographic evidence of infiltrate [7].

Covariates

Other variables that could influence chronic dysphagia and symptom burden were examined and included demographic variables such as age, sex, race and smoking status, disease variables such as tumor subsite, TNM staging, radiotherapy fractionation schedule, total radiotherapy dose and number of fractions [8]. Type and timing of systemic therapy (induction and/or concurrent chemotherapy or targeted therapy) was also taken into account.

Symptom burden assessment

Symptom burden was assessed via a multi-symptom inventory, the MD Anderson Symptom Inventory – Head and Neck Module (MDASI-HN) among a nested subgroup of patients who completed the inventory after consenting to participation in a prospective survey study. The MDASI-HN is a brief 28-item multi-symptom inventory that measures symptom burden and interference and has been validated using principal axis factoring, demonstrating high levels of reliability for each set of items [17]. There are 13 core items representing general cancer related symptoms and 9 head and neck cancer specific items included in the MDASI-HN which are mouth sores, tasting food, constipation, problems with teeth or gums, skin pain, voice or speech difficulties, choking or coughing, chewing or swallowing problems, and increased mucus secretions [17]. The other 6 items rate interference with activity and daily function. Each item is rated on a numeric scale of 1–10, from "not present" for systemic and head and neck symptoms to "as bad as you can imagine" or from "did not interfere" or interfered completely" for interference items. All of the MDASI-HN surveys postdated ORN events in ORN cases.

Statistical methods

Descriptive statistics were calculated. Associations between dysphagia classification and ORN status or grade were examined using bivariate chi-square tests. Mean MDASI-HN summary scores (total symptom burden, local symptom burden, systemic symptom burden, and interference) were computed and compared between groups based on ORN status using two-sample *t*-tests. A non-Bonferroni corrected p value of <0.05 was considered statistically significant for this pilot study. Statistical analyses were performed using the STATA data analysis software, version 14.0 (StataCorp LP, College Station, TX).

Results

Participants

The study sample included 349 patients with a median age of 56 years as detailed in Table 1. Median follow-up was 78 months.