



Long-term toxicities in 10-year survivors of radiation treatment for head and neck cancer



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ABSTRACT

Objectives: To characterize the recognized but poorly understood long-term toxicities of radiation therapy (RT) for head and neck cancer (HNC).

Materials and methods: We retrospectively evaluated patients treated with curative-intent RT for HNC between 1990 and 2005 at a single institution with systematic multidisciplinary follow-up ≥ 10 years. Long-term toxicities of the upper aerodigestive tract were recorded and assigned to two broad categories: pharyngeal-laryngeal and oral cavity toxicity. Kaplan-Meier estimates and Chi-square tests were used for univariable analysis (UVA). Cox model and logistic regression were used for multivariable analysis (MVA). **Results:** We identified 112 patients with follow-up ≥ 10 years (median 12.2). The primary tumor sites were pharynx (42%), oral cavity (34%), larynx (13%), and other (11%). Forty-four percent received postoperative RT, 24% had post-RT neck dissection, and 47% received chemotherapy.

Twenty-eight (25%) patients developed pharyngeal-laryngeal toxicity, including 23 (21%) requiring permanent G-tube placed at median of 5.6 years (0–20.3) post-RT. Fifty-three (47%) developed oral cavity toxicity, including osteoradionecrosis in 25 (22%) at a median of 7.2 years (0.5–15.3) post-RT.

On MVA, pharyngeal-laryngeal toxicity was significantly associated with chemotherapy (HR 3.24, CI 1.10–9.49) and age (HR 1.04, CI 1.00–1.08); oral cavity toxicity was significantly associated with chemotherapy (OR 4.40, CI 1.51–12.9), oral cavity primary (OR 5.03, CI 1.57–16.1), and age (OR 0.96, CI 0.92–1.00).

Conclusion: Among irradiated HNC patients, pharyngeal-laryngeal and oral cavity toxicity commonly occur years after radiation, especially in those treated with chemotherapy. Follow-up for more than five years is essential because these significant problems afflict patients who have been cured.

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Introduction

There are approximately 436,000 HNC survivors living in the United States [1] and it is estimated that more than 60,000 new head and neck cancers (HNC) will be diagnosed in the United States in 2016 [2]. Historically, HNC was a disease of the elderly associated with tobacco/ethanol abuse and comorbidity [3]. Due to changing demographics with increasing human papillomavirus (HPV)-associated oropharyngeal cancer [4–6], patients with HNC are generally younger at diagnosis and living longer after treatment than

historical expectation. While the acute toxicity of HNC treatment has been well studied and reported [7–14], late toxicity data among the large group of HNC survivors are sparse [15].

Long-term toxicity data are difficult to collect. Survivors eschew routine surveillance if they do not understand its importance. They may move and no longer seek care if pursuit of follow-up is not convenient. Head and neck oncologists may erroneously assume that cured patients do not benefit from medical attention. Comorbidity confounds the ability to assign the ‘cause’ of late toxicity. As a consequence, HNC survivor toxicity data beyond five years are limited [16–24]. Available data commonly focus on a specific type of toxicity such as eating/speech [21,25], xerostomia [22], and cranial nerve palsy [23], but head and neck cancer survivors are subject to a variety of frequently overlapping sets of long-term side

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effects. A comprehensive assessment of the burden of long-term toxicity has not been undertaken.

Our tertiary care center practices systematic multidisciplinary (head and neck surgical oncology and radiation oncology) follow-up for all HNC survivors treated with radiation, regardless of whether an operation was performed. Patients are never discharged – follow-up is scheduled in perpetuity. This retrospective study aims to catalog the long-term toxicities of 10-year HNC survivors.

Materials and methods

Participants

We queried our institutional cancer registry for HNC patients treated between 1990 and 2005, a time period during which HPV and/or p16 testing was not performed at our institution. This analysis included HNC survivors managed with external beam radiation (EBRT) as a component of primary treatment who had long-term multidisciplinary follow-up of at least 10 years performed at a single tertiary care cancer center.

Institution standard of care

Most oral cavity tumors were managed with an operation followed by adjuvant therapy according to accepted indications for post-operative therapy [14,26]. Most oropharyngeal tumors were managed with primary (chemo)radiation. Laryngeal and hypopharyngeal tumors were managed with an operation and/or (chemo) radiation based upon multidisciplinary tumor board discussions. Salivary gland and paranasal sinus tumors were managed with an operation followed by adjuvant (chemo)radiation.

After completion of (chemo)radiation, all patients (in absence of problems) were recommended a standardized institutional alternating follow-up schedule with a head and neck surgeon and a radiation oncologist: every 2 months for the first year, every 3 months for years 2–3, every 4 months for years 4–5, and biannually thereafter (one visit with each provider separated by 6 months). Patients were encouraged to report acute problems and clinical decline in function. Referrals to oral maxillofacial surgery, speech language pathology, pulmonary medicine, gastroenterology, physical therapy and neurology were arranged on an as-needed basis predicated upon findings in the clinic appreciated through physical examination and patient history – referrals to speech therapy for a “refresher” are common. All patients are recommended to use supplemental fluoride for the remainder of their lives upon the completion of any head and neck radiation that involves the oral cavity and/or results in xerostomia. Medical oncology follow-up among patients managed with systemic therapy generally persisted for 3–5 years post-treatment, although this was extended according to circumstances as appropriate.

Methods

The medical records, clinic notes, referral records and subsequent evaluations were reviewed retrospectively for each included patient. There was no standardized toxicity rating scale used from 1990–2015; toxicities were identified via chart review. Long-term upper aerodigestive tract toxicities potentially due to radiation and discovered >6 months after completion of RT were recorded as events. Events registered were: permanent gastrostomy tube placement (included if placed prior to 6 months post-RT), permanent tracheotomy, palliative laryngectomy, aspiration pneumonia, asymptomatic osteoradionecrosis, osteoradionecrosis necessitating surgical intervention, hyperbaric oxygen therapy, and trismus.

Laryngeal/pharyngeal toxicity was identified as a “pooled measure” due to the overlap of symptoms, and included aspiration pneumonia, permanent gastrostomy tube, permanent tracheostomy, and palliative laryngectomy. Oral cavity toxicity was identified as osteoradionecrosis (ORN), any hyperbaric oxygen (HBO) therapy, and trismus.

Analysis

In view of the wide range of events recorded and the inherent difficulty in retrospectively recording toxicities over decades, analysis is limited to two broad categories of profound toxicity: pharyngeal-laryngeal and oral cavity toxicity. Kaplan-Meier estimates and Chi-square tests were used for univariable analysis (UVA). Cox model and logistic regression were used for multivariable analysis (MVA). Similar to the above rationale to combine pharyngeal and laryngeal toxicities, we combined pharyngeal and laryngeal primaries on UVA and MVA.

Results

Participants

We identified 1100 consecutive HNC patients managed with EBRT as a component of curative-intent treatment at our institution from 1990 to 2005. In total, 112 patients met inclusion criteria (CONSORT diagram Fig. 1) with a median follow-up of 12.2 years (10.0–22.8 years). The most common primary tumor sites of 10-year survivors were pharynx (n = 47, 42%), oral cavity (n = 38, 34%), and larynx (n = 15, 13%). Consistent with practice patterns, almost half of the patients received radiation after an operation (n = 49, 44%) and almost half of those managed with definitive radiation received a post-treatment neck dissection according to contemporary practice patterns (n = 27, 42% of those managed with primary RT). In total almost half of the patients (n = 53, 47%) received chemotherapy. Among those treated with chemotherapy, the overwhelming majority (n = 45) received concurrent chemotherapy with radiation, most commonly cisplatin as a single agent (n = 30) or in combination with paclitaxel or 5FU (n = 11). Concurrent chemotherapy administration was more frequent in later years of analysis (2000–2005: 35 patients out of 51 patients) than prior years (1990–1999: 10 out of 61 patients). Nearly all patients (96%) were treated with 2D radiation planning with prescription to isocenter, with a median prescribed RT dose of 70 Gy (50–75 Gy). Eight (7%) patients were treated with an accelerated regimen. A majority of patients (n = 75, 67%) had a past history of smoking cigarettes, with a median of 30 (range 0–150) pack-years. Of the smokers, 67 (89%) quit smoking either before to starting RT or within six months after completion of RT (Table 1).

Long-term toxicity

A total of 28 (25%) patients developed pharyngeal-laryngeal toxicity, including 23 (21%) requiring permanent gastrostomy tubes, 15 (13%) with at least one episode of aspiration pneumonia, five (4%) requiring a permanent tracheotomy without a laryngectomy, and three (3%) submitted to palliative laryngectomy. The median time of permanent gastrostomy tube placement among the 23 patients was 5.6 years after the completion of (chemo)radiation. Seven patients with no or minimal dysphagia before radiation had a gastrostomy tube placed prior to completion of RT for prophylactic purpose (n = 2) or acute toxicity (n = 5) that proved to be permanent. Among the 16 who had permanent gastrostomy placed after completion of (chemo)radiation, the median

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