



Patients reported outcomes in head and neck

## Favorable patient reported outcomes following IMRT for early carcinomas of the tonsillar fossa: Results from a symptom assessment study



G. Brandon Gunn<sup>a,\*</sup>, Chase C. Hansen<sup>a,e</sup>, Adam S. Garden<sup>a</sup>, Clifton D. Fuller<sup>a,f</sup>, Abdallah S.R. Mohamed<sup>a,g</sup>, William H. Morrison<sup>a</sup>, Steven J. Frank<sup>a</sup>, Beth M. Beadle<sup>a</sup>, Jack Phan<sup>a</sup>, Gregory M. Chronowski<sup>a</sup>, Erich M. Sturgis<sup>b</sup>, Carol M. Lewis<sup>b</sup>, Charles Lu<sup>d</sup>, Kate A. Hutcheson<sup>b</sup>, Tito R. Mendoza<sup>c</sup>, Charles S. Cleeland<sup>c</sup>, David I. Rosenthal<sup>a</sup>

<sup>a</sup> Department of Radiation Oncology; <sup>b</sup> Department of Head and Neck Surgery; <sup>c</sup> Department of Symptom Research; <sup>d</sup> Department of Thoracic/Head & Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, USA; <sup>e</sup> Texas Tech University Health Sciences Center, School of Medicine, Lubbock; <sup>f</sup> Medical Physics Program, The University of Texas Graduate School of Biomedical Sciences, Houston, USA; and <sup>g</sup> Department of Clinical Oncology, University of Alexandria, Egypt

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### ABSTRACT

**Background:** A questionnaire-based study was conducted to assess long-term patient reported outcomes (PROs) following definitive IMRT-based treatment for early stage carcinomas of the tonsillar fossa.

**Methods:** Participants had received IMRT with or without systemic therapy for squamous carcinoma of the tonsillar fossa (T1-2 and N0-2b) with a minimum follow-up of 2 years. Patients completed a validated head and neck cancer-specific PRO instrument, the MD Anderson Symptom Inventory-Head and Neck module (MDASI-HN). Symptoms were compared between treatment groups of interest and overall symptom burden was evaluated.

**Results:** Of 139 participants analyzed, 51% had received ipsilateral neck IMRT, and 62% single modality IMRT alone (no systemic therapy). There were no differences in mean severity ratings for the top-ranked individual symptoms or symptom interference for those treated with bilateral versus ipsilateral neck IMRT alone. However, 40% of those treated with bilateral versus 25% of those treated with ipsilateral neck RT alone reported moderate-to-severe levels of dry mouth ( $p = 0.03$ ). Fatigue, numbness/tingling, and constipation were rated more severe for those who had received systemic therapy ( $p < 0.05$  for each), but absolute differences were small. Overall, 51% had no more than mild symptom ratings across all 22 symptoms assessed. **Conclusions:** The long-term patient reported symptom profile in this cohort of tonsil cancer survivors treated with definitive IMRT-based treatment showed a majority of patients with no more than mild symptoms, low symptom interference, and provides an opportunity for future comparison studies with other treatment approaches.

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For over five decades, definitive radiation therapy (RT)-based treatment has been the primary treatment approach for the majority of patients with oropharyngeal squamous cell carcinoma (OPC) managed at our institution [1]. Within this organ preservation paradigm, surgery (including neck dissection) has generally been reserved for clinical evidence of residual disease following RT [2]. Recently, given advances in surgical approaches, namely transoral and robotic surgery, patients with OPC are increasingly being considered for primary surgical management at many centers.

Specifically, patients with small primary OPC of the tonsillar fossa may be seen as candidates for either a primary RT-based treatment (with or without systemic therapy) or a primary surgical approach (with or without postoperative therapy) [3].

In addition to those achieved using intensity-modulated RT (IMRT) [4], gains in treatment related-toxicity reduction may be realized through selective reduction of the treatment volumes for patients with early stage tonsil cancer. Specifically, for carefully selected patients with well-lateralized carcinomas of the tonsillar fossa, the RT treatment volume can effectively be restricted to treatment of the primary tumor and ipsilateral cervical lymph nodes, rather than the bilateral cervical nodal basins [5]. This unilateral neck RT approach has been shown to subsequently reduce observer-rated toxicity compared to bilateral neck

\* Corresponding author at: Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.

E-mail address: [gbgunn@mdanderson.org](mailto:gbgunn@mdanderson.org) (G.B. Gunn).

treatment volumes when conventional RT techniques were used [6], but the long-term toxicity outcomes of bilateral versus ipsilateral neck IMRT are needed.

Given the overall younger patient demographic and favorable prognosis for most patients presently presenting with OPC, specifically for those with human papillomavirus (HPV)-associated OPC, and thus the potential to live for decades with sequelae of treatment, toxicity reduction is now the current emphasis in numerous ongoing clinical investigations in OPC [7]. Likewise, considering the OPC patient perspective via patient reported outcomes (PRO(s)) has become increasingly important in both outcomes research and clinical care. Given the recent emphasis on long-term toxicity reduction, evolving and potentially competing treatment modalities, and in the absence of RT versus surgery head-to-head comparison data, OPC site-, stage- and treatment-specific PRO(s) are needed to inform patients, clinicians, and investigators.

Toward this end, the specific goals of the present study were to: (1) characterize the pattern of symptoms in tonsil cancer survivors following treatment with IMRT for selected earlier stage disease; (2) explore symptom burden differentials by selected patient/treatment subgroups, including by RT treatment volume (bilateral neck versus ipsilateral neck-only RT) and by receipt of systemic therapy; (3) identify potential patient-, tumor-, and treatment-related factors associated with long-term symptom severity; and (4) generate testable hypotheses for future clinical studies.

## Materials and methods

### Study design

This single-institution questionnaire-based survivorship study was conducted following approval from our Institutional Review Board. Adults previously treated at our institution for head and neck cancer without evidence of active disease were eligible. Participating survivors provided study-specific informed consent and completed the MDASI-HN, which was either self-administered or completed by telephone-based interview. Patient demographic, tumor, and treatment characteristics were collected.

The target cohort for this study was patients previously treated for squamous carcinoma of the tonsillar fossa of selected early T- and N-categories, who at our institution are generally considered potential candidates for RT-based treatment (with or without systemic therapy) and depending on primary site characteristics, receive either ipsilateral or bilateral neck RT [5]. Therefore, for purpose of this analysis, we evaluated only those previously treated with definitive IMRT for squamous carcinomas of the tonsillar fossa, with or without systemic therapy, with or without prior diagnostic surgical procedures, stages TX/1-2, NX/0-2b, and M0, and with a minimum follow up of two years since completing treatment. As patients with locally advanced primary tumors (T3/4) and more advanced neck disease (N2c/3) are generally treated with concurrent chemotherapy, routinely receive bilateral neck RT, and/or are less often seen as candidates for primary surgical resection, they were excluded from this analysis. Patients who were treated with upfront definitive surgical resection of both the primary tumor and neck disease were excluded. Our general OPC treatment philosophies, including selection of patients for systemic therapy [2], IMRT planning and delivery approach [8], and neck management [9] have been previously detailed.

### The MD Anderson Symptom Inventory-Head and Neck module

The MD Anderson Symptom Inventory-Head and Neck module (MDASI-HN) is a brief, reliable validated patient-reported multi-symptom assessment tool [10]. It contains 13 “core items” representing important symptoms common across all cancer types,

9 “head and neck specific items” that represent both the tumor- and treatment-related toxicities symptoms most important to head and neck cancer patients (including acute and late functionally-oriented symptoms), and 6 items of how these symptoms interfere with major activities of daily functioning. Items are rated on 0–10 numeric scales from “not present” to “as bad as you can imagine”, and the interference items are likewise rated from “did not interfere” to “interfered completely”.

### Statistical analysis

Descriptive statistics were used to summarize cohort characteristics. To illustrate the inter-individual symptom experience, both individual patient and summary MDASI-HN scores are displayed, including outlier box plots, where the box represents the interquartile range (IQR), the horizontal line within the box the median sample value, and the whiskers extend to the outermost data point that falls within 1.5 times beyond the IQR, or if the data points do not reach the computed ranges, then the whiskers are determined by the upper and lower most data point values. Group mean and categorical variables were compared with Student *t*- and Pearson's chi-square tests, respectively. In order to better isolate the impact of the elective neck RT volume and systemic therapy on long-term patient symptoms, our predetermined treatment groups of interest for comparison were: (1) ipsilateral neck RT alone versus bilateral neck RT alone and (2) bilateral neck RT alone versus bilateral neck RT and systemic therapy. We also explored symptom severity according to patient neck dissection status. To explore overall symptom burden, the proportion of patients who were symptom free (all symptom items rated 0), had no more than mild symptoms (defined as all ratings <5), had no more than moderate symptoms (defined as all items <7), or had any single symptom item rated severe (defined as any one item rated ≥7), were calculated. The proportions of patients experiencing each level of symptom severity were calculated and distributions presented as heat maps. Hierarchical cluster analysis of symptoms was used to provide a pictorial representation of how symptoms clustered. Univariate and multivariate logistic regression analyses were performed to determine whether the following variables correlated with composite MDASI-HN score: age, sex, smoking status, T-category, N-category, neck RT volume, RT dose, use of systemic therapy, and neck surgery. For this hypothesis generating dataset, a non-Bonferroni-corrected  $\alpha < 0.05$  was considered statistically significant for all utilized measures. All statistical analyses were performed using JMP Pro version 11.2 (SAS Institute Inc, Cary, NC).

## Results

Overall, of the 996 patients approached, 849 had participated in this questionnaire-based study, and of these 450 (53%) had OPC and 237 (28%) had tonsillar fossa primaries. Of these 237 tonsil cancer patients, 81 were excluded for T3/4 primary site disease, 10 for N2c/N3 disease, and 7 for follow-up less than 2 years. One hundred thirty-nine study participants formed the analyzable cohort and completed the MDASI-HN from 07/2013 through 06/2014.

Cohort characteristics are presented in Table 1. Overall, 84% had a minimum follow up of 3 years. Induction chemotherapy regimens were platinum and taxane-based. Overall, 24% of participants had a neck dissection as part of their evaluation or management. Of the 20 patients who received concurrent systemic therapy, cetuximab was most commonly used (50%), followed by cisplatin (40%). Tumor HPV and/or p16 status was available for 61 of the 139 (44%) participants. Of those, 35 (57%) were positive for p16 by immunohistochemistry, 22 (36%) were positive for both the

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