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

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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.

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Portions of this data were presented at the American Society for Clinical Oncology (ASCO) Annual Meeting, Chicago, Illinois, in June 2012.

Conflicts of interest: The authors have no financial conflicts of interest to disclose.

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 individual symptom and interference ratings 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.

Keywords

tonsil cancer; IMRT; patient reported outcomes; symptoms

Introduction

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 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, which 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 to 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 analysis 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 presence of high-risk HPV DNA by in-situ hybridization and p16, and 4 (7%) were negative for both. No participant had a feeding tube present at the time of MDASI-HN collection.

The mean individual, subscale, and composite MDASI-HN symptom and interference item ratings for entire study cohort are shown in Table 2. The mean individual MDASI-HN item ratings and mean comparison results by treatment group are shown in Supplementary Table 1. Regarding our predetermined treatment groups of interest, no statistically significant difference in the individual MDASI-HN item ratings were detected for those receiving ipsilateral neck RT alone versus bilateral neck RT alone, aside from the skin-related item. Regarding bilateral neck RT alone versus bilateral neck RT and systemic therapy treatment groups, mean MDASI-HN item ratings for fatigue, numbness/tingling, constipation, skin and several symptom interference measures were each more severe for those who received systemic therapy. Analysis of symptom severity by patient neck dissection status revealed no statistically significant difference in mean individual MDASI-HN symptom and interference item ratings for those who had pre- or post-RT neck dissection versus no neck dissection (p -value >0.05 for each).

The number of individual MDASI-HN symptom items rated per patient by symptom severity thresholds for the entire study cohort and treatment groups are shown in Supplementary Figures 1 and 2, respectively. Overall, for the 22 MDASI-HN symptom items, the median number of symptoms rated per patient at 0, 1–4, 5–6, and 7–10 were 16, 4, 0, and 0, respectively. The proportion of patients experiencing each level of overall symptom severity (considering all 22 symptom items) by cut points of “symptom free”, “no more than mild”, “no more than moderate”, and “any single item rated severe”, for the overall cohort and by treatment group are shown in Table 3.

Regarding individual MDASI-HN symptom items, the proportions of patients experiencing each level of symptom severity for the entire study cohort are shown in Figure 1. Overall, for all individual symptoms, the majority of patients reported none to mild symptom severity. Likewise, the proportions of patients experiencing each level of symptom severity by treatment groups are shown in Figures 2 and 3 and Supplementary Table 2. For the individual MDASI-HN symptom items, no statistically significant differences were detected between the treatment groups of interest for the proportions with mild, moderate, or severe ratings aside from dry mouth in those receiving bilateral neck versus ipsilateral neck RT alone, with 40% versus 25% reporting moderate-to-severe levels, respectively (p -value=0.03) and aside from problem with mucus in mouth/throat in those receiving bilateral neck RT alone versus bilateral neck RT and systemic therapy, with 0% versus 8% reporting severe levels, respectively (p -value=0.04).

The long-term symptom cluster analysis is presented in Supplementary Figure 3, showing a singular item cluster for xerostomia along with subclusters, such as those dysphagia-related (e.g. choking and difficulty swallowing/chewing) and general symptoms (e.g. fatigue and

sleep disturbance). On both univariate and multivariate analysis, none of the clinical and treatment related variables interrogated were associated with increased composite symptom scores (p -value >0.05 for each).

Discussion

The long-term patient reported symptom and interference profile following IMRT for early tonsil cancer was favorable with low mean severity ratings across individual symptoms and symptom interference, with the majority of participants reporting no more than milder symptom levels for individual symptoms and overall symptom burden. Regarding the top five reported individual symptom items, assessed >2 years after completion of treatment, a limited proportion of patients reported these at higher severity levels, as only 29, 15, 12, 13, and 15% of participants reported moderate-to-severe levels of dry mouth, difficulty swallowing and chewing, problem tasting food, fatigue, and disturbed sleep, respectively.

As the current standard of care for most patients with OPC, definitive IMRT (either with or without systemic therapy) has achieved impressive results in terms of clinical outcomes [8, 11], salivary functional outcomes [4], and quality of life [12]. Specifically, for patients with small volume primary site disease at presentation, characteristics encompassed by this study cohort, excellent outcomes have been reported using definitive IMRT-based approach, with overall survival of 90% and overall late gastrostomy tube rates of $\sim 2\%$ [8]. The PROs reported here would likely have been deemed unobtainable in the previous treatment eras, as studies conducted as recently as the 1990s showed severe late toxicity rates of 30%, even for patients with T1-2 head and neck cancer [13]. Recently, efforts at toxicity reduction in OPC have begun using novel technologies. Often, these approaches are justified as a method of toxicity reduction using such historical comparators, which bear little resemblance to current, modern IMRT practice outcomes; thus, the present study provides a needed modern comparator in terms of late symptom reports.

Additionally, conglomerate “head and neck cancer” symptom datasets, while useful to demarcate the boundaries of the patient experience, may inadvertently omit anatomically- and spatially-dependent differences in toxicity profiles. As part of a systematic effort of RT-attributable toxicity assessment, we herein present a narrow anatomic subset within OPC; that is to say, the gain in specificity of characterization of the post-RT toxicity profile of the presented series of early stage tonsil patients may not reflect the anatomically-proximate, but symptom-distinct profile of early stage base of tongue cancers. Specifically, for example, at our facility, dose to the base of tongue has been correlated with both objective and subjective measures of swallowing dysfunction [14]; the tonsil cancers included in the current series, while in some cases may have partially extended into the base of tongue, generally required dosimetric coverage with definitive doses to no more than half of the ipsilateral adjacent base of tongue. In contrast, primary base of tongue cases generally necessitate minimum doses to the entire base of tongue of 54–70 Gy in order to ensure coverage of gross disease [8]. Also, patients with T1-2 primary tumor confined to the tonsillar fossa (without clinically evident base of tongue and limited, if any, soft palate involvement), essentially half of the cases in the current series, are often safely treatable with ipsilateral neck RT, obviating meaningful dose to much of the tongue base or

contralateral structures. Comparatively, a similar T1-2 base of tongue or soft palate primary case would necessitate obligate contralateral nodal basin coverage in all cases of at least elective dose. For these reasons, the current series should be seen as a definitive for this select cohort of patients for whom we expect a significantly better dose-dependent toxicity profile even compared to other oropharyngeal sub-sites.

In terms of inter-individual symptom severity, it is notable that the largest number of outliers was observed for the number of items rated per patient at severe levels (Supplementary Figure 1). Considering the homogeneity of our study cohort, this suggests patient-specific rather than treatment-related factors contributed to those few with a multitude of severe symptom reports. In cases where any substantive symptom severity was noted, patients were more likely to report a constellation of symptoms, rather than an isolated single symptom, potentially owing to dysfunction in proximate organs-at-risk (e.g. impact of simultaneous parotid and pharyngeal constrictor damage).

Notably and counterintuitively, no statistically significant differences were observed in terms mean severity for the top-ranked individual symptom severity by neck RT laterality, with mean severity for some symptoms actually numerically rated more severe for those receiving ipsilateral neck RT. Aside from dry mouth, there were no differences in the proportion of patients with moderate-to-severe reports for individual symptoms. These findings are potentially due in part to the overall low symptom reports, even when RT was given to the bilateral neck, and the ability of IMRT to mitigate several long-term effects for most patients, potentially, a lack of a RT dose- or more specifically, RT volume-symptom relationship, or influence of patient expectation. When systemic therapy was included as part of treatment, however, statistically significant differences in mean severity were observed for more general (as opposed to head and neck-specific) symptom and symptom interference items. However, for those individual items with statistically detectable differences by treatment group, the magnitude of differences observed were small (<1.1 increase for each) and may not be clinically meaningful. Given the comparatively small number of patients who received systemic therapy and unilateral neck RT, no direct statistical comparisons were made with this group, but were comparable and presented for completeness.

The inherent limitations of single-institution, cross-sectional, and questionnaire-based studies apply here. While we did focus on a specific OPC sub-site, future studies will seek to incorporate baseline and longitudinal PROs, quantitative dosimetric factors, and objective toxicity and functional endpoints. PRO studies for those with more advanced disease and of other OPC sub-sites are worthy of separate study, and these are planned for serial assessment and presentation in short order.

Despite these caveats, this series represents, to our knowledge, the largest cross-sectional PRO assessment of long-term survivors of tonsillar fossa carcinomas. The presented data has significant utility as both a contemporary series and to inform future toxicity reduction efforts, such as through advanced surgical techniques or beam path dose/toxicity reduction using intensity modulated proton radiotherapy [15], both of which are currently being investigated at our center. In sum, with many patients showing either no symptoms, or self-

characterizing symptom severity as no worse than “mild”, alternate treatment paradigms face a high bar for improvement in this anatomic tumor site for whom excellent oncologic outcomes are expected with IMRT-based treatment, and, in our hands at least, minimal late symptom burden and interference, even with the conservative symptom group thresholds applied in this study. In addition to evaluating acute treatment-related symptoms and toxicity, which have been shown to impact late sequelae [16] future efforts should further investigate potential clinical, demographic, biological, dosimetric, and psychosocial correlates of severe toxicity constellations in the subset of patients who experience substantial post-therapy symptom burden, and are potentially to benefit most from alternate treatment approaches, which are increasingly relying on toxicity prediction models [17].

In conclusion, the long-term patient reported symptom burden in this cohort was very favorable, with the majority of patients experiencing no more than mild symptom severity and low symptom interference, with approximately one third experiencing any moderate-to-severe levels of classic late RT-attributable symptoms. The present study not only provides a dataset for potential comparison with surgically treated cohorts, but also provides an opportunity for comparison with patients treated with advanced RT techniques, which have promise to further reduce acute and late toxicity, certain individual symptoms, as well as the overall symptom burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Heat map of the proportion of patients experiencing each level of symptom severity for the 22 individual MDASI-HN symptom items for the entire study cohort.

Figure 2.

Heat map of the proportion of patients experiencing each level of symptom severity for the 22 individual MDASI-HN symptom items for those who received radiation therapy alone (no systemic therapy), by neck radiation therapy treatment group. (RT = radiation therapy)

Figure 3.

Heat map of the proportion of patients experiencing each level of symptom severity for the 22 individual MDASI-HN symptom items for those who received systemic therapy and radiation therapy, by neck radiation therapy treatment group. (RT = radiation therapy)

Table 1

Patient, tumor, and initial treatment characteristics.

	Entire study cohort			Bilateral neck RT			Ipsilateral neck RT			p-value
	n=139			n=68			n=71			
	n	(%)		n	(%)		n	(%)		
Sex										0.019
Male	109	(78)		59	(87)		50	(70)		
Female	30	(22)		9	(13)		21	(30)		
Age at time of RT (years)										0.200
Median	54			55			53			
Range	25-84			25-74			26-84			
Time from end of treatment to MDASI-HN collection (months)										0.462
Median	61			63			59			
Range	24-112			24-112			26-98			
Ethnicity										0.111
White non-Hispanic	133	(96)		65	(96)		68	(96)		
Hispanic	3	(2)					3	(4)		
Other	3	(2)		3	(4)					
Smoking status										0.193
Never smoker	63	(45)		27	(40)		36	(51)		
Former smoker	52	(38)		34	(50)		18	(25)		
Current smoker	24	(17)		7	(10)		17	(24)		
T-category										0.002
T1	78	(56)		29	(43)		49	(69)		
T2	61	(44)		39	(57)		22	(31)		
N-category										0.522
N0	19	(14)		8	(12)		11	(15)		
N1	35	(25)		11	(16)		24	(34)		
N2a	15	(11)		5	(7)		10	(14)		
N2b	70	(50)		44	(65)		26	(37)		

	Entire study cohort		Bilateral neck RT		Ipsilateral neck RT		p-value
	n=139		n=68		n=71		
	n	(%)	n	(%)	n	(%)	
Neck dissection							
None	105	(76)	52	(76)	53	(74)	0.742
Before RT	19	(14)	10	(15)	9	(13)	
After RT	15	(10)	6	(9)	9	(13)	
Radiation therapy dose (Gy)							
Mean (SD)	66.9 (1.9)		67.5 (2.2)		66.3 (1.3)		
Number of fractions (#)							
Mean (SD)	30.9 (2.2)		31.2 (2.5)		30.5 (1.9)		
Initial treatment							
RT alone	86	(62)	30	(44)	56	(79)	
IC → RT alone	33	(24)	23	(34)	10	(14)	
Concurrent ChemoRT	17	(12)	13	(19)	4	(6)	
IC → ChemoRT	3	(2)	2	(3)	1	(1)	

RT = radiation therapy, IC = induction chemotherapy, ChemoRT = chemoradiation, SD = standard deviation

Table 2

Mean individual MDASI-HN symptom item and symptom interference ratings (and standard deviation) by order of decreasing mean severity for the entire study cohort.

	Entire study cohort	
	<i>n</i> =139	
Core items	Mean	SD
Dry mouth	2.89	2.66
Fatigue	1.54	2.28
Sleep disturbance	1.51	2.51
Difficulty remembering	1.35	2.02
Drowsiness	1.12	2.00
Numbness/tingling	1.06	1.93
Distress	0.96	2.15
Pain	0.85	1.86
Sadness	0.60	1.69
Lack of appetite	0.50	1.67
Shortness of breath	0.47	1.21
Nausea	0.06	0.40
Vomiting	0.05	0.37
SUBTOTAL (13 core items)	0.95	1.95
Head and neck items		
Difficulty swallowing/chewing	1.84	2.38
Problem tasting food	1.58	2.37
Problem with mucus in mouth/throat	1.45	2.15
Choking	1.29	2.20
Problem with teeth/gums	1.01	2.06
Difficulty with voice	0.69	1.59
Constipation	0.65	1.79
Skin pain/burning/rash	0.49	1.52
Mouth/throat sores	0.42	1.45
SUBTOTAL (9 head and neck items)	1.05	2.03
TOTAL (all 22 symptom items)	1.02	2.02
Symptom interference		
Normal work	0.76	1.91
General activity	0.75	2.02
Mood	0.66	1.93
Enjoyment of life	0.65	1.65
Walking	0.43	1.37
Relations with others	0.42	1.42
TOTAL (6 symptom interference items)	0.61	1.74

SD = standard deviation

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Proportion of patients experiencing each level of overall symptom severity (across all 22 MDASI-HN symptom items), by treatment group.

Table 3

	Entire study cohort	Bilateral neck RT (n=68)				Ipsilateral neck RT (n=71)					
		RT alone		Systemic Therapy and RT		RT alone		Systemic Therapy and RT			
		n	(%)	n	(%)	n	(%)	n	(%)		
<hr/>											
		n=139	n=30	n=38	n=56	n=15					
<hr/>											
Symptom free (ratings of all zeros)		14	(10)	1	(3)	1	(3)	11	(20)	1	(7)
<hr/>											
No more than mild (all ratings <5)*		71	(51)	13	(43)	21	(56)	28	(50)	9	(60)
<hr/>											
No more than moderate (all ratings <7)*		102	(73)	25	(83)	26	(69)	38	(68)	13	(87)
<hr/>											
Any single item rated severe (7)		37	(27)	5	(17)	12	(32)	18	(32)	2	(13)
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* absolute number and proportions of patients are inclusive of previous group; cumulative proportions will exceed 100%