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# Intensity-Modulated Proton Therapy (IMPT) versus Intensity-Modulated Photon Radiotherapy (IMRT) for Oropharyngeal Cancer: First Comparative Results of Patient-Reported Outcomes

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## Abstract

**Purpose—**We hypothesized that patients with oropharyngeal cancer treated with intensity-modulated proton therapy (IMPT) would have lower symptom burdens, as measured by patient-reported outcome (PRO) surveys, than patients treated with intensity-modulated photon therapy (IMRT).

**Methods and Materials—**Patients were treated for oropharyngeal cancer from 2006 to 2015 through prospective registries with concurrent chemo-IMPT or chemo-IMRT and completed the MD Anderson Symptom Inventory-Head and Neck Cancer (MDASI-HN) module at various times before treatment (baseline), during treatment (acute), within the first 3 months after treatment (subacute), and afterward (chronic phases). Individual symptoms and the top 5 and top 11 most severe symptoms were summarized and compared between the radiotherapy modalities.

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**Conflicts of Interest**: The MDASI survey is patented and licensed to The University of Texas MD Anderson Cancer Center and Dr. Charles Cleeland. The authors report no other conflicts of interest.

**Results—**PRO data were collected and analyzed from 35 patients treated with chemo-IMPT and 46 treated with chemo-IMRT. Baseline symptom burdens were similar between both groups. The overall top 5 symptoms were food taste problems (mean score 4.91 [on a 0–10 scale]), dry mouth (4.49), swallowing/chewing difficulties (4.26), lack of appetite (4.08), and fatigue (4.00). Among the top 11 symptoms, changes in taste and appetite during the subacute and chronic phases favored IMPT (all $P<0.048$). No differences in symptom burden were detected between modalities during the acute and chronic phases by top-11 symptom scoring. During the subacute phase, the mean (±SD) top 5 MDASI scores were 5.15 ± 2.66 for IMPT vs. 6.58 ± 1.98 for IMRT ($P=0.013$).

**Conclusions—**Using the MDASI-HN, symptom burden was reduced in the IMPT patients during the subacute recovery phase following treatment. A prospective randomized clinical trial is underway to define the value of IMPT in the management of head and neck tumors.

### Keywords

Intensity-modulated proton therapy; intensity-modulated photon therapy; patient-reported outcome; symptom burden; oropharyngeal cancer; radiation therapy; chemoradiation

## INTRODUCTION

Oropharyngeal cancer is one of the most common head and neck squamous cell carcinomas, with an increasing prevalence and substantial morbidity and mortality if left untreated. Radiation therapy remains an integral component of definitive treatment for non-metastatic oropharyngeal cancer, regardless of the human papillomavirus (HPV) status [1, 2]. Survivorship, patient experience, and functioning during and after treatment are important considerations, as these malignancies are both highly curable and can occur in relatively young individuals who may remain in the workforce [3].

Intensity-modulated proton therapy (IMPT) is increasingly being used for oropharyngeal cancer [4–6]. Radiotherapy caused high symptom burden due to local and systemic inflammatory responses, which has been documented under careful assessment with validated PRO tools quantitatively [7, 8]. The hope is that clinical benefit from IMPT may translate into better patient-reported outcomes (PROs) than those obtained after intensity-modulated photon radiation therapy (IMRT), because the physical properties of protons can be exploited to better spare organs at risk from unnecessary radiation, which presumably would reduce clinical symptom burdens. Although IMRT plans are capable of exposing nontarget organ structures such as the anterior oral cavity and brainstem with only low-radiation dose beam path-related toxicity [9], IMPT has clear dosimetric advantages in even better protecting these surrounding normal tissues in patients undergoing treatment for oropharyngeal cancer [4, 10] (Fig. 1).

Here we report PROs obtained via the MD Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) [11, 12] from patients with oropharyngeal cancer treated with either chemo-IMPT or chemo-IMRT. We hypothesized that patients treated with IMPT would have lower symptom burdens as measured by MDASI-HN. The PRO surveys were collected prospectively from patients enrolled in registries, and involved evaluating symptom

burdens at baseline, during therapy, and afterward. Findings from the two groups (IMPT vs. IMRT) were compared in retrospective analyses.

## METHODS AND MATERIALS

### Patient Selection and Treatment Characteristics

This work was approved by the institutional review boards of the participating clinics. All members involved in this research received adequate training regarding protection of human subjects and patient confidentiality. All patients consented to being enrolled in registries at their first clinical appointment with radiation oncology providers. Consecutive patients from both the IMPT (protocol PA11-0803) and the IMRT registries were included if they met the following criteria: (1) older than 18 years old; (2) a tissue diagnosis of squamous cell carcinoma originating in the oropharynx (base of tongue, tonsil, or other subsites); (3) receipt of concurrent chemotherapy as part of definitive therapy (i.e., no surgical resection of either primary tumors or nodal stations at initial management; induction chemotherapy was allowed); (4) no prior radiotherapy; (5) no evidence of distant metastases; (6) receipt of scanning-beam IMPT or photon-based IMRT treatment at a single institution (Fig. 1); and (7) completed the MDASI once before beginning radiotherapy (baseline) and at least 3 of the 6 weekly MDASI surveys scheduled during RT (acute phase) or 1 survey within the first 3 months after radiotherapy (subacute phase); chronic phase data (i.e., surveys collected more than 3 months after radiotherapy) were optional. The acute, subacute, and chronic phases were defined based on the analysis plan for an ongoing trial at the same institution. Patients in the IMPT group completed MDASI forms from June 1, 2012 to July 28, 2015, and follow-up data were available for up to 24 months after treatment; the photon-IMRT group provided MDASI data from Feb 28, 2006 to Feb 26, 2014, with follow-up PRO data available for up to 20 months. Patient and treatment-based information, including demographics, disease stage, tumor histology, and radiotherapy and chemotherapy details were also recorded. No patients received 3D conformal photon-based RT or passive scatter proton therapy.

Baseline PRO findings were typically obtained after induction chemotherapy, if given, or before beginning chemoradiation. Surveys were to be given weekly during the 6- to 7-week radiotherapy period (the acute phase). Data in the subacute phase were obtained during the first 3 months after the end of radiotherapy and grouped into every-2-weeks intervals (2, 4, 6, 8, and 10 weeks after treatment). Finally, in the chronic phase, data were summarized for PROs that had been reported 3 months after treatment, and at 6, 9, 12, 16, 20, and 24 months (6 time points) after completion of the radiotherapy.

The techniques [10], dosimetric and planning considerations [13, 14], and initial clinical outcomes [7] of IMPT for oropharyngeal cancer have been reported elsewhere. The use of modern-era photon-based IMRT and its favorable outcomes [15] have also been reported. To allow adequate follow-up during the subacute and chronic phases, for the IMPT group the first 50 consecutive patients with a biopsy-confirmed diagnosis of oropharyngeal cancer were selected; 48 patients provided PROs at baseline and weekly during treatments. In the IMRT group, 91 consecutive patients with the same diagnosis were similarly selected, based on the availability of completed PRO surveys at baseline and during radiotherapy. Thirty-

five patients in the IMPT group (73%) received concurrent chemotherapy, as did 46 (51%) of the IMRT patients; these patients were the subjects of this planned analysis.

## The MD Anderson Symptom Inventory-Head and Neck Module (MDASI-HN) for Patient-Reported Outcomes

The MDASI-HN survey is a validated symptom burden instrument [7, 12] which reports distress and changes in a patient's condition as related to head and neck cancer and its treatments. Several domains are surveyed including general symptom assessments, psychosocial properties, pain, and functions [16]. The results correlate well with physician-assessed outcomes, e.g., radiation-induced mucositis as determined by National Cancer Institute-Common Terminology Criteria for Adverse Events (ver. 3.0) [11]. The 2-page, easy-to-use MDASI-HN survey asks individual patients to rate the severity of their symptoms over the past 24 hours; individual items are then scored from 0 (not present) to a maximum of 10 (as bad as the individual can imagine). These questionnaires can be completed in person or by mail, over the phone, or via secure electronic methods and are typically arranged by research nurses and coordinators 1 to 3 weeks in advance of the scheduled time points (if they cannot be done in the clinic).

The MDASI-HN includes 22 items that are grouped into two separate domains: core symptoms (13 items) and head and neck cancer module items (9 items) [7]. We did not distinguish between these domains in our analyses. Six (6) additional questions were related to the extent to which symptoms interfered with daily living, but because one of those items (i.e., work interference) was inconsistently recorded in the IMRT database, they were not included in this analysis.

## Statistical Analyses

All 35 patients in the IMPT group had baseline data available, 33 (94%) had acute data, 26 (74%) had subacute data, and 18 (51%) had chronic phase data available. The corresponding numbers for the IMRT group were: 46 (100%) baseline, 46 (100%) acute, 43 (93%) subacute, and 28 (61%) chronic. Of the 22 MDASI items recorded, the top 5 (most severe) symptoms of the current study were extracted based on a previously published strategy [8]; the average of the top 11 (most severe) MDASI items of the current study was also calculated and analyzed with paired Student's *t* tests. Cross-sectional analyses were done in which the proportion of moderate and severe symptoms (defined as scores of 4–10 on any surveyed item) at each time point was evaluated by chi-square regression.

Two separate cutoffs were used, one involving all symptom scores ranging from 0–10, and the other involving only moderate and severe symptoms, i.e., those with a cutoff point of 4 or above; effect sizes (Cohen's *d*) [17] were also estimated and reported. Longitudinal data regression models were included and fit to the specified time-dependent intercept terms. All analyses were done with SAS/STAT for Windows (version 9.2; SAS Institute Inc., Cary, NC).

# RESULTS

## Patient, Tumor and Treatment Characteristics

Patient, tumor and treatment characteristics for both groups are shown in Table 1. The IMPT group included slightly more patients with base-of-tongue tumors, and more patients in the IMPT group had smaller (T1/T2) tumors. TNM staging distribution was more balanced, with most patients in both groups having stage III/IVa-b cancer. Concurrent chemotherapy regimens included cisplatin, cetuximab, or carboplatin-based regimens. More patients received induction chemotherapy in the IMPT (74%) than the IMRT (24%) group, and human papillomavirus (HPV) status was more commonly unknown in the IMRT patients (both characteristics statistically significant between groups). The radiation doses were comparable between the two groups.

## Symptom Burden by Radiation Modality and Temporal Phases

The median follow-up times since the completion of radiation therapy were 7.7 months (25th–75th percentiles, 3.97–22.77 months) for the IMPT group and 2.68 months (0.30–10.27 months) for the IMRT group. The mean scores of the top 11 MDASI symptoms are listed in Table 2 (for all MDASI symptom items, see Supplementary Table 1), separated according to radiation modality and treatment phase. Baseline MDASI scores were balanced between the two treatment groups for 21 of the 22 items, except that the IMRT group had higher scores for difficulty with swallowing/chewing at baseline ($P$=0.041). Symptoms during the acute phase (during treatment) were comparable in both groups, with no differences detected in any item. Among the top 11 symptoms, taste changes (during the subacute period, i.e., within 3 months after treatment) and appetite (during both the subacute and chronic [late after treatment] phases) favored IMPT (all $P$<0.048). No difference in symptom burden was detected between the two radiation modality groups during the acute and chronic phases according to top-11-symptom scoring. However, the top-5-symptom scores were higher during the subacute phase for the IMRT group, indicating a greater burden (mean top 5 scores 5.15 ± 2.66 IMPT vs. 6.58 ± 1.98 IMRT; $P$=0.013; Fig. 2).

## Moderate to Severe Symptoms by Radiation Modality

The numbers of patients with moderate to severe symptoms (i.e., symptoms scored as ≥4) among the top 11 MDASI items are reported in Table 3 (for all MDASI symptom items, see Supplementary Table 2). At baseline, the symptom burden proportions were balanced except for swallowing/chewing ($P$=0.014, favoring IMPT). Similarly, no differences were seen between groups during the acute phase, but during the subacute phase (immediate after treatment) problems with food taste and mucus were significantly better for the patients who received IMPT ($P$<0.039 for both). Significant proportions of patients in both groups still experienced moderate to severe symptoms during the chronic phase (i.e., >3 months after completion of treatment).

## Effect Size Analysis

The overall trend of symptom burden evolution over time, as measured by the top 5 MDASI items, showed an advantage for IMPT in terms of symptom relief during the subacute phase;

the Cohen's *d* effect sizes of the PRO differences between IMPT and IMRT for food taste and lack of appetite were 0.63 and 0.50, respectively, and the Cohen's *d* effect size for the top 5 MDASI scoring comparison between IMPT and IMRT was 0.61.

Even when only moderate and severe symptoms were considered (those with scores of ≥4), this difference during the subacute phase remained significant (IMPT 8.7 ± 8.8 vs. IMRT 36.4 ± 22.4, $P$=0.004, effect size [Cohen's $d$] = 1.63).

## DISCUSSION

Using the MDASI-HN PRO in patients with oropharyngeal tumors treated with concurrent chemoradiation strategies using IMPT and IMRT, a potential reduction in symptom burden during the first 3 months after completing treatment was observed with IMPT, however, no symptom burden reduction was identified in either the acute or chronic phases of treatment. Currently, there are limited PRO data in the literature [18], and this is the first report of IMPT compared to IMRT. The potential advantages of IMPT over IMRT in oropharyngeal tumors arise due to the elimination of unnecessary radiation outside of the clinical target volumes. In this small cohort, we were unable to substantiate an improvement in quality of life using IMPT during treatment and as measured by the MDASI-HN PRO. This observation was unexpected due the fact we have observed a significant reduction of gastrostomy tubes during treatment with IMPT. This may be a reflection of the small sample size in this retrospective cohort, the sensitivity of the PRO instrument, or that no true difference exists in patient-reported quality of life between IMPT and IMRT. A prospective randomized clinical trial is currently underway which will provide more definitive information regarding patient reported outcomes using IMPT.

In addition to PRO reporting, the ongoing clinical trial (NCT01893307) will evaluate long-term cancer outcome, toxicities, and cost-effectiveness to determine if there is substantial value in the use of IMPT in oropharyngeal cancer treatments.

The difference in swallowing/chewing at baseline was likely not clinically significant, as the difference between the two means by modality was 1.04 only (out of a 10-point scale). However, the other differences in the subacute phase (Food Taste, Δ=1.94; Appetite, Δ=1.69) and chronic phase (Appetite, Δ=2.02) appeared larger, which provided a *signal* that this could be clinically significant. The clinical minimally important difference (MID) has been well-studied and summarized previously [34, 35], which stated that if the detected numerical difference reaches or exceeds *half* the standard deviation as recorded by these cohorts, it will need to be considered that such difference may actually be *both* statistically and also clinically significant. Currently, the 3 subacute and chronic phase indices above had corresponding standard deviations ranging from 1.22–3.60, as a result, any PRO difference greater than 0.61–1.80 (*half* of S.D.) should deserve consideration that it may truly be *clinically* significant in this context. By the same token, the difference between the top 5 MDASI scoring in the subacute phase was only 1.43, and this barely met the "half-standard-deviation" rule (S.D. was 2.66 for IMPT, resulting in an MID of 1.33) for which we noted that the actual PRO-based benefit may be small as measured retrospectively in this analysis. For example, while we observed that based on physician-assessed outcomes, 20% of patients

receiving IMPT required a feeding tube versus 48% of those receiving IMRT (P=0.037) [31], by PRO measures the differences in acute and subacute phases seemed to be less. Prospective clinical trials may help decipher and clarify the apparent discrepancies between physician-reported vs. PROs.

Our study had several limitations. First, the analyses were retrospective, even though the data had been collected prospectively via established registries. Second, the patients from the IMRT cohort were diagnosed earlier. The third shortcoming was missing data during the chronic posttreatment phase; this was due predominantly to relatively shorter follow-up, particularly for patients given IMRT. Fourth, more patients received induction chemotherapy in the IMPT group (77% vs. 24% in the IMRT group), which might influence our results. However, when we examined the top 11 MDASI symptoms separately for patients who did *not* receive induction chemotherapy (9 in the IMPT group vs. 35 patients in the IMRT group), no significant differences were found between radiation modalities (data not shown); the increased use of induction chemotherapy was a reflection of our institutional practice particularly in the more modern era. Although receipt of previous systemic treatment has been linked with higher symptom burden [32] which would favor the IMRT cohort, the IMPT group did have smaller tumors (statistically significant, s.s.) and perhaps less nodal cancer burdens (not s.s.); these uncontrolled biases (including types of induction and concurrent chemotherapies) were not adjusted in analyses due to small sample sizes, although there were no overall differences as noted by TNM staging distribution. For future prospective studies, increasing sample sizes and also incorporating Common Terminology for Adverse Events endpoints for additional correlative study as well as other PRO survey tools, such as the MD Anderson Dysphagia Inventory [33], will be helpful for further addressing these issues.

In conclusions, using the MDASI-HN PRO, a reduction in symptom burden was identified in the subacute phase of treatment in patients with oropharyngeal cancer who underwent concurrent chemoradiation with IMPT. IMPT patients may have a more rapid return to normal function during the first 3 months after treatment. Prospective clinical trials with PROs are urgently needed to define the value of proton therapy in the management of oropharyngeal tumors.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## SUMMARY

Using the MDASI-HN patient-reported outcomes survey, a reduction in symptom burden was identified in the subacute phase of treatment in patients with oropharyngeal cancer who underwent concurrent chemoradiation with IMPT. IMPT patients may have a more rapid return to normal function during the first 3 months after treatment. A prospective randomized clinical trial is underway to define the value of IMPT in the management of head and neck tumors.

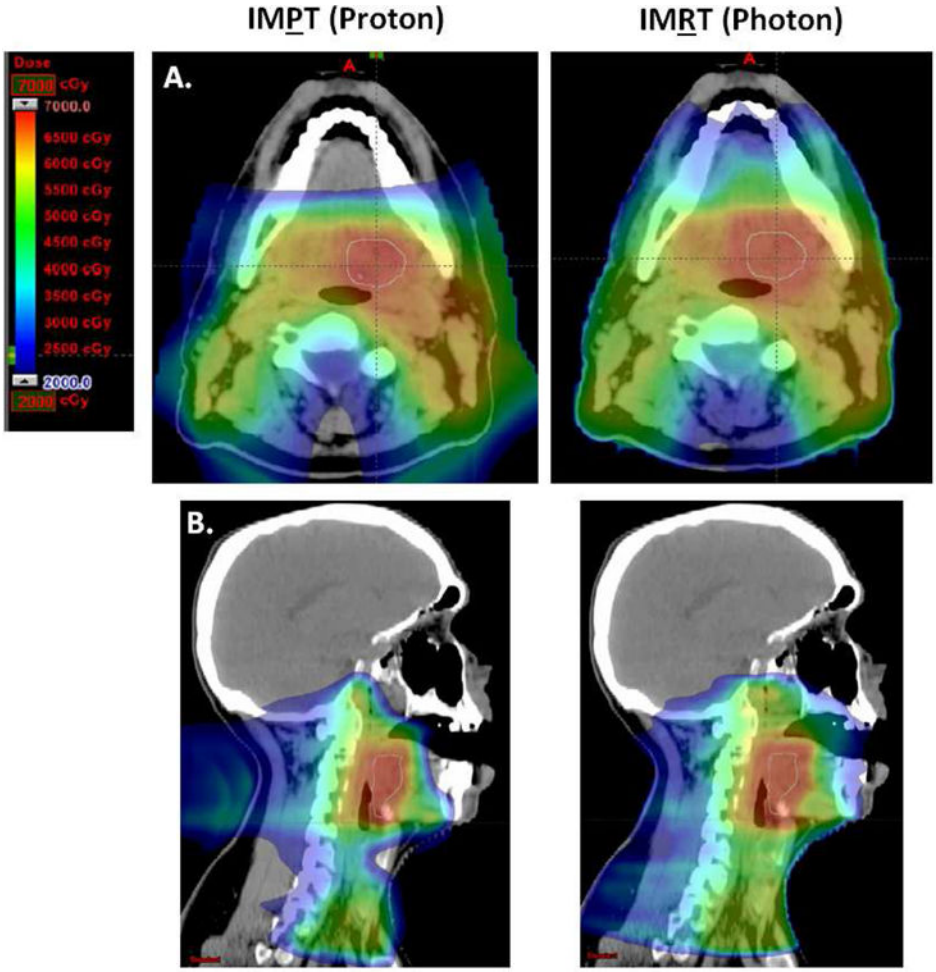


**Fig. 1.**

Axial (row A) and sagittal (row B) CT images of radiation treatment plans for a patient with oropharyngeal cancer illustrate the dosimetric advantages of intensity-modulated proton therapy (IMPT, left) over conventional intensity-modulated photon radiation therapy (IMRT, right).

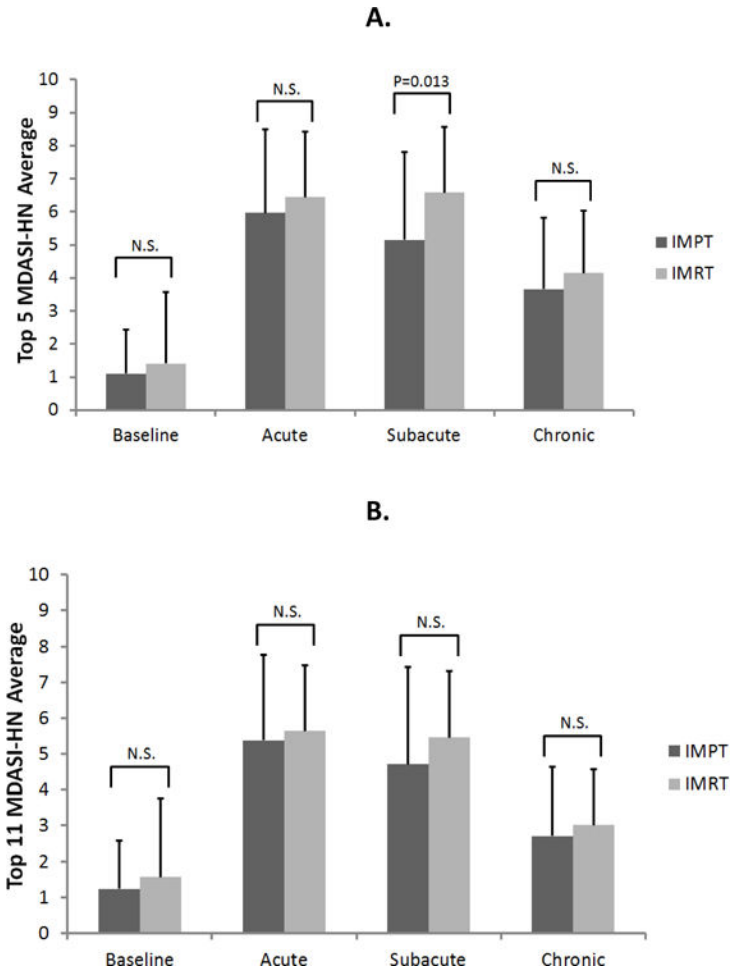


**Fig. 2.**

Mean scores on the top 5 (A) and top 11 (B) items in the MD Anderson Symptom Inventory-Head and Neck Module for intensity-modulated proton versus intensity-modulated (photon) radiation therapy. All temporal phases are included. Error bars represent 1 standard deviation from mean values.

## Table 1

Patient, Tumor and Treatment Characteristics in the IMPT and IMRT groups

| | Treatment Modality | | *P* Values[a] |
|---|---|---|---|
| | IMPT (*n*=35), % | IMRT (*n*=46), % | |
| Mean age, years (SD) | 59.1 (10.2) | 58.2 (9.9) | 0.70 |
| Sex | | | 0.43 |
| Male | 30 (85.7) | 42 (91.3) | |
| Race | | | 0.68 |
| White | 31 (88.6) | 42 (91.3) | |
| Other | 4 (11.4) | 4 (8.7) | |
| Primary tumor location | | | 0.029 |
| Base of tongue | 20 (57.1) | 23 (50.0) | |
| Tonsil | 11 (31.4) | 23 (50.0) | |
| Other | 4 (11.4) | 0 (0.0) | |
| Clinical T status | | | 0.020 |
| T1/T2 | 31 (88.6) | 28 (60.9) | |
| T3/T4 | 4 (11.4) | 17 (37.0) | |
| Clinical N status | | | 0.11 |
| N0-2a | 15 (42.9) | 12 (26.1) | |
| N2b-3 | 20 (57.1) | 34 (73.9) | |
| TNM Stage | | | 0.68 |
| I | 1 (2.9) | 1 (2.2) | |
| II | 1 (2.9) | 2 (4.4) | |
| III | 9 (25.7) | 7 (15.2) | |
| IVA-B | 24 (68.6) | 36 (78.3) | |
| Induction chemotherapy | | | <.0001 |
| Yes | 26 (74.3) | 11 (23.9) | |
| No | 9 (25.7) | 35 (76.1) | |
| Total radiation dose, Gy or Gy(RBE) | | | 0.0019 |
| Mean (SD) | 67.0 (4.1) | 69.3 (2.4) | |
| Median (Min-Max) | 70.0 (59.0–70.0) | 70.00 (58.0–70.0) | |
| HPV_P16 status | | | <.0001 |
| Negative | 2 (5.7) | 2 (4.4) | |
| Positive | 26 (74.3) | 6 (13.0) | |
| Unknown | 7 (20.0) | 38 (82.6) | |

P values were derived from chi-square tests for categorical variables and analysis of variance for continuous variables.

Abbreviations: IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated (photon) radiotherapy; SD, standard deviation; HPV, human papillomavirus.

**Table 2**

Average symptom burden in the top 11 (most severe) items on the MD Anderson Symptom Inventory items, stratified by radiation modality and time

| | Burden at Baseline | | | Burden in Acute Phase | | | Burden in Subacute Phase | | | Burden in Chronic Phase | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Top 11 MDASI-HN Symptoms (In Descending Order by Burden)** | **IMPT (n=35)** | **IMRT (n=46)** | ***P* Value** | **IMPT (n=33)** | **IMRT (n=46)** | ***P* Value** | **IMPT (n=26)** | **IMRT (n=43)** | ***P* Value** | **IMPT (n=18)** | **IMRT (n=28)** | ***P* Value** |
| Food Taste | 1.09 (1.93) | 1.07 (2.34) | | 6.88 (2.75) | 7.65 (2.54) | | 5.76 (3.60) | 7.70 (2.44) | 0.010 | 4.50 (3.43) | 4.43 (2.99) | |
| Dry Mouth | 1.14 (1.96) | 0.91 (2.21) | | 5.55 (3.13) | 6.24 (2.57) | | 5.27 (3.28) | 6.65 (2.51) | | 5.47 (3.06) | 5.79 (2.44) | |
| Swallowing/Chewing | 0.83 (1.22) | 1.87 (2.76) | 0.041 | 6.24 (3.03) | 6.17 (2.81) | | 5.19 (3.07) | 6.40 (2.62) | | 3.76 (3.05) | 3.18 (2.64) | |
| Fatigue | 1.68 (2.00) | 1.80 (2.60) | | 5.33 (3.01) | 6.00 (2.49) | | 4.69 (3.00) | 5.77 (2.47) | | 2.53 (2.18) | 3.14 (2.26) | |
| Pain | 1.77 (2.76) | 1.83 (2.92) | | 5.97 (2.72) | 5.09 (2.41) | | 4.19 (3.18) | 4.05 (2.81) | | 1.59 (2.21) | 1.21 (1.66) | |
| Appetite | 0.89 (1.79) | 1.39 (2.53) | | 5.85 (3.27) | 6.13 (3.04) | | 4.68 (3.53) | 6.37 (3.21) | 0.048 | 2.12 (3.08) | 4.14 (3.01) | 0.036 |
| Mucus | 0.57 (1.17) | 1.35 (2.68) | | 5.73 (2.91) | 6.09 (2.78) | | 4.88 (3.66) | 6.14 (2.92) | | 2.24 (2.84) | 2.89 (2.64) | |
| Sleep | 2.03 (2.58) | 2.11 (2.82) | | 4.36 (3.54) | 4.72 (2.92) | | 4.04 (3.69) | 4.00 (2.68) | | 2.47 (2.98) | 2.57 (2.41) | |
| Mouth Sores | 0.43 (0.95) | 0.93 (2.38) | | 5.48 (2.84) | 5.76 (3.05) | | 5.35 (3.51) | 5.00 (3.23) | | 1.28 (3.20) | 1.39 (1.89) | |
| Drowsiness | 1.46 (2.08) | 1.78 (2.80) | | 4.55 (3.34) | 4.93 (2.83) | | 4.35 (3.16) | 4.63 (2.73) | | 2.18 (2.56) | 2.11 (2.38) | |
| Distress | 1.83 (2.70) | 2.17 (2.46) | | 3.21 (2.90) | 3.24 (2.87) | | 3.42 (3.35) | 3.40 (2.63) | | 2.00 (3.02) | 2.21 (2.57) | |

Values shown are mean symptom scores (SD).

*P* values were derived from analysis of variance or Student's *t* tests for continuous variables.

Abbreviations: IMPT, Intensity-modulated proton therapy; IMRT, intensity-modulated (photon) radiotherapy.

**Table 3**

Numbers of patients with moderate to severe symptoms (scores of 4–10) on the top 11 (most severe) MD Anderson Symptom Inventory items, stratified by radiation modality and time

| | Burden at Baseline | | | Burden in Acute Phase | | | Burden in Subacute Phase | | | Burden in Chronic Phase | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Top 11 MDASI-HN Symptoms (In Descending Order by Burden)** | **IMPT (n=35)** | **IMRT (n=46)** | ***P* Value** | **IMPT (n=33)** | **IMRT (n=46)** | ***P* Value** | **IMPT (n=26)** | **IMRT (n=43)** | ***P* Value** | **IMPT (n=18)** | **IMRT (n=28)** | ***P* Value** |
| Food Taste | 5 (14.3) | 4 (8.7) | | 30 (91.0) | 43 (93.5) | | 17 (65.4) | 40 (93.0) | 0.003 | 9 (50.0) | 17 (60.7) | |
| Dry Mouth | 3 (8.6) | 5 (10.9) | | 23 (69.7) | 40 (87.0) | | 17 (65.4) | 36 (83.7) | | 14 (77.8) | 23 (82.1) | |
| Swallowing/Chewing | 1 (2.9) | 10 (21.7) | 0.014 | 27 (81.8) | 36 (78.3) | | 17 (65.4) | 35 (81.4) | | 7 (38.9) | 10 (35.7) | |
| Fatigue | 8 (22.9) | 9 (19.6) | | 23 (69.7) | 37 (80.4) | | 19 (73.1) | 35 (81.4) | | 5 (27.8) | 14 (50.0) | |
| Pain | 6 (17.1) | 10 (21.7) | | 26 (78.8) | 34 (73.9) | | 13 (50.0) | 23 (53.5) | | 3 (16.7) | 4 (14.3) | |
| Appetite | 1 (2.9) | 7 (15.2) | | 25 (75.8) | 34 (73.9) | | 15 (57.7) | 32 (74.4) | | 4 (22.2) | 14 (50.0) | |
| Mucus | 2 (5.7) | 7 (15.2) | | 24 (72.7) | 34 (73.9) | | 16 (61.5) | 36 (83.7) | 0.038 | 5 (27.8) | 10 (35.7) | |
| Sleep | 9 (25.7) | 11 (23.9) | | 17 (51.5) | 28 (60.9) | | 14 (53.9) | 25 (58.1) | | 6 (33.3) | 10 (35.7) | |
| Mouth Sores | 1 (2.9) | 4 (8.7) | | 26 (78.8) | 35 (76.1) | | 18 (69.2) | 30 (69.8) | | 2 (11.1) | 4 (14.3) | |
| Drowsiness | 5 (14.3) | 9 (19.6) | | 19 (57.6) | 28 (60.9) | | 17 (65.4) | 29 (67.4) | | 4 (22.2) | 6 (21.4) | |
| Distress | 10 (28.6) | 12 (26.1) | | 15 (45.5) | 18 (39.1) | | 11 (42.3) | 21 (48.8) | | 4 (22.2) | 7 (25.0) | |

*P* values derived from chi-square tests for categorical variables.

Abbreviations: IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated (photon) radiotherapy.