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ORIGINAL RESEARCH

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Subjective functional outcomes in oropharyngeal cancer treated with induction chemotherapy using the MD Anderson Symptom Inventory (MDASI)

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Abstract

Objectives: Evaluate the use of induction chemotherapy (IC) in oropharyngeal cancer (OPC) and its impact on subjective functional outcomes using a validated MD Anderson Symptom Inventory-Head and Neck (MDASI-HN) survey tool.

Methods: A single institution retrospective review of OPC patients who received IC, including reasons given for using IC, regimens employed, responses, and patient-reported outcomes (PRO). The latter included pain, distress, dysphagia, xerostomia, and feeding tube placement and dependency. PRO's were assessed using the validated MD Anderson Symptom Inventory-Head and Neck (MDASI-HN) conducted at baseline, during treatment, and at six-month follow up.

Results: One hundred and twenty-five patients were evaluable. They were more likely to have large primary and/or bulky or low neck nodal disease as a reason for IC. A taxane-containing regimen was most common. Primary tumor response was seen in 83.2% and the nodal response in 81.6%. Pain and xerostomia improved with IC, dysphagia was not adversely affected with IC. These symptoms all increased with consolidation chemoradiotherapy (CRT) but returned to baseline by 6 months post treatment. Feeding tube placement did not increase with IC but did with CRT, most patients were no longer feeding tube dependent at 6 months.

Conclusion: This retrospective review of subjective functional outcomes, especially swallowing and feeding tube dependency, using the MDASI survey tool in 125 oropharyngeal cancer patients with large primary tumors and/or bulky adenopathy treated predominantly with platinum-taxane based induction chemotherapy showed

This study was conducted entirely at University of Texas MD Anderson Cancer Center in Houston, TX.

that such outcomes were not adversely impacted. While not standard, such approach may be beneficial in such patients.

Level of Evidence: 2.

KEYWORDS

induction chemotherapy, oropharyngeal carcinoma, patient outcomes

1 | BACKGROUND

Oropharyngeal carcinoma (OPC) is a head and neck squamous cell carcinoma (HNSCC), commonly associated with the Human Papilloma Virus (HPV). It can arise from the soft palate, tonsil, base of the tongue, pharyngeal wall, or the vallecula; although tonsil and base of tongue are the most common primary sites. Approximately 100 000 cases of oropharyngeal cancer are diagnosed on a yearly basis world-wide.[1] There has been a shift over the past decade in the demographics of OPC due to the rise of HPV related cases and the decline of cases associated with tobacco and alcohol. Although HPV is a favorable prognostic factor, the management of HPV positive vs HPV negative cases remains relatively similar. Thus, the choice of systemic therapy for OPC patients is determined based on stage, performance status, and goals of therapy independent of etiology. Per National Comprehensive Cancer Network (NCCN) guidelines, the preferred approach in locally advanced disease is concurrent chemotherapy and radiotherapy (CRT) with cisplatin chemotherapy based on Phase III studies and the comprehensive Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC).[2,3] Cetuximab is an alternative to cisplatin,[4] although recent studies demonstrate better survival with cisplatin than with cetuximab for OPC.[5,6] Multiple clinical trials have failed to show a survival benefit with the use of induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CRT)[7-9] Only the regimen of docetaxel, platinum, 5FU (TPF) is endorsed by the NCCN as an induction option and while associated with reducing loco-regional tumor volume and decreasing risk of distant metastases (DM), the impact on overall survival is uncertain.[10-12] We sought to evaluate acute and chronic feeding tube use and functional outcomes in OPC patients treated at the University of Texas M D Anderson Cancer Center with induction chemotherapy followed by local CRT or RT.

2 | METHODS

We reviewed records of patients enrolled in the University of Texas MD Anderson Cancer Center Oropharynx Cancer Program database; a program generously supported by Mr. and Mrs. Charles W. Stiefel (Institutional Protocol PA14-0947). This database includes all consecutive patients with OPC and squamous cell carcinoma in the neck (unknown primaries) evaluated and/or treated at MD Anderson Cancer Center who were willing to provide consent to be included in the database since March, 2015. This robust database tracks patient demographics such as age, gender, smoking history, HPV-status, and cancer stage. Chemotherapy regimen(s) and radiation treatment dosing and technique as well as response to therapy and survival are tracked. Patient outcomes are also prospectively tracked by the Patient-Reported Outcomes/Function (PROF) core, including variables such as the rate of feeding tube (FT) placement and FT-dependency over time, as well as toxicities using the MD Anderson Symptom Inventory-Head and Neck Module (MDASI-HN).[13,14] MDASI-HN is a validated multi-symptom survey tool which assesses patient reported symptoms in 22 different items including pain, fatigue, nausea and/or vomiting, sleep interference or daytime drowsiness, emotional distress, dyspnea, memory impairment, anorexia, xerostomia, sadness or mood changes or impact on overall enjoyment of life, peripheral neuropathy, dysphagia or choking sensation, mucositis and/or excessive secretions (mucus production), voice changes, skin changes, constipation or diarrhea, dysguesia, dental symptoms, on a scale of 0 ("not present") to 10 ("as bad as you can imagine"), as well as overall activity changes, impact on job/work, impact on relationships, and impact on ambulation.

We conducted a retrospective study of patients enrolled into the MD Anderson Oropharynx Program Database from March, 2015 to January, 2018, including chart review. The study was approved by Institutional Review Board (Institutional Protocol PA18-0197). Our study focused on outcomes in the patients treated with induction chemotherapy (IC). We reviewed demographics, HPV-status, smoking history, and stage. The clinical reason for IC, the IC regimen, and response to IC were reviewed; as well as subsequent choice of radiotherapy (RT) alone, CRT, or surgery. Staging used the American Joint Commission on Cancer (AJCC) Staging 7th Edition and response was measured using RECIST criteria.[15,16]

Patient-reported symptom severity was longitudinally assessed using the MDASI-HN. Prevalence and severity of the following symptom items were considered: pain, dysphagia, xerostomia and FT placement and duration of use. FT placement and MDASI-HN scores were recorded at baseline diagnosis prior to treatment initiation, at the end of induction chemotherapy treatment, at the end of all chemotherapy-radiation treatment, and at 3 to 6 months post-treatment or longer as available.

3 | RESULTS

3.1 | Demographics and stage

During the study period, 684 patients were enrolled in the database. Of these 684 patients, 170 were treated with IC followed by CRT, RT,

or surgery; 125 of them were treated entirely at MD Anderson Cancer Center and with adequate data for analysis. The demographics and staging for these 125 patients are shown in Table 1. Large primary tumors were more common than smaller tumors; 34 (27.2%) had T2 tumors, 25 (20%) had T3 tumors and 44 (35.2%) had T4 tumors. Only 14 (11.2%) patients had T1 primary tumors. Most had advanced nodal disease. Forty-five (36%) patients had N2b nodal stage, 59 (47.2%) had N2c nodal stage, and 13 (10.4%) had N3 nodal stage. Only 8 (6.4%) had N0 (4), N1 (3), or N2a (1) nodal stage.

TABLE 1 Demographics. Staging based on AJCC 7th edition

Characteristics	Number (%) of patients N = 125
Gender	
Male	110 (88%)
Female	15 (12%)
Age (range 34-86)	
34-49	15 (12%)
50-60	45 (36%)
61-86	65 (52%)
Ethnicity	
White	109 (87%)
Hispanic	7 (5.6%)
Black	4 (3.2%)
Asian	1 (0.8%)
Other	4 (3.2%)
HPV status	
Positive	90 (72%)
Negative	20 (16%)
Equivocal	1 (0.8%)
Unknown	14 (11.2%)
Tobacco use	
Current	20 (16%)
Former	62 (49.6%)
Never	43 (34.4%)
T stage	
TX	1 (0.8%)
T0	7 (5.6%)
T1	14 (11.2%)
T2	34 (27.2%)
T3	25 (20%)
T4	44 (35.2%)
N stage	
N0	4 (3.2%)
N1	3 (2.4%)
N2a	1 (0.8%)
N2b	45 (36%)
N2c	59 (47.2%)
N3	13 (10.4%)

3.2 | Treatment

The most common reasons cited for using IC were T3-T4 primary tumors in 33 (26.4%) patients, N2b/c or N3 nodal disease in 41 (32.8%) patients, low neck level 4 nodal disease in 29 (23.2%) patients, and radiation delay due to need for full dental extractions in 19 (15.2%) patients. These were not mutually exclusive reasons and usually overlapped in individual patients resulting in a composite reasoning for recommending IC. A platinum-taxane doublet regimen accounted for 34 (27.2%) patients, docetaxel-platinum-5Flourouracil (TPF) in 47 (37.6%) patients, taxane (paclitaxel in 39 or docetaxel in 5)-carboplatin-cetuximab (PCC) in 44 (35.2%) patients. Some of these regimens were based on a protocol; others were reflective of the more common treatments in use at the time, while some were the preference of the individual providers. Consolidation with concurrent chemo-radiation (CRT) followed IC in 103 (82.4%) patients. Weekly cisplatin was used in 88 patients, weekly Cetuximab in 13, and weekly paclitaxel in two. Twenty patients (16%) received RT alone following IC and two (1.6%) patients had surgery following IC. Three patients also underwent neck dissection following concurrent CRT. All radiation-treated patients received 69 to 70 Gy RT dosing and bilateral neck fields. An overall response (ORR) in the primary site with IC was seen in 104 (83.2%) patients, including 36 complete (CR) and 68 partial (PR) responses. Eight (6.4%) patients had stable disease in the primary site. An ORR with IC was seen in the nodal sites in 102 (81.6%) patients, including 14 CR and 88 PR. Ten (8%) patients had stable nodal disease with IC. Following consolidation, an overall response in the primary site was seen in 109 (87.2%) patients, including 99 CR and ten PR. Overall response to nodal sites was seen in 113 (90.4%) patients, including 84 CR and 29 PR.

3.3 | Symptom survey (MDASI-HN) and FT placement

Table 2 shows patient reported outcomes in 100 patients for pain, dysphagia, xerostomia, mucositis, and distress using the MDASI-HN survey at baseline (pretreatment), end of IC, and end of consolidation. The table shows the percentage of patients who reported any level (1–10) on the variables surveyed. We looked more closely at symptom levels reported for pain, dysphagia, and xerostomia. The median pain score at baseline was 2 and improved to 1 after IC but increased to 5 after consolidation (primarily CRT); however, at 6-months the majority of patients reported a pain score of zero. Dysphagia was present in 51% at baseline but was mild, median score 1. It remained stable after IC, but increased to a median of 7 in 57% of patients after consolidation. By 6 months, dysphagia had improved in the majority with a decrease in median score to 2. Xerostomia was present in 42% at baseline but was very minimal with a median score of 1 and the

TABLE 2 Patient reported outcomes (PROS) to treatment and feeding tube placement

Patient reported outcomes (MDASI)	Baseline	End of induction	End of consolidation
Xerostomia	42%	36%	56%
Dysphagia	51%	29%	57%
Mucositis	31%	24%	56%
Pain	55%	35%	54%
Distress	56%	40%	52%
Feeding tube placement and dependency			
Induction N = 125			**Ratio (%)**
Feeding tube placed			66/125 (52.8%)
Prior to IC			7/66 (10.6%)
During or after IC			8/66 (12.1%)
During or after CRT			46/66 (69.7%)
After relapse			4/66 (6%)
Unknown			1/66 (1.5%)
Feeding tube dependent			30/66 (45.4%)

Note: FT dependent = 6 months after completion of treatment. Data only available for 100 patients. Three patients lost to follow up so unable to determine if FT dependent.

number of patients reporting xerostomia after IC had decreased to 36%. After consolidation, 56% reported xerostomia and the intensity was worse with a median score of 6. This persisted at the 6-month survey with only a slight decrease in the intensity to a median score of 4. Overall, 66 (52.8%) of the 125 patients treated with IC required a FT at some point in their management. Seven of the 66 patients (10.6% or 5.6% overall) had a FT placed prior to starting treatment and eight patients (12.1% or 6.4% overall) had one placed during or immediately after IC. Most of the patients who required a FT had them placed during or immediately after consolidation CRT; 46 patients (69.7% or 36.8% overall) were in this group. At six-month follow up, 30 patients (45.4% or 24% overall) still required a FT.

4 | DISCUSSION

The use of IC in HNC is not considered standard of care. Most trials have failed to show a survival advantage over definitive concurrent chemo-radiotherapy. The Spanish Head and Neck Cancer Cooperative Group conducted one of the largest randomized trials with 439 patients and showed no statistical difference in PFS, TTF, or OS with IC.[7] The DeCIDE trial randomized 285 patients, short of its accrual goal of 400, but also failed to show any statistically significant difference in OS with IC.[8] The PARADIGM trial also showed no statistical difference in three-year OS and the IC group had more febrile neutropenia.[9] On the other hand, a phase II/III Italian trial did suggest a survival advantage for IC in a mixed population of locally advanced head and neck cancers treated with three cycles of docetaxel, platinum, and 5-flourouracil (TPF) followed by concurrent CRT vs concurrent CRT alone. These two groups were again randomized to concurrent chemotherapy with cetuximab or cisplatin and fluorouracil (PF). The results of this study demonstrated improvement in overall survival (median 54 vs 30 months, 3 year survival rate 58 vs 47%, HR 0.74, 95% CI 0.56-0.97), progression free survival (median 30 vs 19 months, 3 year survival 47 vs 39%, HR 0.72, 95% CI 0.56-0.93) and loco-regional failure in the IC arm. Of note, many participants enrolled in this study had T3 or T4 disease (75%) and HPV status was not documented.[17] In our retrospective review at one institution, OPC patients treated with IC were more likely to have bulky T3/T4 tumors or N2b/N2c/N3 nodal disease. Chemotherapy regimens used in induction typically contained a platinum and taxane agent. High response rates were seen in both the primary tumor and the nodal sites. Survival data was good for this group but was expected as most patients with OPC have a good survival prognosis and the follow up interval was too short without a comparator group to determine any conclusive impact on survival with IC in this population. The number of patients who relapsed with distant metastases was higher than expected.

There are also concerns of increased toxicity and failure to fully complete the treatment program with IC due to additional cycles of chemotherapy. In the Spanish trial for example, only 69% of patients in the IC arm completed the full IC followed by CRT program, compared with 92% of patients in the concurrent CRT arm.[7] Proponents of IC; however, claim that IC can reduce subsequent RT dosing and limit toxicities. In a phase II ECOG-ACRIN Cancer Research Group trial, response to IC was utilized to select patients with HPV associated OPC for reduced radiation dose. The trial evaluated 80 patients with HPV-positive resectable stage III/IV OPC who received three cycles of induction cisplatin, paclitaxel, and cetuximab. IC was followed by concurrent CRT with cetuximab. Those who did not achieve a complete response following IC were given a higher dose of radiation (69.3 Gy in 33 fractions) compared to those who achieved a complete response (54 Gy in 27 fractions). Seventy percent of the total patients achieved a complete clinical response after a median

follow up of 35.4 months. In patients who received induction followed by CRT with 54 Gy radiation, the 2 year PFS was 80% and OS was 94%. There were fewer radiation complications in the lower dose radiation group such as dysphagia (40% vs 89%, $P = .011$) and nutritional impairment (10% vs 44%, $P = .025$). Good IC responses treated with lower RT dose had a two-year OS of 94% with less RT-related toxicities.[18] The phase II OPTIMA trial stratified patients with HPV-positive OPC into low or high-risk groups based on tumor size, nodal status, and smoking history. They were then assessed for response after three cycles of induction chemotherapy with carboplatin/nab-placitaxel. Low risk patients with a ≥50% response received 50 Gy radiation dose alone without concurrent chemotherapy; low risk patients with 30% to 50% response and high risk patients with ≥50% response received 45 Gy RT with concurrent chemotherapy. All other patients with lesser responses received CRT with standard of care 75 Gy RT. Two-year progression free survival (PFS) and overall survival (OS) for the low risk group were 95% and 100% respectively; for the high risk group they were 94% and 97% respectively. Grade 3 toxicities, primarily radiation mucositis, based on RT dose were 30% (RT 50Gy), 63% (CRT 45Gy), and 91% (CRT 75Gy). Feeding tube rates were 0% (RT 50 Gy), 31% (CRT 45Gy), and 82% (CRT 75Gy). The authors concluded that their algorithm for dose de-escalation in RT or CRT based on response to IC and risk-stratification was associated with favorable survival outcomes and reduced acute and chronic toxicity.[19] A National Cancer Data Base review of IC did not show a survival impact but patients were more likely to receive a reduced RT dose, <66 Gy, if they received RT; presumably resulting in reduced radiation-associated acute and chronic toxicities.[20] The findings of these three studies suggest a role for a reduced radiation dose in HPV positive patients that demonstrate effective cytoreduction from IC to minimize radiation related toxicities.

The MDASI-HN proved useful in showing that the prevalence of pain and dysphagia (MDASI-HN score > 0) at baseline often reduced after IC. Long-term impact of this early reduction in symptom burden during IC is not clear and requires further investigation, particularly since symptom prevalence and severity both increased on average to moderate/severe symptom levels, as historically expected, during consolidative treatment. Feeding tube placement was required in over half of the patients but most were placed during or after the consolidation phase; very few patients needed FT placement during IC and those placements were related to baseline tumor burden rather than IC toxicity. The number of patients still requiring a FT at 6 months follow up was high, suggesting that it is possible that the cumulative treatment of IC followed by CRT or RT may negatively impact FT outcomes. Based on our findings, it remains unclear whether FT placement and dependence more heavily corresponds to the total amount of chemotherapy received or the relationship between the radiation dose and the chemotherapy received. Bulkier, more advanced disease, more likely to be treated with IC, is well known to associate with a higher toxicity risk. Patients also consistently received 69 to 70 Gy radiotherapy rather than a reduced 60 to 66 Gy dosing which may have impacted need for longer term FT-dependence. Based on MDASI-HN scores from 100 patients, reported outcomes such as dysphagia, xerostomia, mucositis, pain, and distress all improved following IC but worsened following CRT. Implementing a similar approach as the phase II ECOG-ACRIN Research Group and phase II OPTIMA trial, where patients receive a reduced radiation dose based on response to IC and risk stratification, needs further exploration as a potential treatment strategy to minimize treatment related toxicities, feeding tube placement, and improve quality of life for patients. In a 2012 SEER review, analyzing over 16 000 patients with head and neck cancer that received RT between 2000 and 2005, 3617 patients were classified as OPC and of those 1843 (51%) required feeding tube placement with the majority (84%) being placed after treatment. From the 2966 OPC patients that received RT, 57.4% received a FT with 70% placed after treatment. In comparison, from the 1398 OPC patients that received chemotherapy, 66% received a FT with 45.4% placed after treatment.[21] In the OPC population of patients, there are high rates of FT placement but the study does not provide specifics relating to the treatment structure in terms of therapy timing, regimens, and dosing for chemotherapy and RT. In the future, we hope to expand our cohort and assess the differences between OPC patients that received IC + CRT vs CRT alone to better elucidate the impact of treatment approach on FT rates.

In summary, a retrospective study of subjective functional outcomes and practice patterns at one institution in a large database of patients treated with IC demonstrated that the most common practice pattern for choosing IC was in patients with bulky primary and/or nodal disease with baseline pain and/or dysphagia due to disease. Platinum-taxane regimens were most commonly used and generated good responses in both the primary and nodal sites with improvement in baseline symptoms. Feeding tube requirements were still significant in this population of patients presenting with bulky disease burden. The standard of care in OPC continues to be concurrent CRT; the use of IC is based less on survival data and more on clinical decision making in situations that may suggest higher risk of loco-regional toxicity and control due to bulky disease or concern for distant metastases. The use of IC in HNC, while not considered standard, is still prevalent in various clinical situations as outlined in this review and other studies. Given the unclear survival benefit, one must evaluate IC for its potential to reduce toxicities and/or improve other subjective functional outcomes. While other reviews have suggested good IC responses can allow for reduction in subsequent RT dosing, risk-based RT dose de-escalation was not used in this cohort of patients. Thus the feeding tube requirements were still significant in this population of patients but were not significantly worse compared to historical data for OPC patients in general,[22] although patient reported dysphagia may under-estimate physiologic assessment of dysphagia.[23] Our experience has defined patients with T3-4 tumors, those undergoing concurrent chemotherapy with radiation, current active smoking while on therapy, and baseline swallowing dysfunction or weight loss are more likely to have feeding tube placement; however, adherence to an aggressive swallowing program may reduce long-term dependency.[24]

While OS was good, follow up was short, and the number of patients relapsing with distant metastatic disease was concerning.

This could be a reflection of poorer outcomes with high pretreatment risk factors. One must also consider the impact of additional cycles of chemotherapy on chronic toxicities such as xerostomia, neuropathy, hearing, and renal function, and follow up has not yet matured to fully examine late effects associated with this strategy in this database. Additional cost of therapy, increased clinic visits and co-pays, time off work for patients and/or family members, and protracted treatment time are also factors that need to be considered.

Finally, the observation that swallowing function improved after induction chemo only to worsen with CRT was not in itself surprising, but it does raise the question why do induction chemotherapy? Unfortunately, the follow up in the study was too short to determine long-term functional outcomes or even survival results. An ongoing comparison with patients treated with definitive CRT without IC will address response and survival as well as toxicity outcomes and differences in clinical characteristics that may determine the use of IC vs definitive CRT in this population.

CONFLICT OF INTEREST

There are no financial disclosures or conflicts of interest.

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