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Selectively sparing the submandibular gland when level Ib lymph nodes are included in the radiation target volume: An initial safety analysis of a novel planning objective

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ABSTRACT

Background: Submandibular gland (SMG) metastases are extremely rare in head and neck cancer, even in the presence of level Ib lymph node (LN) involvement. In recent years, we have contoured the SMG and specifically attempted to limit its dose exposure even in patients in whom the level Ib LN station is targeted. This study reports our preliminary feasibility and safety experience with selective submandibular gland sparing.
Methods: Patients with squamous cell cancer (SCC) of the oral cavity or oropharynx with T1-2, N0-3, M0 disease in whom at least a single level Ib lymph node region was included in the target volume were identified. All patients were treated from 2009 to 2014 with definitive or postoperative IMRT with or without chemotherapy. Patients with recurrent disease, previous radiation or treated palliatively were excluded.
Results: A total of 174 patients met criteria for inclusion. Among the 185 level Ib LN stations that were deliberately targeted in the clinical treatment volume, 32 submandibular glands were contoured, excluded from the target volume and avoided during treatment planning. Mean dose to the spared SMG were reduced by 12% (66.6 Gy vs. 58.9 Gy, $p < .001$). None of these patients experienced any level 1b LN failures.
Conclusion: Selective sparing of the submandibular gland when targeting the level 1b nodes in oral cavity and oropharynx cancer is feasible, reduces the mean dose to submandibular glands and does not result in increased level 1b nodal failure rates. Additional studies with larger cohorts are needed to validate this preliminary observation.

Introduction

Xerostomia is a common long-term complication of radiation therapy (RT) for oropharyngeal and oral cavity cancers, reducing quality of life and leading to further complications such as dental caries and oral infections [1]. Multiple therapies used to promote salivary flow can be used after the onset of xerostomia, such as cholinergic agonists, acupuncture, and hyperbaric oxygen [2–5]. Just as important is initial prevention of xerostomia, which has been accomplished with the use of amifostine and surgical submandibular salivary gland transfer [6,7]. However, the most important factor in preventing the onset of xerostomia is the use of conformal RT techniques, limiting dosage to the salivary glands [8].

Submandibular gland (SMG) metastases are extremely rare in oropharyngeal and oral cavity cancer, even in the presence of level Ib lymph node (LN) involvement [9–11]. Recently, we have contoured the SMG and specifically attempted to limit its dose exposure in patients with early T-stage oral cavity or oropharyngeal cancer, including patients that required inclusion of the level Ib station in the treatment volume. We hypothesize that carving out the SMG from radiation fields targeting the level 1b LN reduces rates of xerostomia while maintaining equivalent oncologic control. This study reports our preliminary feasibility and safety experience with selective SMG sparing and its dosimetric impact.

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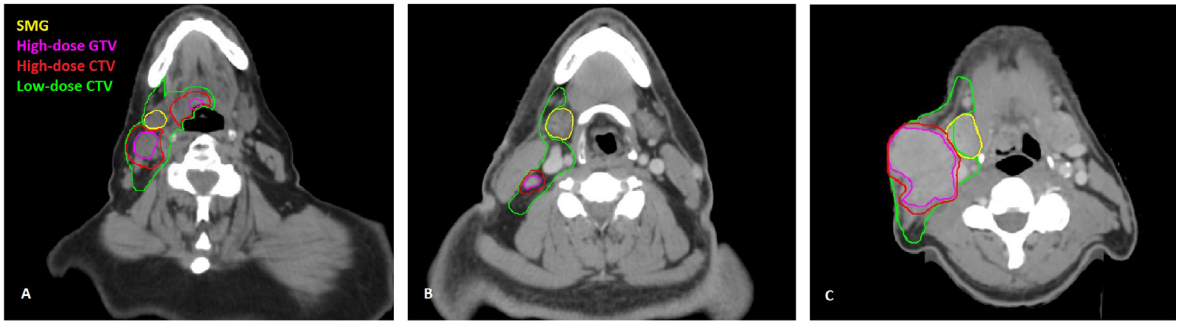

Fig. 1. Selection criteria for whether or not an SMG was considered to be spared or not spared: (A) No sparing was attempted with the SMG lying within the low-dose elective volume; (B) sparing was attempted with the SMG lying outside the low-dose elective volume; (C) sparing was attempted with the SMG lying outside the low-dose elective volume, but without meaningful dose reduction to the SMG due to close proximity to a high-dose nodal target. *GTV: Gross Tumor Volume, CTV: Clinical Target Volume.

Table 1
Comparison of patient, tumor and treatment factors between patients with SMG unspared versus spared.

Factor	Not spared (n = 125)	Spared (n = 19)	p-value
Median age in years (range)	59.7 (34.4–87.1)	57.1 (48.3–96.2)	0.547
Median follow up in months (range)	55 (3–102)	35 (2–93)	< .01
Gender			
Female	19 (15%)	5 (26%)	
Male	106 (85%)	14 (74%)	0.378
Smoking history			
Current use	22 (18%)	3 (16%)	
Former user (quit > 3 months)	64 (51%)	(47%)	
Never smoker	39 (31%)	7 (37%)	0.886
Heavy alcohol use			
Yes	16 (13%)	3 (16%)	
No	109 (87%)	16 (84%)	1
Karnofsky performance status			
90–100	110 (88%)	16 (84%)	
< 90	15 (12%)	3 (16%)	0.926
Tumor site			
Oral Cavity	5 (4%)	1 (5%)	
Oropharynx	120 (96%)	18 (95%)	1
T Classification by 7th edition AJCC staging			
1	59 (47%)	9 (47%)	
2	66 (53%)	10 (53%)	1
N Classification by 7th edition AJCC staging			
0	1 (1%)	1 (5%)	
1	12 (10%)	0 (0%)	
2	102 (82%)	17 (89%)	0.215
a	17	0	
b	65	15	
c	20	2	
3	10 (8%)	1 (5%)	
Intent of radiation			
Definitive	113 (90%)	17 (89%)	
Postoperative	12 (10%)	2 (11%)	1
Median RT dose in Gray (range)	70 (60–78)	70 (60–76)	0.31
Laterality targeted			
Ipsilateral	103 (82%)	15 (79%)	
Bilateral	22 (18%)	4 (21%)	0.965
Chemotherapy			
Yes	112 (90%)	16 (84%)	
No	13 (10%)	3 (16%)	0.76

Methods

From an institutional review board-approved database, 174 patients with squamous cell cancer (SCC) of the oral cavity or oropharynx, with T1-2, N0-3, M0 disease in whom at least a single level Ib lymph node region was included in the target volume were identified. All patients were treated from 2009 to 2014 with definitive or postoperative intensity-modulated radiation therapy (IMRT) with or without chemotherapy. Patients with recurrent disease, or who were treated with re-irradiation or a palliative split course technique were excluded. The treatment plans for each patient were reviewed and verified for level Ib targeting (unilateral vs. bilateral) as well as if the SMG was excluded from the target volume and sparing was attempted during planning (Fig. 1). During analysis, a SMG was considered spared as long as it lay outside of the target volume, regardless of its mean dose. SMG were spared only by one physician (JFG) based on his institutional practice pattern during the latter years of the study. SMG sparing was not attempted in cases where a midline oral cavity or oropharyngeal high-dose (64–72 Gray (Gy)) target volume abutted the SMG, SMG sparing was not attempted. Planning was performed using static IMRT or VMAT with Pinnacle planning system. Treatment was delivered using daily IGRT for image guidance. Simultaneous integrated boost (SIB) planning was the standard, with most patients treated to 70 Gy & 56 Gy or 72 Gy & 58 Gy (definitive plans), or 60–66 Gy and 54–56 Gy (post-operative plans) to the primary and elective volumes respectively.

Xerostomia outcomes were analyzed in a subset of patients (144/174) who had both SMG in situ during IMRT. Patients who had a SMG removed were excluded from this particular analysis as their baseline xerostomia would be affected from a surgical variable and confound interpretation of SMG sparing using IMRT. Xerostomia was defined using the European Organization for Research and Treatment of Cancer's Common Terminology Criteria for Adverse Events, Version 4.0. Acute xerostomia was defined as any grade 2 or higher xerostomia within the first three months of treatment. Intermediate xerostomia was defined as grade 2 or higher xerostomia at 12 months follow-up and late xerostomia was defined as grade 2 or higher xerostomia at 24 months follow up.

Locoregional control (LRC) was calculated from time of diagnosis to the time of recurrence at the primary site or regional lymph nodes, or last oncologic follow-up. Overall survival (OS) was calculated from time of diagnosis to death or date last known alive. Statistical analysis was performed using R software [12]. The Mann-Whitney test was used to detect significant differences in medians of continuous variables while the Chi-squared test was used to detect significant differences in categorical variables. The Kaplan-Meier method and log-rank test was used to assess for differences in LRC and OS between groups. The Fine and Gray method was used to assess for differences in cumulative incidence of locoregional recurrence between groups, using the CMPRSK package in R.

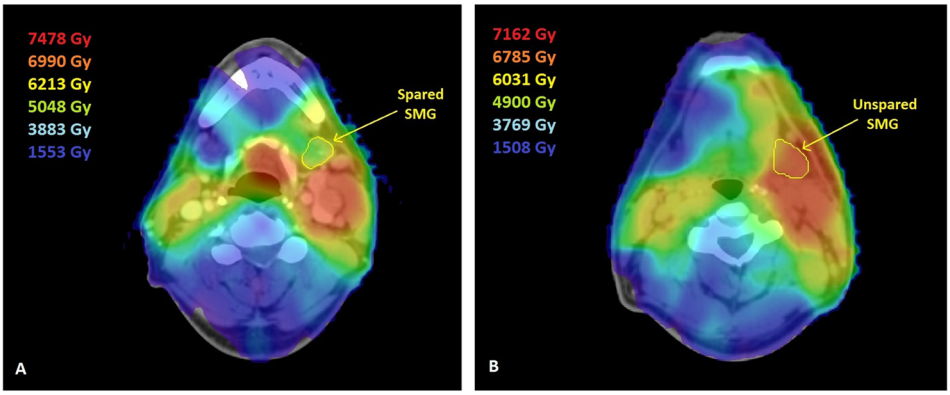

Fig. 2. Dosimetric plans of a patient with submandibular gland (SMG) spared vs. unspared.

Results

A total of 174 patients met criteria for inclusion. Table 1 includes patient, tumor, and treatment factors of the unspared and spared groups and shows that the only factor significantly different between the two groups was median follow up (35 months in the spared group vs. 55 months in the unspared group, $p < .01$), due to adoption of the SMG sparing approach only in recent years. Among these patients, 185 level Ib LN stations were deliberately targeted in the clinical treatment volume, and 32 SMGs were contoured, excluded from the target volume and avoided during treatment planning.

Of 174 patients, 144 patients had both SMGs intact at time of radiation, while the other 33 had at least one SMG removed during surgery. Of these patients, 19 had SMGs adjacent to targeted Ib LNs spared and 125 patients had no sparing of their SMG adjacent to targeted 1b LNs. Of the 19 patients whose SMGs were spared, 18 had clinically positive ipsilateral necks. Of these 18 patients, 13 had positive multilevel disease, most commonly levels II and III. The median of the mean doses of the spared SMGs was able to be reduced by 12% (66.6 Gy vs. 58.9 Gy, $p < .001$) compared to the unspared SMGs (Fig. 2). Additionally, 6 (19%), 6 (19%) and 8 (25%) of those 32 SMGs were spared to < 45 Gy, 45–50 Gy, and 50–60 Gy, respectively.

LRC at 5 years for the 144 patients with both SMGs intact was excellent at 91.4%. LRC was not significantly different between patients with SMGs spared (5 yr LRC – 89%) compared to unspared (5 yr LRC – 95%) with $p = .19$. Also, when accounting for death as a competing risk, cumulative incidence of locoregional recurrence was not significantly different between the SMG spared (5 yr cumulative incidence – 11%) compared to the SMG unspared (5 yr cumulative incidence 5%) group with $p = .20$. Significantly, all of the locoregional failures occurred in the targeted volumes; no patient in the entire cohort experienced any level 1b LN failures. OS at five years was also excellent at 83% and was not significantly different in the spared group (5 yr OS – 87%) compared to the unspared group (5 yr OS − 95%) with $p = .53$.

In the unspared group, 80 (64.5%) of the 124 patients at risk developed acute grade ≥2 xerostomia, 34 (30.4%) of 112 patients at risk developed intermediate xerostomia, and 21 (20.4%) of 103 patients at risk developed late xerostomia. In the spared group, 12 (63.2%) of 19 patients at risk developed acute xerostomia, 3 (17.6%) of 17 patients at risk developed intermediate xerostomia, and 2 (14.3%) of 14 patients at risk developed late xerostomia. On Chi-squared analysis, the unspared and spared groups had no significant difference in xerostomia at any of the three measured time points (Fig. 3).

Discussion

Xerostomia is a common toxicity of radiation therapy to the head and neck, significantly affecting quality of life of patients [1]. This is the preliminary report of our initial experience with a novel technique in which the SMG itself is contoured and avoided during IMRT planning despite targeting the ipsilateral level Ib lymph node. We demonstrate that doing so is safe and does not lead to an increase in level Ib recurrences. The impact on salivary gland dose reduction is modest overall, but substantial in a subset of these patients, which has the potential to lead to meaningful reductions in xerostomia and improved quality of life. In recent years, this practice has been uniformly adopted by all of the head and neck radiation oncology staff at Cleveland Clinic.

While outcomes of parotid gland sparing have been well established to show decreased rates of xerostomia with maintained LRC and OS, there is limited data evaluating the efficacy and safety of sparing the ipsilateral submandibular gland [8]. Collan et al reported outcomes in 80 patients with oropharyngeal, nasopharyngeal, and hypopharyngeal cancer with low risk of recurrence in the contralateral level I and II nodes, who's contralateral SMGs were spared in IMRT planning by avoiding targeting of the level Ib node [13]. In patients whose ipsilateral level I and II nodes were also considered to be of low risk of recurrence, the ipsilateral SMG was spared in the same manner as well. Local control and overall survival at 5 years were 88% and 85%, respectively, for the whole cohort, with no local recurrences located at the vicinity of the spared SMG. However, there was no control group and no reporting of xerostomia outcomes. Chajon et al. analyzed outcomes in 70 patients with both early and late stage head and neck cancer of various subsites [14]. By avoiding the adjacent level Ib node, contralateral SMGs were spared in 18 patients and ipsilateral SMGs were spared in 5, specifically in patients whose level II and III nodes were considered to be low risk. No failures occurred in tissues surrounding the spared SMGs. Although recurrence, survival, and xerostomia outcomes were excellent among the whole cohort, there was no statistical analysis comparing the spared and unspared groups. Other studies have spared just the contralateral SMG to doses below 39 Gy by avoiding the contralateral level Ib node, and have noted decreased rates of xerostomia between the spared and non-spared groups, with no recurrences in the contralateral 1b node [15–17]. These studies, however, describe SMG sparing in patients that do not require targeting of the level Ib nodes on the same side as the gland. Our study is unique in that precisely this scenario is what we describe. This study contends that even when level Ib is targeted, sparing the gland itself is safe and is not associated with increased failures.

Studies have demonstrated a dose-response relationship for the SMG, correlating increased radiation dose with decreased salivary flow rates [18,19]. Mean doses of less than 39 Gy to the SMG appear to be most effective in minimizing xerostomia [20]. Because the adjacent level Ib node was targeted, dose reduction to SMG in our study was more modest with median of the mean doses reduced from 66.6 Gy to 58.9 Gy, likely too high of a mean dose to produce appreciable differences in rates of xerostomia. However, a subset of SMGs achieved more substantial dose reductions, with 19% of patients achieving doses between 45 Gy and 50 Gy and 19% below 45 Gy. Although the mean dose

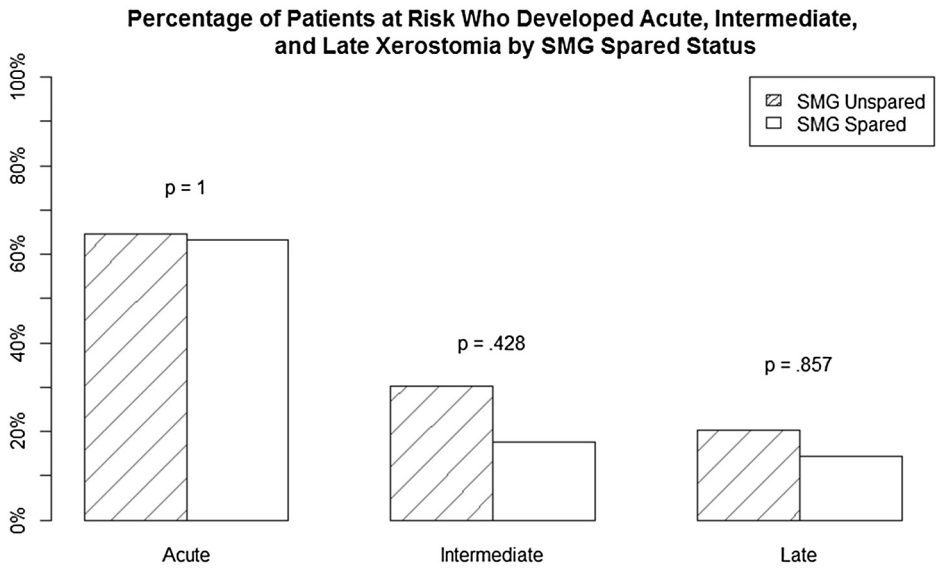

Fig. 3. Rates of acute, intermediate, and late xerostomia in patients treated with RT for oral cavity or oropharyngeal cancer by submandibular gland spared status (125 non-spared vs. 19 spared).

to the SMG was not reduced to 39 Gy, the cutoff identified for meaningful reductions in clinical xerostomia [20], the dose reductions experienced by these subset of patients are still significant. Other studies have demonstrated a continuous relationship between dose to the SMG and saliva production, demonstrating that patients with less than 50 Gy to the SMG experienced significant increases in salivary flow compared to patients with a dose of 68 Gy or higher [21]. There is a clear need to optimize selection criteria to identify those patients most likely to benefit from this technique.

This study has several limitations. First, it is a single-institution retrospective study representing an initial report of patient outcomes with this experience. Also, there was a wide range of doses achieved to the ipsilateral SMG as the heterogeneity of cases was significant. Some patients had large nodes targeted to full dose adjacent to the SMG, for example, while others received elective nodal radiation with moderate doses. As such, the dosimetric outcomes of this study are hard to interpret. Similarly, we used observer graded xerostomia scores which are imperfect. Patient reported quality of life instruments would add to the robustness of these findings. With additional patients and follow up, we hope to be able to refine our selection of patients who stand to benefit from this technique, demonstrate more substantial dose reductions to the SMG in these properly selected patients, and provide longer follow up on larger numbers of patients to validate the safety signal of this initial report.

Conclusion

Selective sparing of the SMG when targeting the level Ib nodes in oral cavity and oropharynx cancer is feasible, reduces the mean doses to SMGs, and does not result in increased level Ib nodal failure rates. Future studies with larger numbers are needed to validate this preliminary finding and examine the impact of this technique on functional outcomes.

Conflicts of interest

Dr. Shlomo Koyfman – Research support from Merck.

Dr. Mathew Ward – My professional group has received honoraria related to advisory board participation for AstraZeneca, unrelated to this project.

No other authors have conflicts of interest.

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