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FULL PAPER

Can sparing of the superficial contralateral parotid lobe reduce xerostomia following radiotherapy for head and neck cancer?

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Objective: The purpose of this study is to see whether sparing the superficial contralateral parotid lobe can help limiting xerostomia following radiotherapy for head and neck cancer.

Methods: 88 patients that were included in two prospective randomized studies were analysed in the current study. Using the dosimetry of both the parotid glands, we divided our patients in four groups. Group 1 includes patients where we were able to reduce the radiation dose below the threshold in order to spare both the ipsilateral and contralateral parotid glands, Group 2 consists of patients where only the contralateral parotid gland could be spared. Group 3 consists of patients where only the contralateral superficial parotid lobe could be spared, while in Group 4 not even the contralateral superficial lobe could be spared.

Results: When we compared Group 1 and Group 2, we did not observe a significant difference between both groups in terms of xerostomia scores at 6 or 12 months. When we compared these groups with Group 3, we observed significant differences with more xerostomia in Group 3 where only the contralateral superficial lobe was spared. A significant difference was also observed between Group 3 and Group 4 with more xerostomia in Group 4.

Conclusion: Sparing of just one superficial parotid lobe results in less xerostomia when compared to not sparing any lobe of both parotid glands.

Advances in knowledge: When sparing of the whole contralateral parotid gland is not possible, delineating both the superficial parotid glands and trying to spare at least one of them can mean a way forward in limiting xerostomia in head and neck cancer patients treated with radiotherapy.

INTRODUCTION

Radiotherapy (RT) is an important treatment modality in the management of head and neck cancer (HNC). RT can be used as a single modality or in combination with surgery and/or chemotherapy. One of the most frequently reported side effects following RT in patients with HNC is hyposalivation and subsequent xerostomia due to co-irradiation of the salivary glands.^{1,2} Xerostomia significantly impairs the patient's quality of life due to the many secondary effects such as impairment of taste, swallowing and speech.^{2–6} Approximately 40% of patients with HNC will experience xerostomia to some degree after treatment with RT.^{7–11} The introduction of new techniques such as parotid-sparing intensity-modulated RT has resulted in less xerostomia; however, toxicity outcome is still far from perfect.¹² The consensus has been reached that xerostomia can be substantially reduced by limiting the mean parotid gland dose to < 26–30 Gy as a planning criterion.¹³

Xerostomia can occur early during RT treatment. It is suggested that early damage may be due to damage to the plasma membrane of acinar cells, compromising the receptor-mediated signalling pathways of water excretion. Late damage, on the other hand, may be explained by (DNA) damage to the salivary gland stem cells (SCs) and subsequent lack of proper cell renewal.^{14–16} Sparing of SC-rich regions within the parotid gland could thus theoretically help in preventing xerostomia following RT.¹⁷ The specific location of these SCs and therefore the region to spare has been the subject of debate. The data from the group in Groningen suggest that SCs are located in the vicinity of the major ducts residing in the superficial lobe.¹⁴ Miah et al found that sparing the superficial lobe of both parotid glands may offer a higher incidence of recovery of salivary function compared to whole contralateral parotid gland sparing alone in oropharyngeal cancers.¹⁸

The purpose of this study is to see whether sparing the superficial contralateral parotid lobe can help limiting xerostomia following RT for HNC.

METHODS AND MATERIALS

Patients

88 patients that were included in two prospective randomized studies were analysed in the current study (ClinicalTrials.gov Identifier: NCT01287390)].^{19,20} The inclusion criteria were previously untreated, histologically proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx or cervical lymph node metastases of unknown primary cancer. All patients were treated with definitive RT or chemoradiotherapy for HNC between 2009 and 2015. In all patients, the intention was to limit the irradiation to at least one parotid gland to a mean dose less than 26 Gy and doses to the submandibular glands were kept as low as possible.

The delineation of the parotid lobe, and superficial and deep lobes were done retrospectively by one observer after the planning. The planning was thus performed without optimization for these structures. Parotid tissue lateral to the retromandibular vein was defined as the superficial lobe (Figure 1).²¹ All patients were treated with IMRT using a commercially available treatment planning system (Eclipse®). The following dose-volume parameters were extracted from the treatment plans: Dmean ipsilateral parotid gland, Dmean contralateral parotid gland, Dmean of the superficial contralateral and deep parotid lobe and the Dmean of the superficial ipsilateral and deep parotid lobe. These structures were considered to be spared when the mean dose was less than 26 Gy. Using the dosimetrical information, we divided our patients in four groups. Group 1 includes patients where we achieved to spare both the ipsilateral and contralateral parotid gland, Group 2 consists of patients where only the contralateral parotid gland could be spared, Group 3 consists of the patients where only the contralateral superficial parotid lobe

could be spared (Figure 1), while in Group 4 not even one superficial lobe could be spared.

Xerostomia was scored by physicians using the RTOG/EORTC scoring system for late toxicity at 6 and 12 months of follow-up. Proportional odds models were used to look at the link between the different groups and xerostomia at 6 and 12 months. The interaction with time was tested. A significant interaction with time means that the association between the variables is different between the 3 time points (6 months, 12 months). All tests are two-sided, a 5% significance level is assumed for all tests. Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows).

RESULTS

Patient characteristics can be found in Table 1.

Table 1. Patient and treatment characteristics

Patient and treatment characteristics	
Sex	
Female	17/88 (19.3%)
Male	71/88 (80.7%)
Age	
Mean	63.4
Median	62.1
Range	(38.0; 80.0)
Location	
CUP	5/88 (5.7%)
Hypopharynx	22/88 (25.0%)
Larynx	15/88 (17.0%)
Oropharynx	46/88 (52.3%)
T	
CUP	5/88 (5.7%)
1	6/88 (6.8%)
2	36/88 (40.9%)
3	29/63 (33.0%)
4	12/63 (13.6%)
N	
0	13/88 (14.8%)
1	14/88 (15.9%)
2a	5/88 (5.7%)
2b	31/63 (35.2%)
2c	25/63 (28.4%)
Chemotherapy	
No	30/88 (34.1%)
Yes	58/88 (65.9%)

CUP, cancer of unknown primary.

Figure 1. Example of a patient of group 3 where only the contralateral superficial parotid lobe could be spared (arrow).

We included a total of 88 patients in our study and divided these patients in 4 groups. In 21 patients, both the ipsilateral and contralateral parotid glands could be spared (Group 1). In 41 patients the contralateral parotid gland could be spared, but the ipsilateral could not be spared (Group 2). Thus, in 62 patients at least the contralateral lobe could be spared, meaning that in the remaining 26 patients the contralateral parotid gland could not be spared entirely. In 14 of these patients the superficial contralateral parotid lobe could be spared (Group 3), while in 12 patients not even the superficial lobes could be spared (Group 4).

Incidences of xerostomia at 6 and 12 months are presented in Table 2.

We observed a statistically significant global effect between the four groups and the xerostomia scores with a p -value of 0.02. Therefore, we performed a subsequent pairwise comparison between the four groups. We observed a p -value for interaction of $p = 0.11$; meaning that the observed effect between the four groups and xerostomia was the same at 6 and 12 months of follow-up.

The pairwise comparison is presented in Table 3. When we compared Group 1 and Group 2 (sparing of both parotid glands versus sparing of the contralateral parotid gland), we did not observe a significant difference between both groups in xerostomia at 6 or 12 months. When we compared Group 1 and Group 2 with Group 3, we observed significant differences with more xerostomia in Group 3 where only the contralateral superficial lobe was spared. When we correlated Group 1 and Group 2 with Group 4, we observed a similar result with more xerostomia in Group 4 when compared to Group 1 and Group 2. Furthermore a significant difference was observed between Group 3 and Group 4 with more xerostomia in Group 4.

DISCUSSION

Severe xerostomia following RT in HNC can be avoided by sparing one parotid gland.^{13,14} The patient cohort of this study was therefore planned trying to spare at least one parotid gland. However, in 26 patients (29% of the patients) the contralateral parotid gland could not be spared entirely. In these patients we need to find other ways to limit xerostomia. Therefore, the purpose of this study is to see whether sparing the superficial contralateral parotid lobe can help limiting xerostomia following RT for HNC.

Table 2. Incidences of xerostomia (RTOG/EORTC scoring) at 6 and 12 months

Xerostomia	6 months ($n = 88$)	12 months ($n = 84$)
Grade 0	21 (24 %)	24 (27%)
Grade 1	40 (45%)	38 (45%)
Grade 2	21 (24%)	19 (22%)
Grade 3	6 (7%)	3 (4%)
Grade 4	0	0

Table 3. Pairwise comparison of the different groups of the study

Comparison	Estimate (95% CI)	p -value
Group 1 vs Group 2	-1.033 (-2.693, 0.626)	0.22
Group 1 vs Group 3	-1.250 (-2.405, -0.096)	0.04
Group 1 vs Group 4	-1.473 (-2.391, -0.555)	0.01
Group 2 vs Group 3	-7.467 (-14.90, -0.034)	0.05
Group 2 vs Group 4	-0.804 (-1.506, -0.103)	0.02
Group 3 vs Group 4	-1.167 (-2.249, -0.085)	0.04

CI, confidence interval; Estimate < 0 means lower score of xerostomia for first level.

Group 1: Both the ipsilateral and contralateral parotid lobes could be spared; Group 2: Contralateral parotid gland could be spared, but the ipsilateral could not be spared; Group 3: Only contralateral superficial parotid lobe could be spared; Group 4: Both parotid lobes, and both superficial lobes could not be spared.

When we compared Group 1 and Group 2 (sparing of both parotid gland versus sparing of the contralateral parotid gland), we did not observe a significant difference between both groups in xerostomia at 6 or 12 months. Sparing of both the parotid glands versus only one entire parotid gland did not result in less xerostomia at 6 and 12 months of follow-up in our patient population. However sparing both parotid glands or just one proved to be better in terms of xerostomia outcome when compared to just sparing one superficial parotid gland or not being able to spare a superficial parotid gland at all. Interestingly, a significant difference was also observed when we compared Group 3 and Group 4. These data suggest that when we cannot spare both or one parotid gland from high dose irradiation, sparing of the contralateral superficial parotid gland results in less xerostomia after 6 and 12 months of follow-up. Delineating both the superficial parotid glands and trying to spare them can thus mean a way forward in limiting xerostomia in HNC patients treated with RT in patients where an entire parotid gland cannot be spared.

Data on superficial parotid lobe sparing in literature are scarce. In a recent study, contralateral parotid sparing was compared to bilateral superficial lobe parotid sparing. The results of this study showed that bilateral superficial parotid lobe sparing results in less high-grade xerostomia.^{18,21} In this study they advocate delineation of the superficial parotid lobes, a suggestion that we, based on our results, agree upon.

A strong point of this paper is the prospective scoring of toxicity, and the uniform delineation by one observer. Possible limitations are the fact that we did not take the dose to the submandibular glands and oral cavity into account. Dijkema et al stated that sparing of the contralateral submandibular gland, in addition to parotid gland sparing might result in less xerostomia.²² Little et al found that mean doses to the parotid glands, submandibular glands and oral cavity are significant predictors of xerostomia, with oral cavity doses remaining significant after adjusting for the parotid gland and submandibular gland doses.²³ Jellema et al found that the mean dose

to the parotid and submandibular glands could influence the risk of xerostomia at 6 months; no significant differences were found when xerostomia was correlated with the oral cavity dose.⁹ These results support efforts to spare all the salivary glands as much as possible, as was done for the patients in our study. Given the relatively small patient population and the fact that we had already four groups when we took the dose to the parotid glands into account, we were not able to further

subgroup the patients taking into account dose to other relevant organs in the current study.

CONCLUSION

When sparing of the whole contralateral parotid gland is not possible, delineating the superficial parotid glands and trying to spare at least one of them can mean a way forward in limiting xerostomia in HNC patients treated with RT.

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