Editorial

Can xerostomia be further reduced by sparing parotid stem cells?

Avraham Eisbruch

Department of radiation Oncology, University of Michigan, MI, USA

Correspondence to: Avraham Eisbruch. Department of radiation Oncology, University of Michigan, MI, USA. Email: eisbruch@umich.edu.

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Reducing xerostomia by sparing the parotid glands (PGs) has been the main rationale for intensity modulated radiotherapy (IMRT) in patients with head and neck cancer (HNC). Sparing the PGs by IMRT has indeed improved xerostomia compared with conventional radiotherapy in randomized studies (1-3), and has achieved even further improvement over time (4). However, these achievements have been relatively modest. While whole-mouth salivary output and observer-rated xerostomia such as the Radiation Therapy Oncology (RTOG) scales have consistently been significantly better using IMRT, a rate of post-IMRT xerostomia grade ≥2 as high as 40% at 12 months, reported in one of the randomized studies (3), is typical. It has been even harder to demonstrate significant improvements in patient-reported xerostomia. Kam et al reported no advantage of IMRT over 2D radiotherapy (RT) in patient-reported xerostomia (1), and Nutting *et al*. reported that the advantage through 12 months for IMRT compared with conventional radiotherapy post-therapy was smaller than 10 points on a 0-100 scale, regarded as less than clinically relevant difference (3). Thus, IMRT aiming to spare the PGs achieves partial gains in observer-rated, and even smaller gains in patient-reported xersotomia. What is the reason for this only partial success?

Recent advances in RT treatment planning include the ability to construct dose-volume histograms (DVHs), facilitating an accurate assessment of the dose distributions in the glands. Several recent studies have been published assessing dose-response relationships based on DVHs (5-10). The common finding in all these studies is the correlation of the post-RT gland function with the mean gland dose. This is expected in an organ with a "parallel" organization of its functional subunits (11). The studies differ in the methods of salivary collection: selective parotid flows (5,7-8) or whole mouth saliva (9), and in the RT technique: standard 3-field RT (7-8) or various methods of IMRT (5,8-9), causing different spatial dose distributions within the glands. Different models have been fitted in these studies to the resulting data. As would be expected from this variability, these studies have reported different relationships between the mean doses and residual gland function. Defining as an end-point a reduction of the salivary output to ≤25% of the pre-RT flow rate (RTOG/EORTC xerostomia grade IV), the mean parotid gland doses reported in these studies were in the range of 26–39 Gy. Similar dose range (12,13) or higher (14) were reported to cause long-term dysfunction in previous studies, which used crude estimates of the gland doses. Studies are have also been conducted using salivary gland single photon emission computed tomography (SPECT), assessing the relationships between the 3-dimensional scintigraphy results and the mean parotid gland dose (15).

In this issue of *Sci Transl Med*, van Luijk *et al*., present data from irradiated rat and human PGs suggesting that that stem and progenitor cells of the PGs reside in the region of the gland which contains the major ducts (16). Partial irradiation of the rat parotid resulted in different salivary function depending on the site irradiated, rather than on the mean gland dose. Similarly, in patients, the dose to the stem-cell containing region of the parotid gland, which is the region where the first branching of Stensen's duct occurs, was highly predictive of subsequent gland function. This prediction of function was better than the prediction using the mean dose to the gland, and suggests that sparing this particular region should be the most important goal of RT optimization. Thus, if we make efforts to spare this specific region in the parotid gland, rather than using just the mean dose for optimization, as commonly practiced, we may gain higher salivary output and further reduce xerostomia.

How reliable are these findings? The experience of this group assessing rat parotid RT are quite convincing (17), however, further studies in humans are required to compare targeted sparing of the stem-cell region to sparing of the whole gland aiming to reduce its mean dose. Other groups assessing the identification of stem cells in salivary glands reported that these cells were present in the intercalated ducts of the rat glands (18), meaning that they are distributed throughout the gland rather than being confined to a specific anatomical region. Furthermore, if the findings by van Luijk *et al*. will be confirmed, their clinical utility will depend on adequate imaging to identify the major parotid ducts. Using CT scan, the common method used clinically to identify and contour the target and organs for RT planning, is complicated by inter-observer errors in delineation of the parotid gland (19) and cannot serve adequately to define the major intra-parotid ducts. Sialography, especially MRI-based sialography, is a reliable method but require radiologic expertise and is best after salivary stimulation (20), which are not prevalent in clinical practice. Moreover, high resolution MRI of the parotid ducts detected the main intra-parotid ducts in only 66% of subjects (21). Thus, defining the stem-cell region based on parotid major ducts would require additional imaging beyond clinical standard practice.

Beyond methods to improve parotid gland output using targeted sparing, suggested by van Luijk *et al*., it is necessary to appreciate the fact that the parotid gland is not the only source of saliva. While it produces most saliva output during eating, its secretions are purely serous. The submandibular glands produce most of the saliva while not eating and their secretions contain mucins. In addition, the minor salivary glands, dispersed within the oral cavity, while producing only 10% of the salivary volume, produce most of the salivary mucins (4). Mucins are glycoproteins which adhere to the oral mucosal surfaces and absorb water molecules, providing a sense of hydration to the patient. Thus, sparing of all the salivary glands, including the parotid, submandibular, and minor salivary glands, is expected to provide maximal reduction in patient-reported RT-associated xerostomia.

We have recently assessed prospectively the predictors of xerostomia in patients with HN cancer treated with IMRT. We have found that statistically significant predictors of patient-reported xerostomia scores included oral cavity, PGs, and submandibular glands mean doses, as well as baseline XQ score, time since RT, and both stimulated and unstimulated PG saliva flow rates. Similar factors were statistically significant predictors of observer-graded xerostomia (22).

In conclusion, better sparing of the parotid gland focusing on the presumed sites of parotid stem cells offers improvement in serous parotid secretions, if confirmed. Importantly, efforts to also spare the other major, as well as minor, salivary glands, are likely to result in significant improvement of xerostomia, and, subsequently, patient-reported quality of life (23).

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Footnote

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