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In Reply to Sari and Yazici

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finding in the current study. However, we would like some points to be clarified.

First, the authors used selected questions in the European Organisation for Research and Treatment of Cancer's Head and Neck 43 (EORTC HN43) questionnaire and the Groningen questionnaire. Although not directly asking about dry mouth, all questions in the Groningen questionnaire and more than half in the EORTC questionnaire investigate xerostomia, asking about swallowing, talking, teeth problems, and sticky saliva. As Steenbakkers et al stated, the role of the parotid glands is primarily during eating and drinking; therefore, using all questions in both questionnaires might have changed the results.³ Was there a specific reason for choosing those questions only? Second, parotid stem cells are reported to be located in the vicinity of the Stensen duct.⁴ The authors chose to automatically delineate the stem cell region. However, this led to a large field to be spared and may have been the reason for statistically nonsignificant outcomes.

We think this may be a valuable study that could change routine practice and help minimize parotid toxicity. However, probably due to the selected questions from the questionnaires and the size of the delineated region of the parotid gland, the study may have resulted in nonsignificant findings. Nonetheless, the mean dose to the stem cell region seems important.

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References

1. Steenbakkers R, van Rijn-Dekker MI, Stokman MA, et al. Parotid gland stem cell sparing radiotherapy for head and neck cancer patients: A double-blind randomized controlled trial [e-pub ahead of print]. *Int J Radiat Oncol Biol Phys* 2022. <https://doi.org/10.1016/j.ijrobp.2021.09.023>. Accessed October 8, 2021.
2. Sari SY, Yilmaz MT, Elmali A, et al. Parotid gland stem cells: Mini yet mighty. *Head Neck* 2021;43:1122–1127.
3. Aps JK, Martens LC. Review: The physiology of saliva and transfer of drugs into saliva. *Forensic Sci Int* 2005;150:119–131.
4. Pringle S, Van Os R, Coppes RP. Concise review: Adult salivary gland stem cells and a potential therapy for xerostomia. *Stem Cells* 2013;31:613–619.

In Reply to Sari and Yazici



To the Editor: We thank Dr Sari and Dr Yazici for their interest¹ in our double-blind randomized controlled trial testing the effect of stem cell sparing radiation therapy (RT).²

We fully agree that it would be very interesting to consider more toxicity outcomes, such as dysphagia or sticky saliva. Unfortunately, the number of events in our study was too small to allow drawing reliable conclusions. For example, 21 patients experienced physician-rated grade 2 dysphagia³ (8 events in the standard RT arm and 13 events in the stem cell sparing RT arm) and 22 patients experienced patient-rated moderate-to-severe sticky saliva⁴ (10 and 12 events, respectively, in the standard RT and stem cell sparing RT arm), both outcomes measured at 12 months after treatment. In addition, these prevalence rates were in line with earlier publications (Table 1). In conclusion, the number of events for these endpoints was insufficient to allow meaningful analyses. Moreover, they were not defined as secondary endpoint in advance.

We also agree that our automatic delineation of the stem cell rich (SCR) region likely reduced the power of our study. However, to our knowledge, currently no modality can

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Table 1 Prevalence of dysphagia and sticky saliva: comparison of our study and literature

Study	Outcome	Time point	Prevalence
Physician-rated dysphagia			
Steenbakkers et al (2021) ²	Grade ≥ 2 according to the CTCAE ³	M06	33%
<i>Unpublished data</i>		M12	25%
		M24	21%
Van den Bosch et al (2021) ⁶	Grade ≥ 2 according to the CTCAE ³	M06	33%
		M12	30%
		M24	32%
Hansen et al (2019) ⁷	Grade ≥ 2 according to the RTOG/EORTC ⁸	M06	33%
Blanchard et al (2016) ⁹	Grade ≥ 2 according to the RTOG/EORTC ⁷	M06	30%
Patient-rated sticky saliva			
Steenbakkers et al (2021) ²	Moderate-to-severe according to the EORTC QLQ-HN35 ³	M06	32%
<i>Unpublished data</i>		M12	27%
		M24	27%
Van den Bosch et al (2021) ⁶	Moderate-to-severe according to the EORTC QLQ-HN35 ³	M06	33%
		M12	25%
		M24	29%
Beetz et al (2012) ¹⁰	Moderate-to-severe according to the EORTC QLQ-HN35 ³	M06	36%
<i>Abbreviations:</i> CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-HN35 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module; M06 = 6 months after radiation therapy; M12 = 12 months after radiation therapy; M24 = 24 months after radiation therapy; RTOG/EORTC = toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer.			

image the cell population we aimed to spare in a clinical setting. In addition, at the time we designed our study, the performance of ductal imaging (eg, magnetic resonance imaging) was insufficient to reliably define the stem cell region. Therefore, we reverted to the definition developed in previous work,⁵ further optimized by using knowledge on anatomic information.² However, this resulted in a structure that typically contained 25% to 35% of the parotid gland. Because larger volumes are harder to spare, further optimization of techniques to identify and contour the stem cell region may increase the effect of stem cell sparing on outcome. Nonetheless, intra-arm variation in dose to normal tissues inherently limits the power for detecting study arm differences, even after more exact delineation of the SCR region.

However, we would like to stress that despite these limitations, our multivariable analysis still showed a significant role for the SCR region in the development of radiation-induced xerostomia.² Therefore, we will continue our research into the impact of this SCR region by

further optimizing the definition of the SCR region using radiomics and machine learning techniques. We hope that our future research will further elucidate the role of the parotid gland SCR region and lead to improvement of clinical practice.

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References

1. Sari SY, Yazici G. In regard to Steenbakkers et al. *Int J Radiat Oncol Biol Phys* 2022;112:1290–1291.
2. Steenbakkers RJHM, Rijn-Dekker MI van, Stokman MA, et al. Parotid gland stem cell sparing radiation therapy for patients with head and neck cancer: A double-blind randomized controlled trial. *Int J Radiat Oncol Biol Phys* 2022;112:306–316.
3. U.S. Department of Health and Human Services. *National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE)*; 2021. version 4.0. 2009. Available at; https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf. Accessed November 19, 2021.
4. Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H and N35) in head and neck patients. *Eur J Cancer* 2000;36:1796–1807.
5. van Luijk P, Pringle S, Deasy JO, et al. Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer. *Sci Transl Med* 2015;7:305ra147.
6. Van den Bosch L, der Schaaf A van, der Laan HPI van, et al. Comprehensive toxicity risk profiling in radiation therapy for head and neck cancer: A new concept for individually optimised treatment. *Radiother Oncol* 2021;157:147–154.
7. Hansen CR, Friborg J, Jensen K, et al. NTCP model validation method for DAHANCA patient selection of protons versus photons in head and neck cancer radiotherapy. *Acta Oncologica* 2019;58:1410–1415.
8. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–1346.
9. Blanchard P, Wong AJ, Gunn GB, et al. Toward a model-based patient selection strategy for proton therapy: External validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort. *Radiother Oncol* 2016;121:381–386.
10. Beetz I, Schilstra C, der Schaaf A van, et al. NTCP models for patient-rated xerostomia and sticky saliva after treatment with intensity modulated radiotherapy for head and neck cancer: The role of dosimetric and clinical factors. *Radiother Oncol* 2012;105:101–106.