In Reply to Kashid et al.

To the Editor: We thank Kashid et al1 for their interest (ref Kashid et al.) in our double-blind randomized controlled trial testing parotid gland stem cell sparing (SCS) radiation therapy (RT).2

The authors suggest to consider the stem cell rich (SCR) region as a serial structure and consequently use maximum dose (Dmax) as predictor (reference Kashid et al). However, loss of parotid gland function involves effects of dose to the stem cell region on regenerative function, as well as a dose to the remainder of the parotid gland directly on salivary function. Such a situation is not captured by a serial or parallel organization of functional subunits. Practically, using Dmax has several disadvantages. Being a point dose, Dmax is very sensitive to small changes in treatment planning, as well as per-treatment anatomical changes. Accordingly, we did not find a significant association between the Dmax of the SCR regions and xerostomia (Table 1).

We agree with Kashid et al that the tissue microenvironment strongly influences the stem cell’s behavior. Although this cannot be exploited in treatment planning directly, investigating interventions modulating the microenvironment are indeed of interest and research is in progress.3,4

We are aware of the multifactorial etiology of xerostomia. We minimized potential bias from the effects of chemotherapy by stratifying randomization for systemic treatment. Moreover, further analysis of the relation between systemic treatment and xerostomia using univariable logistic regression did not reveal significant associations (Table 1).

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Multivariable analysis, including doses to the submandibular glands and other relevant organs at risk3-7 showed that doses to the submandibular glands and buccal mucosa were independent predictors, next to doses to the SCR regions and pretreatment xerostomia.2

Lastly, Kashid et al wondered whether SCS-RT might influence pattern of failure. Therefore, we updated the survival data. Almost 5 years after the last patient inclusion 17 patients were deceased in both study arms, indicating no difference (Fisher’s exact test \( P = .68 \)). Locoregional failure was only proven in 18 patients. Only in 7 did this occur near the parotid glands. However, in both study arms these failures were in the high-dose area, where doses were not compromised by SCS-RT.

To conclude, mean dose to the SCR region was an independent prognostic factor for radiation-induced xerostomia.2 Moreover, SCS-RT did not compromise other oncological outcomes. We intend to publish our follow-up research shortly, further elucidating the role of the SCR

Table 1  Additional univariable logistic regression analysis of xerostomia endpoints

<table>
<thead>
<tr>
<th>Univariables</th>
<th>OR (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-rated xerostomia*</td>
<td>M12 (n = 81, 30 events)</td>
<td></td>
</tr>
<tr>
<td>SCR region CL, Dmax</td>
<td>0.99 (0.96-1.03)</td>
<td>.68</td>
</tr>
<tr>
<td>SCR region IL, Dmax</td>
<td>1.00 (0.97-1.03)</td>
<td>.99</td>
</tr>
<tr>
<td>Systemic treatment (yes vs no)</td>
<td>1.40 (0.55-3.57)</td>
<td>.48</td>
</tr>
<tr>
<td>Daytime xerostomia</td>
<td>M12 (n = 81, 29 events)</td>
<td></td>
</tr>
<tr>
<td>SCR region CL, Dmax</td>
<td>1.01 (0.98-1.04)</td>
<td>.51</td>
</tr>
<tr>
<td>SCR region IL, Dmax</td>
<td>1.00 (0.96-1.03)</td>
<td>.86</td>
</tr>
<tr>
<td>Systemic treatment (yes vs no)</td>
<td>0.72 (0.27-1.95)</td>
<td>.52</td>
</tr>
<tr>
<td>Nighttime xerostomia</td>
<td>M12 (n = 81, 37 events)</td>
<td></td>
</tr>
<tr>
<td>SCR region CL, Dmax</td>
<td>1.00 (0.97-1.03)</td>
<td>.89</td>
</tr>
<tr>
<td>SCR region IL, Dmax</td>
<td>1.02 (0.99-1.05)</td>
<td>.27</td>
</tr>
<tr>
<td>Systemic treatment (yes vs no)</td>
<td>0.82 (0.32-2.10)</td>
<td>.68</td>
</tr>
<tr>
<td>Physician-rated xerostomia</td>
<td>M12 (n = 84, 17 events)</td>
<td></td>
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<tr>
<td>SCR region CL, Dmax</td>
<td>1.04 (1.00-1.08)</td>
<td>.07</td>
</tr>
<tr>
<td>SCR region IL, Dmax</td>
<td>1.05 (1.00-1.10)</td>
<td>.07</td>
</tr>
<tr>
<td>Systemic treatment (yes vs no)</td>
<td>0.36 (0.09-1.38)</td>
<td>.14</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; CL = contralateral; Dmax = maximum point dose; IL = contralateral; M12 = 12 months after treatment; OR = odds ratio; SCR = stem cell rich.

Xerostomia scored according to the:

* European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Head and Neck.

1 Groningen Radiation Induced Xerostomia Questionnaire.

1 Common Terminology Criteria for Adverse Events.

1
region in relation to other organs at risk and how this can improve clinical practice.

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