# The First Prognostic Tool to Estimate the Risk of Late Grade ≥3 Xerostomia in Patients Irradiated for Head-and-Neck Cancer

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**Abstract.** *Background/Aim: Xerostomia is a serious complication following radiotherapy of head-and-neck cancers. A prognostic tool was developed for estimating its risk. Patients and Methods: In our previous study, age, tumor site, bilateral lymph node involvement, definitive radiotherapy, and addition of systemic therapies showed significant associations with grade ≥3 late xerostomia or trends. In additional analyses, mean radiation dose to ipsilateral parotid gland was significant (p=0.011). These six factors were included in the prognostic tool. Scoring points of 0 (lower risk) or 1 (higher risk) were assigned to each factor and added for each patient. Results: Patient scores ranged between 0 and 6; Grade ≥3 xerostomia rates were 0%, 8%, 24%, 26%, 25%, 42%, and 100%, respectively. Three groups were designed (0-1, 2-4, and 5-6 points) with grade ≥3 xerostomia rates of 5%, 25%, and 50%, respectively (p<0.001). Conclusion: This new tool helps estimating the risk of radiation-induced grade ≥3 xerostomia. It can support physicians and other medical staff members during treatment planning.*

Xerostomia is considered one of the most dreaded late complications after irradiation of head-and-neck cancers (1). Furthermore, a dry mouth persisting for years can trigger further oral complications such as increased susceptibility to infections, radiation caries, and tooth loss (2-4). Grade ≥2 xerostomia was reported to occur in a considerable proportion of patients irradiated for malignancies in the head-and-neck region, particularly if 3-dimensional conformal radiotherapy (3D-CRT) was used (5-9). For optimization of radiation treatment planning in terms of appropriate coverage of the target volumes and sparing of the organs at risk, comprehensive information regarding the risk of late complications is important. This is particularly true for higher-grade (grade ≥3) toxicities that are serious or potentially life threatening. Grade ≥3 xerostomia is characterized by complete dryness of the mouth, which can be non-debilitating (grade 3) or debilitating (grade 4) for patients (10). Several risk factors have already been identified that can help estimate the risk of radiation-induced xerostomia. The most recognized of these factors is the mean radiation dose to one or both parotid glands (7, 11-14). Moreover, concurrent systemic therapy, and occasionally older age, female sex, tumor sites cranial to the hypopharynx, advanced stage, and bilateral treatment were observed as risk factors for xerostomia (9, 14-16). However, an easy-to-use prognostic tool would be more practical for treating physicians and other medical staff members than separate prognostic factors. Therefore, the present study aimed to create a tool that facilitates estimation of the risk of grade ≥3 late xerostomia after radiotherapy for head-and-neck cancers.

## Patients and Methods

In our previous study of 159 patients irradiated for head-and-neck cancers, significant associations with grade ≥3 late xerostomia or trends were found for age ≥61 years (*p*=0.035), location of the tumor in the nasopharynx, oropharynx and/or oral cavity/floor of mouth (*p*=0.088), bilateral involvement of lymph nodes (*p*=0.093), definitive radiotherapy (*p*=0.082), and the addition of systemic therapies (*p*=0.055) (5). These five characteristics were used to develop the prognostic tool. Late xerostomia was defined as dryness occurring ≥6 weeks after radiotherapy. It was graded based on the subjective criteria of the Late Effects of Normal Tissues (LENT)/Subjective Objective Management Analytic (SOMA) system with respect to dryness of mouth (as reported by the patients during follow up visits): 0=no dryness; 1=occasional; 2=partial,

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Table I. *Associations between mean radiation doses to ipsilateral, contralateral or both parotid glands and grade ≥3 late xerostomia following radiotherapy.*

| | Grade ≥3 xerostomia, n (%) | | |
| --- | --- | --- | --- |
| | Yes | No | *p*-Value |
| Mean dose to ipsilateral parotid gland | | | |
| ≤34 Gy | 11 (31) | 69 (56) | **0.011** |
| >34 Gy | 24 (69) | 55 (44) | |
| Mean dose to contralateral parotid gland | | | |
| ≤23 Gy | 13 (37) | 67 (54) | 0.078 |
| >23 Gy | 22 (63) | 57 (46) | |
| Mean dose to both parotid glands | | | |
| <29 Gy | 13 (37) | 68 (55) | 0.064 |
| ≥29 Gy | 22 (63) | 56 (45) | |

*p*-Values were calculated with the Chi-square test. Significant *p*-values are shown in bold.

persistent; 3=complete and not debilitating; 4=complete but debilitating (10). The highest grade of xerostomia observed between 6 weeks and 24 months after radiotherapy was included.

In the present study, which was approved by the ethics committee of the University of Lübeck (AZ 21-108), additional analyses were performed in the initial cohort (n=159) with respect to associations between grade ≥3 xerostomia and the mean radiation doses to the ipsilateral (≤34 *vs.* >34 Gy, median=34 Gy), the contralateral (≤23 *vs.* >23 Gy, median=23 Gy) or both (<29 *vs.* ≥29 Gy, median=28.9 Gy) parotid glands (Table I). A significant association was found for the mean dose to the ipsilateral gland (*p*=0.011, Chi square test), and trends for associations with the mean dose to the contralateral gland (*p*=0.078) and both parotid glands (*p*=0.064). Since these three factors were likely confounding variables, only the significant factor, i.e., the mean dose to the ipsilateral gland, was included in the prognostic tool. Of the patients of the previous study (n=159), complete data regarding the six factors included in the tool were available for 141 patients. Of these patients, 109 received upfront resection of the primary tumor with or without lymph node dissection, and 76 received systemic therapies in addition to radiotherapy. The distributions of these and other patient characteristics are shown in Table II. Details regarding radiotherapy, surgery, and systemic therapies were previously described (5).

For the development of the prognostic tool, the data of these 141 patients were used. For each factor included in the tool, scoring points of 0 (lower risk of xerostomia) or 1 (higher risk) were assigned (Table III) and summed for each patient (patient scores). The creation of prognostic groups was based on the grade ≥3 late xerostomia rates related to the patient scores. The prognostic groups were compared for grade ≥3 late xerostomia rates using the Chi-square test or, in case of <5 patients in one group, the Fisher's exact test. *p*-Values <0.05 were considered demonstrating significance and *p*-values <0.10 showing a trend.

Table II. *Distribution of the potential risk factors in the cohort of 141 patients.*

| Potential risk factor | Frequency, n (%) |
| --- | --- |
| Age | |
| ≤60 Years | 76 (54) |
| ≥61 Years | 65 (46) |
| Sex | |
| Female | 28 (20) |
| Male | 113 (80) |
| Tumor site | |
| Nasopharynx | 7 (5) |
| Oropharynx and/or oral cavity/FoM | 73 (52) |
| Hypopharynx | 16 (11) |
| Larynx | 32 (23) |
| Hypopharynx plus larynx | 13 (9) |
| Primary tumor stage | |
| T1-2 | 63 (45) |
| T3-4 | 78 (55) |
| Nodal stage | |
| N0 | 38 (27) |
| N1-2b | 72 (51) |
| N2c | 31 (22) |
| Bilateral nodal involvement | |
| No | 110 (78) |
| Yes | 31 (22) |
| Underlying pathology | |
| SCC | 136 (96) |
| Other | 5 (4) |
| Histologic grading | |
| G1-2 | 85 (60) |
| G3 | 54 (38) |
| Unknown | 2 (1) |
| Upfront resection | |
| No | 32 (23) |
| Yes | 109 (77) |
| Systemic therapies | |
| No | 65 (46) |
| Yes | 76 (54) |
| Type of radiotherapy | |
| EBRT alone | 131 (93) |
| EBRT + BT | 10 (7) |
| Total dose of EBRT | |
| 60 Gy | 77 (59) |
| >60 Gy | 54 (41) |
| Mean dose to ipsilateral parotid gland | |
| ≤34 Gy | 75 (53) |
| >34 Gy | 66 (47) |
| Mean dose to contralateral parotid gland | |
| ≤23 Gy | 75 (53) |
| >23 Gy | 66 (47) |
| Mean dose to both parotid glands | |
| <29 Gy | 75 (53) |
| ≥29 Gy | 66 (47) |

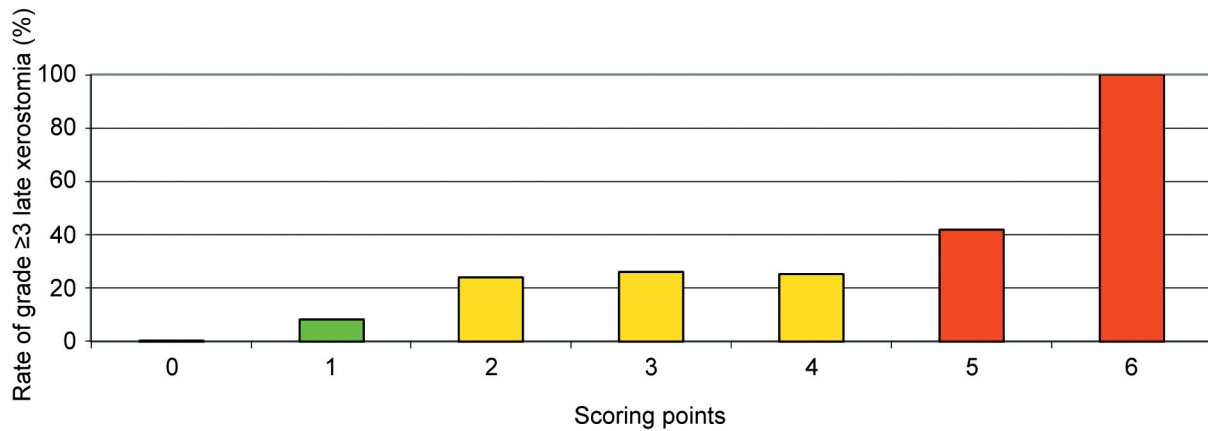FoM: Floor of mouth; SCC: squamous cell carcinoma; EBRT: external beam radiotherapy; BT: brachytherapy boost.

Figure 1. *The grade ≥3 late xerostomia rates related to the patient scores.*

Table III. *Risk factors for grade ≥3 late xerostomia and related scoring points.*

| Prognostic factor | Scoring points |
|---|---|
| Age | |
| ≤60 Years | 0 |
| ≥61 Years | 1 |
| Tumor site | |
| Hypopharynx/Larynx Nasopharynx/Oropharynx/ | 0 |
| Oral cavity/Floor of Mouth | 1 |
| Bilateral nodal involvement | |
| No | 0 |
| Yes | 1 |
| Upfront resection | |
| Yes | 0 |
| No | 1 |
| Systemic treatment | |
| No | 0 |
| Yes | 1 |
| Mean dose to ipsilateral parotid gland | |
| ≤34 Gy | 0 |
| >34 Gy | 1 |

## Results

Patient scores ranged between 0 and 6 points. The corresponding grade ≥3 late xerostomia rates were 0% (0/14), 8% (2/26), 24% (7/29), 26% (10/38), 25% (5/20), 42% (5/12), and 100% (2/2), respectively (Figure 1). Based on these rates, three prognostic groups were designed (0-1, 2-4, and 5-6 points) with grade ≥3 late xerostomia rates of 5% (2/40), 25% (22/87), and 50% (7/14), respectively. The overall difference was significant ($p=0.001$, Chi square test). The differences of 0-1 *vs*. 2-4 points ($p=0.007$, Fisher's exact test) and 0-1 *vs*. 5-6 points ($p<0.001$, Fisher's exact test)

were also significant, and the difference of 2-4 *vs*. 5-6 points showed a strong trend ($p=0.057$, Chi square test).

## Discussion

Following radiotherapy of head-and-neck cancers, patients may experience late xerostomia, which can result in significant additional complications including oral mucosal discomfort and infections, dysgeusia, weight loss, and carious destruction of teeth (2-4). This is particularly true for grade ≥3 xerostomia, which is defined as complete dryness of mouth (10). Thus, grade ≥3 xerostomia should be avoided, whenever reasonably possible. Since the risk of late xerostomia increases with the mean radiation dose at the parotid glands, it is important to spare these glands when planning the treatment (7, 11-14). In head-and-neck cancer patients with lymph node involvement, particularly in case of N2c or N3 disease, sparing of parotid glands may have a negative impact on the dose coverage of the target volumes resulting in a higher risk of loco-regional recurrences. For optimal results of radiation treatment planning, it would be helpful to be able to estimate a patient's risk of developing grade ≥3 late xerostomia. A higher risk would mean a greater need of sparing the parotid glands.

In addition to the mean dose to the parotid glands, other risk factors for post-radiotherapy xerostomia have been reported (7, 11-16). However, it may be difficult to estimate the risk with separate prognostic factors for each individual patient. More practical for clinical use would be an easy-to-use scoring system combining prognostic factors. The present study was performed to develop such a tool in a cohort of patients receiving radiotherapy plus/minus chemotherapy for head-and-neck cancers. The prognostic tool was based on six factors that were significantly associated with the occurrence of grade ≥3 xerostomia or

showed a corresponding trend. These factors included age, location of the tumor, bilateral lymph node involvement, definitive treatment, addition of systemic therapies, and mean radiation dose to the ipsilateral parotid gland. Considering the rates of grade ≥3 xerostomia related to these factors, three prognostic groups were designed, namely 0-1, 2-4, and 5-6 points. In the 0-1 points group, the risk of grade ≥3 late xerostomia was low. The 5% probability represents the complication rate, which is generally considered tolerable (tolerance dose=TD5/5) (17). Therefore, one may consider to focus more on the coverage of the target volumes during radiation treatment planning in these patients. In the 2-4 points group, the probability of developing grade ≥3 late xerostomia was 25%. This rate is a bit higher than the 20% considered acceptable in the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) (18). Thus, sparing of the parotid glands becomes more important in this group. In the 5-6 points group, every second patient developed grade ≥3 late xerostomia. Therefore, sparing of the parotid glands is of great importance for these patients. However, when one has to weigh between sparing of the parotid glands and coverage of the target volumes, it is very important that the patient participates in the decision process. The patients' preference regarding better loco-regional control of the disease *versus* less toxicity including xerostomia must have the highest priority.

When planning to use this prognostic tool, one should be aware of the limitations of the present study. These limitations include the retrospective nature of the data used for the tool (risk of hidden selection biases) and the fact that grading of xerostomia was limited to subjective criteria of the LENT/SOMA system. Moreover, validation of this new tool is warranted.

In summary, a prognostic tool including three groups was developed to estimate the risk of grade ≥3 late xerostomia after radiotherapy of head-and-neck cancers. This new tool can support physicians, dosimetrists, and medical physicists during treatment planning. However, the limitations of this study should be considered when using this new tool that should be validated. It is important that patients participate in the decision process regarding improved loco-regional control *versus* less xerostomia.

## Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

## Authors' Contributions

All Authors participated in the design of the study. The data were provided by B.W. and interpreted by all Authors. D.R. and S.E.S. drafted the article, which was reviewed and approved by all Authors.

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