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Impact of Dose-Volume Parameters of Parotid Glands on Xerostomia in Patients Irradiated for Head-and-Neck Cancer

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Abstract. *Background/Aim: Optimal planning of radiotherapy for head-and-neck cancers should consider the risk of xerostomia. This study investigated the prognostic value of dose-volume parameters of the parotid glands. Patients and Methods: Dose-volume parameters were evaluated for xerostomia in 145 patients including D40 (minimum dose to 40% of corresponding parotid volume), D60 (minimum dose to 60%), D80 (minimum dose to 80%), and mean dose of ipsilateral, contralateral, and bilateral parotid glands. Results: Grade ≥2 xerostomia was significantly associated with D40 of ipsilateral and all parameters of bilateral glands; trends were found for all other parameters. Grade ≥3 xerostomia was significantly associated with D80 of bilateral glands; trends were found for other parameters of ipsilateral and bilateral glands. Conclusion: Since grade ≥2 xerostomia was associated with all parameters, D40, D60, and D80 did not provide additional information to mean doses. D80 of bilateral glands is a new factor and more predictive than mean dose regarding grade ≥3 xerostomia.*

Radiotherapy alone or in combination with systemic therapies, mainly cisplatin-based chemotherapy, is a common treatment for head-and-neck cancers (1). It is often associated with significant toxicity, particularly if administered with concurrent systemic treatment. Acute toxicity includes radiation dermatitis and oral mucositis that usually resolve within a few weeks (2-4). In contrast, late toxicity frequently persists for several years or even for the entire lifespan (5). Therefore, it is very important to reduce the risk of late toxicities. In a previous retrospective study, xerostomia (dry mouth) was identified as a debilitating late effect in patients with head-and-neck cancer after chemoradiation (5). In addition, a permanent decrease in saliva can result in subsequent complications including oral infections or demineralization and loss of teeth (6-8).

In order to provide optimal personalized radiation treatment, it is important to estimate an individual patient's risk of xerostomia. The implications of xerostomia need to be discussed with patients, especially with those at highest risk. Reduction of the risk of xerostomia can be achieved by sparing one or both parotid glands. However, this can often only be realized if the distribution of the radiation dose at the target volume is compromised, which may result in a higher risk of a loco-regional recurrence of the cancer. Several clinical factors have been reported as predictors of xerostomia after radiotherapy of head-and-neck cancers including tumor site (oropharynx, oral cavity), advanced stage, bilateral involvement of lymph nodes and/or irradiation, more advanced age, and concurrent systemic therapies (9-13). Regarding the impact of dose-volume parameters of radiotherapy on xerostomia, the mean dose to parotid glands was identified as significantly associated with the risk of xerostomia in several studies (10, 14-19).

However, in addition to mean doses, other dose-volume parameters of the parotid glands may also play a role in the development of xerostomia, but only few studies have investigated such parameters. In a retrospective study of 88 patients from 1999, saliva output decreased substantially, if at least 67%, 45%, and 24% of the parotid glands received 15 Gy, 30 Gy, and 45 Gy, respectively (17). In 2018, a retrospective study of 21 patients with cancer of the nasopharynx found associations between xerostomia and V20 (proportion of the volume of the parotid gland receiving at least 20 Gy), V30 (proportion receiving at least 30 Gy), V40 (proportion receiving at least 40 Gy), and D50 (minimum dose to 50% of the parotid volume) in addition to the mean dose (18). In another retrospective study of 195 patients who

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Key Words: Xerostomia, radiotherapy, head-and-neck cancer, parotid glands, dose-volume parameters.

Table I. *Patient and treatment characteristics*.

Characteristic	Subgroup	Frequency, n (%)
Age	≤60 Years	77 (53)
	≥61 Years	68 (47)
Sex	Female	31 (21)
	Male	114 (79)
Tumor site	Nasopharynx	7 (5)
	Oropharynx and/or oral cavity/FoM	70 (48)
	Hypopharynx	16 (11)
	Larynx	30 (21)
	Hypopharynx plus larynx	10 (7)
	Other multiple sites	12 (8)
Primary tumor stage	T1-2	62 (43)
	T3-4	83 (57)
Nodal stage	N0	32 (22)
	N+	113 (78)
Histology	SCC	140 (97)
	Other	5 (3)
Histologic Grading	G1-2	80 (55)
	G3	63 (43)
	Unknown	2 (1)
Upfront resection	No	38 (26)
	Yes	107 (74)
Systemic therapies	No	62 (43)
	Yes	83 (57)
Type of radiotherapy	EBRT alone	138 (95)
	EBRT + BT	7 (5)
Total dose of EBRT	60 Gy	77 (56)
	>60 Gy	61 (44)

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

developed xerostomia following radiotherapy for nasopharynx cancer, the V30 of the contralateral parotid gland was an independent predictor of recovery of xerostomia over time (19). More research is required evaluating the prognostic value of additional dose-volume parameters of the parotid glands regarding radiation-related xerostomia. Therefore, this study was performed to investigate the potential impact of D40, D60, and D80 (dose to 40%, 60%, and 80%, respectively, of the parotid volume) in addition to mean doses separately for ipsilateral, contralateral, and bilateral (both) parotid glands.

Patients and Methods

In addition to previously identified clinical risk factors of radiation-related xerostomia, this retrospective study (reference no. 21-108, ethics committee of the University of Lubeck) investigated dose-volume parameters of the parotid glands for associations with grade ≥2 and grade ≥3 xerostomia in 145 patients irradiated for head-and-neck cancer (11). The characteristics of these patients and their treatment are summarized in Table I.

External beam radiation therapy (EBRT) alone, performed as 3D-conformal radiotherapy (linear accelerator) with generally more than ten radiation fields for each plan, was administered to 138 patients (95%). In 127 of these patients, it started with conventional fractionation over 5 weeks (50 Gy in 25 fractions) to primary tumor and lymph nodes. Additional doses (sequential boosts) were delivered to the primary tumor and to intermediate-risk and high-risk lymph node areas. Depending on the extent of resection, these doses were 10 Gy (microscopically complete resection), 14-16 Gy (microscopically incomplete resection) or 20 Gy (macroscopically incomplete resection or definitive treatment). Lymph node areas with extracapsular spread received a boost of 14-16 Gy.

Seven of the 138 patients treated with EBRT alone received conventionally fractionated radiotherapy (30 Gy in 15 fractions over 3 weeks) followed by a concomitant boost resulting in a cumulative dose of 69.6 Gy (20, 21), three patients received conventionally fractionated radiotherapy (30 Gy in 15 fractions over 3 weeks) followed by hyperfractionated-accelerated irradiation (2×1.4 Gy per day) resulting in a cumulative dose of 70.6 Gy (22), and one patient received conventionally fractionated radiotherapy (52 Gy in 26 fractions) followed by hyperfractionated-accelerated irradiation (2×1.5 Gy per day) resulting in a cumulative dose of 70.0 Gy. In the 7 patients receiving a brachytherapy boost (high-dose rate with iridium-192), EBRT doses ranged between 50 and 66 Gy and brachytherapy doses (mainly administered to the primary tumor) between 10 and 15 Gy (2×2.5 Gy per day).

In the 107 patients (74%) receiving upfront resection, microscopically complete resection was achieved in 90 patients. Resection was microscopically incomplete in ten, macroscopically incomplete in two, and unclear in five patients, respectively. Eighty-three patients (57%) received additional systemic treatment including concurrent cisplatin alone (n=51), cisplatin-based treatment (n=14), or other regimens (n=13). Five patients received induction chemotherapy (docetaxel, cisplatin, fluorouracil) followed by concurrent chemoradiation (cisplatin alone).

Xerostomia was assessed 6 weeks to 24 months after completion of the radiation treatment. Grading was performed according to the subjective criteria of the Late Effects of Normal Tissues (LENT)/Subjective Objective Management Analytic (SOMA) system as reported by the patients: Grade 0=no dryness of mouth; grade 1=occasional dryness; grade 2=partial dryness, persistent; grade 3=complete dryness, not debilitating; grade 4=complete, debilitating (23). The highest grade of xerostomia reported by the patients at follow-up visits 6 weeks to 24 months after radiotherapy was used for the analyses.

Analyses of potential associations between the investigated dose-volume parameters of the parotid glands and grade ≥2 or grade ≥3 xerostomia were performed with the Chi-square test. When applying the Bonferroni adjustment for 12 tests, p-values of <0.0042 were considered significant representing an alpha level of <0.05. p-Values <0.06 indicated a trend. Investigated dose-volume parameters included D40 (dose to 40% of parotid volume), D60 (dose to 60% of parotid volume), D80 (dose to 80% of parotid volume), and mean dose to parotid gland(s). Separate analyses were performed for the ipsilateral parotid gland (receiving the higher dose of both glands), the contralateral parotid gland, and bilateral (both) parotid glands.

Results

After Bonferroni adjustment, grade ≥2 xerostomia occurred in 82 patients (57%) and was significantly associated with D40 of the ipsilateral parotid gland (p=0.0030) and with D40

Table II. *Associations between dose-volume parameters and grade ≥2 xerostomia after radiotherapy.*

Dose-volume parameter		Grade ≥2 Xerostomia, n (%)		*p*-Value
		Yes (n=82)	No (n=63)	
Parotid gland, ipsilateral				
D40	≤37 Gy (n=74)	33 (40)	41 (65)	**0.0030**
	>37 Gy (n=71)	49 (60)	22 (35)	
D60	≤26 Gy (n=74)	34 (41)	40 (63)	0.0085
	>26 Gy (n=71)	48 (59)	23 (37)	
D80	≤18 Gy (n=75)	35 (43)	40 (63)	0.0129
	>18 Gy (n=70)	47 (57)	23 (37)	
Mean dose	≤33 Gy (n=71)	32 (39)	39 (62)	0.0063
	>33 Gy (n=74)	50 (61)	24 (28)	
Parotid gland, contralateral				
D40	≤23 Gy (n=74)	34 (41)	40 (63)	0.0085
	>23 Gy (n=71)	48 (59)	23 (37)	
D60	≤17 Gy (n=73)	35 (43)	38 (60)	0.0353
	>17 Gy (n=72)	47 (57)	25 (40)	
D80	≤12 Gy (n=73)	34 (41)	39 (62)	0.0147
	>12 Gy (n=72)	48 (59)	24 (38)	
Mean dose	≤22 Gy (n=72)	32 (39)	40 (63)	0.0035
	>22 Gy (n=73)	50 (61)	23 (37)	
Parotid glands, bilateral				
D40	≤30 Gy (n=74)	31 (38)	43 (68)	**0.0003**
	>30 Gy (n=71)	51 (62)	20 (32)	
D60	≤20 Gy (n=72)	29 (35)	43 (68)	**<0.0001**
	>20 Gy (n=73)	53 (65)	20 (32)	
D80	≤14 Gy (n=74)	32 (39)	42 (67)	**0.0010**
	>14 Gy (n=71)	50 (61)	21 (33)	
Mean dose	≤28 Gy (n=67)	27 (33)	40 (63)	**0.0003**
	>28 Gy (n=78)	55 (67)	23 (37)	

After Bonferroni adjustment, *p*-values <0.0042 were considered significant and are given in bold.

(p=0.0003), D60 (p<0.0001), D80 (p=0.0010), and the mean dose (p=0.0003) of bilateral (both) parotid glands (Table II). In addition, trends were found for D60 (p=0.0085), D80 (p=0.0129), and the mean dose (p=0.0063) of the ipsilateral parotid gland, and for D40 (p=0.0085), D60 (p=0.0353), D80 (p=0.0147), and mean dose (p=0.0035) of the contralateral parotid gland (Table II).

Thirty-one patients (21%) experienced grade ≥3 xerostomia. It was significantly associated with D80 (p=0.0015) of bilateral parotid glands (Table III). In addition, trends were found for D40 (p=0.0508), D60 (p=0.0183), D80 (p=0.0044), and mean the dose (p=0.0358) of the ipsilateral parotid gland, and for D40 (p=0.0057), D60 (p=0.0096), and the mean dose (p=0.0305) of bilateral parotid glands (Table III).

Discussion

Xerostomia can be a debilitating late complication of radiotherapy and chemoradiation in patients with local advanced head-and-neck cancers (1, 5). Sparing of the parotid glands during radiotherapy can decrease the risk of xerostomia. However, the price for sparing the parotid glands often is a suboptimal coverage of the treatment volume close to the glands, which could impair loco-regional control and even survival. Therefore, it is important to identify patients who have a high risk of developing xerostomia. The pros and cons of sparing the parotid glands should be discussed in greater detail with these patients.

In order to identify high-risk patients, several studies identified clinical factors associated with the development of xerostomia. In a study from 2012 including data from 167 patients irradiated for different head-and-neck cancers, xerostomia was associated with older age (p=0.014) in the multivariable analysis, and with addition of chemotherapy (p=0.02) and bilateral neck irradiation (p<0.01) on univariable analyses (10). These three factors were also associated with xerostomia in a cohort of 434 head-and-neck cancer patients who received radiotherapy and/or chemotherapy and completed

Table III. *Associations between dose-volume parameters and grade ≥3 xerostomia after radiotherapy.*

Dose-volume parameter		Grade ≥3 Xerostomia, n (%)		*p*-Value
		Yes (n=31)	No (n=114)	
Parotid gland, ipsilateral				
D40	≤37 Gy (n=74)	11 (35)	63 (55)	0.0508
	>37 Gy (n=71)	20 (65)	51 (45)	
D60	≤26 Gy (n=74)	10 (32)	64 (56)	0.0183
	>26 Gy (n=71)	21 (68)	50 (44)	
D80	≤18 Gy (n=75)	9 (29)	66 (58)	0.0044
	>18 Gy (n=70)	22 (71)	48 (42)	
Mean dose	≤33 Gy (n=71)	10 (32)	61 (54)	0.0358
	>33 Gy (n=74)	21 (68)	53 (46)	
Parotid gland, contralateral				
D40	≤23 Gy (n=74)	12 (39)	62 (54)	0.1216
	>23 Gy (n=71)	19 (61)	52 (46)	
D60	≤17 Gy (n=73)	11 (35)	62 (54)	0.0620
	>17 Gy (n=72)	20 (65)	52 (46)	
D80	≤12 Gy (n=73)	11 (35)	62 (54)	0.0620
	>12 Gy (n=72)	20 (65)	52 (46)	
Mean dose	≤22 Gy (n=72)	11 (35)	61 (54)	0.0751
	>22 Gy (n=73)	20 (65)	53 (46)	
Parotid glands, bilateral				
D40	≤30 Gy (n=74)	9 (29)	65 (57)	0.0057
	>30 Gy (n=71)	22 (71)	49 (43)	
D60	≤20 Gy (n=72)	9 (29)	63 (55)	0.0096
	>20 Gy (n=73)	22 (71)	51 (45)	
D80	≤14 Gy (n=74)	8 (26)	66 (58)	**0.0015**
	>14 Gy (n=71)	23 (74)	48 (42)	
Mean dose	≤28 Gy (n=67)	9 (29)	58 (51)	0.0305
	>28 Gy (n=78)	22 (71)	56 (49)	

After Bonferroni adjustment, *p*-values <0.0042 were considered significant and are given in bold.

quality of life questionnaires (12). In this study, xerostomia was additionally associated with female sex ($p<0.05$), tumor site (oral cavity or oropharynx, $p<0.05$), and nodal stage (N2c or N3, $p<0.05$) (12). A retrospective study from 2017 with 63 head-and-neck cancer patients also identified the addition of chemotherapy ($p<0.05$) as a risk factor of xerostomia (13). In a large retrospective cross-sectional study from 2021, patient-reported data regarding xerostomia were available for 877 long-term survivors after treatment of oropharynx cancer (9). Approximately 99% of these patients had received radiotherapy. Xerostomia was reported by 39% of the patients (n=343) and associated with female sex ($p=0.006$), advanced primary tumors ($p=0.027$), and smoking at the time when completing the questionnaires ($p=0.04$). In addition, a trend was found for definitive treatment ($p=0.063$). In our recent study that included 159 patients, grade ≥2 xerostomia was significantly associated with tumor site ($p=0.049$), and grade ≥3 xerostomia with age ≥61 years ($p=0.035$) (11). Trends were found for associations between grade ≥3 xerostomia and tumor site ($p=0.088$), bilateral nodal involvement ($p=0.093$), definitive treatment ($p=0.082$), and addition of (mainly concurrent) systemic treatment ($p=0.055$).

In addition to these clinical factors, several studies identified the mean radiation dose to the parotid glands as a significant predictor of xerostomia. In 1999, Eisbruch *et al*., identified threshold doses to the parotid glands of ≤24 Gy for unstimulated saliva and ≤26 Gy for stimulated saliva, after which a substantial preservation of the saliva flow was observed (17). In the study of Blanco *et al*., a mean parotid dose of 25.8 Gy was likely to decrease the saliva flow of a parotid gland to 25% of the pre-radiotherapy flow (14). Moreover, Dijkema *et al*. calculated complication (xerostomia) probabilities of 17 to 26% for a mean dose at the parotid glands of 25 to 30 Gy (15). In the study of Moissenko *et al*., a xerostomia rate of <20% was achieved when the mean dose to the contralateral parotid gland was <20 Gy (16). Lou *et al*., found that patients developing xerostomia had received a mean dose to parotid glands between 30.6 and 33.6 Gy, compared to

26.3 to 28.0 Gy in patients not developing xerostomia (18). Finally, Pan *et al*. found a mean dose to the ipsilateral parotid gland to be an independent protective factor for improvement of xerostomia during the follow up after radiotherapy for nasopharyngeal carcinoma (19).

Very few studies have investigated the potential impact of other dose-volume parameters of the parotid glands on the development of xerostomia. In the study of Eisbruch *et al*., a substantial decrease in saliva flow was observed, when ≥67%, ≥45%, and ≥24% of the parotid glands had received 15, 30, and 45 Gy, respectively (17). In a small retrospective study, the dose-volume parameters of the parotid glands V20 ($p<0.01$), V30 ($p=0.05$), V40 ($p=0.06$), and D50 ($p<0.01$) were significantly or almost significantly associated with the occurrence of xerostomia (18). In another retrospective study of patients irradiated for nasopharyngeal carcinoma, a V30 of the contralateral parotid gland of ≤52% (*i.e*., ≤52% of the gland received 30 Gy) was an independent predictor of resolution of xerostomia during further follow up (19).

However, since associations between additional dose-volume parameters of the parotid glands and xerostomia are limited, additional studies are warranted. The present study added the evaluation of the role of D40, D60, and D80. Grade ≥2 xerostomia was significantly associated with D40 of ipsilateral and all studied parameters of bilateral glands. In addition, trends were found for all other investigated parameters. Thus, with respect to grade ≥2 xerostomia, the highest levels of significance (lowest p-values) were found for bilateral parotid glands (Table II). Moreover, the dose-volume parameters D40, D60, and D80 did not provide significant information in addition to the information obtained from the mean doses to the parotid glands (Table II). This finding agrees with the results of the study of Eisbruch *et al*., who found that the threshold values of the parotid gland volumes receiving 15 Gy, 30 Gy, and 45 Gy, respectively, did not add significantly to their model predicting the saliva flow (17).

In the present study, occurrence of grade ≥3 xerostomia was significantly associated with D80 of bilateral glands, and trends were found for all other parameters of the ipsilateral parotid gland and bilateral parotid glands. No such associations were observed for the contralateral parotid gland. Therefore, the D80 of bilateral parotid glands appeared to provide additional information to that obtained from the mean dose. In the study of Lou *et al*. the D50 was significantly associated ($p<0.01$) with xerostomia (18). Since this also held true for the mean dose ($p<0.01$), one may question whether calculation of the D50 is necessary? However, in contrast to the present study, Lou *et al*. did not evaluate the prognostic role of the D80 (18). Therefore, the results of the present study contribute to the body of knowledge, and the D80 of bilateral parotid glands appears to be an important additional factor to predict the risk of grade ≥3 xerostomia following radiotherapy for head-and-neck cancer. However, the limitations of the present study need to be considered when interpreting its results. These include the retrospective design, which bears the risk of hidden selection biases, and the fact that the patients received 3D conformal radiotherapy. Xerostomia rates would have been significantly lower if precision radiation techniques such as intensity-modulated radiation therapy and volumetric modulated arc therapy were used (24, 25). However, the use of modern techniques should not have a significant impact on the relationship between dose-volume parameters of the parotid glands and the subsequent development of xerostomia.

In conclusion, since grade ≥2 xerostomia was associated with all parameters, the additionally investigated parameters D40, D60, and D80 did not provide additional information when compared to the prognostic value of the mean doses. D80 of bilateral glands was more predictive than the mean dose regarding grade ≥3 xerostomia and appears to be an important new prognostic factor. Prospective studies using precision radiation techniques are warranted to better define the role of further dose-volume parameters in addition to mean doses of the parotid glands to predict xerostomia after radiotherapy of head-and-neck cancers.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there are no conflicts of interest related to this study.

Authors' Contributions

The study was designed by all Authors. B.W. provided the data that were analyzed by D.R. and interpreted by all Authors. D.R. and S.E.S. drafted the manuscript, which was reviewed and finally approved by all Authors.

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