PATIENTS WITH HEAD AND NECK CANCER CURED BY RADIATION THERAPY: A SURVEY OF THE DRY MOUTH SYNDROME IN LONG-TERM SURVIVORS

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Abstract: *Background.* Xerostomia can have a significant impact on the quality of life of patients treated by radiation therapy (RT) for cancer in the head and neck. The first aim of the study was to evaluate the degree of xerostomia in 39 long-term survivors treated between 1965–1995 by conventional two-dimensional radiation therapy and currently without evidence of disease. The second aim was to develop a concise instrument to evaluate the subjective aspects of xerostomia.

Methods. A newly developed questionnaire and a visual analog scale (VAS) were used in analyzing the degree of dry mouth and xerostomia-related problems. The radiation dose received by the major salivary glands was estimated by analyzing two-dimensional simulation films.

Results. Sixty-four percent of the patients experienced a moderate to severe degree of xerostomia. In the multivariate analysis, three questions regarding dry mouth, eating, and speech were particularly discriminatory for establishing the degree of xerostomia as expressed by the VAS score.

Conclusions. In this survey, 64% of the long-term survivors, after treatment by conventional two-dimensional radiation therapy for a malignancy in the head and neck region, still experienced a moderate to severe degree of permanent xerostomia. A simplified instrument to evaluate xerostomia subjectively can consist of the VAS score and three graded questions. © 2002 Wiley Periodicals, Inc. *Head Neck* **24:** 737–747, 2002

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The dry mouth syndrome is one of the most frequently encountered late side effects and usually a combination of interrelated side effects after conventional radiation therapy of tumors in the head and neck.[1–5] Xerostomia has implications for important basic functions such as speech, chewing, and swallowing and can have major consequences for dentition.[6–13] Quality of life in patients treated for head and neck tumors is strongly influenced by xerostomia and all its ramifications.[14–20] An effective therapy to treat salivary gland dysfunction and xerostomia does not exist as yet; prevention is mandatory.[21–35] At present, implemented advanced radiation techniques, such as three-

dimensional (3D) conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT), focus on sparing (part of) the major salivary glands from radiation and thus reducing xerostomia.[36–43] Altered fractionation schemes, such as accelerated fractionation and hyperfractionation, as well as combined modality treatment (chemoradiation), are currently implemented in multimodality treatment of cancer of the head and neck. These newer strategies have the potential of improving tumor control and survival with preservation of organ function. However, in particular regarding accelerated fractionation schedules and/or concomitant chemotherapy (chemoradiation), there is an associated risk of increasing the acute and late morbidity as well.[44–46] Introduction of any new treatment requires evaluation of the effectiveness of the treatment in terms of tumor control, functional status, and overall well-being of the patients. To determine the most effective treatment with the least amount of side effects, it is of utmost importance to have a disease-specific, health related quality-of-life instrument and a reliable system for grading and registration of acute and late treatment-related side effects. However, not only is an objective evaluation of side effects important but also the subjective impact of the somatic problems must be evaluated.[47,48] With respect to grading and registration of late radiation sequelae, major efforts have been put into development of comprehensive system(s).[48–50] The SOMA-LENT system addresses late effects per organ system and/or structure.[49] The subjective and objective aspects of xerostomia are scored in the salivary gland section. This scoring system still needs further validation. Also, knowledge concerning the tolerance dose and volume of the parotid gland is increasing; for instance Eisbruch calculated that to maintain a stimulated salivary parotid flow the mean dose of the parotid gland must be kept below 26 Gy and for the unstimulated flow the mean dose may not exceed 24 Gy.[41,43,51] However, the correlation between objective measured parotid salivary flow rate, the dose distributions (DVH) of the major salivary glands, and the severity of subjective complaints of a dry mouth seems not to be unequivocal.[9,27,52–56] Apparently, with regard to xerostomia, the subjective appreciation is what matters most to a patient. This article is mainly focused on subjective parameters regarding chronic xerostomia.

MATERIAL AND METHODS

Questionnaire (see Appendix). The main goal of this investigation was to interview patients by telephone on the issue of xerostomia, who were previously irradiated for a tumor in the head and neck region. A questionnaire was developed for that purpose and divided into three sections: The first section contained administrative data only. The second section consisted of questions about housing, occupation, and general health. The third section addressed the specific xerostomia-related issues and, in particular, the consequences of xerostomia on speech, swallowing, eating, and dentition. The answers of section three were graded from grade 1 to 4 or 5.

In addition to the questionnaire, the patients were asked to indicate the overall severity of their xerostomia problem on the linear visual analog scale (VAS). With respect to the VAS: A 10-point scale reflecting the severity of the dry mouth syndrome was used; zero equals no complaints; 10 reflects severe complaints of a totally dry mouth. The VAS score can be arbitrarily translated into a 4-grade xerostomia scale:

G1 = VAS score of 2.4 or less
G2 = VAS score between 2.5 and 4.9
G3 = VAS score between 5.0 and 7.4
G4 = VAS score of at least 7.5

Patient Selection. The patients were selected from three different, partially overlapping, databases taken from the main database of the department of Medical Statistics of the Erasmus Medical Center-Daniel, spanning a time period of 30 years (1965–1995). Each of the three databases had been used previously for the purpose of evaluating particular clinical issues in different tumor sites treated by radiation therapy. The first database consisted of 151 patients treated for nasopharyngeal carcinoma between 1965–1995.[57] The patients of the second database (n = 110) were treated for an oropharyngeal carcinoma by external radiation therapy (ERT) between 1975–1985 or by the combination of ERT and interstitial radiation therapy (IRT) between 1990–1994.[58]

The third database contained all patients (n = 1493) treated in our institution between 1965–1985 for a head and neck malignancy by radiation therapy with curative intent.[59] The data set of the third database was partly corrected because of overlapping the other two databases. Patients selected from these three

databases had to meet the following criteria: primary radiation therapy to the primary tumor with at least one side of the neck receiving a dose of 40 Gy or more; follow-up time since end of radiation therapy of at least 2 years; no signs or history of recurrence or second primary tumor in the head and neck region. Because of the long time span of 30 years, most of the patients had already died at time of this inquiry, resulting in a list of only 87 patients after the first selection from the three databases. Of these 87 patients, 47 could be reached by phone, and 41 consented to participate in the inquiry. After oral consent, the questionnaire was sent out; a return envelope was included for return of the VAS form; and an appointment was made for evaluation of the questionnaire by telephone 1 week later. Thirty-nine patients responded to the telephone appointment, and 36 returned their VAS form. Table 1 summarizes the patient and treatment characteristics.

TABLE 1. Patient characteristics.

Parameter	Study group $n = 39$
Age	31–85 y mean 64.7 y
Gender: male/female	27/12
Follow-up at time of evaluation since end of mean 9.6 years radiotherapy	3–22 years
Tumor site/stage (TNM 1997)	
Nasopharynx	14
T1	
T2	9
T3	4
T4	1
Oropharynx	15
T1	
T2	4
T3	7
T4	4
Larynx	9
T1	4
T2	3
T3	1
T4	1
Hypopharynx	1
T2	
T4	1
Node stage	
N0	20
N1	6
N2	13*
Radiation dose definitive ERT	
60–69 Gy	8
70 Gy	18
>70 Gy	3
ERT (46 Gy) + IRT	10†
Surgery	
Neck dissection	
None	32
Unilateral	4
Bilateral	3

**N2 stage, not further specified.*
†Exclusively patients with an oropharyngeal carcinoma of the tonsillar fossa or soft palate.

Radiation Therapy Technique. All patients were treated by conventional two-dimensional radiation therapy techniques and conventional fractionation schedules. Patients were treated in the supine position using an immobilizing head cast. The primary and the upper and middle cervical node levels were generally treated with two lateral parallel-opposed photon beams (4 or 6 MV); when necessary, an abutting anterior photon beam was added to cover the lower cervical node levels. The posterior neck was taken off cord after 40 or 46 Gy and was supplemented with 10 MeV electrons if appropriate. In four patients with a nasopharyngeal tumor, the nasopharynx was boosted after a dose of 70 Gy ERT with intracavitary brachytherapy. Of further relevance is that 29 patients were irradiated to the primary and (bilateral) upper neck by ERT to a cumulative tumor dose of 60 to 70 Gy. In 10 patients with an oropharyngeal tumor, the primary tumor and the neck were irradiated to a dose of 46 Gy using ERT; subsequently, the booster dose to the primary tumor was given by IRT (24–26 Gy). Five of these 10 patients underwent a neck dissection at time of the implantation for IRT.

Estimation of Irradiated Salivary Gland Volume. The irradiated volume of the major salivary glands (ie, both parotid and submandibular glands) was estimated for each radiation portal on simulation films using a 2D template. The template was composed of 10 randomly chosen lateral beams-eye-view (BEV) projections of the parotid and submandibular glands. From these 2D projections, an average standard salivary gland "volume" was chosen. A superimposable template with grids of 1×1 cm was used to estimate the irradiated gland "volume" (surface) and was expressed as a percentage of the total salivary gland standard "volume." The salivary gland "volume" receiving a dose of 40 Gy or more was recorded.

TABLE 2. Results of a selection of the questionnaire and the VAS score.

Question*	Nasopharynx (number of patients)	Oropharynx (number of patients)	Larynx (number of patients)
Dry mouth			
G1G2	3	6	5
G3G4	11	9	5
Night rest			
0	3	6	3
1–2	5	5	5
>3	6	2	2
Unknown		2	
Drink to speech			
G1G2	3	8	7
G3G4G5	11	6	3
Unknown		1	
Drink to eat			
G1G2	4	6	5
G3G4	10	9	5
Feeding pattern			
G1G2	13	10	9
G3G4	1	4	1
Unknown		1	
Bottle of fluid			
G1G2	5	10	8
G3G4G5	9	5	2
Tooth decay			
n/n	9/9	4/6	2/2
VAS-score			
G1 = VAS ≤ 2.4	0	4	4
G2 = VAS 2.5–4.9	3	3	2
G3 = VAS 5–7.4	4	5	1
G4 = VAS ≥ 7.5	5	3	2
Unknown	2		1
Mean VAS	6.7	5.3	4.1
Range	3.6–9.8	0.5–9.7	0.4–9.4

**Dry mouth = how much does a dry mouth bother you? Night rest = how often do you wake up because of a dry mouth? Drink to speech = do you have to sip water to facilitate speech? Drink to eat = do you have to sip water to facilitate chewing and swallowing? Feeding pattern = did you change your feeding pattern? Bottle of fluid = do you carry a bottle of fluid when going out? Tooth decay = did your teeth deteriorate? (only applicable when having own dentition before radiation therapy)?*

Because all patients were treated by conventional 2D radiation therapy techniques, no information from CT scans was available. Because of this lack of CT information, that is precise CT-based dose and volume calculations, a dose-volume histogram (DVH) analysis of the salivary glands could not be calculated. Instead of DVH calculations, we used, as a crude substitute, a 2D estimation for the "radiation burden" of each salivary gland. The radiation "burden" is the product of the 2D estimated irradiated gland volume (Vi) as a percentage of the total volume and the external radiation dose (Di) for that specific radiation field. The total radiation burden (B) is the sum of all partial radiation burdens:

$$B = \sum_{i=1}^{n} Vi.Di$$

Statistical Considerations. Two separate analyses were performed. First, the value of the various questions on the questionnaire was evaluated with respect to their impact on grading xerostomia as expressed by the VAS score. Second, correlations between subjective xerostomia, as assessed by the VAS score, and radiation therapy parameters were analyzed.

RESULTS

Questionnaire and VAS Score. Table 2 summarizes the results of a selection of the most important questions of the questionnaire and the results of the VAS score. All 39 patients complained of a dry mouth; 28% (11 patients) had considerably more complaints than before radiation therapy (G3); and 36% (14 patients) had

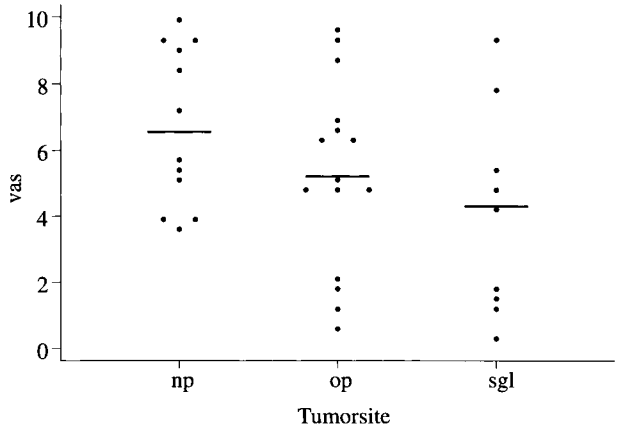

FIGURE 1. The correlation between VAS score and tumor site shows a trend without reaching statistical significance. The horizontal bars indicate the mean values. Each dot represents one patient. np = nasopharynx; op = oropharynx; sgl = supraglottic larynx.

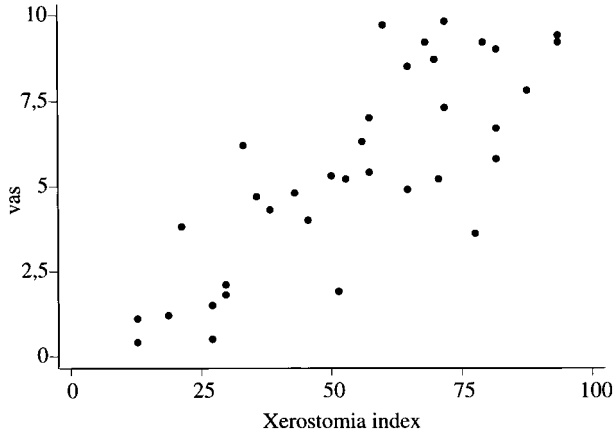

FIGURE 2. Graph shows the linear correlation between the VAS score and the overall xerostomia index (I). I = Q1 × g1 + Q2 × g2 + Q3 × g3 + K. Q1, Q2, and Q3 are the severity grades of three questions; g1, g2, and g3 are weighing factors of, respectively, 15.8, 8.5, and 5.9; K is a constant factor (−33.2). Each dot represents one patient.

permanent complaints of a very dry mouth (G4). The overall severity of xerostomia as expressed by the VAS varied from 0.4–9.8, with a mean of 5.4. Distribution by tumor site: The mean VAS score increased with localization of the tumor (4.1 for the larynx, 5.3 for the oropharynx, and the highest score of 6.7 for the nasopharynx subgroup). A statistically significant difference between the subgroups, however, was not found (Figure 1). In the univariate analysis, most graded questions of the third section showed a significant correlation with the VAS score. The strongest correlation was found between the VAS score and the question addressing xerostomia in general (p = .0001). In the multivariate regression analysis, three questions contributed significantly to the severity of xerostomia as expressed by the VAS score:

"How severe is your dry mouth problem" (G1 = normal; G2 = more xerostomia than before radiation; G3 = considerably worse than before radiation; G4 = permanent complaints of an extreme dry mouth)?

"Do you need to sip water to facilitate eating" (G1 = no; G2 = sometimes, depending on the quality of food; G3 = more than previously; G4 = a sip of water with every bite of food)?

"Do you need to drink to facilitate speech" (G1 = never; G2 = occasionally; G3 = regularly; G4 = always; G5 = even have to interrupt speaking to take a sip of water)?

An overall xerostomia index (I) was calculated on the basis of these three questions:

$$I = Q1 \times g1 + Q2 \times g2 + Q3 \times g3 + K$$

Q1 = grade of question 1
Q2 = grade of question 2
Q3 = grade of question 3

g1, g2, and g3 are weighing factors of, respectively, 15.8, 8.5, and 5.9.
K = a constant factor of −33.2.

Figure 2 shows the significant linear correlation between the VAS score and this overall xerostomia index. For further analysis, the VAS score was used as a standard to rate the degree of xerostomia and to evaluate the relation between xerostomia and radiation therapy parameters.

Radiation Therapy Parameters (Table 3). The initial radiation portals were irradiated to a cumulative dose of 40 to 50 Gy and encompassed at least 65% of the left parotid gland volume, at least 45% of the right parotid gland volume, and more than 95% of the submandibular gland volumes. After the field reduction, a considerable part of the salivary glands was still within the treatment portals, with the exception of the 10 oropharyngeal patients who received IRT. The parotid glands were not encompassed by the reduced booster fields of the laryngeal cancer patients; however, the submandibular glands could not be spared. Moreover, five oropharyngeal patients underwent a neck dissection with removal

Table 3. Radiation parameters of the major salivary glands.

% of irradiated salivary gland volume	Nasopharynx mean % (range)	Oropharynx mean % (range)	Larynx mean % (range)
Initial radiation portal (46–50 Gy)			
Left parotid gland	95% (65–100)	90%* (75–100)	79% (65–95)
Right parotid gland	96% (50–100)	75% (50–100)	69% (45–85)
Left submandibular gland	98% (70–100)	100%*	98% (95–100)
Right submandibular gland	100% (95–100)	100% (95–100)	99% (95–100)
Boost volume (46/50–60/70 Gy)			
Left parotid gland	79% (40–100)	53%† (30–70)	18% (0–40)
Right parotid gland	84% (50–100)	56%† (35–75)	18% (5–35)
Left submandibular gland	69% (0–100)	95%† (85–100)	79% (65–92)
Right submandibular gland	76% (5–100)	96%† (85–100)	77% (55–95)
Radiation burden			
Left parotid gland	59 (40–71)	43* (24–58)	37 (27–43)
Right parotid gland	59 (40–68)	37 (23–56)	35 (19–59)

**One patient received radiation therapy to the right side only.*
†Ten patients were boosted by IRT and five patients received an ERT booster dose; two of these five were irradiated to one side of the neck (one left and one right).

of the submandibular gland(s). The radiation "burden" of the parotid glands shows the same trend as the VAS score: the lowest values in the laryngeal group and the highest values in the nasopharyngeal group. Statistical significance between the tumor site subgroups and the radiation burden was not found, neither was a significant correlation detected between radiation burden and VAS score (Figure 3).

DISCUSSION

Xerostomia is a serious, permanent, and almost ubiquitous problem in patients treated by full-course radiation therapy for a head and neck malignancy, especially when using conventional parallel-opposed beam arrangements. In concordance with the literature, in our study, the most severe complaints were observed in patients treated for cancer of the nasopharynx and oropharynx (mean VAS score of 6.7 and 5.3, respectively).[60] In contrast, radiation therapy for laryngeal cancer is generally well tolerated (mean VAS score of 4.1).[14] As observed by others, this survey also showed the impact of xerostomia on basic functions of life such as eating, speech, and sleep.[14,15,19] Although xerostomia is generally recognized as a complication of (conventional 2D) radiation therapy in the head and neck region, little information is available about the quality of life (QOL) in long-term survivors of head and neck cancer and the impact of xerostomia on QOL. Despite the impression that the severity of the problems decreases with time (habituation) and the retrospective nature of our survey, 64% of the interviewed long-term survivors still experienced moderate to severe xerostomia (≥grade 3). This high percentage of long-lasting xerostomia warrants the continuing efforts put into the development of salivary gland–sparing radiation therapy techniques (ie, 3DCRT and IMRT). Furthermore, ongoing research is necessary to explain the pathogenesis of xerostomia and the complex relationships between objective function (ie, salivary flow) and subjective complaints. A reliable clinical instrument is needed for xerostomia evaluation. An important aim of our study was therefore to select the most relevant queries from a large number of questions to constitute a simple, but reliable, in-

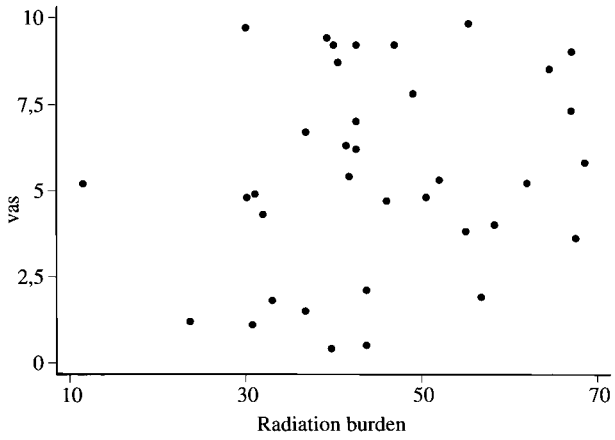

FIGURE 3. The lack of correlation ($r = 0.16$; $p = .35$) between the VAS score and the mean radiation burden of the parotid glands is shown in this graph. Each dot represents one patient.

strument for the evaluation of the subjective aspects of xerostomia. The VAS score seemed to have a significant correlation with most questions in the univariate analysis. In the multivariate regression analysis, three questions correlated significantly with the VAS score. It was therefore believed that the VAS score adequately reflected the subjective aspects of the xerostomia problem. The relevance of the VAS score is also demonstrated by the linear correlation, with an overall xerostomia index based on these three questions. However, as a general rule, we do not advocate the use of this particular "severity index" only to grade the problem of xerostomia. It carries the risk of losing essential information of individual parameters, as is the case with all composite scores.[19,47,50] The SOMALENT scoring system for similar reasons also advises against the use of the total composite score that was included in the original version.

We believe that the VAS score and the three selected questions of our questionnaire could be added to the commonly used QOL instruments particularly developed for head and neck cancer patients.[9,19,47,61] In fact, these four items by themselves can be used to obtain a quick scan of the xerostomia problem in the individual patient.

In the second part of the analysis, an attempt was made to correlate 2D dose and volume parameters ("radiation burden") with the degree of xerostomia (VAS score). Being aware of the flaws in the method of assessing the "radiation burden" and the small number of patients, it is not surprising that no significant correlation was found between subjective (ie, VAS score) and objective 2D dose and volume parameters ("radiation burden"). The estimation of the parotid gland "volume" with a uniform 2D template is a crude estimate and does not take into account the wide variation in parotid gland volume in three dimensions. The large range in the VAS values also contributes to the lack of significance. Finally, missing salivary flow rate measurements makes further conclusions with regard to correlations between objective and subjective parameters not relevant.

Precise 3D CT-based DVH analysis and larger numbers of patients are needed to establish correlations between dose and volume parameters of the parotids (and other salivary glands), salivary flow rates, and xerostomia complaints.[51] In our study, based on crude 2D estimations, most of the patients received a dose of at least 40 Gy to more than 50% of the bilateral parotid glands. The tolerance dose of the parotid glands (ie, according to Eisbruch et al, at least 55% of the parotid gland volume must receive a dose less than 30 Gy)[41] was thus surpassed in most of the patients. Recently, the importance of the submandibular, sublingual, and especially minor salivary glands for maintaining oral comfort was re-emphasized by Eisbruch et al.[52,64–66] According to their findings, the mean radiation dose received by the oral cavity, as a substitute for the minor salivary glands, correlated significantly with the subjective xerostomia score ($p = .002$). The same holds for the submandibular gland ($p = .009$), whereas the mean parotid gland dose was only marginally significant ($p = .05$).

The importance of the minor salivary glands is ascribed to the mucin production by these glands. Seventy percent of the mucin content of saliva is produced by the minor salivary glands; the remainder is produced by the sublingual and to some extent by the submandibular gland. Mucin is the most important constituent of saliva to maintain lubrication of the mucosa. Lubrication of the oral mucosal membranes is essential for oral comfort and the prevention of xerostomia. The relevance of the minor salivary glands explains also why in our study fewer complaints (lower VAS score) were observed in the patients irradiated for a laryngeal cancer opposed to an oropharyngeal cancer and cancer in the nasopharynx, despite surpassing the tolerance dose of the major salivary glands (parotid and submandibular glands). This is largely explained by better sparing of the oral cavity.

CONCLUSION

Our retrospective analysis on the extent of xerostomia in long-term survivors confirmed that xerostomia is a major late sequela of radiation therapy of tumors in the head and neck region. Although this was not a formal QOL study, our results indicate that xerostomia has a major impact on QOL by influencing basic functions such as eating and speaking.

The most important questions distilled from our questionnaire were the questions addressing dry mouth in general and the questions regarding the necessity to drink water to facilitate eating and speech. These three questions together with the VAS score constitute a simplified instrument for subjectively scoring xerostomia. In fact, the impact of the appreciation of the complaints by

our patients is in agreement with the philosophy of Bjordal et al,[15,16] which was nicely summarized as follows: "In every QOL assessment the patients should be the primary source of data collection."

There is an increased awareness of the importance of scoring treatment-related morbidity at present. Also given, for example, the use of higher doses of radiation and chemoradiation for better tumor control and organ preservation, QOL analysis will be of increasing importance.[19,20,61–70] Finally, in any study on oral function and xerostomia, the contribution of all salivary glands must be analyzed, and especially the role of the minor salivary glands should be taken into account.

APPENDIX: QUESTIONNAIRE

Part I. Administrative data

Part II.

II. A. Questions concerning occupation and occupational environment
II. B. Questions about housing
III. C. General health questions

1. How is your appetite? bad/moderate/normal/very good
2. What is your body weight? kg
3. Did your body weight change in the last year? If, yes, how much did your weight change?
4. What kind of medication do you use?
5. Have you undergone surgery after radiation therapy?

Part III. Xerostomia

1. How severe is your dry mouth problem?
   G1 = normal, as before radiation therapy (RT)
   G2 = somewhat more complaints than before RT
   G3 = considerable more complaints than before RT
   G4 = permanent complaints of a very dry mouth
2. Under which circumstances does the dry mouth problem occur? Answer each question with yes/no/or not applicable.
   In the open air
   In the open air in case of wind and cold
   In air-conditioned spaces
   Especially dry mouth during daytime
   Especially dry mouth at nighttime
   Always dry mouth night and day
   Especially bother of the dry mouth during meals
3. How often do you wake up at night because of a dry mouth?
4. How would you describe the quality of your saliva?
   G1 = normal, watery fluid
   G2 = normal watery but too little volume
   G3 = sticky saliva
   G4 = no saliva at all
5. Do you have difficulties with speech because of the dry mouth?
   G1 = no problems; unchanged with respect to situation before radiation therapy (RT)
   G2 = occasionally some difficulty with speech
   G3 = frequently speech problems
   G4 = always difficulties with speech
   G5 = always major speech problems
6. Do you need to sip water to facilitate speech?
   G1 = never
   G2 = occasionally
   G3 = frequently
   G4 = always
   G5 = even have to interrupt speaking to take a sip of water
7. Is swallowing changed because of the dry mouth problem?
   G1 = no problems; unchanged with respect to situation before radiation therapy (RT)
   G2 = occasionally some difficulty with swallowing
   G3 = frequently problems with swallowing
   G4 = always swallowing difficulties
   G5 = swallowing is seriously impaired because of the dry mouth problem
8. Has the dry mouth a negative influence on chewing?
   G1 = no change in chewing capability
   G2 = some difficulty with chewing
   G3 = frequently difficulties with chewing
   G4 = always difficulties with chewing
   G5 = chewing is seriously hampered because of the dry mouth problem
9. Do you need to sip water to facilitate eating?
   G1 = no never
   G2 = sometimes, depending on the quality of the food
   G3 = frequently; more often than before radiation therapy
   G4 = always need to take a sip of water/ fluid with every bite of food
10. Did you change your feeding habits?
    G1 = no change

G2 = minor changes, such as avoiding some products
G3 = can eat only mashed food
G4 = can eat only liquid food
G5 = tube feeding

11. Do you have painful, dry, or crusted lips?
G1 = never
G2 = sometimes, depending on the weather and environmental circumstances
G3 = frequently
G4 = always, day and night
12. Do you need to carry a bottle of fluid with you when leaving home?
G1 = never
G2 = occasionally
G3 = frequently
G4 = very often
G5 = always
13. What do you use to alleviate the complaints of a dry mouth? Please specify.
14. Do you have a sore or painful mouth?
G1 = never
G2 = occasionally
G3 = frequently
G4 = very often
G5 = always
15. Did your taste change?
G1 = no change; normal taste sensation
G2 = some reduction in taste discrimination and sensation
G3 = considerable change in taste
G4 = no taste sensation at all
G5 = always a bad taste in the mouth
16. Do you often have an infected oral mucosa or irritated gums?
G1 = never
G2 = occasionally
G3 = frequently
G4 = very often
17. Did your teeth deteriorate after radiation therapy?
Yes/no
Not applicable

REFERENCES

1. Shannon IL, Trodahl JH, Starcke EN. Radiosensitivity of the human parotid gland. Proc Soc Exp Biol Med 1978;157: 50–53.
2. Cheng VST, Downs J, Herbert D, Aramany M. The function of the parotid gland following radiation therapy for head and neck cancer. Int J Radiat Oncol Biol Phys 1981;7: 253–258.
3. Franzen L, Funegard U, Ericson T, Henriksson R. Parotid gland function during and following radiotherapy of malignancies in the head and neck. Eur J Cancer 1992;28: 457–462.
4. Leslie MD, Dische S. Parotid gland function following accelerated and conventionally fractionated radiotherapy. Radiother Oncol 1991;22:133–139.
5. Liu RP, Fleming TJ, Toth BB, Keene HJ. Salivary flow rates in patients with head and neck cancer 0.5 to 25 years after radiotherapy. Oral Surg Oral Med Oral Pathol 1990;70:724–729.
6. Cooper JS, Fu K, Marks J, Silverman S. Late effects of radiation therapy in the head and neck region. Int J Radiat Oncol Biol Phys 1995;31:1141–1164.
7. Beeken L, Calman F. A return to "normal eating" after curative treatment for oral cancer. What are the long-term prospects. Oral Oncol Eur J Cancer 1994;30B: 387–392.
8. Ship JA, Fox PC, Baum BJ. How much saliva is enough? Normal function defined. JADA 1991;122:63–69.
9. Fox PC, Busch KA, Baum BJ. Subjective reports of xerostomia and objective measures of salivary gland performance. JADA 1987;115:581–584.
10. Markitziu A, Zafiropoulos G, Tsalikis L, Cohen L. Gingival health and salivary function in head and neck-irradiated patients. Oral Surg Oral Med Oral Pathol 1992;73: 427–433.
11. Roos DE, Dische S, Saunders MI. The dental problems of patients with head and neck cancer treated with CHART. Oral Oncol Eur J Cancer 1996;32B:176–181.
12. Garg AK, Malo M. Manifestations and treatment of xerostomia and associated oral effects secondary to head and neck radiation therapy. JADA 1997;128:1128–1133.
13. Hamlet S, Faull J, Klein B, et al. Mastication and swallowing in patients with postirradiation xerostomia. Int J Radiat Oncol Biol Phys 1997;37:789–796.
14. Jensen AB, Hansen O, Jorgensen K, Bastholt L. Influence of late side-effects upon daily life after radiotherapy for laryngeal and pharyngeal cancer. Acta Oncol 1994;33: 487–491.
15. Bjordal K, Kaasa S, Mastekaasa A. Quality of life in patients treated for head and neck cancer: a follow up study 7 to 11 years after radiotherapy. Int J Radiat Oncol Biol Phys 1994;28:847–856.
16. Bjordal K, Freng A, Thorvik J, Kaasa S. Patient self-reported and clinician-rated quality of life in head and neck cancer patients: a cross sectional study. Oral Oncol Eur J Cancer 1995;31B:235–241.
17. D'Antonio LL, Zimmerman GJ, Cella DF, Long SA. Quality of Life and functional status measures in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 1996;122:482–487.
18. Harrison LB, Zelefsky MJ, Pfister DG, et al. Detailed quality of life assessment in patients treated with primary radiotherapy for squamous cell cancer of the base of the tongue. Head Neck 1997;19:169–175.
19. Terrell JE, Nanavati KA, Esclamado RM, et al. Head and neck cancer-specific quality of life. Instrument validation. Arch Otolaryngol Head Neck Surg 1997;123:1125–1132.
20. Epstein JB, Emerton S, Kolbinson DA, et al. Quality of life and oral function following radiotherapy for head and neck cancer. Head Neck 1999;21:1–11.
21. Weerkamp AH, Wagner K, Vissink A, 's-Gravenmade EJ. Effect of the application of a mucin-based saliva substitute on the oral microflora of xerostomic patients. J Oral Pathol 1987;16:474–478.
22. Stephens LC, Schultheiss TE, Ang KK, Peters LJ. Pathogenesis of radiation injury to the salivary glands and potential methods of protection. Cancer Bull 1989;41: 106–111.
23. Fox PC, Atkinson JC, Macynski AA, et al. Pilocarpine treatment of salivary gland hypofunction and dry mouth (xerostomia). Arch Intern Med 1991;151:1149–1152.
24. Rieke JW, Hafermann MD, Johnson JT, et al. Oral pilocarpine for radiation-induced xerostomia: integrated efficacy

and safety results from two prospective randomized clinical trials. Int J Radiat Oncol Biol Phys 1995;31:661–669.
25. Zimmerman RP, Mark RJ, Tran LM, Juillard GF. Concomitant pilocarpine during head and neck irradiation is associated with decreased posttreatment xerostomia. Int J Radiat Oncol Biol Phys 1997;37:571–575.
26. Roesink JM, Konings AWT, Terhaard CHJ, Battermann JJ, Kampinga HH, Coppes RP. Preservation of the rat parotid gland function after radiation by prophylactic pilocarpine treatment: radiation dose dependency and compensatory mechanisms. Int J Radiat Oncol Biol Phys 1999;45:483–489.
27. Horiot JC, Lipinski F, Schraub S, et al. Post-radiation severe xerostomia relieved by pilocarpine: a prospective French cooperative study. Radiother Oncol 2000;55: 233–239.
28. Rudat V, Meyer J, Momm F, et al. Protective effect of amifostine on dental health after radiotherapy of the head and neck. Int J Radiat Oncol Biol Phys 2000;48:1339–1343.
29. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 2000;18:3339–3345.
30. Visch LL, 's-Gravenmade EJ, Schaub RMH, Putten van WLJ, Vissink A. A double-blind crossover trial of CMC- and mucin-containing saliva substitutes. Int J Oral Maxillofac Surg 1986;15:395–400.
31. Aagaard A, Godiksen S, Teglers PT, Schiodt M, Glenert U. Comparison between new saliva stimulants in patients with dry mouth: a placebo-controlled double-blind crossover study. J Oral Pathol Med 1992;21:376–380.
32. Epstein JB, Stevenson-Moore P. A clinical comparative trial of saliva substitutes in radiation-induced salivary gland hypofunction. Spec Care Dent 1992;12:21–23.
33. Johnstone PAS, Peng YP, May BC, Inouye WS, Niemtzow RC. Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. Int J Radiat Oncol Biol Phys 2001;50:353–357.
34. Greer JE, Eltorky M, Robbins KT. A feasibility study of salivary gland autograft transplantation for xerostomia. Head Neck 2000;22:241–246.
35. Jha N, Seikaly H, McGaw T, Coulter L. Submandibular gland transfer prevents radiation-induced xerostomia. Int J Radiat Oncol Biol Phys 2000;46:7–11.
36. Wu Q, Manning M, Schmidt-Ullrich R, Mohan R. The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: a treatment design study. Int J Radiat Oncol Biol Phys 2000;46:195–200.
37. Eisbruch A, Ship JA, Martel MK, et al. Parotid gland sparing in patients undergoing bilateral head and neck irradiation: techniques and early results. Int J Radiat Oncol Biol Phys 1996;36:469–480.
38. Jones RE, Takeuchi T, Eisbruch A, D'Hondt E, Hazuka M, Ship JA. Ipsilateral parotid sparing study in head and neck cancer patients who receive radiation therapy. Results after 1 year. Oral Surg Oral Med Oral Pathol Oral Radiol Endodont 1996;81:642–648.
39. Ship JA, Eisbruch A, D'Hondt ED, Jones RE. Parotid sparing study in head and neck cancer patients receiving bilateral radiation therapy: one-year results. J Dent Res 1997;76:807–813.
40. Eisbruch A, Marsh LH, Martel MK, et al. Comprehensive irradiation of head and neck cancer using conformal multisegmental fields: assessment of target coverage and noninvolved tissue sparing. Int J Radiat Oncol Biol Phys 1998;41:559–568.
41. Eisbruch A, Ten Haken RK, Kom HM, Marsh LH, Ship JA. Dose, volume and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45:577–587.
42. Dieren EB, Nowak PJCM, Wijers OB, et al. Beam intensity modulation using tissue compensators or dynamic multileaf collimation in three-dimensional conformal radiotherapy of primary cancers of the oropharynx and larynx, including the elective neck. Int J Radiat Oncololgy Biol Phys 2000;47:1299–1309.
43. Chao KSC, Deasy JO, Markman J, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys 2001;49:907–916.
44. El-Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. A meta-analysis of prospective and randomized trials. J Clin Oncol 1996;14:838–847.
45. Skladowski K, Maciejewski B, Golen M, et al. Randomized clinical trial on 7-day-continuous accelerated irradiation (CAIR) of head and neck cancer—report on 3-year tumour control and normal tissue toxicity. Radiother Oncol 2000;55:101–110.
46. Kaanders JH, van der Kogel AJ, Ang KK. Altered fractionation: limited by mucosal reactions? Radiother Oncol 1999;50:247–260.
47. Karnell LH, Funk GF, Hoffman HT. Assessing head and neck cancer patient outcome domains. Head Neck 2000; 22:6–11.
48. Wasserman T, Mackowiak JI, Brizel DM, et al. Effect of amifostine on patient assessed clinical benefit in irradiated head and neck cancer. Int J Radiation Oncol Biol Phys 2000;48:1035–1039.
49. Pavy JJ, Denekamp J, Letschert J, et al. EORTC late effects working group. Late effects toxicity scoring: the SOMA scale. Radiother Oncol 1995;35:11–15.
50. Trotti A. Toxicity in head and neck cancer: a review of trends and issues. Int J Radiat Oncol Biol Phys 2000;47: 1–12.
51. Roesink JM, Moerland MA, Batterman JJ, Hordijk GJ, Terhaard CH. Quantitative dose-volume response analysis of changes in the parotid function after radiotherapy in the head-and-neck region. Int J Radiat Oncol Biol Phys 2001;51:938–946.
52. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 2001;50:695–704.
53. Wescott WB, Mira JG, Starcke EN, Shannon IL, Thornby JI. Alterations in whole saliva flow rate induced by fractionated radiotherapy. Am J Roentgenol 1978;130: 145–149.
54. Johnson JT, Ferretti GA, Nethery WJ, et al. Oral Pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. N Engl J Med 1993;329:390–395.
55. McDonald S, Meyerowitz C, Smudzin T, Rubin P. Preliminary results of a pilot study using WR-2721 before fractionated irradiation of the head and neck to reduce salivary gland dysfunction. Int J Radiat Oncol Biol Phys 1994;29:747–754.
56. Kuten A, Ben-Aryeh H, Berdicevsky I, et al. Oral side effects of head and neck irradiation: correlation between clinical manifestations and laboratory data. Int J Radiat Oncol Biol Phys 1986;12:401–405.
57. Levendag PC, Schmitz PI, Jansen PP, et al. Fractionated high dose rate brachytherapy in primary carcinoma of the nasopharynx. J Clin Oncol 1998;16:2213–2220.
58. Levendag PC, Schmitz PIM, Jansen PP, et al. Fractionated high-dose-rate and pulsed-dose-rate brachytherapy: first clinical experience in squamous cell carcinoma of the tonsillar fossa and soft palate. Int J Radiat Oncol Biol Phys 1997;38:497–506.

59. Levendag PC, Nowak PJC, van der Sangen MJC, et al. Local tumor control in radiation therapy of cancers in the head and neck. Am J Clin Oncol 1996;19:469–477.
60. Huguenin PU, Taussky D, Moe K, et al. Quality of life in patients cured from a carcinoma of the head and neck by radiotherapy: the importance of the target volume. Int J Radiat Oncol Biol Phys 1999;45:47–52.
61. Gotay CC, Moore TD. Assessing quality of life in head and neck cancer (review). Qual Life Res 1992;1:5–17.
62. Medbery R, Yousem DM, Needham MF, Kligerman MM. Variation in parotid gland size, configuration, and anatomic relations. Radiother Oncol 2000;54:87–89.
63. Roesink JM, Terhaard CHJ, Moerland MA, et al. CT-based parotid gland location: Implications for preservation of parotid function. Radiother Oncol 2000;55:131–134.
64. Eliasson L, Birkhed D, Heyden G, Strömberg N. Studies on human minor salivary gland secretions using the Periotron method. Arch Oral Biol 1996;41:1179–1182.
65. Tylenda CA, Ship JA, Fox PC, Baum BJ. Evaluation of submandibular salivary flow rate in different age groups. J Dent Res 1988;67:1225–1228.
66. Jacob R, Weber RS, King GE. Whole salivary flow rates following submandibular gland resection. Head Neck 1996;18:242–247.
67. Browman GP, Levine MN, Hodson DI, et al. The Head and Neck Radiotherapy Questionnaire: a morbidity/quality-of-life instrument for clinical trials of radiation therapy in locally advanced head and neck cancer. J Clin Oncol 1993;11:863–872.
68. Bjordal K, Hammerlid E, Ahlner-Elmqist M, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Questionnaire-H&N35. J Clin Oncol 1999;3:1008–1019.
69. Rathmell AJ, Ash DV, Howes M, Nicholls J. Assessing quality of life in patients treated for advanced head and neck cancer. Clin Oncol 1991;3:10–16.
70. Trotti A, Johnson DJ, Gwede C, et al. Development of a head and neck companion module for the quality of life-radiation therapy instrument (QOL-RTI). Int J Radiat Oncol Biol Phys 1998;42:257–261.