Xerostomia

Delineation guidelines for organs at risk involved in radiation-induced salivary dysfunction and xerostomia

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Abstract

Background and purpose: It is believed that minimizing inconsistencies in OAR-volume definition will help to improve adequate reporting and interpreting of radiation treatment results. The aim of this paper is to introduce computed tomography (CT)-based delineation guidelines for organs at risk (OARs) in the head and neck area, associated with radiation-induced salivary dysfunction and xerostomia.

Material and methods: After analyses of the human anatomy of the head and neck area, computed tomography (CT)-based guidelines for delineation of the most relevant OARs were described by a panel of experts.

Results and conclusions: The provided OAR guidelines are accompanied by CT-based illustrations presenting examples of the delineated structures and their corresponding anatomic boundaries. The parts of the tongue bearing minor salivary glands could not be outlined. Difficulties and uncertainties in defining these minor salivary glands on CT remain to be resolved. Implementation of these guidelines in practice should lead to a reduction in inter- and intra-observer variability and therefore unambiguous reporting of possible dose-volume effect relationships.

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Xerostomia is the most frequently reported side effect after irradiation of the head and neck region [19,21,24] and has a significant adverse effect on health-related quality of life [24,27]. Radiation induces a decrease in salivary output and a change in salivary composition, resulting in the sense of a dry mouth and sticky saliva [5,41]. Salivary dysfunction may result in considerable additional morbidity, including severe oral discomfort, problems with speaking, dysphagia, and an increased incidence of caries and mucosal infections [41]. Therefore, radiation oncologists have mainly focussed on the prevention of radiation-induced xerostomia.

Radiotherapy is an important treatment modality in the management of patients with head and neck cancer. In the last decade, the clinical introduction of new and advanced radiation delivery techniques, such as 3D-conformal radiotherapy (3D-CRT) and Intensity Modulated Radiotherapy (IMRT), allows for a better dose conformation to the planning target volume (PTV) while reducing the normal tissue dose.

The probability of xerostomia depends on the dose distributions in the salivary glands and therefore, precise delineation of these anatomic structures at the planning-CT scan is a prerequisite for treatment planning optimization [9,10,23,30,34]. In most studies reporting on the results of head and neck radiotherapy, a detailed description of the way in which organs at risk (OARs) are defined and delineated is not provided. However, in order to report, compare and interpret the results of radiation treatment adequately, it is extremely important to delineate OARs according to well defined and uniform guidelines. This may even be the case for apparently simple anatomic structures. For example, sometimes, parotid gland tissue extends laterally from the masseter muscle following the parotid gland duct, while radiation oncologists do not always include this part in the delineation of the parotid gland (personal observation). Similar discrepancies are noted for the medial extension in the parapharyngeal space. The evaluation of the parotid gland dose, e.g., the mean parotid dose, may be hampered when these parts of the parotid glands are not taken into account.

A number of authors reported on inter- and intra-observer variability in the delineation of the gross tumour volume (GTV) and clinical target volume (CTV), indicating that in some cases, important differences among the different observers may exist [20,26,32]. Similar results were found by others for OARs [4,14,36]. Wong et al. showed that delineation guidelines may help improve uniformity among radiation oncologists [44]. Guidelines to delineate CTVs in head and neck cancer already exist [15,16]. However, they do not exist for the OARs involved in xerostomia.

Therefore, the purpose of this paper is to present CT-image based delineation guidelines for anatomic structures involved, or
potentially involved, in salivary dysfunction and xerostomia that eventually permit unambiguous reporting of dose-volume effect relationships for these OARs.

Procedure

The first step in this project was to define which anatomic structures should be considered as OAR for salivary dysfunction and patient-rated and physician-rated xerostomia.

Second, the boundaries of these OARs were described by a panel of experts, including two specialised head and neck radiation oncologists (H.B. and J.L.) and an experienced head and neck radiotherapist (H.W.).

Third, all anatomic structures were then delineated on a contrast-enhanced planning-CT scan from an edentate male patient with a T2aN0 glottic tumour that did not affect the anatomic structures concerned. The planning-CT scan was made with the patient in supine position at the University Medical Center Groningen with a multidetector-row spiral CT machine (Somatom Sensation Open, 24 slice configuration; Siemens Medical Solutions, Erlangen, Germany). The acquisition parameters were: gantry un-angled, spiral mode rotation time 0.5 s, 24 detector rows at 1.2 mm intervals, table speed 18.7 mm/rotation, reconstruction interval 2 mm at Kernel B30 (displaying soft tissue) and 120 kVp/195 mA. The CT-scan had a slice separation of 2 mm. The matrix size was 512 × 512, with a pixel spacing of 0.97 × 0.97 × 2.0 mm in the x, y and z directions, respectively. iodine containing contrast medium was applied intravenously.

Contouring was performed in the Pinnacle treatment planning system, version 8.0 h (Pinnacle-TPS). The OARs were delineated by one radiation oncologist and reviewed by the other experts. Overall, the center and width values (window settings) used to delineate the OARs were set to 839 Hounsfield Unit (HU) and 370 HU, respectively. In some cases these specific values were changed to improve the visualization of certain anatomic structures and/or boundaries. These settings were not specified as the exact values resulting in the best display may vary among different patients. Besides, image contrast also varies for each scanner, independent of the window settings.

Potential OARs for salivary dysfunction and xerostomia

Salivary dysfunction can be defined in different ways, using different clinical endpoints, including: (1) objective analytical endpoints (e.g. stimulated salivary flow) [2,10,34]; (2) physician-rated endpoints graded according to toxicity classification systems (e.g. the Common Toxicity Criteria for Adverse Effects, CTCAE); and (3) patient-rated endpoints determined by questionnaires [3,9,25,31] (Fig. 1). The first class of endpoints investigates only the relationship between the dose distribution in one specific OAR and the function of that specific OAR. Assessment of physician-rated and patient-rated endpoints is clinically more relevant but much more complex, and the development of these endpoints does not necessarily depend on only one OAR. This was illustrated by the findings of Jellema et al. [23] showing that patient-rated xerostomia was significantly associated with both the mean parotid and mean submandibular dose.

Based on the results of a number of clinical studies reporting on the relationship between dose–volume parameters and radiation-induced salivary dysfunction and xerostomia, we concluded that the parotid and submandibular glands should be considered as relevant OARs [3,9,23,28,35].

We did not retrieve any data on dose-volume effects of the sublingual salivary glands in relation to xerostomia. However, given that approximately 7–8% [7,22,40] of the total salivary flow is produced by these smaller salivary glands, they should be considered as potential OARs.

The question arises, which other salivary glands in the oral cavity should be considered as OAR as well. Unfortunately, studies investigating the role of the minor salivary glands lining the oral cavity, in relation to radiation-induced salivary dysfunction or xerostomia, are scarce. One example of such a study is the study of Eisbruch et al. [9]. They found a significant association between the dose in the oral cavity, representing the minor salivary glands, and the probability of patient-rated xerostomia. In fact, these minor salivary glands are scattered in the lamina propria of the entire oral mucosa. Large numbers of minor salivary glands are present in the tongue, the cheek, the lips and the palate [33,39,40]. The minor salivary glands in the inner surface of the lips, the cheeks and the soft palate are associated with salivary dysfunction and/or xerostomia [6,8,11,13].

In order to identify other OARs than the parotid, the submandibular and sublingual glands for salivary dysfunction and subsequent patient-rated and/or physician-rated xerostomia, we decided to focus on those regions that (1) contain high densities of minor salivary glands, and (2) can be distinguished on contrast-enhanced CT-scan and thus allow reproducible delineation. This was the case for the minor salivary glands located in the mucosa of the soft palate, the inner surface of the lips and in mucosa of the cheeks. During the development of this protocol, we experienced major problems with the minor glands of the tongue. It is true that the tongue also contains a certain amount of minor salivary glands. However, it remains unclear which part of the tongue exactly contains minor salivary glands that are most important in relation to xerostomia. Secondly, and this is actually even more important, defining these areas on planning-CT turned out to be extremely difficult and we did not succeed to delineate these salivary glands in a consistent way. Therefore, we decided not to include the minor salivary glands of the tongue in the paper.

Fig. 1 displays all OARs that were considered relevant in relation to different clinical endpoints.

Guidelines for the delineation of OARs

Guidelines for the delineation of the salivary glands and salivary gland regions are presented below. Table 1 presents an overview of all OARs and their corresponding anatomic borders.

Parotid gland

The parotid gland is enclosed by the parotid fascia derived from the superficial layer of the deep cervical fascia. This gland, serous in
The submandibular gland is one of the three large paired salivary glands and is mixed serous and mucinous in type (predominantly serous). It is composed of a large superficial lobe and a smaller deep process that are continuous with each other around the posterior border of the mylohyoid muscle. The superficial lobe is located in the fascial-lined submandibular space that is cranially demarcated by the mylohyoid muscle. The smaller deep process protrudes in the posterior aspect of the nonfascial-lined sublingual space that has an open connection with the submandibular space [18]. The submandibular salivary gland is often, but not always, hypodense on CT and can be distinguished relatively easily from its surrounding structures. 

The anatomic boundaries of the submandibular gland are specified in Table 1 and illustrated in Figs. 2 and 3.

Sublingual gland

The sublingual glands are the smallest of the previously described major salivary glands, and are more difficult to distinguish from surrounding tissues on a planning-CT scan. These glands are predominantly mucous in type and are located in the anterior part of the oral cavity in the sublingual space [18].

Table 1 and Figs. 2 and 3 display the relevant anatomic structures demarcating the sublingual gland. The following notes may be of help defining the sublingual glands in a consistent way. In cranial direction, these glands are demarcated by the mucous membrane covering the floor of the mouth. However, this membrane cannot be properly visualized on CT-scan. Therefore, in case...
these glands are not clearly visible, the crossing of the lingual septum (Fig. 3: hypodense vertical line in coronal view) with the intrinsic tongue muscles can be used as a reference to define the cranial border of the sublingual glands.

Soft palate

The mucosa of the soft palate encloses many minor salivary glands. Fig. 4 and Table 1 display the relevant anatomic structures specifying the anatomic boundaries. In most cases the soft palate can be well distinguished from the tongue in the anterior direction by a hypodense line on CT or even by air present in the oral cavity. The pharyngeal lumen represents the posterior border of the soft palate. In caudal direction, the uvula should be included for delineation of the soft palate. Visualization of the soft palate and demarcating structures may be improved by using the sagittal plane as well. For delineation of the soft palate minor salivary glands, we enclosed the entire soft palate, as the salivary glands of the soft palate secreting to the oral cavity site are distributed to almost the full thickness of the soft palate [1] and these glands will most likely be more relevant for xerostomia, as compared to the relatively small amount of nasal glands secreting to the nasal cavity site.

Minor salivary glands at the inner surface of the lips and cheeks

In general the labial and buccal minor salivary glands are located between the mucous membrane of the oral cavity and the muscle layer and are surrounded by connective tissue, while some of the glands are located inside the muscle layer [17,39]. The maximal thickness of the lower and upper labial gland layers is approximately 4 mm (thicknesses of the lower labial area were significantly higher as compared to the upper labial area) [39].

In the delineation guidelines, we decided to use a similar thickness for the regions containing minor salivary glands in the labial and buccal mucosa, for practical reasons. As a result, both the inner surface of the lip and inner surface of the cheek structures have a constant thickness of 4 mm. Delineations were started medially of the mucosal layer of the oral cavity.

Inner surface lower lip

The inner surface of the lower lip is relatively hard to distinguish from its surrounding tissues. For delineation, the anatomic structures demarcating the orbicularis oris muscle are used as reference. Table 1 and Fig. 5 display the relevant structures used as anatomic boundaries. The following notes may help improve delineation consistency when defining the lower lip minor salivary glands. The upper edge of the lower lip can be defined most easily by using the sagittal plane. The lips can be distinguished from the tongue in the posterior direction by a thin hypodense line visible on CT, enclosed for delineation, corresponding to subcutaneous fatty tissue located posterior to the orbicularis oris muscle in the lower lip structure (Fig. 5). The region of interest is delineated to the level of the caudal edge of the teeth sockets (or the cranial edge of the mandibular body, in case of edentate patients).

Inner surface upper lip

For delineation of the minor salivary glands in the upper lip, the anatomic structures demarcating the upper orbicularis oris muscle are used to define the anatomic boundaries as specified in Table 1 and Fig. 5. The following notes may help improve delineation consistency when defining the upper lip structure. In the cranial direction this structure is demarcated by the anterior nasal spine that is not enclosed in the delineated structure. Posteriorly, the lips can be distinguished from the tongue by a thin hypodense line visible on CT that is enclosed in the upper lip (Fig. 5). In caudal direction, this structure is delineated to the level of the inner surface lower lip structure which is visible most clearly in the sagittal plane.
Discussion

In the current paper, we defined guidelines for the delineation of OARs that are involved in radiation-induced salivary dysfunction and/or xerostomia [9,10,23,24,34]. Application of these guidelines in clinical practice will help to reduce inter- and intra-observer variability in OAR delineation and therefore help to improve the comparison and interpretation of results from different studies allowing for unambiguous reporting of dose-volume effect relationships for these OARs.

Delineation of the major salivary glands, including the parotid and submandibular glands, may appear relatively straightforward. However, in our department, we noticed that these delineated OARs frequently differed among experienced radiation oncologists involved in head and neck cancer. This was particularly the case regarding (1) the medial extension of the deep lobe of the parotid gland; (2) whether or not the parotid blood vessels were included in the parotid gland; (3) the anterior boundaries of the parotid gland in case of a more pronounced anterior extension of the parotid gland alongside the masseter muscle, and; (4) regarding the superior extension of the submandibular glands, which is sometimes difficult to distinguish from the medial pterygoid muscle.

Furthermore, delineation of OARs may be hampered when the tumour extends in OARs such as the parotid and submandibular glands. In general, one could argue that those parts of an OAR that are invaded by the tumour (GTV) should not be included in the OAR. This is, however, not the case for the CTV and PTV.

Data about the role of the minor salivary glands with respect to radiation-induced salivary dysfunction and xerostomia are limited. Therefore, we decided to include only those anatomic structures of the oral mucosa that contain relatively high concentrations of minor salivary glands and are possibly associated with xerostomia, i.e. the minor salivary glands located at the inner surface of the lips, the hard palate and the cheek [6,8,11–13]. In addition to these structures, the hard palate secretion rate was also associated with xerostomia [29,43], though in a recent study of Eliasson et al. [12] no such association was found. We have chosen not to consider the hard palate structure, as first of all, it is hard to define correctly the soft tissue area of the hard palate on CT without including bony parts of this structure. In addition, the hard palate contains very few minor salivary glands and it is assumed that the saliva film layer thickness of this structure will mainly be dependent on the transfer of saliva from other sites of the oral cavity, such as the soft palate [6] or the accumulated saliva in the anterior part of the floor of the mouth [43].

The minor salivary glands located in the posterior part of the mobile tongue are potentially relevant structures, which have not been included in these guidelines. The most important reason for this was that we were unable to accurately visualize and define the regions of interest in the oral tongue on CT. Although there are minor salivary glands located in the tongue, there are just a few studies that investigated the function and distribution of the lingual salivary glands [33,38,40]. Van Amerongen et al. stated that the contribution of the lingual saliva to the total oral saliva production was low. However, Sivarajasingam et al. found that the anterior lingual glands had a similar secretion rate as the buccal glands and a higher secretion rate than the minor salivary glands of the hard palate and lips. These flow rate measurements were, however, difficult to perform and therefore prone to errors. Furthermore, Riva et al. stated that the posterior superficial lingual glands (located at the level of the lingual tonsils and circumvallate papillae) were more numerous than the anterior lingual glands (located in the ventral part of the tongue on either sides of the frenulum). These findings illustrate that uncertainties in defining which areas of the tongue will be most relevant in relation to xerostomia remain to be resolved. Therefore, these regions were not included in these guidelines.

Whether the considered structures play a significant role in developing radiation-induced salivary dysfunction and/or xerostomia still remains to be determined. However, the presented delin-
Delineation guidelines for salivary glands

The importance of the role of the minor salivary glands with respect to the development of patient-rated xerostomia has also been suggested by the results of a recently published study [25]. Kam et al. reported on a prospective trial in which IMRT was compared with conventional radiotherapy (CRT) for nasopharyngeal carcinoma. Although IMRT could reduce the parotid gland dose significantly, corresponding to an increased flow rate as compared to CRT, no differences were observed with regard to patient-rated xerostomia. Similar results were found by Pow et al. [31]. These discrepancies in outcome may be explained by the fact that parotid gland sparing alone is not sufficient enough to reduce the probability of patient-rated xerostomia, reflecting the need for enhanced protection of other salivary glands.

Other investigators pointed out the problem of inter- and intra-observer variability in the delineation of target volumes for radiotherapy [42]. Wong et al. showed that by using delineation guidelines (for target volume definition for partial breast radiotherapy), inter-observer variation in tumour delineation could be reduced significantly [44]. There are only a few studies reporting on the variation in OAR delineation [4,36] showing that even in apparently straightforward anatomic structures, such as the heart, oesophagus and spinal cord, inter- and intra-observer variability can be significant. More specifically, Geets et al. [14] observed a small but significant variability among various observers regarding the mean parotid and mean spinal cord volume. As a consequence, this variability in size, shape and geometrical location of both OARs and target volumes may result in different dose–volume histograms that are used to evaluate treatment plans.

Delineation guidelines for clinical target volumes already exist [15,16] and are now commonly used in daily practice and clinical trials. However, to our knowledge, delineation guidelines for the OARs as presented in this paper do not exist.

It should be noted that other imaging modalities than CT, such as Magnetic Resonance Imaging (MRI), may improve the visualization of relevant anatomic structures. MRI can help to discriminate the salivary glands from surrounding tissues such as muscles or the parapharyngeal space. On CT-scan, salivary gland tissues sometimes have similar density values as their surrounding tissues, which may hamper distinguishing salivary gland tissue from these tissues. Therefore, the use of co-registered MRI in conjunction with CT may facilitate the delineation of salivary tissues.

However, as the CT-scan currently is the standard for target volume and OAR delineation, we decided to define CT-image based
delineation guidelines, despite the potential additional value of MRI. It is strongly recommended, though, to use contrast-enhanced CT-scans, while this will improve the discrimination between relevant structures and therefore the accuracy of delineation of the considered OARs.

As the clinical introduction of new and advanced radiation delivery techniques allows for a better conformation of the radiation dose to the planning target volume (PTV) and a reduction of the dose to normal tissues it has become important to accurately define the structures of interest. Standardization of delineation protocols for both target volumes and OARs should help improve optimization of radiation therapy in head and neck cancer and permit unambiguous reporting of dose-volume effect relationships for OARs.

Conclusion

Implementation of the presented delineation guidelines should help facilitate and improve delineation of OARs that are related to radiation-induced salivary dysfunction and subsequent side effects and help reduce intra- and inter-observer variability. Minimizing inconsistencies in OAR-volume definition is a prerequisite for adequate reporting, comparing and interpreting of radiation treatment results.

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