STANDARD FOLLOW UP PROGRAM (SFP) FOR HEAD AND NECK CANCER PATIENTS TREATED WITH CURATIVE PRIMARY OR POSTOPERATIVE RADIOTHERAPY OR CHEMORADIATION

(SFP HEAD & NECK)

Standaard Follow up Programma (SFP) voor patiënten met een tumor in het hoofdhalsgebied die curatieve primaire of postoperatieve radiotherapie of chemoradiatie ondergaan

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1. General introduction

1.1. Treatment of head and neck cancer

Head and neck cancer accounts for approximately 5% of all cancers in the Netherlands, with 2.500 to 3.000 new cases annually. The majority of these cases include squamous cell carcinoma (HNSCC) originating in the oral cavity, oropharynx, nasopharynx, hypopharynx and larynx.

In the Netherlands, the majority of patients (approximately 90%) are referred to and treated in eight specialised centers, the so called “Hoofd Hals Oncologische Centra (HHOC)”. These centres fullfill a large number of quality criteria, such as a the presence of a multidisciplinary team (head and neck surgeons, maxillofacial surgeons, radiation oncologists and medical oncologists, radiologists and pathologists all specialised in head and neck oncology). This centralisation of medical care for head and neck cancer patients may be responsible for the fact that overall survival of head and neck cancer patients in the Netherlands is highest among all European countries (EUROCARE project).

1.2. The role of radiotherapy

Radiotherapy plays a pivotal role in the treatment of HNSCC both in the primary setting as well as in the adjuvant setting after primary surgery. Growing evidence indicates that more aggressive treatment regimens, either the delivery of radiotherapy with concomitant chemotherapy or cetuximab or altered fractionation schedules, improve loco-regional tumour control and overall survival of HNSCC patients.(1-4) However, these new treatment regimens have come to the expense of increased morbidity, such as persistent swallowing dysfunction, laryngeal dysfunction, severe fibrosis, hypothyriodism and xerostomia occurring in a considerable proportion of patients (5-9) and significantly affecting patient’s quality of life (QoL).(10)

1.3. Prevention of radiaton-induced side effects

Radiation-induced side effects can be subdivided in both acute and late side effects. Acute side effects occur during or immediately after the course of radiation and are clinically relevant as they limit the dose that can be administered. In some cases, acute side effects progress into late side effects (so-called consequential side effects). Late side effects can occur several months or sometimes even years after completion of the radiation course and may prove to be irreversible or even progressive over time, e.g. the development of cardiovascular events after irradiation of the chest. For virtually all critical organs or normal tissues, the probability of radiation-induced side effects depends on the radiation-dose distribution and the relative volume of an Organ at Risk (OAR) that receives a certain dose, with higher radiation doses and larger irradiated volumes leading to higher risks on radiation-induced side effects. Thus, radiation-induced side effects can be prevented by optimize the dose distribution, i.e. minimizing the dose to OARs without compromising the dose to the target volume (including the tumour and elective target areas) by the clinical introduction of new radiation delivery techniques.

Technical innovations over the last two decades have tremendously changed the practice in radiation oncology of HNSCC. Nowadays, the cornerstone of modern radiotherapy treatment planning is computed tomography (CT), providing a fully three-dimensional (3D) anatomical model of the patient, which can be co-registered with other imaging modalities, such as Magnetic Resonance Imaging (MRI) and functional imaging studies, including Positron Emission Tomography (PET), allowing radiation oncologists to more accurately identify tumour volumes and their spatial relationship with critical organs. The availability of modern 3D-treatment planning systems allows full integration of these imaging advances into treatment delivery and has facilitated the implementation of 3D-conformal radiation therapy (3D-CRT) and Intensity-Modulated Radiotherapy (IMRT) which is now firmly in place as the standard of practice, in particular in the curative setting. Emerging radiation delivery techniques such as Image-Guided Radiotherapy (IGRT), Adaptive Radiotherapy (ART) and radiation with charged particles, such as protons, will allow further optimization of radiation dose delivery.

1.4. Introduction of new radiation techniques

In radiotherapy, many new radiation delivery techniques are clinically introduced in order to reduce the dose to critical anatomical structures or Organs at Risk (OARs) and subsequently

to prevent acute and late radiation-induced side effects without compromising the dose to the target volume (including the tumour). Most of these new techniques have been accepted as the new standard without any clinical validation. In recent years, there has been a profound discussion among radiation oncologists concerning the question whether or not new techniques should be clinically introduced as the standard of care, without this having been finally confirmed by proper randomized controlled trials (RCT's). Indeed, this debate focuses in particular on the fact that the new technology is introduced primarily with the aim to reduce the dose to OARs and thus to prevent side effects. Several authors have stated that the appraisal of RCT's for new radiation technologies that aim primarily at the reduction of side effects (including secondary tumours), is actually based on the wrong paradigm. And indeed, the original 'rules of evidence' (as formulated by David Sackett) were in the first place intended to evaluate evidence pertaining to the differential benefits of therapeutic interventions, that is: treatment efficacy (in radiotherapy e.g. improvement of local tumour control). These rules were specifically not intended for evaluating evidence pertaining to the risks of exposure to potentially avoidable hazards, such as ionizing radiation (that is: treatment quality). It is important to note that for virtually all critical organs or normal tissues, the probability of radiation-induced side effects depends on the radiation dose distribution and the relative volume that receives a certain dose. These dose-volume-effect relationships can be described mathematically in so-called Normal Tissue Complication Probability (NTCP) models (see: Figure 1). The prognostic value of these dose-volume parameters has been found to be consistent in numerous prospective cohort studies and for some side effects has also been confirmed by systematic reviews (providing level I evidence for prognostic factors).

This background knowledge with respect to dose-volume-effect relationships is already generally exploited in daily practice of radiation oncology. Whenever available, radiation oncologists and patients will choose the radiation technique that yields an equivalent dose to the target volume with the lowest dose to critical organs, when that reduced dose to critical organs will result in a profound and clear reduction of radiation-induced side effects. Randomizing patients between two radiation treatment delivery technologies that yield the same tumour dose distribution but with a clear left-shifted dose–volume histogram in critical OARs, is not consistent with the general ethical principle of equipoise (balanced uncertainty). As a consequence, practically a limited number of RCTs investigating the added value of new radiation techniques with regard to reduction of side effects is currently available.

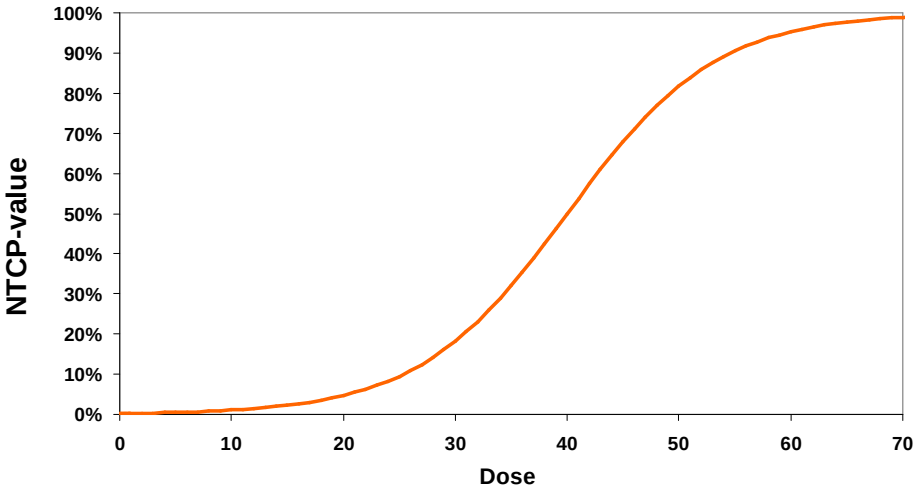
1.5. Validation of new radiation technology aiming at reduction of side effects

Starting from the observation that RCT's are currently not available and, more importantly, not the most suitable methodology for validating new radiation technology aiming at reduction of side effects, an alternative validation methodology has been developed, which has now also been adopted by the Dutch Health Insurance Board (CVZ) and the Health Council (Gezondheidsraad). This methodology contains 4 steps.

1.6. Step 1: Development of Normal Tissue Complication Probability (NTCP) Models

The basic principle in the development of new radiation delivery techniques is the existence of validated relationships between dose distributions in critical organs and the probability of radiation-induced side effects (i.e. Normal Tissue Complication Probability (NTCP)). In general, the NTCP will increase with increasing dose and increasing volume that receives a certain dose (see Figure 1). For some side effects, these dose-volume effect relationships are clear (e.g. the risk of radiation-induced xerostomia is significantly associated with the mean dose in the parotid gland). However, for other side effects, such as swallowing dysfunction, the exact OAR remains to be determined as well as the most relevant dose-volume parameter. Knowledge of these two factors, i.e. which dose-volume parameters in which OARs are most relevant for the development of a certain side effect, is essential to be able to optimize the radiation technique and is required for the second step of this methodology. Furthermore, before these NTCP-models can be generally introduced in routine clinical practice, they should be externally validated in separate patient cohorts preferably in other treatment centers.

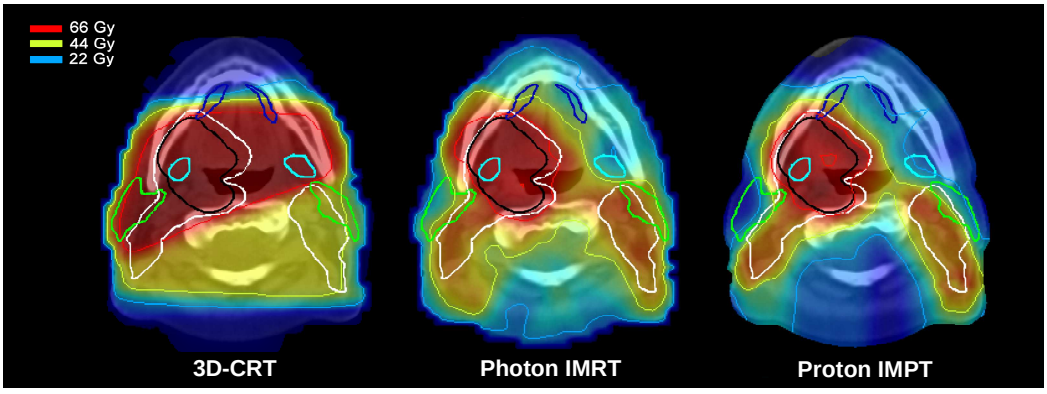
Figure 1: Example of a NTCP-curve (Normal Tissue Complication Probability) describing the probability of a complication as a function of the dose in a critical organ. The NTCP-value increases with increasing dose.



1.7. Step 2: In silico planning comparative (ISPC) studies

With respect to reduction of side effects, the potential benefit of new radiation technology is mainly based on the assumption that this new technique achieves a more optimized dose distribution, resulting in an at least equivalent dose to the target volume with a lower radiation dose to critical organs. These kinds of studies are referred to as '*in silico planning comparative studies'* (see Figure 2). In such study, the new technique is tested on its ability to reduce the most relevant dose-volume parameters obtained from step 1. In general, ISPC studies are performed in 10-30 patients, using existing planning-CT scans of patients already treated with the conventional technique. The endpoints of an ISPC-study are the absolute and relative reductions of the most relevant dose-volume parameters.

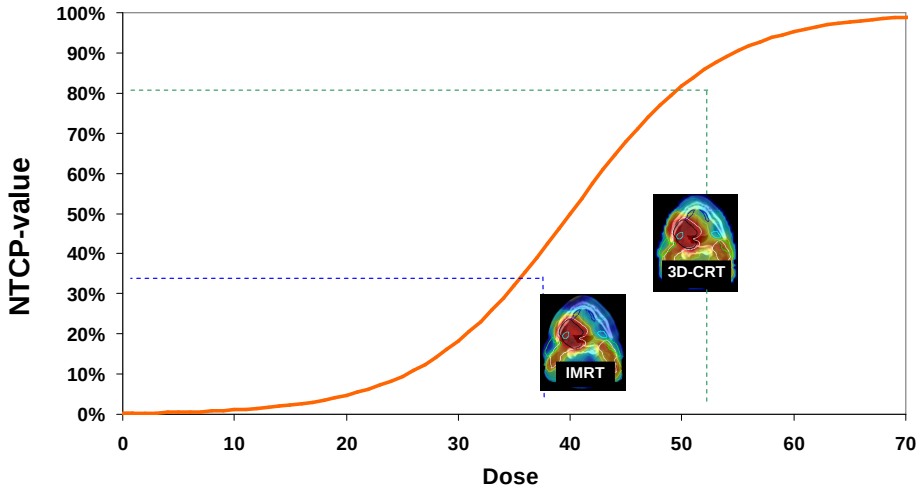
Figure 2. Example of a 'in silico planning comparative study' comparing 3D-conformal radiotherapy with intensity modulated radiotherapy (IMRT). Presented is a case with a oropharyngeal tumour (black). The red area represents the high dose area. The light green structures on both sides represent the salivary glands. These structures should be spared as much as possible to prevent lifelong xerostomia. With 3D-CRT the dose to the parotid glands are highest. A significant reduction can be obtained with IMRT (current standard), while with IMPT (protons) a further reduction of the mean dose to the parotid glands can be obtained.



1.8. Step 3: In silico planning comparative (ISPC) studies

The final step will be to determine to what extent the optimised physical dose distributions will translate into a clinically relevant beneficial effect, using the combination of data from existing NTCP-models (step 1) and in silico planning comparative studies (step 2) which is illustrated above (see Figure 3). Step 3 has to be performed in each individual patient, as a dose reduction of e.g. from 50 Gy to 40 Gy (10 Gy difference) translates into a different NTCP reduction than a dose reduction from 20 y to 10 Gy (10 Gy difference).

Figure 3: Translation of differences in dose distribution into clinical benefit in terms of the probability of complications. The reduction of the dose in the parotid glands obtained with IMRT (photons) compared to 3D-CRT photons results in a reduction of the NTCP-value from 80% to 33%.



1.9. Step 4: Clinical validation

The first 3 steps of this 4-step methodology are in fact hypothesis generating. They provide information on the expected NTCP-reduction that can be obtained with the new radiation technology based on the integration of the results of in silico planning comparative studies into externally validated NTCP-models. If individual in-silico planning comparative analysis indicates a significant difference in NTCP-value, there are two possibilities, including: 1) let this patient participate in an RCT, or, 2) provide treatment with the new technique within the framework of a so *called sequential prospective observational study with a standard follow up program*. The following considerations should be taken into account when selecting patients for either of these strategies:

- Some late radiation-induced complications have very long latency times, e.g. the development of vascular complications generally takes at least 5 to 10 years, and the incidence in particular continues to increase up to twenty years after initial treatment. In such cases, an RCT would take at least 15 to 20 years to come up with useful information regarding the primary endpoint. Therefore, when the new radiation technology is predicted to significantly reduce the risk of such complications based on step 3 results, patients will be treated with the new technique based on the ALARA-principle.
- In some patients, the individual in silico planning comparative analysis may reveal a substantial predicted difference in NTCP-value between the new and the old radiation technique for a given side effect, while the dose to the target volume stays the same, e.g. an expected difference in severe swallowing dysfunction after radiotherapy of the head and neck region. Enrolling this patient in an RCT would not be consistent with the general ethical principle of ‘equipoise’ (balanced uncertainty), in particular when the expected side effect would significantly and severely impact on health-related quality of life. When clinically available, these patients will be offered the new technique within the framework of a prospective observational study. The same applies even to relatively small differences in

observed NTCP-values, when this particular side effect is expected to have major impact on health-related quality of life, e.g. radiation myelopathy with total paraplegia or radiation retinopathy with severe visual impairment or complete blindness.

A prerequisite of historical comparisons between old and new radiation techniques is that the assessment of all relevant endpoints takes place in a similar and standardized manner. Therefore, the backbone of the 4-step approach as previously described is the Standard Follow up Program (SFP). In an SFP, endpoints related to treatment efficacy, such as locoregional tumour control and overall survival are systematically scored and collected besides endpoints related to acute and late radiation-induced toxicity and patient-rated quality of life and symptoms. The latter endpoints can only be reliably assessed in a prospective program.

In step 1, prospective collection of data on acute and late toxicity is required for the development and external validation of NTCP-models. For step 4, the SFP is necessary to allow for a reliable comparison of the results between the old and new technique (see Figure 4). The direct comparison between the old and new technique will be done using matched controls based on the estimated NTCP-values for each individual patient with the radiation technique that will be actually applied and the estimated NTCP-reductions of the old and new technology for both groups.

1.10. Rationale for implementation of SFP as standard of care

Given that the aforementioned methodology for the clinical validation of new radiation technology has now been adopted by the Health Council, Dutch Health Insurance Board (CVZ) and the Dutch Society for Radiation Oncology (NVRO), the departments of radiation oncology of some HHOC's have decided to develop and implement SFP's for all head and neck cancer patients that are treated with curatively intended radiotherapy. The data from the prospective collection included in this SFP are considered standard of care and can be used for the following purposes:

- The prospective collection of data on tumour response, locoregional tumour control, distant metastases and survival will be used to evaluate treatment results of the different HHOC's and to use these results as a benchmark for other institutions;
- The prospective collection of data on acute and late toxicity and 3D-dose distributions will be used to develop and externally validate NTCP models for a large variety of endpoints;
- The prospective collection of data on acute and late toxicity for a longer period of time will be used to compare the results of new and emerging radiation delivery techniques after they have been clinically introduced by comparing these results obtained in patients treated with the current technique
- The prospective collection of patient-rated quality of life will be used to determine if the introduction of new technology actually actually translates into better quality of life as reported by patients. In addition, it will enable the development of NTCP-models for patient-rated head and neck cancer symptoms that eventually can be used to further optimize radiation treatment.

2. Objectives of the SFP

2.1. General objective

The primary and general objective of the clinical introduction of the SFP as the current standard of care is to improve the quality of radiotherapy for head and neck cancer patients by reducing radiation-induced side effects without hampering treatment efficacy in terms of locoregional tumour control and overall survival and to systematically evaluate the beneficial effect of newly introduced radiation technology for this particular group of patients. The clinical introduction of the SFP will allow for a systematic and broad scale quality improvement cycle for head and neck cancer patients treated with radiotherapy. In fact, this methodology can be considered a kind of quality circle for the clinical introduction of new radiation techniques, aiming at continueous efforts for further improvement.

2.2. Specific objectives

- To develop, validate, and improve NTCP models for a wide variety of acute and late radiation-induced side effects relevant for head and neck cancer patients (step 1);

- To use the outcome of the NTCP models to better inform patients on the risks on acute and late toxicity;
- To use the outcome of the NTCP models for the definition of dose constraints for radiotherapy treatment planning in current practice;
- To use the outcome of the NTCP models for the development and investigation of the potential benefit of new and emerging radiation delivery technique, such as swallowing-sparing IMRT and proton radiotherapy.
- To compare the outcome of new radiation delivery techniques that are clinically introduced with the current standard in terms of radiation-induced toxicity, patient-rated symptoms and quality of life and in terms of locoregional tumour control and overall survival

3. Endpoints

3.1. SFP general

The SFP includes a prospective assessment of baseline characteristics, treatment-related factors, including dose distribution parameters, acute and late radiation-induced toxicity, and health-related quality of life. In the following paragraphs, the assessments will be described in more detail.

3.2. Baseline characteristics

The baseline characteristics that are considered relevant are part of the Electronic Patient File of the Department of Radiation Oncology and will be completed by the treating physician and will not burden patients. Pre-existing co-morbidity will be scored according to the ACE-27 using a questionnaire (appendix A)

3.3. Treatment-related factors

The treatment-ralated factors that are considered relevant are part of the Electronic Patient File of the Department of Radiation Oncology and will be completed by the treating physician More detailed information regarding the 3D-dose distribution and the Dose Volume Histograms (DVH) from the relevant OARs will be automatically extracted from the Treatment Planing System and transferred to the database. This will not be any burden to patients.

3.4. Acute toxicity

Acute toxicity will be scored before, weekly during radiation therapy and at 6 weeks after completion of treatment by the treating physicians and are part of the Electronic Patient File of the Department of Radiation Oncology. These assessments are determined during the routine follow up visits at the department of Radiation Oncology (see Table 1). This follow up schedule is standard for all patients and established by the Multidisciplinaire Werkgroep Hoofdhals Tumoren of the UMCG. Acute toxicity will be scored on the ACUTE TOXICITY form (appendix B). The following scales will be scored:

- Dry mouth (according to CTCAE v4.02)
- Dysphagia (according to CTCAE v4.02)
- Dysphagia (according to EORTC/RTOG)
- Mucositis oral (according to CTCAE v4.02)
- Oral pain (according to CTCAE v4.02)
- Dermatitis radiation (according to CTCAE v4.02)
- Weigh loss (according to CTCAE v4.02)
- Tube feeding dependence (0=no, 1=nasogastric tube, 2=PEG)
- Aspiration (according to CTCAE v4.02)
- Laryngeal edema (according to CTCAE v4.02)
- Laryngeal mucositis (according to CTCAE v4.02)
- Pharyngeal mucositis (according to CTCAE v4.02)
- Pharyngolaryngeal pain (according to CTCAE v4.02)
- Voice alteration (according to CTCAE v4.02)

ZORGACTIVITEITEN	BEHANDELSTRATEGIE															
	Chirurgie			Radiotherapie			Chemoradiatie				Chirurgie + postoperatieve radiotherapie			Chirurgie + postoperatieve chemoradiatie			
	KNO	MHK	RTH	KNO	MHK	RTH	KNO	MHK	RTH	ONC	KNO	MHK	RTH	KNO	MHK	RTH	ONC
DIAGNOSTISCHE FASE																	
Intake / MDS	HB			HB			HB				HB			HB			
Diagnostiek	HB			HB			HB				HB			HB			
MDO	HB			HB			HB				HB			HB			
DIAGNOSTISCHE FASE																	
Preoperatieve fase	HB										HB			HB			
CHIRURGIE	HB										HB			HB			
Postoperatieve fase	HB										HB			HB			
MDO	HB										HB			HB			
Prechemoradiatiefase				HB			HB				HB			HB			
RADIOTHERAPIE ± CHEMOTHERAPIE				HB [1] →		HB	HB [1] →			HB	HB [1] →		HB	HB [1] →			HB
Week 1						HB				HB			HB				HB
Week 2						HB				HB			HB				HB
Week 3						HB				HB			HB				HB
Week 4						HB				HB			HB				HB
Week 5						HB				HB			HB				HB
Week 6						HB				HB			HB				HB
Week 7						HB				HB			HB				HB
Week 12				HB [2] ←		HB	HB [2] ←			HB	HB [2] ←		HB	HB [2] ←			HB
FOLLOW UP FASE																	
3 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
6 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
9 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
12 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
15 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
18 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
21 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
24 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
30 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
36 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
42 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
48 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
54 maanden na CHRT/CHI	HB			HB			HB				HB			HB			
60 maanden na CHRT/CHI	HB			HB			HB				HB			HB			

HB = hoofdbehandelaar
Noot 1: In geval van primaire of postoperatieve radiotherapie of chemoradiatie gaat het hoofdbehandelaarschap over van KNO/MHK naar radiotherapie respectievelijk medische oncologie op de eerste dag van de radiotherapie of chemoradiatie. De datum van start (chemo)radiatie wordt door radiotherapie ingevoerd in PoliPlus onder kopje Behandelplan Radiotherapie.
Noot 2: Na het einde van de primaire of postoperatieve radiotherapie wordt het hoofdbehandelaarschap weer terug overgedragen naar KNO/MHK na de poliklinische controle bij de radiotherapie in week 12 (5 tot 6 weken na einde radiotherapie). Dit wordt door radiotherapie aangegeven in PoliPlus. Afspraak 3 maanden na einde (chemo)radiatie wordt gemaakt vanuit polikliniek RT.

Table 1: Standard Follow up Schedule for Head and Neck Cancer patients of the UMCG.

3.5. Late toxicity

Late toxicity will be scored before after completion of treatment by the treating physicians and are part of the Electronic Patient File of the Department of Radiation Oncology. These assessments are determined during the routine follow up visits (see Table 1). Late toxicity will be scored on the LATE TOXICITY form (appendix B). The following scales will be scored:

- Dry mouth and salivary flow (according to CTCAE v4.02)
- Dysphagia (according to CTCAE v4.02)
- Dysphagia (according to EORTC/RTOG)
- Oral pain (according to CTCAE v4.02)
- Tube feeding dependence (0=no, 1=nasogastric tube, 2=PEG)
- Aspiration (according to CTCAE v4.02)
- Laryngeal edema (according to CTCAE v4.02)
- Pharyngolaryngeal pain (according to CTCAE v4.02)
- Voice alteration (according to CTCAE v4.02)
- Hypothyroidism (according to CTCAE v4.02)
- Dental caries (according to CTCAE v4.02)
- Edema face (according to CTCAE v4.02)
- Head and neck soft tissue necrosis (according to CTCAE v4.02)
- Osteonecrosis of jaw (according to CTCAE v4.02)
- Trismus (according to CTCAE v4.02)
- Lhermitte's sign (0=1, 1=yes)

3.6. Patient-rated symptoms and quality of life

Patient-rated symptoms and quality of life will be measures by the EORTC QLQ-C30 (Appendix E) and by the site-specific module, the EORTC QLQ-H&N35 (Appendix F). The questionnaires will be filled in by patients at the time points mentioned in Table 1. Filling out these questionnaire will take approximetaly 10-15 minutes every time and will take place prior to the visit to the treating physician.

The EuroQol-5D questionnaire (Appendix G) is a small, standardized generic quality-of-life questionnaire consisting of two parts. The first part is a 5-dimensional questionnaire, the EQ-5D. The five dimensions are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [Essink-Bot 1993, Brooks 1996, Kind 1996]. With regard to each of those dimensions, the patient is asked to indicate if he or she experiences no problems, some problems, or major problems. The resulting profile of answers (one of 243 possibilities (3^5)) can be transformed to a value given by the general public: the $EQ\text{-}5D_{index}$ [Dolan 1997]. The second part of the EuroQoL questionnaire is a visual analogue scale, the EQ_{VAS}, which represents the patient's judgement of his own health state. The advantage of the EuroQoL-questionnaire is its feasibility to yield utility scores expressing the health state of patients, which can be used to calculate Quality Adjusted Life Years (QALYs). QALYs combine the number of life years gained and the quality of life during these years in one single measure.

3.7. Efficacy endpoints

The following endpoints related to treatment efficacy will also be determined:

3.8. Overall survival

The overall survival will be calculated from the first day of treatment, either the first day of induction chemotherapy or the first day of radiotherapy in case of concomitant chemoradiation or radiation alone. An event is defined as death of any cause.

3.9. Locoregional tumour control

Loco-regional control will be calculated from the first day of treatment, either the first day of induction chemotherapy or the first day of radiotherapy in case of concomitant chemoradiation or radiation alone. An event is defined as local recurrence and/or regional recurrence. These two events will be separately scored.

3.10. Laryngo-oesophageal dysfunction-free survival

Laryngo-oesophageal dysfunction-free survival will be calculated from the first day of treatment, either the first day of induction chemotherapy or the first day of radiotherapy in case of concomitant chemoradiation or radiation alone. This endpoint is specifically develop for patients undergoing non-surgical (larynx preservation) treatment for laryngeal or hypopharyngeal cancer.(42) The event is defined as death, local relapse, total or partial laryngectomy, tracheotomy at 2 years or later, or feeding tube at 2 years or later. The rationale of this endpoint is that it provides direct information regarding the probability of being alive with a functional larynx without local recurrence, which is actually the main goal of larynx preservation strategies.

4. Patient selection criteria

4.1. Inclusion criteria

All patients planned for curatively intended primary or postoperative radiotherapy will be included. At he first visit, patients are informed about the standard follow up program by the treating physician.

4.2. Exclusion criteria

All patients planned for palliative radiotherapy will not be included in the SFP.

4.3. Relation with other studies

Inclusion in clinical trials is not an exclusion criterion. It is possible to add additional assessments required for the clinical study.

5. Therapeutic regimens

Patients will be treated according to the institutional protocol, or if applicable according to the clinical trial protocol. Each centre should define its standard protocols. If the patient is treated otherwise than this standard protocol, this has to be specified. At least the following information is needed for all treatments.

5.1. Radiotherapy

– Definitions of GTV's, CTV's, and PTV's of the primary tumour, pathological lymph nodes and elective lymph node areas;
– Prescribed total dose, fraction dose, number of fractions per week and overall treatment time to the primary tumour, the pathological nodes and the elective nodal areas;

5.2. Chemotherapy

– Type of systemic therapy (induction, concomitant or both)
– Type of drugs, with total dose, dose reductions, dose delays, and overall treatment time.

5.3. Cetuximab

– Type of drugs, with total dose, dose reductions, dose delays, and overall treatment time.

5.4. Dental examination

All patients receiving radiotherapy should have an oral and dental examination including clinical and radiological examination. Usual management consists of:

– Avulsions when preservation is not possible;
– Other dental restoration procedure for superficial caries not involving pulpal tissue;
– Endodontic treatment for caries involving pulpal tissue;
– Maintenance of optimal hygiene and systematic lifetime fluoride topical application methods.

When avulsions are required, they should be performed according to well established procedures and should be as non-traumatic as possible. Alveolectomy and primary closure should be attempted at the time of extraction. If the site of extraction is within the irradiated volume, surface coverage of exposed bone should be obtained before starting radiotherapy, which usually requires 10 days.

5.5. Patient immobilisation

All patients will be irradiated in supine position. Immobilisation devices such as customised masks have to be used to secure the accuracy and reproducibility of patients positioning during radiotherapy. Preferably, mask immobilisation of the head, neck and shoulders will be used.

5.6. Planning CT scan acquisition

For all patients, Planning Computed Tomography (Planning CT), using a set of slices extending from the level of the base of skull to the lower border of the clavicle, will be required. Slice thickness of preferably 3 mm will be used.
CT will be performed in treatment position with a flat tabletop and with the immobilisation device in place.
To enhance vascular and soft tissue contrast and to facilitate delineation of both target volumes and organs at risk (OAR's), the use of intravenous contrast enhancement is mandatory.
Images will be constructed with at least 512 x 512 pixel matrix.

5.7. PET procedure

A static 3D ^{18}F-FDG PET scan is made with the patient in treatment position with immobilisation device after acquiring the planning CT scan. The PET scan should be made according to the NEDPAS protocol [10], with an injected dose of FDG of 2.5 x Body Weight MBq. PET-CT scanner will be calibrated in order to provide the most accurate and comparable SUV values. This is current routine practice.

5.8. Delineation of target volumes

Target volumes are delineated according to the centres protocol. For the purpose of this project, delineation should at least include the following structures:

– GTV of the primary tumour (cc)
– Composed GTV of the pathological lymph nodes volume in the ipsilateral neck (cc)

– Composed GTV of the pathological lymph nodes volume in the contralateral neck (cc)

5.9. Delineation of Organs at risk

These are the normal tissue structures whose radiation sensitivity may significantly influence the treatment planning and/or the prescribed dose. For the purpose of this study, OAR's that may affect treatment planning should be delineated by the local investigators, including:

- The spinal cord (from the tip of the dens to the level of TH3, should be outlined preferably using the osseous borders of the vertebral canal);
- Brainstem;
- Parotid glands and submandibular (when applicable) on both sides (for guidelines see: appendix F)
- Structures involved in swallowing, i.e., the pharyngeal constrictor muscles superius, medius and inferius, the musculus cricopharyngeas, the upper esophageal sphincter, the base of tongue, the supraglottic region and the glottic region (appendix G)

5.10. Treatment technique

The treatment technique is left at the discretion of each physician, provided that constraint doses to the field arrangement and conformality respect normal tissues.

5.11. Dose computation

- Dose Volume Histograms (DVH) are to be used for assessing dose to the PTVs and all normal tissues at risk.
- All treatment plans should be calculated using an advanced dose calculation algorithm, such as collapsed cone or convolution/superposition algorithm.

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Appendix

Appendix A: ACE-27 co-morbidity scoring

Appendix B: Radiation-induced side effects to be scored (CTCAE v4.0)

Appendix C: Delineation guidelines for the salivary glands

Appendix D: Delineation guidelines for swallowing structures

Appendix E: EORTC QLQ-C30

Appendix F: EORTC QLQ-H&N35

Appendix G: EuroQol-5D

Appendix A: ACE co-morbidity scoring

Vragenlijst COMORBIDITEIT (ACE-27)

1 / 5

UMCG-nummer ☐☐☐☐☐☐☐ - ☐

Geboortedatum ☐☐ - ☐☐ - ☐☐☐☐

Datum van vandaag ☐☐ - ☐☐ - ☐☐☐☐

Deze vragenlijst is om uw medische voorgeschiedenis en huidige medische conditie te inventariseren. Wilt u alle vragen zelf beantwoorden door het antwoord aan te kruisen dat het meest op u van toepassing is. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

DEEL 1 (HART EN BLOEDVATEN)

1. Heeft u in het afgelopen jaar een hartinfarct gehad? O Ja O Nee

Zo ja, datum ☐☐ - ☐☐ - ☐☐☐☐

2. Heeft u pijn/druk op de borst gerelateerd aan het hart (angina pectoris)? O Ja O Nee

Zo nee, ga door met vraag 6

3. Heeft u pijn op de borst bij inspanning of in rust? O Inspanning O Rust

4. Bent u in het ziekenhuis opgenomen geweest voor uw pijn op de borst? O Ja O Nee

5. Heeft u een operatie gehad voor uw hartklachten? O Ja O Nee

Zo ja, datum ☐☐ - ☐☐ - ☐☐☐☐

6. Heeft u hartfalen? O Ja O Nee

Zo nee, ga door met vraag 11

7. Bent u kortademig tijdens inspanning/of wordt u 's nachts buiten adem wakker? O Ja O Nee

8. Beperkt uw kortademigheid uw activiteiten? O Ja O Nee

9. Heeft uw kortademigheid- veroorzaakt door hartfalen- goed gereageerd op behandeling? O Ja O Nee

10. Bent u in het ziekenhuis opgenomen geweest voor uw hartfalen? O Ja O Nee

11. Heeft u een onregelmatige hartslag? O Ja O Nee

Zo nee, ga door met vraag 13

12. Heeft u hiervoor een pacemaker gekregen? O Ja O Nee

Wilt u a.u.b. naar de volgende bladzijde gaan

Vragenlijst COMORBIDITEIT (ACE-27)

2 / 5

UMCG-nummer ☐☐☐☐☐☐☐ - ☐

13. Heeft u een hoge bloeddruk? O Ja O Nee

Zo nee, ga door met vraag 18

14. Gebruikt u medicatie voor de behandeling van uw hoge bloeddruk? O Ja O Nee

15. Heeft u last van duizeligheid, bloedneuzen of hoofdpijn veroorzaakt door uw hoge bloeddruk? O Ja O Nee

16. Heeft u oog- of zenuwproblemen gehad door uw hoge bloeddruk? O Ja O Nee

17. Bent u in het ziekenhuis opgenomen geweest voor behandeling van uw hoge bloeddruk? O Ja O Nee

18. Heeft u ooit een trombose been gehad? O Ja O Nee

Zo nee, ga door met vraag 21

Zo ja, datum ☐☐ - ☐☐ - ☐☐☐☐

19. Gebruikt u sindsdien bloedverdunners? O Ja O Nee

20. Bent u geopereerd aan uw trombose been? O Ja O Nee

Zo ja, wat voor soort operatie? ☐

21. Heeft u ooit een longembolie gehad (bloedpropje in de longen)? O Ja O Nee

Zo ja, datum ☐☐ - ☐☐ - ☐☐☐☐

22. Heeft u last van pijn in uw onderbenen tijdens wandelen (etalagebenen)? O Ja O Nee

Zo nee, ga door met vraag 25

23. Heeft u hiervoor een operatie gehad? O Ja O Nee

24. Heeft u een beenamputatie gehad voor uw problemen met uw bloedvaten? O Ja O Nee

Zo ja, datum ☐☐ - ☐☐ - ☐☐☐☐

25. Heeft u een aneurysma (verwijdt bloedvat) in uw borstkast of buik? O Ja O Nee

Zo nee, ga door met vraag 27

26. Heeft u een behandeling gehad voor een aneurysma? O Ja O Nee

Wilt u a.u.b. naar de volgende bladzijde gaan

Vragenlijst COMORBIDITEIT (ACE-27)

3 / 5

UMCG-nummer ☐☐☐☐☐☐☐ - ☐

DEEL 2 (LONGEN)

27. Heeft u chronische bronchitis, emfyseem of astma? O Ja O Nee

Zo nee, ga door met vraag 32

28. Heeft uw kortademigheid - veroorzaakt door longproblemen- goed gereageerd op behandeling? O Ja O Nee

29. Beperkt uw kortademigheid uw activiteiten? O Ja O Nee

30. Heeft u in rust last van uw kortademigheid? O Ja O Nee

31. Gebruikt u regelmatig extra zuurstof? O Ja O Nee

DEEL 3 (LEVER, MAAG EN PANCREAS)

32. Heeft u chronisch leverfalen (hepatitis, cirrose)? O Ja O Nee

Zo nee, ga door met vraag 35

33. Bent u in het ziekenhuis opgenomen geweest voor een maagbloeding? O Ja O Nee

Zo ja, datum ☐☐ - ☐☐ - ☐☐☐☐

34. Heeft u een levertransplantatie gehad? O Ja O Nee

Zo ja, datum ☐☐ - ☐☐ - ☐☐☐☐

35. Heeft u een maagzweer? O Ja O Nee

Zo nee, ga door met vraag 38

36. Gebruikt u hiervoor medicatie? O Ja O Nee

37. Bent u geopereerd aan uw maagzweer? O Ja O Nee

38. Heeft u een darm-absorptie stoornis of een inflammatoire darmziekte (ziekte van Chrohn of Collitis Ulcerosa)? O Ja O Nee

39. Heeft u ooit problemen gehad met uw alvleesklier (pancreas) en/of bent u hiervoor opgenomen geweest in het ziekenhuis? O Ja O Nee

DEEL 4 (NIEREN)

40. Heeft u problemen met uw nieren? O Ja O Nee

Zo nee, ga door met vraag 43

41. Heeft u een niertransplantatie gehad? O Ja O Nee

Zo ja, datum ☐☐ - ☐☐ - ☐☐☐☐

Wilt u a.u.b. naar de volgende bladzijde gaan

Vragenlijst COMORBIDITEIT (ACE-27)

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UMCG-nummer ☐☐☐☐☐☐☐ - ☐

42. Dialyseert u? ○ Ja ○ Nee

Zo ja, sinds wanneer (datum) ☐☐ - ☐☐ - ☐☐☐☐

DEEL 5 (DIABETES)

43. Heeft u suikerziekte (diabetes)? ○ Ja ○ Nee

Zo nee, ga door met vraag 47

Zo ja, is de suikerziekte goed onder controle? ○ Ja ○ Nee

44. Gebruikt u hiervoor tabletten? ○ Ja ○ Nee
Spuit u insuline? ○ Ja ○ Nee

45. Bent u in het ziekenhuis opgenomen geweest voor complicaties van uw suikerziekte? ○ Ja ○ Nee

46. Heeft u problemen in andere organen (b.v. ogen, zenuwen, nieren, hart) veroorzaakt door uw suikerziekte? ○ Ja ○ Nee

DEEL 6 (HERSENEN EN ZENUWEN)

47. Heeft u ooit een beroerte gehad (CVA of TIA)? ○ Ja ○ Nee

Zo nee, ga door met vraag 49

Zo ja, datum ☐☐ - ☐☐ - ☐☐☐☐

48. Heeft u verlamming/restverschijnselen van uw beroerte? ○ Ja ○ Nee

49. Heeft u volledige hulp nodig bij eten, uw verzorging, aankleden, toiletgang? ○ Ja ○ Nee

50. Heeft u MS (multiple sclerose), ziekte van Parkinson of myasthenia gravis (spierzwakte)? ○ Ja ○ Nee

51. Heeft u last van een depressie of een psychiatrische stoornis? ○ Ja ○ Nee

Zo nee, ga door met vraag 53

52. Gebruikt u medicatie voor uw depressie/psychiatrische stoornis? ○ Ja ○ Nee

DEEL 7 (GEWRICHTEN EN SPIEREN

53. Heeft u reumatoïde artritis of andere gewrichts-of spierproblemen? ○ Ja ○ Nee

Zo nee, ga door met vraag 56

Wilt u a.u.b. naar de volgende bladzijde gaan

Vragenlijst COMORBIDITEIT (ACE-27)

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UMCG-nummer ☐☐☐☐☐☐☐ - ☐

54. Welke medicijnen gebruikt u hiervoor?

55. Heeft u nier-, long- of hartproblemen door uw reumatoïde artritis of gewrichts- of spierproblemen? O Ja O Nee

DEEL 8 (MALIGNITEIT)

De komende vragen gaan niet over de tumor/kanker waarvoor u hier behandeld gaat worden

56. Heeft u ooit kanker, leukemie of een lymfoon gehad? O Ja O Nee

Zo nee, ga door met vraag 59

Zo ja, datum ☐☐ - ☐☐ - ☐☐☐☐

57. Bent u nog onder behandeling hiervoor? O Ja O Nee

58. Is het goed onder controle? O Ja O Nee

DEEL 9

59. Drinkt/dronk u alcohol? O Ja O Nee

Zo nee, ga door met vraag 62

Zo ja, aantal glazen per week ☐☐

60. Heeft/had u problemen in uw sociale leven gerelateerd aan uw alcohol gebruik? O Ja O Nee

61. Heeft u ooit onttrekkingsverschijnselen gehad na het stoppen met alcohol? O Ja O Nee

62. Gebruikt u drugs? O Ja O Nee

Zo nee, Einde vragenlijst

63. Heeft/had u problemen in uw sociale leven gerelateerd aan uw drugs gebruik? O Ja O Nee

64. Heeft u ooit onttrekkingsverschijnselen gehad na het stoppen met drugs? O Ja O Nee

Appendix B: Radiation-induced side effects according to CTCAEv4.0 head and neck

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	
Hearing impaired	Adults enrolled on a monitoring program (a 1, 2, 3, 4, 6 and 8 kHz audiogram): threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear or subjective change in the absence of a Grade 1 threshold shift	Adults enrolled in monitoring program (a 1, 2, 3, 4, 6 and 8 kHz audiogram): threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear Adult not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL.	Adults enrolled in monitoring program (a 1, 2, 3, 4, 6 and 8 kHz audiogram): threshold shift of >25 dB veraged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adults not enrolled in monitoring program: hearing loss with hearing aid or intervention indicated; limiting self care ADL.	Adults: profound bilateral hearing loss (>80 dB at 2 kHz and above); non-serviceable hearing
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	
Mucosal oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	
Neck edema	Localized facial edema	Edema Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Osteonecrosis of the jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally	
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Laryngeal edema	Asymptomatic; clinical or diagnostic observations only;intervention not indicated	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine,antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Pharyngeal mucositis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limitinginstrumental ADL	Severe pain; unable to adequately aliment or hydrateorally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Voice alteration	Mild or intermittent changefrom normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	

Appendix C: Delineation guidelines for the parotid and submandibular glands

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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

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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 radiologist (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 $0.97 \times 0.97 \times 2.0$ 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.

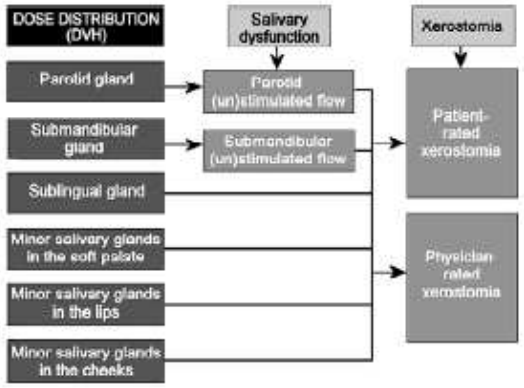

Fig. 1. Theoretical model relating the organs at risk as found in the literature and potential organs at risk for different endpoints involved in salivary dysfunction. DVH, dose–volume histogram.

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

Table 1
Delineation guidelines: The anatomic boundaries of the organs at risk involved in radiation-induced salivary dysfunction and xerostomia.

Organ at risk	Anatomic boundaries					
	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Parotid gland	External auditory canal, mastoid process	Post. part submandibular space	Masseter m., post. border mandibular bone, medial and lateral pterygoid m.	Ant. belly sternocleidomastoid m, lat side post belly of the digastric m. (posterior-medial)	Subcutaneous fat, platysma	Post. belly of the digastric m., styloid process, parapharyngeal space
Submandibular gland	Medial pterygoid m., mylohyoid m.	Fatty tissue	Lat. surface mylohyoid m., hyoglossus m.	Parapharyngeal space, sternocleidomastoid m.	Med. surface medial pterygoid m., med. surface mandibular bone, platysma	Lat. surface mylohyoid m., hyoglossus m., superior and middle pharyngeal constrictor m., anterior belly of the digastric m.
Sublingual gland	(Mucous membrane covering the floor of the mouth), crossing lingual septum – intrinsic tongue muscles	Ant. part mylohyoid m., geniohyoid m.	Ant. part surface mandibular bone, mylohyoid m.	Hyoglossus m.	Ant. part med. surface mandibular bone, mylohyoid m.	Genioglossus m.
Soft palate	Hard palate, nasopharyngeal mucosal space/air lumen	Tongue base, palatine tonsils, oropharyngeal mucosal space/air lumen	Hard palate, tongue/tongue base, air present in oral cavity or pharyngeal lumen	Superior pharyngeal constrictor m., pharyngeal mucosal space/air lumen	Pterygoid process, medial pterygoid plate, superior pharyngeal constrictor m., medial pterygoid m., parapharyngeal space, palatine tonsil, pharyngeal lumen	
Inner surface lower lip[a]	Upper edge lower lip	Lower edge teeth sockets, cranial edge mandibular body	Orbicularis oris m., subcutaneous tissue/fatty skin	Mandibular body, teeth, tongue, air (if present)	Depressor anguli oris m., buccinator m.	
Inner surface upper lip[a]	Hard palate (lateral), anterior nasal spine (at the midline)	Lower edge upper lip	Orbicularis oris m., subcutaneous tissue/fatty skin	Teeth, maxillary bone, hard palate, tongue	Depressor anguli oris m., buccinator m., levator anguli oris m./risorius m.	
Inner surface cheeks[a]	Transition between maxillary sinus and alveolar process maxilla	Alveolar process mandible	Orbicularis oris m.	Post. edge mandibular body, post. edge maxilla	Buccinator muscle, fatty tissue	Mandibular body, teeth, tongue

Abbreviations: m., muscle; med., medial; lat., lateral; post., posterior; ant., anterior.
[a] These structures have a constant thickness of 4 mm.

type, consists of a deep and superficial lobe (separated by the extracranial facial nerve passing through the gland).

Figs. 2 and 3 and Table 1 depict the relevant anatomic structures used as reference for delineation of the parotid gland. The following notes may help improve consistency when defining the parotid gland: in 20% of the cases, the parotid gland extends anteriorly over the surface of the masseter muscle following the parotid duct [18] (Fig. 2); in the anterior direction the deep lobe of the parotid gland may extend alongside the medial border of the mandible and the posterior-medial border of the medial pterygoid muscle; medially, this structure may be demarcated by the parapharyngeal space characterised by a hypodense region on CT, which in some cases can be difficult to distinguish from the parotid gland itself. In the lateral direction, the parotid gland is demarcated by a hypodense area corresponding to subcutaneous fat and more caudally by the platysma. The superior aspect of the parotid gland is related to the external auditory canal and mastoid process. Caudally, the gland protrudes into the posterior submandibular space inferior to the mandibular angle [18,37].

Note that the external carotid artery, the retromandibular vein and the extracranial facial nerve are enclosed in the parotid gland (Fig. 2). If no contrast-enhanced CT is used, these structures are generally hard to distinguish from the parotid gland tissue. The use of contrast agents, which is highly recommended, improves the discrimination between the vessels and salivary tissue (not accounting for the extracranial nerve), but, unfortunately, contrast agents are not always applied. Therefore, for the purpose of consistency, we decided to enclose these structures in the parotid gland.

Submandibular gland

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

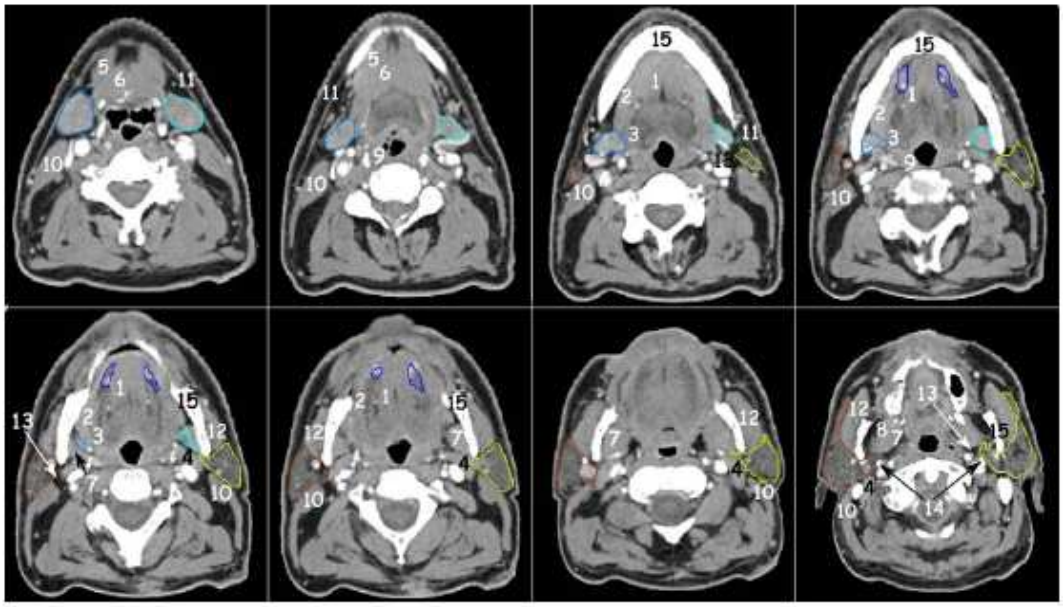

Fig. 2. Major salivary glands: the parotid glands are depicted in brown (left) and green (right), the submandibular glands are depicted in blue (the left one is brighter than the right one) and the sublingual glands are coloured dark blue (anterior part oral cavity). (1) Genioglossus m., (2) mylohyoid m., (3) hyoglossus m., (4) posterior belly digastric m., (5) anterior belly digastric m., (6) geniohyoid m., (7) medial pterygoid m., (8) lateral pterygoid m., (9) pharyngeal constrictor m., (10) sternocleidomastoid m., (11) platysma, (12) masseter m., (13) parapharyngeal space, (14) styloid process, (15) mandibular bone.

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.

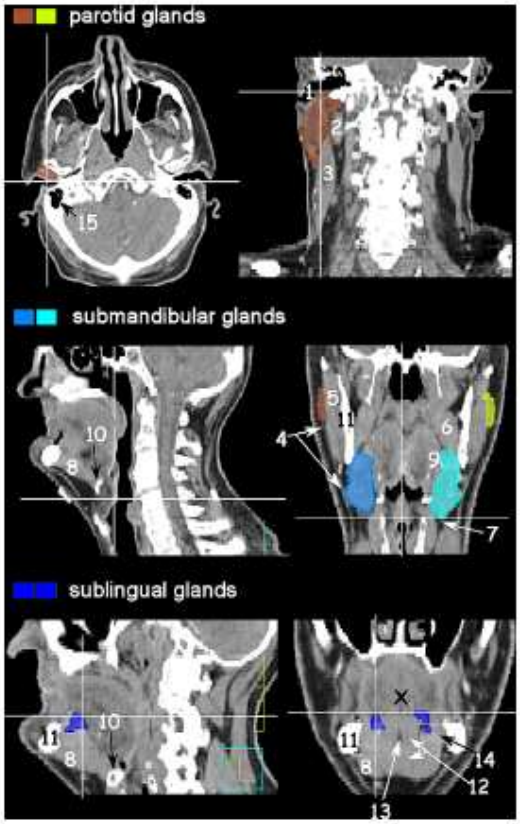

Fig. 3. Coronal and sagittal images displaying the cranial and caudal borders of the major salivary glands. The black cross (×) indicates the crossing of the lingual septum with the intrinsic tongue muscles. (1) External auditory canal, (2) posterior belly digastric m., (3) sternocleidomastoid m., (4) platysma, (5) masseter m., (6) medial pterygoid m., (7) fatty tissue, (8) anterior belly digastric m., (9) hyoglossus m., (10) hyoid bone, (11) mandibular bone, (12) genioglossus/geniohyoid m., (13) lingual septum, (14) mylohyoid m. and (15) mastoid process.

Inner surface cheek

For delineation of the minor salivary glands in the buccal mucosa, the anatomic structures demarcating the buccinator muscles are used as reference. In general, the buccal mucosa containing the minor salivary glands is relatively hard to distinguish from its surrounding tissues. Table 1 and Fig. 5 display the relevant anatomic boundaries. Visualization of the upper, lower and medial borders of this structure may be improved by using a coronal plane (Fig. 5). The cheeks can be distinguished from the tongue by a fatty tissue layer, corresponding to fatty tissue anteriorly to the buccinator muscle followed by a very thin mucous layer of the oral cavity, both enclosed in the structure (Fig. 5, coronal plane). In caudal direction, the buccal structure is delineated until the buccinator muscle is not visible anymore (Fig. 5).

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 soft 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-

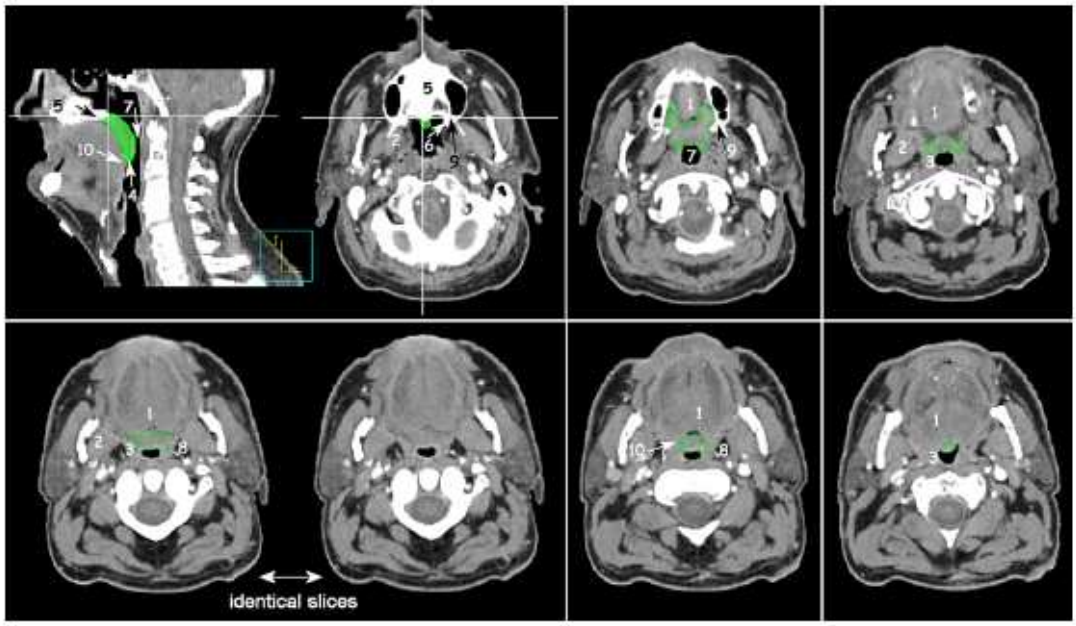

Fig. 4. Soft palate: the soft palate structure is depicted by the green contour. The sagittal view is depicted in the upper left corner, displaying the cranial border of the soft palate: the nasopharyngeal mucosal space/air lumen and the hard palate (see corresponding transversal plane). The two lower left pictures display the same axial CT-slice: one including and one not including the delineated soft palate structure. (1) Tongue, (2) medial pterygoid m., (3) superior pharyngeal constrictor m., (4) uvula, (5) hard palate, (6) medial pterygoid plate, (7) pharyngeal lumen, (8) parapharyngeal space, (9) pterygoid process and (10) level of the palatine tonsil.

eation guidelines will improve the uniformity in defining these OARs and will allow for a more accurate comparison of dose–volume parameters among the different studies.

Only a few studies have investigated the relationship between dose distributions in the minor salivary glands in relation to radiation-induced xerostomia. Eisbruch et al. [9] found a significant relationship between the mean oral cavity dose (representing the dose given to the minor salivary glands) and patient-rated xerostomia. However, limited information was provided regarding the exact anatomic boundaries of this oral cavity structure. Moreover, these investigators also included parts of the oral cavity that do not contain salivary gland tissue such as air gaps and teeth. Jellema et al. [23] also investigated the relationship between the mean oral cavity dose and patient-rated xerostomia. In this study, the authors referred to the paper of Eisbruch et al. [9] for definition of the oral cavity structure. In contrast to the results of Eisbruch et al., Jellema et al. did not find a significant association between the mean oral cavity dose and patient-rated xerostomia. These apparently conflicting results may be due to differences among these studies with regard to the way in which the oral cavity was delineated. Furthermore, it remains unclear as to whether the oral cavity structure as delineated in both studies properly represents the minor salivary glands lining the oral cavity.

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

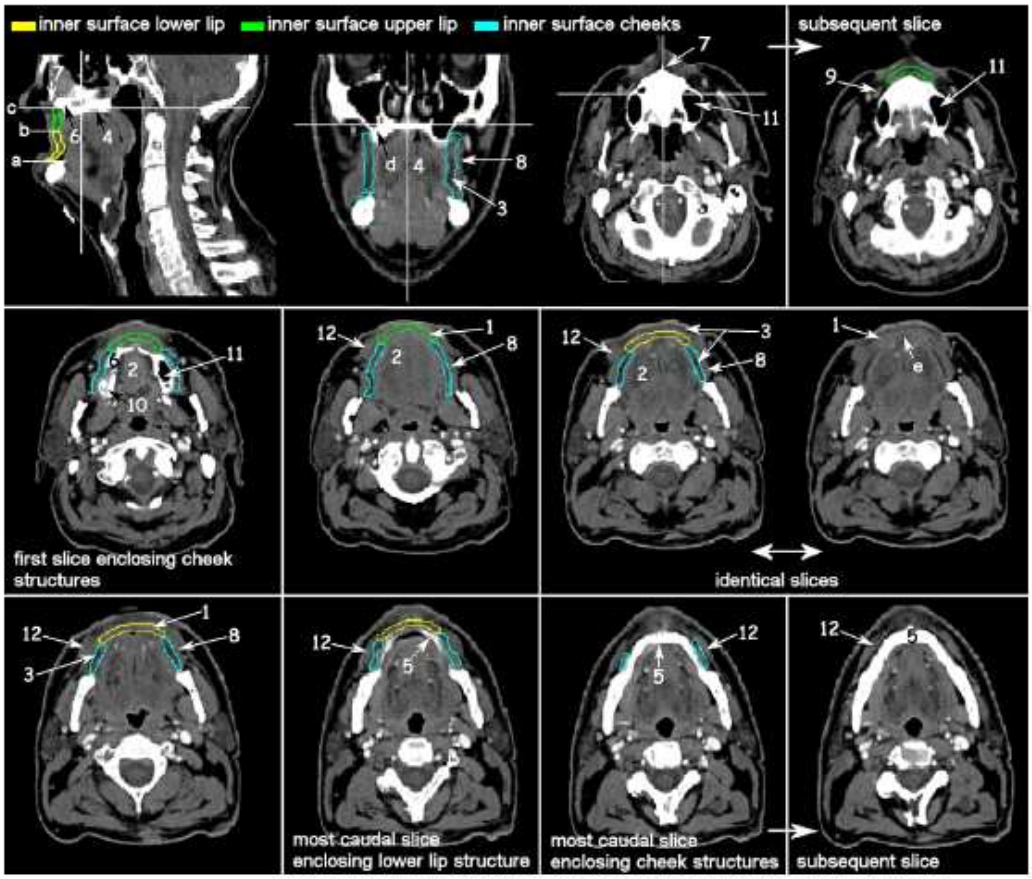

Fig. 5. Inner surface of the lower and upper lip plus cheek structure: (a) depicts the caudal border of the lower lip; (b) the cranial border of the lower lip and caudal border of the upper lip; (c) depicts the cranial border of the upper lip; (d) the upper edge of the inner surface cheek structure (transition between alveolar process maxilla – maxillary sinus); (e) the fatty tissue present posterior to the orbicularis oris muscle (m.). (1) Orbicularis oris, (2) tongue, (3) fatty tissue, (4) hard palate, (5) mandibular body, (6) maxillary bone, (7) anterior nasal spine, (8) buccinator m., (9) levator anguli oris/risorius m., (10) alveolar process maxilla, (11) maxillary sinus and (12) depressor anguli oris muscle.

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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Appendix D: Delineation guidelines OAR involved in swallowing

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Morbidity in head and neck radiotherapy

Delineation of organs at risk involved in swallowing for radiotherapy treatment planning

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ABSTRACT

Background and purpose: Radiotherapy, alone or combined with chemotherapy, is a treatment modality used frequently in head and neck cancer. In order to report, compare and interpret the sequelae of radiation treatment adequately, it is important to delineate organs at risk (OARs) according to well-defined and uniform guidelines. The aim of this paper was to present our institutional Computed Tomography (CT)-based delineation guidelines for organs in the head and neck at risk for radiation-induced swallowing dysfunction (SWOARs).

Material and methods: After analyses of the human anatomy of the head and neck area and literature review, CT-based guidelines for delineation of the most relevant SWOARs were described by a panel of experts.

Results and conclusions: This paper described institutional guidelines for the delineation of potential SWOARs, accompanied by CT-based illustrations presenting examples of the delineated structures and their corresponding anatomic borders. This paper is essential to ensure adequate interpretation of future reports on the relationship between dose distribution in these SWOARs and different aspects of post-treatment swallowing dysfunction.

Many head and neck cancer (HNC) patients treated with (chemo) radiation ((CH) RT) have to deal with devastating side-effects of their treatment [1]. In particular, a significant increase in the incidence of swallowing dysfunction after intensified regimens, such as the addition of concurrent chemotherapy to radiotherapy, has been observed [2]. Numerous studies revealed that swallowing dysfunction after completion of treatment has a significant impact on the general dimensions of quality of life [2–4], which is probably even more important than radiation-induced xerostomia [1,5].

Studies on swallowing dysfunction using videofluoroscopy after (CH) RT for HNC revealed a large variety of motility disorders [2,6–17]. These swallowing disorders can lead to clinically apparent as well as silent or subclinical aspiration or continued alternate feeding such as placement of a nasogastric or a percutaneous endoscopic gastrostomy tube [2,4,6–8,16–18].

Given the complexity of swallowing and the large variety of disorders after (CH) RT, there are a large number of potential organs at risk (OARs) for radiation-induced swallowing dysfunction. Several authors investigated the relationship between the dose distributions in potential swallowing organs at risk (SWOARs) and different aspects of swallowing dysfunction [5,19–28]. These studies retrieved different results, which may be due to a number of methodological issues, including the relatively small number of patients in most of these studies, differences in eligibility criteria and differences in study design and endpoints chosen. Even more important, the definition and delineation of the SWOARs among the studies that reported on dose–volume–effect relationships differ which may also account for different outcomes in terms of associations between dose volume histogram (DVH) parameters and swallowing dysfunction. Therefore, in order to compare and interpret the results among studies, it becomes increasingly important to accurately describe the way potential SWOARs are defined and delineated.

The past 3 years, a number of prospective studies on risk factors for post-treatment swallowing dysfunction have been carried out at the departments of Radiation Oncology of the VU University Medical Center (VUMC) and the University Medical Center Groningen (UMCG), including studies on dose effect relationships. To ensure proper interpretation of the results of these studies in future publications, we felt it was important to describe how the different structures were defined and delineated, in particular for potential SWOARs.

Therefore, the main objective of this paper was to present our institutional CT-image based delineation guidelines for anatomic structures involved, or potentially involved in radiation-induced swallowing dysfunction that eventually permit unambiguous

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interpretation of dose–volume–effect relationships for SWOARs as will be reported in a number of upcoming publications.

The normal swallowing process

Swallowing involves multiple muscles and other structures. The pharyngeal musculature, including the circular constrictors (the superior, middle and inferior pharyngeal constrictor muscle (PCM)) and longitudinal muscles (the stylopharyngeal, salpingopharyngeal, and palatopharyngeal muscles) are required to prevent food from entering the nose (in collaboration with the soft palate) and for peristalsis and synchronization among the pharyngeal contraction wave. In addition, they are responsible for the opening of the cricopharyngeal sphincter, and closure of the larynx. The base of tongue drives the bolus through the pharynx and makes contact with the posterior pharyngeal wall assuring that no residue remains in the vallecula. Glottic adductor muscles (the thyroarytenoid, lateral cricoarytenoid, and transverse arytenoid muscles) and supraglottic adductors (oblique arytenoids and aryepiglottic muscles) take care of glottic closure and adduction of the supraglottic larynx during swallow. The cricopharyngeal sphincter opens by relaxation of the cricopharyngeal muscle, upward and forward motion of the cricoid cartilage by the suprahyoid muscles (the geniohyoid, mylohyoid, and digastric muscles), and the pressure generated on the bolus which widens both the cricopharyngeal sphincter and the inlet muscles of the esophagus [29–32].

Thus, a number of valves are involved to direct food into the esophagus and prevent food from entering the airway or the nose. These valves include (1) the velopharyngeal valve, which is comprised of the soft palate and the pharyngeal walls; (2) the larynx, operating at the levels of epiglottis and aryepiglottic folds, the false vocal folds and arytenoid cartilages, and the true vocal folds; (3) the base of tongue; and (4) the cricopharyngeal sphincter, which is comprised of the cricoid cartilage and the cricopharyngeal muscle [29,30,32].

Guidelines for SWOARs

General methodology

In the next paragraph, we present our guidelines for SWOARs based on normal anatomy and function, while at the same time keeping as close as possible to the definitions used in former studies when appropriate.

The definitions of the SWOARs were described by a panel of experts, including two specialised head and neck radiation oncologists (HB and JL) and an experienced head and neck radiologist (HW).

In addition, the SWOARs were delineated on a contrast-enhanced planning CT-scan from an edentate female patient with a T2N0 nasal cavity tumour that did not affect the shape of the anatomic structures concerned.

Contouring was carried out using the Pinnacle treatment planning system (TPS) (version 8.0 h, Philips Radiation Oncology Systems, Fitchburg, WI). The SWOARs were delineated by one radiation oncologist and reviewed and adjusted when considered appropriate by the other experts. Overall, the centre and width values (window settings) used to delineate the SWOARs were set to 900 Hounsfield Unit (HU) and 326 HU, respectively. In some cases these specific values were changed to improve the visibility of certain anatomical structures and/or boundaries. We did not specify these settings as the exact values resulting in the best display may vary among different patients.

A general overview of potential SWOARs are depicted in Fig. 1. For each SWOAR included in this paper, we described the normal anatomy and guidelines used by other authors (Table 1) which were taken into account, ultimately ending up with the definitions and delineation guidelines for each SWOAR (Table 2 and Fig. 2).

Pharyngeal constrictor muscles

The pharyngeal wall is composed of two layers of muscles, including an external circular layer consisting of the pharyngeal

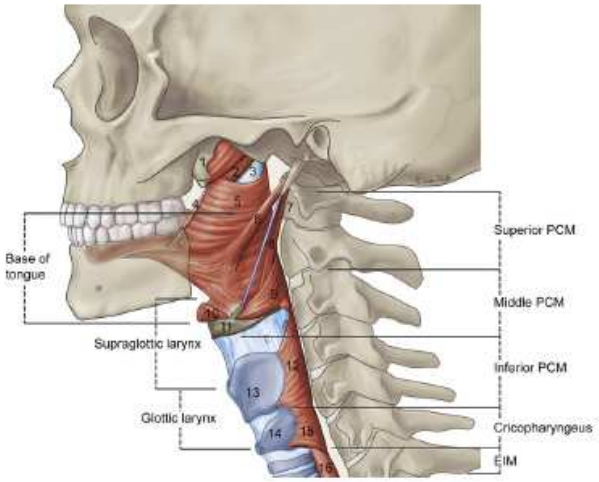

Fig. 1. General overview of anatomical structures involved in swallowing. The following reference anatomical structures are shown: (1) processus pterygoideus, (2) levator veli palatine, (3) fascia pharyngobasilaris, (4) raphe pterygomandibularis, (5) superior PCM, (6) styloglossus, (7) anterior tubercle of atlas, (8) stylopharyngeus, (9) middle PCM, (10) geniohyoideus (cut), (11) hyoid, (12) inferior PCM (thyropharyngeal part), (13) thyroid cartilage, (14) cricoid cartilage, (15) cricopharyngeus, and (16) esophagus.

constrictor muscles (PCM) and an internal mainly longitudinal layer consisting of the two levators. The PCM can be divided in a superior, middle and inferior part. The distal parts of the levators (the stylopharyngeal, salpingopharyngeal, and palatopharyngeal muscles) approach and blend with the PCM. In general, it is hard to distinguish these longitudinal muscles from the PCM. Therefore, we decided not to contour these two structures separately as the most distal parts of these longitudinal muscles are already enclosed in the PCM.

The superior PCM

The superior PCM is a quadrilateral sheet of muscles originating from the pterygoid hamulus of the sphenoid bone. The insertion of all fibres unites in the median raphe and in the aponeurosis that is attached to the pharyngeal tubercle on the basilar part of the occipital bone.

Levendag et al. [25] defined the cranial border of the superior PCM in the middle of the 2nd vertebra, which is lower than the actual cranial border of the superior PCM. In most studies, the authors defined the caudal tip of the pterygoid plates as the cranial border of the superior PCM [20,23,26]. Indeed, the caudal tip of the pterygoid plates corresponds with the pterygoid hamulus of the sphenoid bone and thus with the actual cranial border of the most cranial fibres of the superior PCM (Fig. 3). Some authors only mentioned the pterygoid plates as cranial border [21,28]. However, the pterygoid plate generally extents through a number of slides in cranial–caudal direction and therefore provides a less accurate definition of the cranial border of the superior PCM. Therefore, we decided to define the cranial border of the superior PCM as the caudal tip of the pterygoid plate, i.e., the pterygoid hamulus (Table 2).

The lowest fibres of the superior PCM are roughly separated from the middle PCM by the stylopharyngeal muscle and the glossopharyngeal nerve but also partly overlap with the highest fibres of the middle PCM. However, it is hardly possible to distinguish these structures on CT. Most authors defined the caudal border of the superior PCM as the upper edge of the hyoid bone, although the most caudal fibres of the superior PCM attach to the hyoid bone. If the upper edge of the hyoid bone would be defined as the lower border, almost half of the middle PCM will be missed (see Fig. 1). Therefore, we decided to define the lower border of the 2nd cervical vertebra as the caudal border of the superior PCM.

The posterior border of the superior PCM is defined by the prevertebral muscles and fascia, from which it is separated by the retropharyngeal space.

Anteriorly, the superior PCM is attached to the pterygoid hamulus (clearly visible on CT), the pterygomandibular raphe (not visible on CT), the posterior end of the mandible (to which the pterygomandibular raphe is attached), and to the base of tongue. However, it is difficult to define exactly how these structures can be used on CT to define the anterior borders of the superior PCM. We assume, that for this reason, two authors [5,20] decided to define the anterior border as the widest diameter of the rhinopharynx, the base of tongue and the hyoid bone as the anterior border as surrogate anterior borders, which approximately corresponds with the actual anterior border of the superior PCM (Table 1). With regard to the part of the superior PCM anteriorly from the prevertebral muscles, the anterior border is defined as the pharyngeal lumen. As a consequence, the pharyngeal mucosa overlying the superior PCM will be included in this structure.

The middle PCM

The middle PCM originates from the lesser horns and the greater horns of the hyoid bone. The insertion of all fibres unites in the median pharyngeal raphe. The lower fibres descend deep to the inferior PCM to reach the lower end of the pharynx and thus overlap in the transverse plane with the fibres of the inferior PCM, while the highest fibres ascend and overlap with the fibres of the superior PCM. Therefore, it should be noted that cranial and caudal borders of these anatomical structures are always somewhat arbitrary.

The upper border of the middle PCM corresponds with the lower border of the superior PCM.

In most studies, the caudal border of the middle PCM was defined as the lower edge of the hyoid bone, which roughly corresponds with the actual caudal border of the PCM.

In addition, the anterior borders for the middle PCM were defined in a similar way as for the superior PCM, including the widest diameter of the base of tongue, the hyoid bone and the larynx, which approximately corresponds with the actual anterior border of the middle PCM, while the posterior border is defined by the prevertebral muscles (Table 2).

The inferior PCM

The inferior PCM is the thickest of the three constrictor muscles. It is composed of the thyropharyngeal part originating from the linea obliqua of the thyroid cartilage and the cricopharyngeal part originating from the lateral edges of the cricoid cartilage. In some studies, the thyropharyngeal part (often referred to as inferior PCM) and the cricopharyngeal part (often referred to as cricopharyngeal muscle) are defined as two separate anatomical structures [20,25,26]. From a functional point of view, it makes sense to distinguish these two structures as lack of relaxation of the cricopharyngeal muscle in particular plays a role in the pathophysiology of aspiration during swallow [31,33]. The borders of the cricopharyngeal muscle will therefore be discussed in a separate paragraph, while the definition of the borders of the inferior PCM, as described here, actually corresponds with the thyropharyngeal part of the inferior PCM.

In line with most authors, the cranial border of the inferior PCM is defined as the caudal border of the middle PCM, starting at the lower edge of the hyoid bone. Practically, the delineation should start at the first slice caudally from the lower edge of the hyoid bone.

As we defined the cricopharyngeal muscle as a separate SWOAR, we defined the caudal border of the inferior PCM as the upper edge of the cricoid cartilage just below the lower edge of the arytenoid cartilage. This is somewhat different from the definitions used by other investigators who made a distinction between the thyropharyngeal part of the inferior PCM and the cricopharyngeal muscle, since they all referred to the caudal edge of the cricoid as the caudal border of the inferior PCM [20,25,26]. In fact, the cricopharyngeal muscle fibres are horizontal in direction and are mainly located posteriorly from the cricoid cartilage.

Anteriorly, the inferior PCM attaches to the posterior edge of thyroid cartilage, which can be recognised easily on CT, while the posterior border is defined by the prevertebral muscles.

The cricopharyngeal muscle

The cranial border of the cricopharyngeal muscle is similar to the caudal border of the inferior PCM as described in the former paragraph. Practically, the delineation should start at the first slice caudal to the arythenoid cartilages.

Caudally, the cricopharyngeal muscle blends with the circular esophageal fibres around the narrowest part of the pharynx. The lower border of the cricoid cartilage corresponds with the caudal border of the cricopharyngeal muscle.

The cricopharyngeal muscle attaches anteriorly to the outer posterior edge of the cricoid cartilage. The posterior border is defined by the prevertebral muscles.

Esophagus inlet muscles (EIM)

The most proximal part of the esophagus, is the most frequently involved area of radiation-induced strictures. As the dose given to

Table 1
Anatomical borders of swallowing organs at risk used in the eight studies published between 2000 and 2010.

Author	Pharyngeal constrictor muscles			Cricopharyngeus	Esophagus inlet muscle	Cervical esophagus	Base of tongue	Larynx	
	Superior PCM	Middle PCM	Inferior PCM					Supraglottic	Glottic
Bhide (2009)*	Cranial: base of the skull Caudal: superior end of the hyoid bone Posterior: pre-vertebral muscles Anterior: pharyngeal lumen (mucosa included)	Cranial: superior end of the hyoid bone Caudal: caudal end of the hyoid bone	Cranial: caudal end of the hyoid bone Caudal: caudal end of cricoid cartilage	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Caglar (2008)*	Cranial: pterygoid plates Caudal: upper edge of the hyoid bone	Cranial: upper edge of the hyoid bone Caudal: lower edge of the hyoid bone	Cranial: inferior edge of the hyoid bone Caudal: lower edge of the cricoid cartilage	Not mentioned	Not mentioned	Cranial: lower edge of the cricoid Caudal: caudal-most extent of the low-neck target	Not mentioned	Cranial: upper edge of the thyroid cartilage Caudal: upper edge of the cricoid	
Caudell (2010)*	Cranial: pterygoid plates Caudal: superior portion of hyoid bone	Cranial: cranial portion of hyoid bone Caudal: inferior portion of hyoid bone	Cranial: inferior portion of hyoid bone Caudal: inferior edge of cricoid cartilage	Not mentioned	Not mentioned	Cranial: inferior edge of the cricoid cartilage Caudal: superior extent of the aortic arch	Cranial: intersection of a vertical plane projected from the posterior hard palate to the tongue Caudal: vallecula Lateral: glossopharyngeal sulcus	Cranial: epiglottis Caudal: vocal cords	
Dirix (2009)	Cranial: caudal tip of the pterygoid plates (hamulus) Caudal: upper edge of hyoid bone Posterior: cervical vertebra or prevertebral muscles Anterior: widest diameter of rhinopharynx, base of tongue, hyoid bone and larynx	Cranial: upper edge of hyoid bone Caudal: lower edge of hyoid bone	Cranial: lower edge of hyoid bone Caudal: lower edge of cricoid cartilage	Cranial: lower edge of cricoid cartilage Caudal: upper edge of trachea Posterior: cervical vertebra Anterior: subglottic larynx		Cranial: upper edge of trachea Caudal: first 2 cm Posterior: cervical vertebra Anterior: trachea	Cranial: below soft palate (uvula) Caudal: upper edge of hyoid bone Anterior: posterior third of tongue	Cranial: top of the piriform sinus and aryepiglottic fold Caudal: upper edge of the cricoid cartilage Posterior: cornu of thyroid cartilage Anterior: anterior tip of thyroid cartilage Lumen excluded	Level of the cricoid cartilage Lumen excluded
Feng (2007)*	Cranial: caudal tips of the pterygoid plates Caudal: upper edge of the hyoid bone	Cranial: upper edge of the hyoid bone Caudal: lower edge of the hyoid bone	Cranial: below the hyoid Caudal: inferior edge of the cricoid	Not mentioned	Not mentioned	Cranial: inferior border of the cricoid Caudal: caudal-most extent of the low-neck targets	Not mentioned	Contoured as a single structure	
Jensen (2007)	Cranial: lower part of transverse process of C2 Caudal: top of the cricoid cartilage Anterior: widest diameter of rhinopharynx, base of tongue, hyoid bone and larynx			Not mentioned	At the level of the cricoid cartilage Posterior: cervical vertebra Anterior: larynx	Not mentioned	Cranial: below soft palate Caudal: first slice with epiglottis Anterior: posterior 0.5–1.0 cm rim of the tongue	Cranial: top of the piriform sinus Caudal: top of the cricoid cartilage Anterior: cornu of hyoid bone / thyroid cartilage	Level of the cricoid cartilage Lumen excluded

(*continued on next page*)

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Table 1 (continued)

Author	Pharyngeal constrictor muscles			Cricopharyngeus	Esophagus inlet muscle	Cervical esophagus	Base of tongue	Larynx	
	Superior PCM	Middle PCM	Inferior PCM					Supraglottic	Glottic
Levendag (2007)	Cranial: mid C2 Caudal: upper C3	Cranial: upper C3 Caudal: upper C4/ caudal part corpus hyoid	Cranial: upper C4(caudal part corpus hyoid Caudal: mid C6 / caudal edge cricoid	Cranial: mid C6/ caudal edge cricoid Caudal: lower border first trachea ring	Cranial: lower border first trachea ring Caudal: 1 cm caudal from lower border first trachea ring	Not mentioned	Not mentioned	Lumen excluded Not mentioned	Not mentioned
Li (2009)	Cranial: caudal tips of the pterygoid plates Caudal: lower edge of the hyoid bone		Cranial: below the hyoid Caudal: inferior edge of the cricoid	Cranial: caudal cricoid Caudal: first tracheal ring, 1 cm caudal from cranial border	Not mentioned	Cranial: 1 cm caudal from the caudal cricoid Caudal: thoracic inlet	Not mentioned	Not mentioned	Not mentioned

* Refers to guidelines as defined by Eisbruch 2004.

the esophagus drops rapidly in the lower parts of the esophagus, this suggests a dose response relation for stricture [34,35]. According to Levendag et al. [25], we defined the first centimeter of the esophagus as a separate SWOAR, the EIM. The cranial border of the esophagus starts immediately caudally from the caudal border of the cricopharyngeal muscle. Practically, the cranial border of the EIM is the first slice caudal from the lower edge of the cricoid cartilage.

The anterior border is formed by the trachea and the posterior border is defined by the prevertebral muscles.

Cervical esophagus (CE)

Some authors also took into account the dose distributions in the CE [20,21,23,26,28], which certainly makes sense as in the case of elective nodal irradiation, the CE may receive a clinically relevant dose, in particular when IMRT is used. However, the definition of the CE differed widely among the different studies (Table 1).

For the purpose of consistency, the cranial border of the CE was defined as 1 cm caudal from the lower edge of the cricoid cartilage which corresponds with the caudal border of the EIM. Generally, the CE is defined as the part of the esophagus extending from the pharynx to the thoracic inlet. Therefore, we decided to use the thoracic inlet as the caudal border of the CE which, on CT, corresponds with the sternal notch. Normally, in the transversal plane, the CE can be easily recognized on CT, so we did not define anterior and posterior borders.

Base of tongue

The base of tongue is the posterior part of the tongue as it curves down into the throat. It composes the anterior wall of the oropharynx and is attached to the hyoid bone and mandible [32]. Guidelines for the anatomical borders of the base of tongue were only provided in three studies [5,20,28]. In these studies the cranial border was defined as below the soft palate. Since this border is hard to distinguish on CT, and often is made invisible due to artefacts, we decided to take a cranial border which is clearly visible on CT, the lower edge of the anterior tubercle of the 1st cervical vertebra (Fig. 3), which actually resembles the same level.

However, the caudal border of the base of tongue was defined differently as the upper edge of the hyoid bone [20], the vallecula [28], and the first slice with epiglottis [5]. We decided, again, for the purpose of consistency, to define the upper edge of the body of the hyoid bone as the caudal border.

The anterior part of the tongue, including the genioglossal, the hyoglossal, the pataloglossal and the styloglossal muscle, are not part of the base of tongue. However, these muscles are often hard to distinguish on CT-scan, therefore, for the purpose of consistency; we created a surrogate structure which includes the posterior one third of the tongue measured from the inner side of the mandibular bone to the pharyngeal lumen, just above the hyoid bone on the sagittal view of the CT as illustrated in Fig. 3.

Larynx

The larynx includes the supraglottic, the glottic and subglottic region. The supraglottis encompasses the epiglottis, the supraglottic adductor muscles, the aryepiglottic folds, the arytenoids, and the false vocal cords. The glottis is composed of the true vocal cords. The region extending from the lower boundary of the glottis to the lower edge of the cricoid cartilage is the subglottis.

A limited number of authors provided definitions of the boundaries of the glottic and supraglottic larynx [5,20,21] which were slightly different.

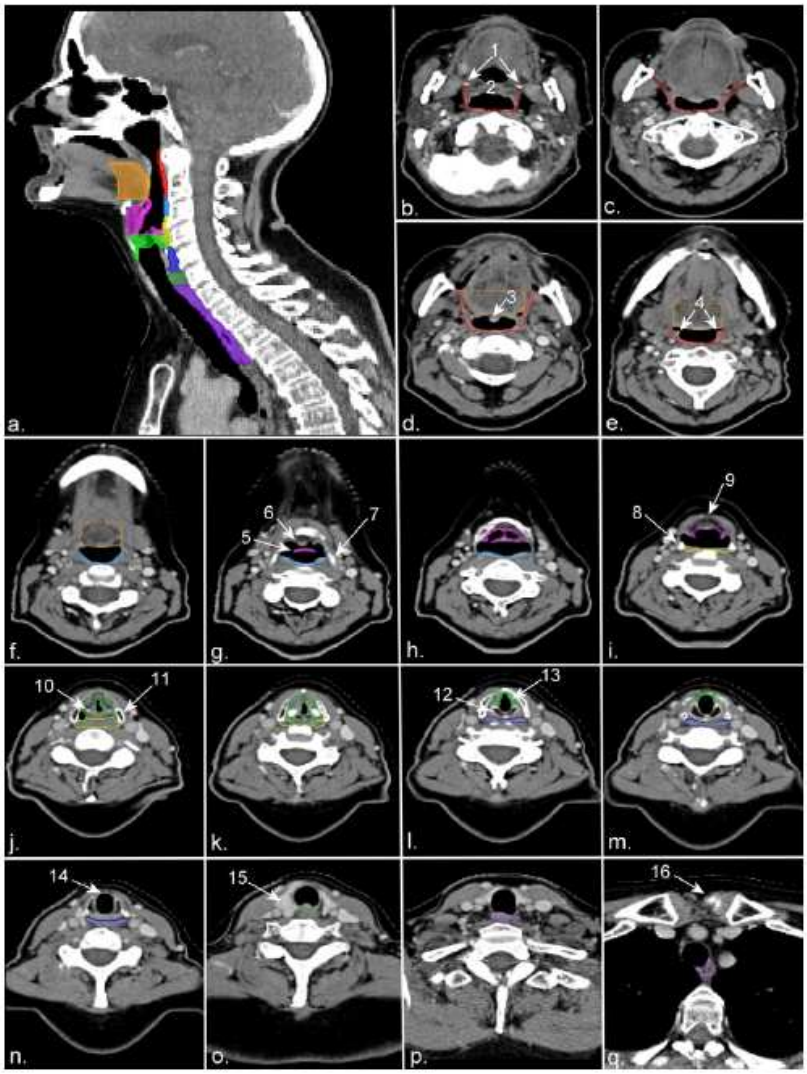

Fig. 2. Most relevant CT-slices for the delineation of SWOARs, including: superior PCM (red); middle PCM (light blue); inferior PCM (thyropharyngeal part) (yellow); cricopharyngeus (dark blue); EIM (dark green); CE (purple); base of tongue (orange) and: supraglottic (pink) and glottic larynx (light green). The following reference anatomical structures are shown: (1) hamulus of pterygoid plates; (2) soft palate, (3) uvula, (4) palatopharyngeal folds, (5) tip of epiglottis, (6) lingual tonsil, (7) greater horn of hyoid bone, (8) superior horn of thyroid cartilage, (9) pre-epiglottic space, (10) arytenoid cartilage, (11) thyroid cartilage, (12) cricoid cartilage, (13) soft tissue of lower larynx, (14) no soft tissue present anterior to cricoid cartilage, (15) thyroid gland, and (16) sternal notch.

differences in DVH-parameters from the same treatment plan. As a consequence, the results of the different studies that investigate the relationship between DVH-parameters and swallowing function after radiotherapy will be hard to compare. Furthermore, translation of the results of dose–volume–effect relationship studies into clinical practice can only be introduced safely, if radiation oncologists use the similar guidelines in clinical practice. Therefore, delineation guidelines are the first prerequisite for

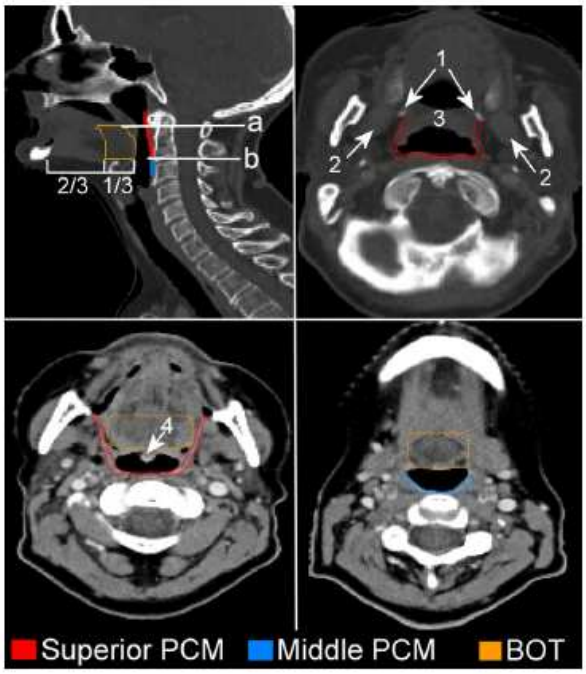

Fig. 3. Superior PCM, middle PCM and base of tongue (BOT) in sagittal and coronal CT-slices. The upper two CT-slices are in bone-setting. Two cranial borders are shown: (a) lower edge of anterior tubercle of atlas (cranial border of BOT) and (b) upper edge of C3 (cranial border of middle PCM). The following reference anatomical structures are shown: (1) hamulus of pterygoid plates, (2) medial pterygoid muscles, (3) soft palate, and (4) uvula.

unambiguously contouring of SWOARs and for a reliable comparison and interpretation of results from different studies.

As the CT-scan currently is the gold standard for target volume and OAR delineation, therefore we decided to define CT-image based delineation guidelines. However, it should be noted that the visualization of relevant anatomic swallowing structures could be improved by using Magnetic Resonance Imaging (MRI). MRI can help to discriminate the muscles from surrounding tissues in more detail. Therefore, the use of co-registered MRI in conjunction with CT may improve and facilitate the delineation of the pharyngeal muscles.

Furthermore, when the tumour extends in one of the SWOARs, or when the tumour or involved lymph nodes alter the normal anatomy, delineation of the SWOARs may be burdensome. Hampered interpretation could also be the case when the CT-scan images are blurred due to artefacts. To delineate in a consistent way, the solution would be to delineate the contours in the well perceptible slices, and interpolate the delineations in between.

Conclusion

This paper described institutional guidelines for the delineation of potential SWOARs in order to ensure adequate interpretation of future reports on the relationship between dose distribution in these SWOARs and different aspects of post-treatment swallowing dysfunction.

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Appendix E: EORTC QLQ-C30

DUTCH

EORTC QLQ-C30 (version 3)

Wij zijn geïnteresseerd in bepaalde dingen over u en uw gezondheid. Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is. Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

Wilt u uw voorletters invullen: _____
Uw geboortedatum (Dag, Maand, Jaar): _____
De datum van vandaag (Dag, Maand, Jaar): 31 _____

		Helemaal niet	Een beetje	Nogal	Heel erg
1.	Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?	1	2	3	4
2.	Heeft u moeite met het maken van een lange wandeling?	1	2	3	4
3.	Heeft u moeite met het maken van een korte wandeling buitenshuis?	1	2	3	4
4..	Moet u overdag in bed of in een stoel blijven?	1	2	3	4
5.	Heeft u hulp nodig met eten, aankleden, u zelf wassen of naar het toilet gaan?	1	2	3	4

Gedurende de afgelopen week:		Helemaal niet	Een beetje	Nogal	Heel erg
6.	Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?	1	2	3	4
7.	Was u beperkt in het uitoefenen van uw hobbies of bij andere bezigheden die u in uw vrije tijd doet?	1	2	3	4
8.	Was u kortademig?	1	2	3	4
9.	Heeft u pijn gehad?	1	2	3	4
10.	Had u behoefte te rusten?	1	2	3	4
11.	Heeft u moeite met slapen gehad?	1	2	3	4
12.	Heeft u zich slap gevoeld?	1	2	3	4
13.	Heeft u gebrek aan eetlust gehad?	1	2	3	4
14.	Heeft u zich misselijk gevoeld?	1	2	3	4

Wilt u a.u.b. naar de volgende bladzijde gaan

DUTCH

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
15. Heeft u overgegeven?	1	2	3	4
16. Had u last van obstipatie? (was u verstopt?)	1	2	3	4
17. Had u diarree?	1	2	3	4
18. Was u moe?	1	2	3	4
19. Heeft pijn u gehinderd in uw dagelijkse bezigheden?	1	2	3	4
20. Heeft u moeite gehad met het concentreren op dingen, zoals een krant lezen of televisie kijken?	1	2	3	4
21. Voelde u zich gespannen?	1	2	3	4
22. Maakte u zich zorgen?	1	2	3	4
23. Voelde u zich prikkelbaar?	1	2	3	4
24. Voelde u zich neerslachtig?	1	2	3	4
25. Heeft u moeite gehad met het herinneren van dingen?	1	2	3	4
26. Heeft uw lichamelijke toestand of medische behandeling uw familieleven in de weg gestaan?	1	2	3	4
27. Heeft uw lichamelijke toestand of medische behandeling u belemmerd in uw sociale bezigheden?	1	2	3	4
28. Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?	1	2	3	4

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is

29. Hoe zou u uw algehele gezondheid gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

30. Hoe zou u uw algehele "kwaliteit van het leven" gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

Appendix F: EORTC QLQ-H&N35

DUTCH

EORTC QLQ - H&N35

Soms zeggen patienten dat ze de volgende klachten of problemen hebben. Wilt u aangeven in welke mate u deze klachten of problemen gedurende de afgelopen week heeft ervaren door het getal te omcirkelen dat het meest op u van toepassing

Gedurende de afgelopen week:		Helemaal niet	Een beetje	Nogal	Heel erg
31.	Heeft u pijn in uw mond gehad?	1	2	3	4
32.	Heeft u pijn in uw kaak gehad?	1	2	3	4
33.	Was uw mond gevoelig?	1	2	3	4
34.	Heeft u een pijnlijke keel gehad?	1	2	3	4
35.	Heeft u moeite gehad met slikken bij het drinken?	1	2	3	4
36.	Heeft u moeite gehad met slikken bij het eten van gepureerd voedsel?	1	2	3	4
37.	Heeft u moeite gehad met slikken bij het eten van vast voedsel?	1	2	3	4
38.	Heeft u zich verslikt?	1	2	3	4
39.	Heeft u last gehad van uw gebit?	1	2	3	4
40.	Heeft u moeite gehad uw mond wijd open te doen?	1	2	3	4
41.	Had u een droge mond?	1	2	3	4
42.	Was uw speeksel kleverig?	1	2	3	4
43.	Had u problemen met uw reukvermogen?	1	2	3	4
44.	Had u problemen met uw smaakvermogen?	1	2	3	4
45.	Heeft u gehoest?	1	2	3	4
46.	Bent u hees geweest?	1	2	3	4
47.	Heeft u zich ziek gevoeld?	1	2	3	4
48.	Heeft u zich gestoord aan uw uiterlijk?	1	2	3	4

Wilt u a.u.b. naar de volgende bladzijde gaan

DUTCH

Gedurende de afgelopen week:		**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
49.	Heeft u moeite gehad met eten?	1	2	3	4
50.	Vond u het moeilijk te eten in het bijzijn van uw gezin?	1	2	3	4
51.	Vond u het moeilijk te eten in het bijzijn van andere mensen?	1	2	3	4
52.	Had u er moeite mee van uw maaltijden te genieten?	1	2	3	4
53.	Had u er moeite mee met andere mensen te praten?	1	2	3	4
54.	Had u moeite met het voeren van een telefoongesprek?	1	2	3	4
55.	Had u moeite met sociale contacten met uw naaste familie?	1	2	3	4
56.	Had u moeite met sociale contacten met vrienden?	1	2	3	4
57.	Had u moeite de straat op te gaan?	1	2	3	4
58.	Had u moeite met lichamelijk contact met naaste familie of vrienden?	1	2	3	4
59.	Had u minder belangstelling voor seks?	1	2	3	4
60.	Heeft u minder plezier beleefd aan seks?	1	2	3	4

Gedurende de afgelopen week:		**Nee**	**Ja**
61.	Heeft u pijnstillers gebruikt?	1	2
62.	Heeft u voedingssupplementen (bijvoorbeeld Nutridrink of Fortimel) gebruikt (behalve vitaminen)?	1	2
63.	Heeft u sondevoeding (voeding door middel van een slangetje in de maag) gebruikt?	1	2
64.	Bent u afgevallen?	1	2
65.	Bent u aangekomen?	1	2

Appendix G: EuroQOL-5D

Gezondheidsvragenlijst

We willen onderzoeken hoe mensen denken over gezondheid. Op de volgende bladzijden beschrijven we enkele gezondheidstoestanden waar mensen zich zoal in kunnen bevinden. We willen u vragen hoe goed of hoe slecht u iedere gezondheidstoestand voor iemand als uzelf zou vinden. Er zijn geen goede of foute antwoorden, het gaat ons alleen om uw persoonlijke mening. Om te beginnen willen we u vragen om aan te geven (op de volgende pagina) hoe uw eigen gezondheidstoestand vandaag is.

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje achter de zin die het best past bij uw eigen gezondheidstoestand vandaag.

Mobiliteit
Ik heb geen problemen met lopen ☐
Ik heb enige problemen met lopen ☐
Ik ben bedlegerig ☐

Zelfzorg
Ik heb geen problemen om mijzelf te wassen of aan te kleden ☐
Ik heb enige problemen om mijzelf te wassen of aan te kleden ☐
Ik ben niet in staat mijzelf te wassen of aan te kleden ☐

Dagelijkse activiteiten *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*
Ik heb geen problemen met mijn dagelijkse activiteiten ☐
Ik heb enige problemen met mijn dagelijkse activiteiten ☐
Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ☐

Pijn/klachten
Ik heb geen pijn of andere klachten ☐
Ik heb matige pijn of andere klachten ☐
Ik heb zeer ernstige pijn of andere klachten ☐

Stemming
Ik ben niet angstig of somber ☐
Ik ben matig angstig of somber ☐
Ik ben erg angstig of somber ☐

Vergeleken met mijn gezondheidstoestand gedurende het afgelopen jaar is mijn gezondheidstoestand vandaag:

beter ☐

ongeveer hetzelfde ☐

slechter ☐

Om mensen te helpen bij het aangeven hoe goed of hoe slecht een gezondheidstoestand is, hebben we een meetschaal (te vergelijken met een thermometer) gemaakt. Op de meetschaal hiernaast betekent "100" de beste gezondheidstoestand die u zich kunt voorstellen, en "0" de slechtste gezondheidstoestand die u zich kunt voorstellen.

We willen u vragen op deze meetschaal aan te geven hoe goed of hoe slecht volgens u uw eigen gezondheidstoestand vandaag is. Trek een lijn van het hokje hieronder naar het punt op de meetschaal dat volgens u aangeeft hoe goed of hoe slecht uw gezondheidstoestand vandaag is.

Uw gezondheidstoestand vandaag