Late Morbidity (Dysphagia) in Head and Neck Cancer after Radiotherapy using various Treatment Techniques

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The work described in this thesis was performed at the Department of Radiation Oncology in Erasmus MC - Daniel den Hoed Cancer Center, Rotterdam, the Netherlands.

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Late Morbidity (Dysphagia) in Head and Neck Cancer after Radiotherapy using various Treatment Techniques

Late bijwerkingen (dysphagia) bij hoofd-hals kanker
na radiotherapie bij gebruik van verschillende bestralingstechnieken

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Introduction

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Head & Neck Cancer

Patients with head & neck cancer (HNC) can have a variety of malignancies which originate from the paranasal sinuses, nasal cavity, oral cavity, oro-, naso- or hypopharynx, larynx, thyroid gland or from the major or minor salivary glands. Except for the thyroid gland, the great majority of these cancers are of squamous cell type origin. HNC is the sixth most common type of cancer in humans, representing about 6% of all malignancies and accounting for an estimated 650,000 new cancer cases and 350,000 cancer deaths worldwide, annually. Moreover, an increase in cancers of the base of tongue, and tonsillar fossa and/or soft palate has been noted, especially in young adults in the USA and in some European countries [1]. A high number of cases are reported in particular areas of the Western world, e.g. in France (oral cavity tumors), in the Mediterranean basin (cancer of the nasopharynx), and in countries like India (oral cavity tumors), and East and South East Asia (Hong Kong, Indonesia; cancer of the nasopharynx). This geographical variation is likely to be related to the high incidence of risk factors in these areas. Tobacco and alcohol consumption are implicated in 75% of all HNC and have a multiplicative combined effect. In non-smokers, substantial alcohol consumption (≥ 3 drinks per day) has been associated with increased risk of developing HNC [2]. On the other hand, consumption of fruits and vegetables has been associated with a reduced risk of HNC. Familial inheritance has also been noted as a risk factor. The role of certain viral agents in the pathogenesis of HNC is well appreciated (Human papillomavirus (HPV), type 16 and – to a lesser extent – type 18). The association between HPV and HNC is strongest for cancers of the tonsil, intermediate for the rest of the oropharynx and weakest for the oral cavity and larynx. HPV positivity is a favorable prognostic factor in HNC [3]. These patients respond better to radiotherapy (RT), chemotherapy (CHT) or both. Epstein-Barr virus (EBV) has long been associated with nasopharyngeal carcinoma. Antibody titers to EBV have been found to be elevated in nasopharyngeal carcinoma regardless of their ethnic and geographic origin.

The median age of patients with HNC is early 60, with a male predominance. More than 50% of the new cases have locally advanced disease and require an aggressive combined modality treatment approach. Early recognition of symptoms and signs of HNC is important for prompt diagnosis. Accurate staging is in fact the most important factor in HNC that guides therapeutic decision making. Distant metastases at initial presentation are uncommon, arising in about 10% of the patients [3]. Second primary tumors develop at a rate of 3–5% every year [4]. Surgery is one of the two standard treatment options for HNC, but its execution is frequently limited by the anatomical extent of the tumor and by the desire to achieve organ (function) preservation.

Radiotherapy

Radiotherapy is next to surgery one of the two most effective modalities for treating HNC. In fact, in this era of organ (function) preservation, radiotherapy has even replaced surgery with regard to long-term tumor control, cosmesis and quality of life (QoL) in some HNC sites (e.g. the oropharynx). Chapter 2 will describe in depth the treatment of oropharyngeal cancer, which is taken from our chapter 42 of Perez and Brady's Principles and Practice of Radiation Oncology 2007. Due to the routine

implementation of sparing techniques, such as IMRT; they play a crucial role in the improvement of dose distributions (sparing) and ability to dose escalate beyond dose-levels that are conventionally achieved. Although side-effects (dysphagia / xerostomia / trismus) are not negligible as will described in more detail in chapters 3-7. 4D treatment plans can now be generated, enabling a dedicated Linac mounted on a robotic C-arm, to deliver with sub-millimeter accuracy highly focused doses of radiation to a moving target (Cyberknife, Accuray Inc.). Additional ways to apply RT are brachytherapy (chapters 8-10) and stereotactic radiotherapy. The introduction of chemotherapeutic agents has emerged as the third main treatment mode to a point where many, often cisplatin-based regimes, are routinely integrated in the treatment protocols in a neoadjuvant and/or concomitant setting. Particularly in academic centers, further development in clinical cancer care is increasingly emerging from studies in basic sciences, often referred to as translational research. An example of this would be the efficacious role of targeted therapy (Cetuximab) in HNC. However, one has to keep in mind that clinical investigators have frequently reported that combined treatment can be more expensive and/or results in excess of (late) side effects. Between 40% and 60% of HNC will be treated with RT in a curative setting. In recent years, noteworthy strategies such as altered fractionation have emerged. To obtain better tumor control rates, in recent years more aggressive regimes have been implemented in the treatment for cancer of the head and neck. The aggressive nature of the treatment modalities is exemplified by using high doses of radiation per se, and/or (altered) fractionation regimen. For example, Bourhis et al showed in a meta-analyses an increase in local control of 6.4%, and an increase in overall survival of 3.4%, by using hyperfractionated or accelerated RT in the cancer of the head and neck [5].

Contouring, Dose Distributions and Quality of Life

Most effective way of improving cure rates is by quality assurance in the prescription and delivery of the radiation dose-plan. Questions like ‘How to define the target?’ and ‘What are the boundaries of relevant organs at risk (OAR)?’ are of fundamental importance from a quality assurance perspective. In chapters 3-7 of this thesis some delineation examples are given for ‘new’ organs at risks and dose-effect relationships studies of these OARs are described. A potential solution for these morbidities are described in chapters 8 and 10 published before as chapter XI in ‘Function Preservation and Quality of Life in Head and Neck Radiotherapy’, edited by P.M. Harari et al. and as chapter 11 of ‘Head and Neck Cancer: Multimodality Management’, edited by J. Bernier and in chapter 11 regarding the use of brachytherapy and the role of hyperbaric oxygen treatment after radiotherapy in preventing /reducing the side-effects.

Contouring the many described OARs is often a painstaking and time-consuming task if clinically used in a radiotherapy department, the time that is needed for contouring each IMRT case could entail inaccuracies from the clinician’s side and/or lead to cuing in the treatment planning room with increasing waiting times as a consequence. Regarding contouring in head and neck cancer patients for treatment with radiotherapy, extensive guidelines are published in the book ‘Contouring in Head & Neck Cancer’ from Peter Levendag, Abrahim Al-Mamgani and David Teguh [6]. It deals with practical issues concerning delineation and contains the original descripti-

ons by Robbins of surgical boundaries of the neck levels I–VI, the CT based boundaries derived from surgical anatomy for the CTV of neck levels I–VII, and its validation of the level-contouring in clinic. The lack of standardization in delineation and dose prescription illustrates the need for rigid guidelines. A promising atlas-based auto segmentation tool is a welcoming tool for a busy radiotherapy department. This tool is described in chapter 14 (ABAS). The fundamentals of non-rigid registration being the basis of auto-contouring are reported in chapter 12. Here the non-rigid registration method is used to quantify the anatomic changes caused by external beam radiotherapy in HNC patients in full three dimensions and to relate the local anatomic changes to the planned mean dose. Another application of the non-rigid registration tool is to accurately sum different dose distributions from brachytherapy and IMRT as described in chapter 13.
With the current developments in image guided radiotherapy (IGRT), modern linear accelerators are equipped with kV imaging devices and cone-beam CT (CBCT). With CBCT, not only bony anatomy but also soft tissues are visible. It is now possible to trace potential changes in patient anatomy due to e.g. weight loss, edema or other (medical) reasons. This could lead to the development of on-line positioning protocols with smaller PTV margins and thus more sparing of normal tissues. Tools, such as functional imaging, non-rigid registration (chapters 12 and 13) and atlas-based auto-segmentation (chapter 14), play an important role in analyzing the data for IGRT.

Outline Thesis

In summary the current thesis covers a wide range of aspects regarding radiotherapy of cancer in the head and neck. Several aspects were covered:

First, chapter 2 describes the treatment of oropharyngeal cancer. In chapters 3 to 7 the quality of life (dysphagia and trismus) endpoints and the FEES procedure are described in relation to radiation dose to the particular normal tissues. Also site and treatment techniques influencing the dose in the normal tissue structures are discussed. Chapters 8 to 10 will describe brachytherapy in oral cavity and oropharyngeal cancer. Main focus will be on the quality of life of patients treated by brachytherapy. Chapter 11 describes the hyperbaric oxygen trial in reducing late side-effects of radiotherapy. More technical papers regarding adding 3D brachytherapy dose to the external beam dose and non-rigid registration being the basis of auto-segmentation are described in chapters 12 to 14.

Thesis Chapters:

Oropharyngeal Cancer
Chapter 2

Quality of Life: Dysphagia
Chapters 3-6

Quality of Lfe: Trismus
Chapter 7

Brachytherapy
Chapters 8-10

Hyperbaric Oxygen
Chapter 11

Non-Rigid Registration / Atlas-Based Auto-Segmentation
Chapters 12-14

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Oropharynx

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Perez and Brady's Principles and Practice of Radiation Oncology; 5th edition,
Edward C. Halperin, Carlos A. Perez, Luther W. Brady; Lippincott Williams and Wilkins;
December 2007. Chapter 42. ISBN: 978-0-7817-6369-1

Epidemiology

The oropharynx is the posterior continuation of the oral cavity and connects with the nasopharynx (above) and laryngopharynx (below). It is located between the soft palate superiorly, and the hyoid bone inferiorly. The main sites of the oropharynx consist of the posterior and lateral pharyngeal wall, faucial arches, tonsillar fossa (TF), soft palate (SP), and the base of tongue (BOT). These structures play a crucial role in swallowing and speech. By obstructing the "air space" or by infiltrating muscles or nerves, locally advanced oropharyngeal tumors can significantly impede these functions. The same holds for intensive treatment regimen: it can cause deformities and/or impairment of particular functional (sub) units, resulting eventually in severe (late) side effects. It has long been known that patients with a history of smoking or excessive consumption of alcohol are believed to be at increased risk for developing cancer in the oropharynx [31,37]. Overall these cancers comprise less than 0.5% of all cancers in men in the United States, which amounts to approximately 5000 new cases each year [319]. According to the Surveillance, Epidemiology, and End Results report of the National Cancer Institute, in 2001 the age-adjusted incidence was 1.5 per 100,000 white men and 3.2 per 100,000 black men [271]. These cancers more often afflict men (4:1); they are diagnosed most frequently in the sixth and seventh decades of life. Oropharyngeal cancers are readily accessible to clinical examination and staging. Historically, in the early stage and in the moderately advanced tumors, radiation therapy (RT) has been the preferred therapy mode because of its organ function-preservation properties [300,321]. Most (±95%) oropharyngeal cancers are squamous cell carcinomas (SCC). Although reports can be found of other histologic subtypes [1,14,72,93,158], such as minor salivary gland tumors, lymphoepitheliomas, malignant lymphomas, mesenchymal tumors, or metastases from other extracranial tumor sites, these will not be discussed in great detail as they are considered beyond the scope of the present chapter.

Anatomy

The SP, anterior faucial pillar, and the retromolar trigone are embryologically connected to the oral cavity. However, because of their clinical behavior, tumors of these structures are preferably classified with oropharyngeal malignancies. The inferior part of the TF is referred to as the glossopalatine sulcus (Fig. 1). The lateral border of the retromolar trigone extends upward into the buccal mucosa, medially it blends with the anterior tonsillar pillar. Its base is formed by the last lower molar and the adjacent gingivolingual surface. The lateral walls of the oropharynx are limited posteriorly by the TF proper and the posterior tonsillar pillar. The anterior and posterior tonsillar pillars are the folds of mucous membrane that cover the underlying glossopalatine and pharyngopalatine muscles, respectively. Deep to the lateral wall of the TF are major vessels (Figs. 2 and 3) and muscular components such as the superior constrictor muscle, the upper fibers of the middle constrictor muscle, the pharyngeus and stylopharyngeus muscles, and the glossopalatine and pharyngopalatine muscles. Stratified squamous epithelium covers all of these structures. The tonsil has a heavy lymphoid network. The pharyngeal wall is related to the second and third cervical vertebrae. Nerve supply is from the cranial nerves IX and X. The BOT lies posterior and inferior to the palatoglossal arch. It is bounded anteriorly by the circumvallate papillae, laterally by the glossopharyngeal sulci and oropharyn-

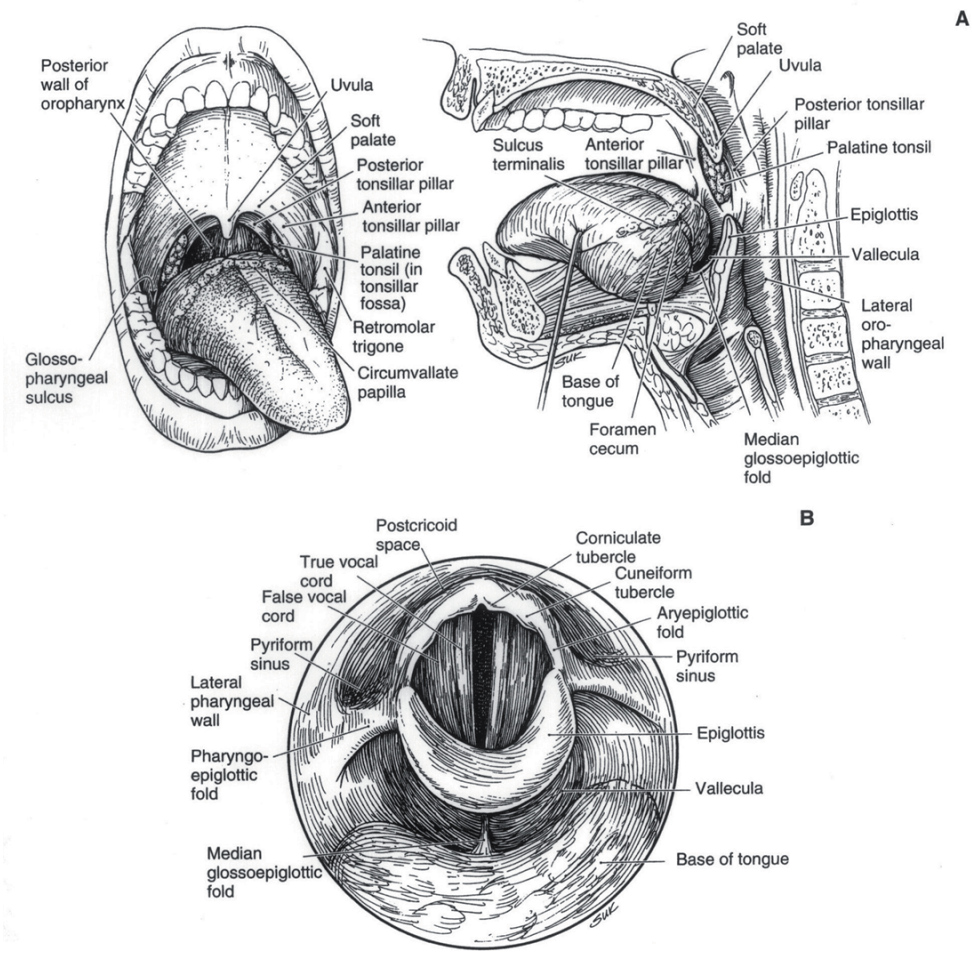


Figure 1: Anatomy oropharynx Book: Radiation Oncology, Rationale, Techniques, Results (Cox, 2003, p.197, Mosby, St. Louis).

geal, walls and inferiorly by the valleculae and the pharyngoepiglottic fold. Embryologically, its epithelium is derived from the entoderm, unlike that from the oral tongue (ectoderm). The body of the BOT is formed by thick muscles, the The genioglossus, palatoglossus, and hypoglossus muscles. The muscles originate from the margins of the mandible and are attached to the hyoid bone. The blood supply and the innervation are by the lingual arteries and hyoglossal nerve, respectively genioglossus, styloglossus, palatoglossus, and hypoglossus muscles. The muscles originate from the margins of the mandible and are attached to the bone. The blood supply and hyoid the innervation are by the lingual arteries and hypoglossal nerve, respectively.

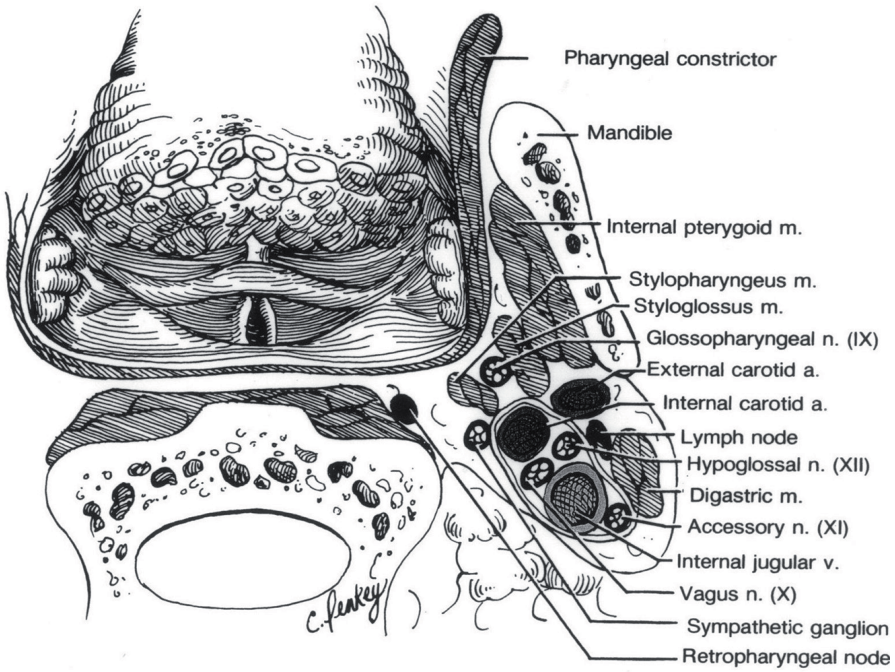
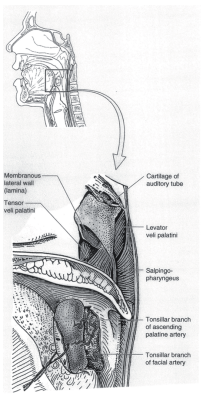


Figure 2: Cross-section mid-oropharynx. Book: Management of Head and Neck Cancer: a multidisciplinary approach.(Million,1994, p.402, figure 17.2 Lippincott Company Philadelphia).



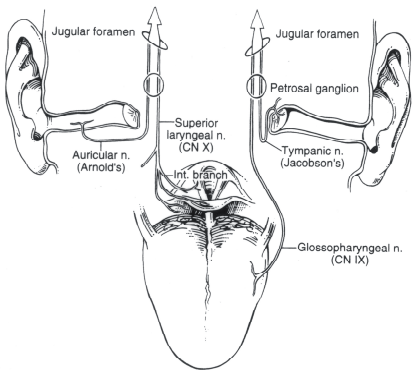


Figure 3: Inside view of lateral oropharangeal wall. Note major vessels in parapharangeal Space.Book: Clinically Oriented Anatomy 4th Edition, 1999 (Moore KL, Dalley AF. p.1059, Lippincott Williams & Wilkins, Philadelphia)

Figure 4: Neural pathways of referred otalgia. Book: Clinical Radiation Oncology (Leibel, 204, p.605, figure 28 7 Lippincott, Williams and Wilkins, Philadelphia)

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Natural History

In general, tumors of the anterior tonsillar pillar and soft palate are better differentiated and biologically less aggressive than those of the TF. For example, 50% to 60% of patients with primary tumors in the anterior tonsillar pillar, retromolar trigone, and SP had necks with clinically negative findings, in contrast to only 24% of those with TF primaries [149]. Lesions of the TF [231], retromolar trigone [39], and BOT tend to grow more extensively. Perez et al. [234] observed that the primary tumor was confined to the TF in only 5.4%. Byers et al. [171] described 14% mandibular invasion in carcinomas of the retromolar trigone. At diagnosis, 75% of BOT cancers have invaded adjacent structures, including the glossopharyngeal sulcus, pharyngeal wall, larynx, and/or faucial arches. The most common complaint at presentation of tumors in the oropharynx is pain; this pain is either attributed to (severe) mucositis, deep infiltration of the tumor or is referred (Fig. 4). However, patients with primary tumors of the oropharynx can also be asymptomatic or have only vague discomfort at presentation. BOT tumors, for example, typically grow insidiously. Because the BOT is devoid of pain fibers, they are mostly asymptomatic until they have progressed significantly. With local advancement and/or with infiltration of the pterygoid muscles, patients can experience trismus and, ultimately, bleeding or swallowing problems, or can have difficulty with speech. Diagnosis is typically established by clinical examination in the outpatient clinic and/or examination under general anesthesia, including morphologic confirmation (biopsy) of the lesion and tattooing of the clinical target volume (CTV). In the Erasmus Medical Center—Daniel den Hoed, Rotterdam (Erasmus MC), at the time of diagnosis/staging, with the patient still under general anesthesia, the lesion is frequently marked with marker seeds. This enables the extensions of the lesion to be visualized on x-ray films. From a series of patients implanted with platinum markers, we found, for example, that the TF significantly moves during swallowing and even in rest (because of respiration). Maximum excursions in rest were found to be 3.6 mm. This type of information contributes to a more accurate determination of the planning target volume (PTV) margin (Figs. 5 and 6). Conventionally, platinum (Pt) or gold (Au) marker seeds were used, particularly for those patients to be boosted by brachytherapy (BT) [175]. Because of significant scattering properties on computed tomography (CT), nonmetallic seeds are being tested. Panendoscopy can reveal synchronous second primaries. Ultrasound fineneedle aspiration biopsy has become an indispensable tool for pro diagnosis and for staging, especially where it concerns the lymph nodes. Multislice CT and magnetic resonance imaging (MRI) scans are now obligatory imaging tools. CT scanning with contrast enhancement using 2-mm slices is better for detecting lymph nodes and for bone detail. MRI is preferred for the evaluation of the parapharyngeal space. Axial slices are usually sufficient; sagittal MRI is helpful for detecting early pre-epiglottic space infiltration. CT combined with positron emission tomography scanning seems an extremely promising, powerful tool for diagnostic and simulation purposes, but is not

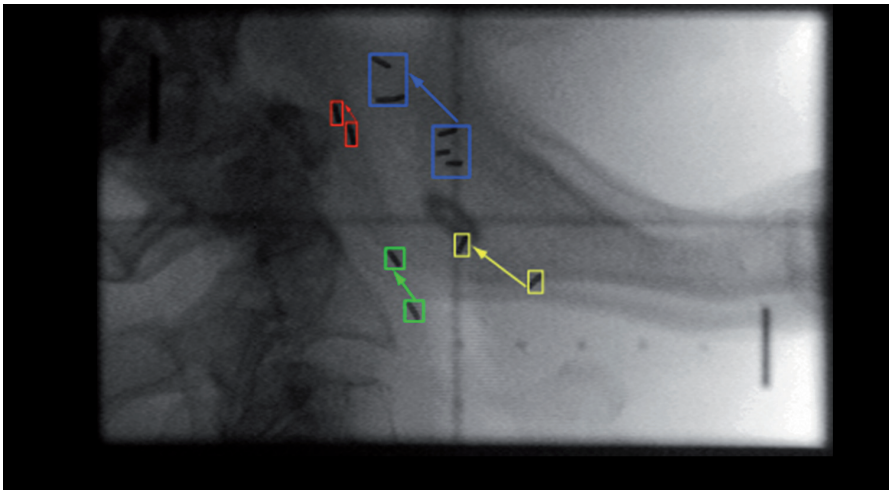

Figure 5: Motion with swallowing. Lateral fluoroscopic images of two different moments in time projected over each other. The patient was instructed to swallow. The images are acquired 0.5 seconds apart. The colored rectangles indicate the motion of the markers. The arrow indicates the direction of movement (from equilibrium to extreme position during swallowing). For the yellow, green and red markers the amplitude in the lateral view was respectively 13.4, 9.3 and 2.4 mm. For the markers in the blue rectangle the amplitude of the most cranial marker was 15.6 mm.

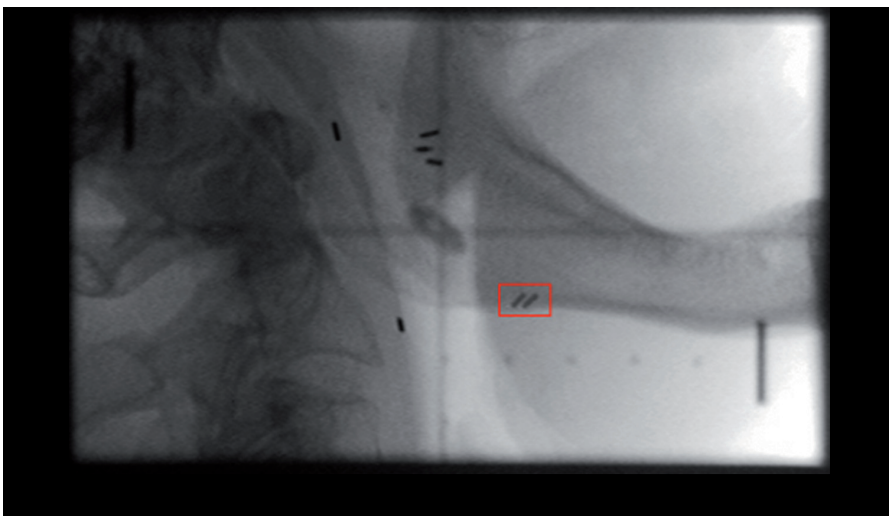

Figure 6: Motion without swallowing. Lateral fluoroscopic images of two different moments in time projected over each other. The patient was asked not to swallow. The images are acquired 7.5 seconds apart. All markers where stationary except for the marker indicated with the red rectangle. The motion of this marker is 2.0 mm in the anterior-posterior direction and 0.4 mm in the cranial-caudal direction. Based on the frequency of the observed motion this is most probably caused by respiration.

yet available in every institution. Several textbooks contain helpful overviews [8,59,123,171,208,232]. Tumors are staged according to the American Joint Committee on Cancer classification system (Table 1) [6]. Dentulous patients are at increased risk for caries and osteoradionecrosis from the reduction and qualitative change of salivary flow, change in pH, and proliferation of bacteria believed to be responsible for caries. Panorex x-ray films, identification of nonrestorable teeth for pretreatment extraction, dental trays for fluoride rinse, protection against scatter radiation, as well as education about long-term oral hygiene, should be engaged before RT and/or chemotherapy (CHT) is applied. In fact, the quite common development of osteoradionecrosis in the past [17] should be prevented by adequate measures. Finally, given the complexity of head and neck tumors, all patients should be formally discussed in a head and neck tumor board, with or without the patient being present, before the initiation of any treatment.

Primary tumor (T)	
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not >4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4a	Tumor invades the larynx, deep/extrinsic muscle of the tongue, medial pterygoid, hard palate, or mandible
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Regional lymph nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral node, ≤3 cm
N2a	Metastasis in a single ipsilateral node, >3 cm but <6 cm
N2b	Metastasis in multiple ipsilateral nodes, >3 cm but <6 cm
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm
N3	Metastasis in a lymph node >6 cm
Distant metastasis (M)	
M0	No distant metastasis present
M1	Distant metastasis present

Stage			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1-3	N1	M0
Stage IVa	T4a	N0	M0
	T4a	N1	M0
	T1-3	N2	M0
	T4b	Any N	M0
Stage IVb	Any T	N3	M0
Stage IVc	Any T	Any N	M1

Table 1: 2002 edition of American Joint-Committee on Cancer Classification of Oropharyngeal Cancer. (From: Greene F, Page D, Fleming I, et al. AJCC cancer staging manual, 6th ed. New York; Springer-Verlag, 2002) Book Greene F, Page D, Fleming I, et al. AJCC cancer staging manual, 6th ed. New York; Springer-Verlag, 2002.

Lymphatics of the Oropharynx

The lymphatic drainage of the oropharynx and the neck was first described by Rouviere [262] in 1938 and has been refined since by others [113,149]. The nodal groups in the neck were originally described along the lines of lymph node chains, located in particular anatomic regions and draining specific (sub) sites. Instead of using the term jugular chain nodes, Robbins et al. [255,256,254] proposed the “level system” for classifying the location of lymph nodes in the neck relative to surgical –anatomic landmarks (Table 2). The level classification (levels I to VI) was recently refined with the addition of sublevels (Ia/Ib, IIa/IIb, and Va/Vb), also using some of the radiologically defined landmarks as proposed by Som et al. [283]. The probability of lymphatic (regional) metastasis is re lated to size and location of the primary site within the oropharynx. The order of progression of metastatic cells is systematic, that is, it usually proceeds from the upper jugular chain nodes superiorly (level I/II; first echelon), to midcervical (level III) and to lower cervical nodes (level IV), inferiorly. Candela et al. [44], for that purpose , evaluated 333 untreated primary SCCs of the oropharynx and hypopharynx

Levels	Cranial	Caudal	Anterior(Medial)	Posterior (Lateral)
IA	Symphysis of madible	Body of hyoid	Anterior Belly Digastric M	Anterior Belly Digastric M
IB	Body of madible	Posterior Belly of Digastric Muscle	Anterior Belly Digastric M	Stylohoid M
IIA	Base of Skull	Inferiro Body of Hyoid	Stylohyoid M	SAN
IIB	Base of Skull	Inferior Body of Hyoid	SAN	Lateral Border SCMM
III	Inferior Body of Hyoid	Inferior Cricoid	Lateral Border Sternohyoid M	Lateral Border SCMM
IV	Inferior Body of Hyoid	Clavicle	Lateral Border Sternohyoid M	Lateeral Border SCMM
VA	Apex Convergence SCMM and Trapezius M	Inferior Cricoid	Posterior Edge SCMM	Anterior Border Trapezius M
VB	Lower Border Cricoid	Clavicle	Posterior Edge SCMM	Anterior Border Trapezius M
VI	Hyoid bone	Suprasternal notch	Common Carotid Artery	Common Carotid Artery

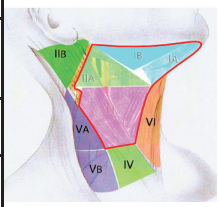

Table 2: Anatomical structures defining surgical levels (modified after Robbins, 2002. see also references Robbins et al., 1991, 1999). ([SCMM] Sterno-Cleido Mastoid Muscle; [SCJ] Sterno Clavicular Joint; [M] Muscle; [SAN] Spinal Accessory Nerve; [RPh] Retropharyngeal; [RSS] Retro-Styloid Space; [SCF] Sub-Clavicular Fossa) See also references Robbins et al., 1991, 1999, 2002.

and ascertained the prevalence of neck node metastasis by neck level. Isolated skip metastases occurred in only one patient (0.3%); level I or level V involvement was always associated with metastases at other levels. Another important finding is that tumors in the midline or of the posterior pharyngeal wall exhibit a higher propensity for bilateral lymphadenopathy.

Delineating and Validation of Neck Node Levels

Node-Negative Neck

From a comprehensive review of the literature regarding the incidence of regional metastasis [16,40,44,45,52,178,276,277,279], a few observations can be made. First, for most of the tumor sites in the oropharynx, when using RT one needs to irradiate the neck either electively (46 to 50 Gy node-negative [N0] neck) or boost the lymph nodes to high cumulative doses (60 to 70 Gy neck nodes). Second, in organ functionpreservation RT, image-based technology has become paramount. Third, in order to adequately spare the critical healthy tissues, the clinician needs to be as selective as possible with the levels incorporated in the irradiated volumes (standardization of treatment volumes; e.g., ipsilateral vs. bilateral neck). Finally, the lymph nodal drainage per tumor site follows a predictable pattern, such that the concept of selective treatment has a legitimate rationale for surgery as well as for RT (Tables 3 and 4). Nowak et al. [222] reported on an inventory in The Netherlands, showing a lack of

standardization even when experienced physicians were asked to delineate the portals designed to cover the primary and neck (Fig. 7). They argued that a more precise three-dimensional definition on CT of the lymph node levels in the neck allows for a better standardization of the treatment portals and, in addition, for the development and application of more conformal (selective) RT techniques. Conceptually, with the radical and modified neck dissection, all lymph nodes are routinely removed [255,256]. In contrast, selective neck dissection refers to preservation of one or more of the lymph node groups (for example, see Table 2 for selective neck dissection levels I, II, and III). In order to be as selective as with surgery, first the clinical (research) groups of Rotterdam and Brussels have translated the surgical-anatomy boundaries (Table 2) to corresponding borders on CT [108,223].

The Rotterdam guidelines have further evolved into a "simplified version" for routine clinical practice (Fig. 8) [318]. In fact, the proposed simplified delineation guidelines were based on easy-to-identify anatomic landmarks on CT, leading to a simple-to-execute delineation procedure ("learning curve"). Besides the Rotterdam system being more generous, the comparison with the Brussels guidelines revealed small but essential discrepancies (Fig. 9). After adjustments, a common set of recommendations for the delineation of neck node levels for the N0 neck was proposed [110]. This proposal was discussed with major cooperative groups in Europe (DAHANCA, EORTC, GORTEC, NCIC, RTOG) and after some minor modifications, it was fully endorsed (Table 5, Fig. 10). Finally, a series of clinical experiments was performed

	Levels involved (%)				
Tumor Site	I	II	III	IV	V
Oral Cavity	20	17	9	3	0.5
Oropharynx	2	25	19	8	2
Hypopharynx	0	13	13	0	0
Larynx	5	19	20	9	2.5

Table 3: Incidence and distribution of regional metastasis for levels I-V for clinically N0 neck. (See references: Bataini, Byers, Candela Chao, Lindberg,, Shah, Shah). Gregoire V, Couche E, Cosnard et al, Radiotherapy and Oncology, 2000;56(2):135-150.

	Levels Involved (%)				
Tumor Site	I	II	III	IV	V
Oral Cavity	48	39	31	15	4
Oropharynx	15	71	42	27	9
Hypopharynx	10	75	72	45	11
Larynx	6	61	54	30	6
Nasopharynx	13	95	60	21	44

Table 4: Incidence and distribution of regional metastasis for levels I-V for clinically N+ neck. (See references: Bataini, Byers, Candela Chao, Lindberg,, Shah, Shah, Sham). Gregoire V, Coche E, Cosnard et al, Radiother and Oncology, 2000;56 (2):135-150.

to validate the “international consensus guidelines” on the delineation of the CT-based lymph node levels [174,173]. In the first experiment, the superior border of the N0 neck (cranial border level II) was determined. In 10 consecutive patients, clips were placed at the most cranial border of the neck at the time of a neck dissection. Antero-posterior and lateral x-ray films were obtained intraoperatively. The clips lined up at the caudal part of the transverse process of C1 (Fig 11). Thus, the cranial border is situated much lower than the base of skull. From the position of the parotid gland, one can appreciate that this is of great importance when sparing the major salivary

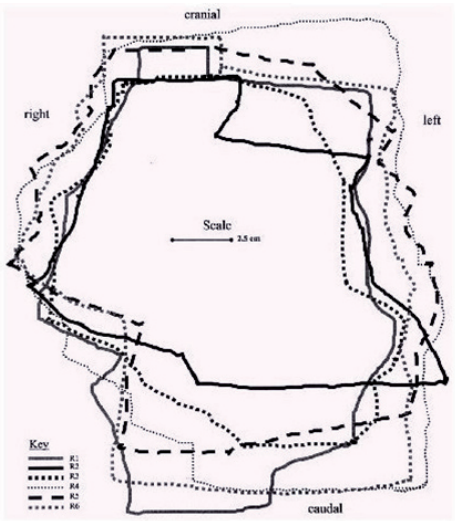

Figure 7: Due to lack of standardization variation in RT portals as depicted on lateral X-ray films by radiation oncologists of different institutions for same clinical indication. Inventory in the Netherlands. Radiotherapy and Oncology, volume 43(1)1997:81-86.

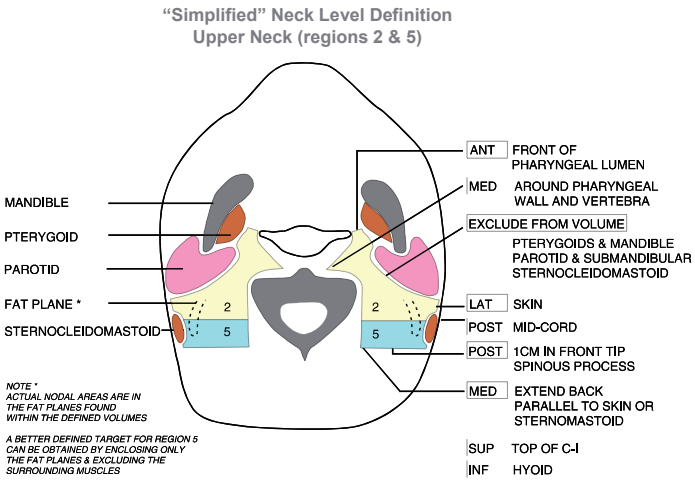

Figure 8: Simplified CT-based definition of the lymphnode levels in the superior part of the node negative Neck. (middle- and inferior part neck not shown) Radiotherapy and Oncology 1999;1:35-42.

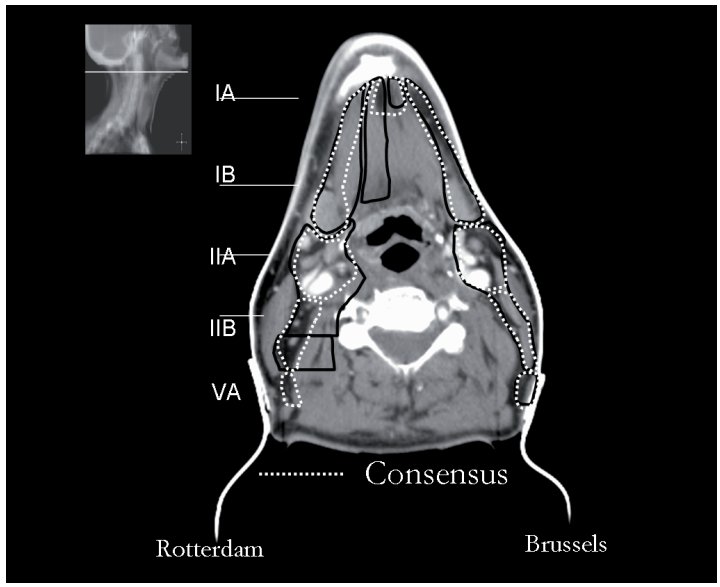

Figure 9: Axial CT slice upper neck region, with levels Ia, Ib, II and V (solid black lines) contoured according to Rotterdam (right neck) and Brussels (left neck) delineation protocols. Rotterdam and Brussels delineation protocols were meticulously compared and adapted to surgical level definitions as defined by 2002 AAO-HNS classification. International consensus was reached. Stipulated white lines (both necks) demarcate contours of levels and sublevels as defined by international consensus protocol. This figure illustrates contours of levels Ia, Ib, IIa, IIb and Va (middle- and inferior neck guidelines not shown). I.J.R.O.Biol. Phys 2004;58:1:113-123.

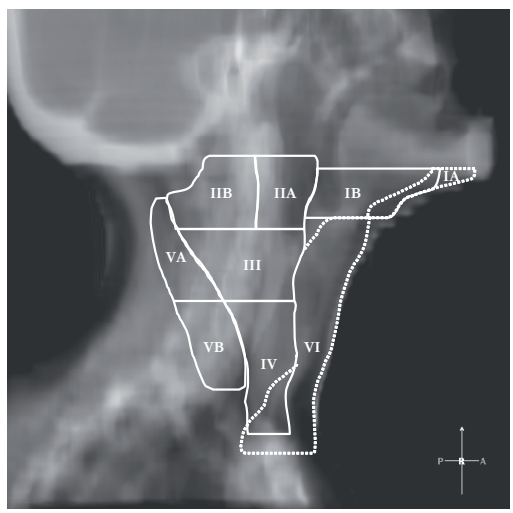

Figure 10: Digital Reconstructed Radiograph levels I-VI.

Levels	Cranial	Caudal	Medial to iCA	Posterior	Lateral	Medial
IA	Caudal Madible	Body hyoid	Platysma, Symphysis	Body Hyoid	Symphis - Anterior Belly DM	
IB	Cranial SMG, Mylohyoid M	Central hyoid bone	Platysma, Symphysis	Posterior SMG	Madible, Skin, Platysma	Symphysis - DM
IIA	Transverse Process C1 (caudal border)	Caudal Border Hyoid	Posterior SMG	Posterior IVJ	Medial Edege SCMM	Medial to ICA
IIB	Transverse Process C1 (caudal border)	Caudal Border Hyoid	Posterior IJV	Posterior Edge SCMM	Medial Edege SCMM	Deep Cervical Mm
III	Inferior Hyoid	Inferior Cricoid	Anterior Edge SCMM	Posterior Edge SCMM	Medial Edege SCMM	Medial to ICA Deep Cervical Mm
IV	Inferior Cricoid	2 cm Superior SCJ	Anteriomedial SCMM	Posterior Border SCMM	Medial Edege SCMM	Medial to ICA Paraspinal Mm
VA	Cranial Hyoid	Inferior Cricoid	Posterior Edge SCMM	Al-Trapezius M	Skin, Platysma	Deep Paraspinal Mm
VB	Inferior Cricoid	Transverse Cerv. A.	Posterior Edge SCMM	Virtual Line Al-Trapezius M	Skin, Platysma	Deep Paraspinal Mm
VI	Caudal Thyroid	Sternal Manubrium	Skin	Esophagus/Trachea	Medial Edege SCMM, Thyroid G	Trachea
RSS	Base of skull (jugular foramen)	Upper limit of level II	Parapharyngeal Space	Vertebra Bse of Skull	Parotid Space	Retropharyngeal nodes
SCF	Lower border IV/Vb	Sternoclavicular joint	SCMM, Skin, Clavicle	Anterior Border Posterior Scalenus M	Lateral Edge Posterior Scalenus M	Trachea/ Thyroid
RPhs	Base of skull	Cranial Edge Hyoid	Fascia Pharynx Mucosa	Longus Coli / Capitus M	Medial Edge Internal Carotid A	Midline

Table 5: International consensus guidelines regarding translation of surgical-anatomy boundaries of lymphnodal levels I-VI in clinically node negative(N0) neck to CT-based borders. Also depicted are retrostyloid space, subclavicular fossa and retropharyngeal space (see text). ([SCMM] Sterno-Cleido Mastoid Muscle; [SCJ] Sterno Clavicular Joint; [RPhS] Retropharyngeal Space; [RSS] Retro-Styloid Space; [SCF] Sub-Clavicular Fossa; [C-I] Vertebra Corpus C-I; [SMG] Sub-Mandibular Gland; [IJV] Internal Jugular Vein; [Mm] Muscles; [a] artery; [AL-Trap.M] Antero Lateral Edge Trapezius Muscle; [G] Gland.

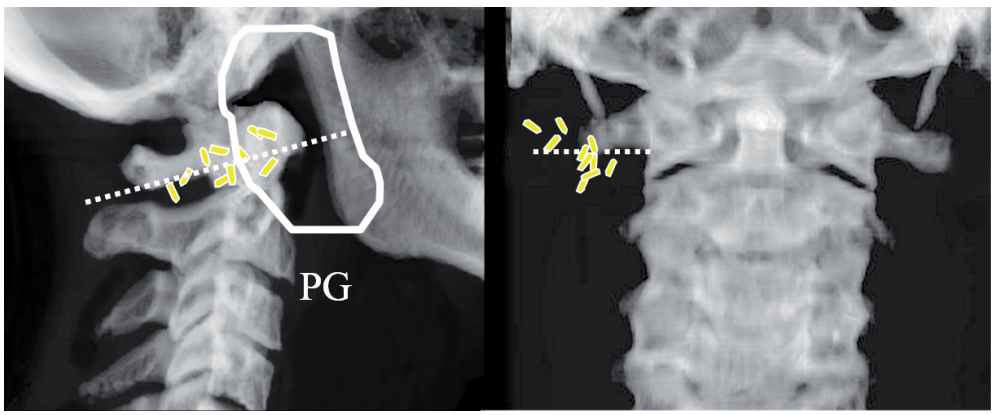

Figure 11: Projection of clips (AP and Lateral X-ray films) placed intra-operatively at cranial border node negative neck. Clips cluster around caudal border transverse process corpus vertebra C-I. See also projection of circumference of parotid gland (PG) as determined by CT.

gland. In a second series of experiments, the neck levels I-VI in three patients first were contoured on preoperative contrast-enhanced CT scans according to the international consensus guidelines. Of each of these three patients, after placing clips at relevant surgical-anatomic–based level boundaries, an intraoperative CT scan was also obtained. The preoperative (CTbased delineated boundaries) and intraoperative (surgical-anatomic defined level boundaries) CT scans were then fused. The caudal border of level IV can be identified by the clips positioned next to traverse cervical artery (Fig. 12). The posterior border of level IV and Vb is determined by a virtual line drawn between the heads of the trapezius muscle (Fig. 12). The posterior border of surgical level IIa (spinal accessory nerve) did not fully match with posterior border of CT-based level IIa (internal jugular vein); the other surgical boundaries and CT-based contours were in perfect agreement (Fig. 13). This second series of experiments was also designed to examine whether the subdivision into sublevels IIa and IIb, as suggested by Robbins [256], is of any benefit in selective RT. It can be argued that because of the heavy infestation of occult metastatic cells in the lymph channels around the IJV and carotid artery, the division of level II into radiologic sublevels IIa and IIb may not be relevant and may even be risky [174] (Figs. 14 and 15). In contrast to CT-based contoured sublevels in cases of selective RT, the division into surgical sublevels IIa/IIb makes sense as this could reduce serious morbidity, that is, could prevent potential damage to the spinal accessory nerve [174].

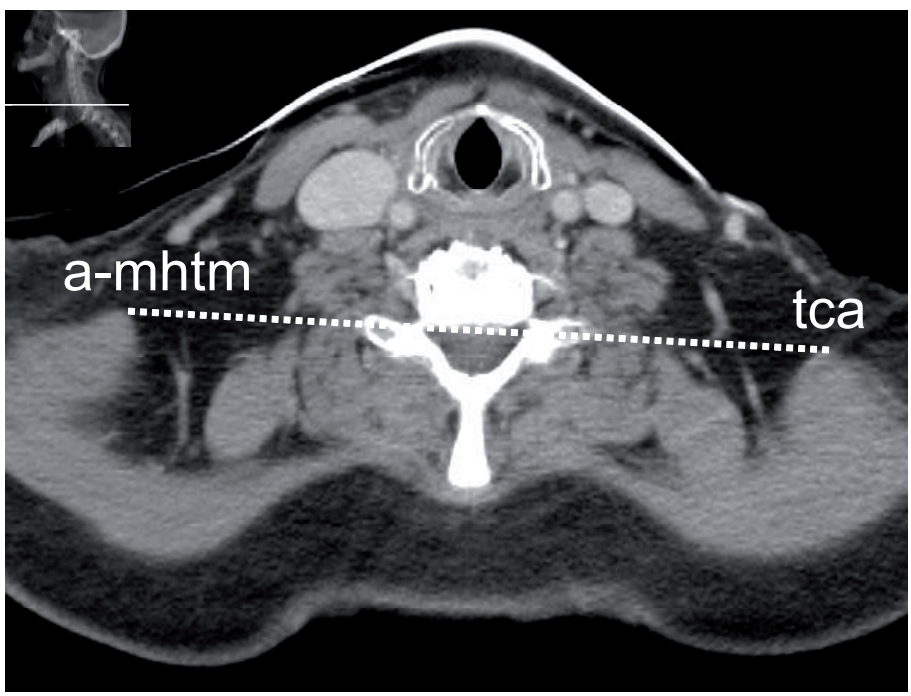

Figure 12: Caudal border level IV (CT-slice at the level of transverse cervical artery [tca]). Posterior border level IV and Vb (virtual line anterior medial heads of trapezius muscle [a-mhtm]).

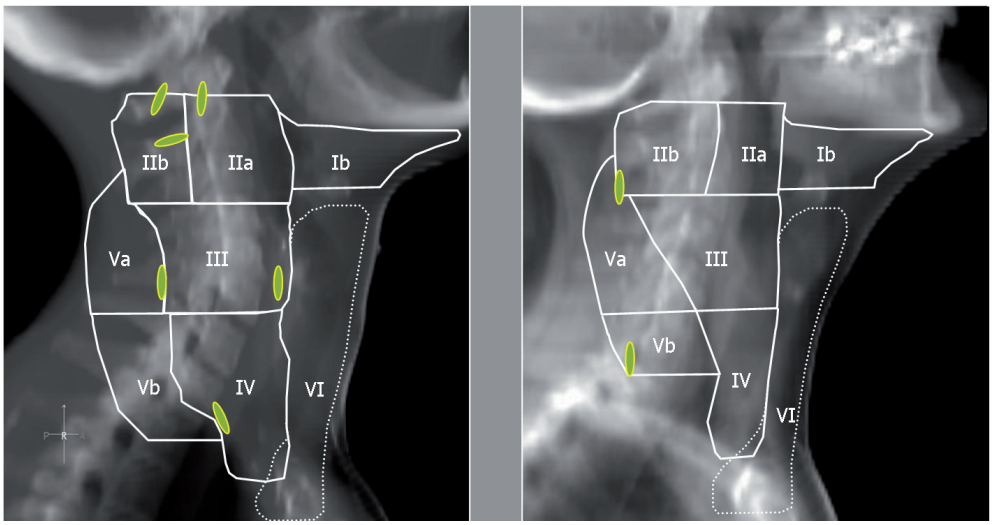

Figure 13: Digitally reconstructed radiographs validated the position of clips at cranial border IIa, IIb and boundaries level III, Va, and IV, Vb. (left panel). Digitally reconstructed radiographs validated the position of intra-operatively defined clips, demarcating boundaries of levels IIb, Va and Vb, as they were in good agreement with previously contoured (and matched) CT-base boundaries (right panel). I.J.R.O.Biol. Phys 2005;62:3:690-699.

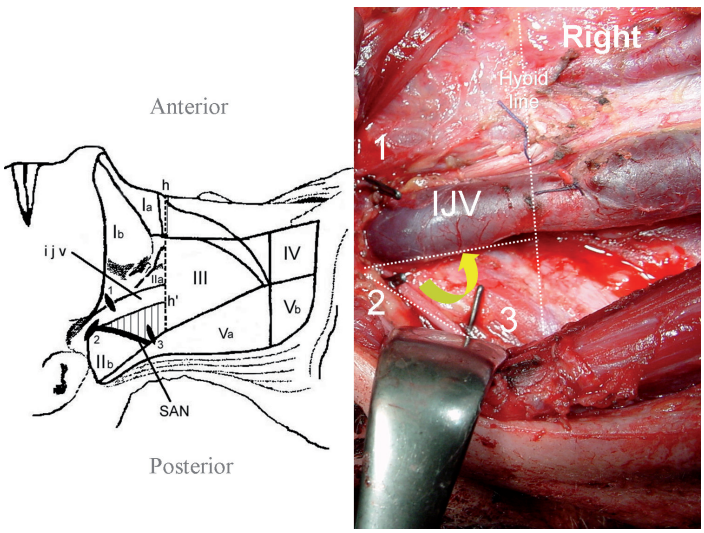

Figure 14: Photograph and schematic drawing of right upper-neck region in patient with right radical neck dissection (RND). Radiopaque surgical clips positioned at the most cranial part of the neck, anterior (#1) and posterior (#2) to the internal jugular vein (IJV). Also seen is a clip (#3) at the site where the spinal accessory nerve (SAN) enters the sterno cleido mastoid muscle (SCMM). The triangular area, denoted as “no-man’s land”, belongs to either the posterior part of surgical level IIa or the ventral (anterior) part of CT-based level IIb. The triangular area is formed by SAN, clips #2 and #3, the posterior boundary of the IJV, and part of the hyoid line. I.J.R.O.Biol. Phys 2005;62:3:690-699.

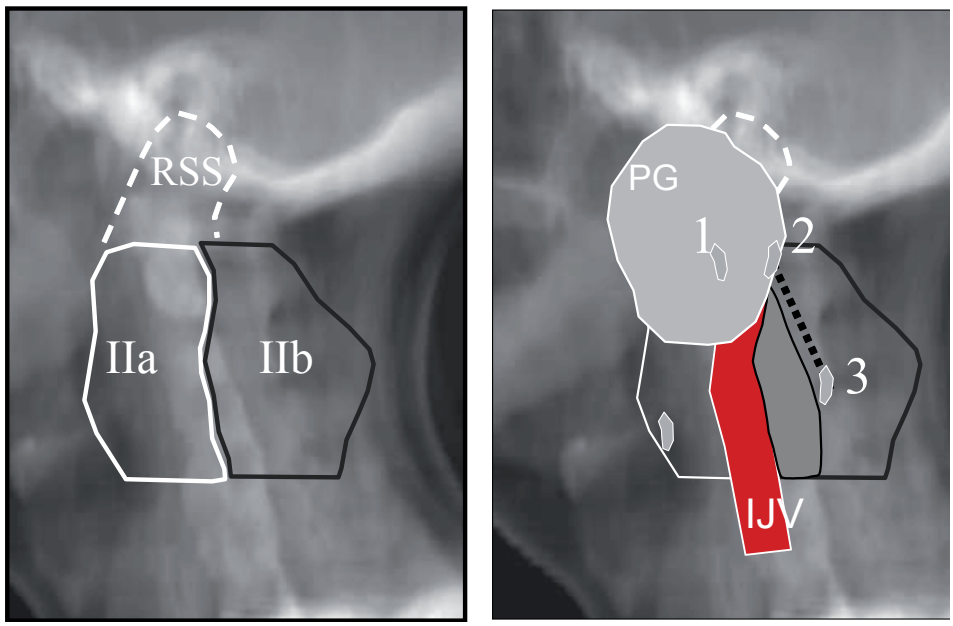

Figure 15: Digitally reconstructed radiograph (left panel) is shown of the computed tomography (CT)-based contoured sublevels IIa and IIb, and the retro-styloidspace (RSS). Right panel: superimposed on the delineated sublevels, the contoured IJV and the clips positioned intra-operatively at the relevant surgical boundaries of sublevels IIa/IIb and the hyoid (clips #1, #2, #3, #5). The stipulated line demarcates the position of the boundary between the surgically defined sublevels IIa and IIb (SAN). The "no-man's land" zone is the triangularly shaped, cross-hatched area between the posterior border of the surgically defined sublevel IIa (SAN) and the posterior border of the CT-based level IIa (posterior boundary of the IJV). I.J.R.O.Biol. Phys 2005;62:3:690-699.

Node-Positive Neck

Retrospective intensity-modulated radiation therapy (IMRT) series have reported marginal recurrences in the neck of node-positive (N+) patients treated primarily or postoperatively with radiotherapy. Eisbruch et al. [74] reported a series of 135 patients treated bilaterally from 1994 to 2002 with three-dimensional conformal radiation therapy or IMRT for primary tumors located mainly in the oropharynx. With a median follow-up of 32 months, 21 patients had a locoregional recurrence, 4 of which were marginal. Some of the marginal recurrences were observed near the base of skull above the upper limit of the delineated level II. Thus, it seems reasonable, as a first modification in case of infiltration of the upper part of level II, to include in the CTV the fatty space around the internal jugular vein and internal carotid artery up to the jugular foramen (base of skull) in the N+ neck [109]. From an anatomic point of view, this space belongs to the upper most part of the retrostyloid space (Fig. 16). Also included are the tumor-infiltrated nonlymphoid structures. As a third modification with respect to the N+ neck, the guidelines for the caudal limits were modified. For the N+ neck, the caudal border was modified basically by lowering it down to the sternoclavicular joint. For a boost volume, the involved level and the directly surrounding uninvolved neck node levels are used [109]. The optimal management of cervical me-

tastases is still subject to considerable debate. For example, Roy et al. [263] reported on patients with TF/SP and BOT tumors and N2 neck disease. After a full course of RT, 65% of these patients still had pathologically confirmed disease in cases of clinical and/or CT-based evidence of persistent disease. For those patients with no evidence of residual disease, 33% still had remaining disease in the neck dissection specimen. Their data lend support to a planned neck dissection. In contrast, Su et al. [291] argued that for patients with oropharyngeal tumors, a neck dissection only improves regional control for those patients with a complete clinical response. In fact, a close follow-up is advocated for this category.

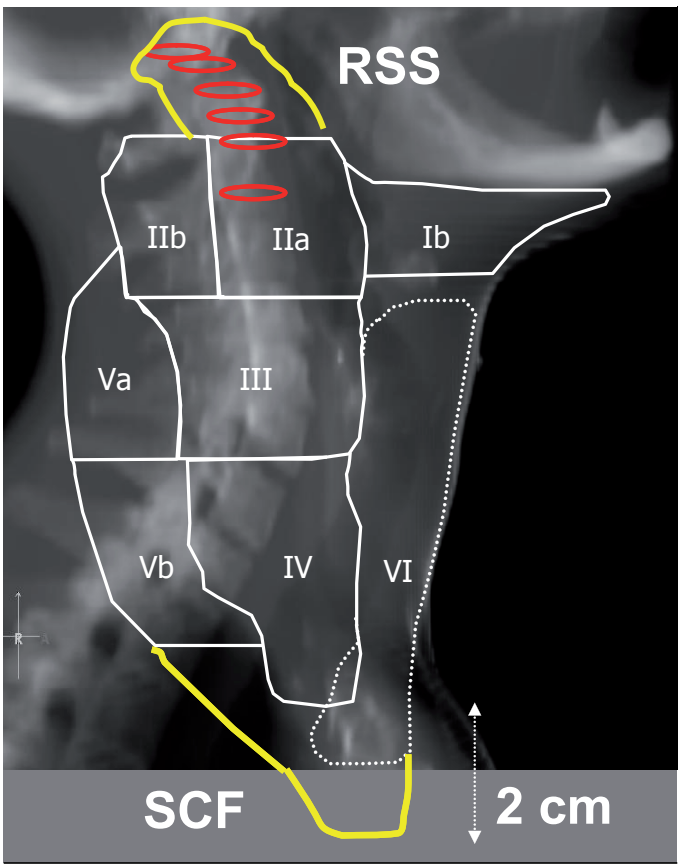

Figure 16: Digital Reconstructial Radiograph with levels Ib-VI, including delineation of the Retro-Styloid Space (RSS) and Subclavicular Fossa (SCF).

Postoperative Neck

In cases of postoperative RT (PORT), one relies on the long-established institutional guidelines [24,109]. As an example, the routine clinical criterion for PORT as used in the Erasmus MC, Rotterdam, and those established by the University of Texas, M.D. Anderson Cancer Center, Houston, are summarized in Table 6. Basically, with regard to the tumor bed, if feasible, in PORT one tries to mirror the contralateral noninvolved neck. Finally, the previously discussed consensus guidelines established for the N0 neck will remain the foundation for PORT (and N+ neck).

PORT: Risk groups		
Hard criteria: Irradical resection Lym node metastases with ECE Two or more nodes	High risk	66 Gy (66 Gy EQD2,33) 6 fx/week
Soft criteria: Perineural growth Close margins T3-T4	Intermediate risk	60 Gy (60 Gy EQD2,33) 6 fx/week
No riskfactors:	Low risk	No PORT

PORT: Risk groups	
High-risk group: >= 2 factors Oral cavity primary Mucosal margins close or positive Nerve invasion Largest node > 3 cm >= 2 Positive lymph nodes Treatment delay greater than 6 weeks Zubrod performance status >= 2	63 Gy 5 fx/week (53.2 Gy EQD2,33) 63 Gy 5 fx/week (63 Gy EQD2,33) 3 weeks 1 fx/day, 2 wks 2 fx/day
Intermediate-risk: 1 Adverse feature other than ECE	57.6 Gy 5 fx/week (61.8 Gy EQD2,33)

Table 6: Indications for postoperative radiation therapy (PORT). Criteria used in Erasmus MC – Daniel den Hoed Cancer Center, Rotterdam.(upper panel) and University of Texas, MD Anderson Cancer Center, Houston (lower panel).

Clinical Presentation

Patients with carcinoma of the oropharynx present most frequently with a sore throat. They also may complain of difficulty swallowing or pain in the ear, which is related to the anastomotic–tympanic nerve of Jacobson. Carcinomas of the tonsil usually are ulcerated and sometimes exophytic. They infiltrate the glossopharyngeal sulcus and BOT, many times with little or no mucosal involvement. Trismus may be a late manifestation of the disease if the masseter or pterygoid muscle is involved. Cancers of the BOT, unlike those of the oral tongue, rarely are visualized by the patient and may grow to a large size before detection. The patient usually can point to the site of pain and the location of the tumor. Difficulty in swallowing because of pain is common, but dysphagia and impaired deglutition caused by massive infiltration of the tongue by tumor are less so. In advanced tumors that fix the root of the tongue, poor articulation is caused by impaired tongue mobility. It is common for patients with oropharyngeal cancer to notice a mass in the cervical region, usually subdigastric (jugulodigastric), as the first manifestation of disease. Initially, distant metastases are extremely rare.

Diagnostic Work-Up

The evaluation of patients with carcinoma of the oropharynx always begins with a complete history and physical examination. The next step is a comprehensive examination of the head and neck, including oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx. Mirror or fiberoptic examination of the nasopharynx, hypopharynx, and larynx always should be performed to detect any tumor extension or associated pathology. In many centers, panendoscopy has become a routine procedure because of the risk of second primaries in the upper digestive tract. After indirect laryngoscopy, careful digital examination with a gloved finger should evaluate submucosal invo.lvement of the glossopalatine sulcus, base of the tongue, buccal mucosa, or lateral pharyngeal wall. Direct laryngoscopy under anesthesia seldom is required for carcinoma of the faucial arch, but it is very useful to evaluate patients with larger tonsillar or BOT lesions. Physical examination should include a thorough evaluation of the neck for detection of metastatic lymph nodes as well as a search for distant metastases. Examination of the neck should be done with the physician standing behind the seated patient. Anatomic position, size, consistency, tenderness, and mobility of palpable cervical lymph nodes should be recorded. Histologic confirmation of a clinically suspicious malignant lesion always must be obtained, and biopsies should be performed, preferably at the margins of the tumor. Incisional or punch forceps biopsies can be performed with local anesthesia on an outpatient basis. When a lymphoma is suspected, the lesion may be submucosal; a large amount of tissue may be required for electron microscopy and immunologic typing of the tumor. Fine-needle aspiration biopsy of suspicious palpable neck nodes may be used to make the initial diagnosis. Complete blood counts, chemistry profiles, and urinalysis should be obtained. Plain films of the soft tissues of the neck or mandible may show involvement of soft tissues or bony structures. CT with contrast has become standard in delineating the extent of tumor and evaluating involvement of the mandible or extension into the base of the skull. MRI scans and positron emission tomography with their superior soft tissue contrast can be quite sensitive in detecting tumor extension and lymph node distributions [232]. Criteria used for tumor involvement are abnormal contrast enhancement, soft tissue thickening, presence of a bulky mass, infiltration of lymphatic tissues (even without distortion of surrounding tissues), or a combination of these. Neck lymph nodes are considered pathologic when the smallest diameter is greater than 1 cm. In other studies, the presence of hypodense areas in more than 33% of the lymph nodes has been defined as nodal necrosis. Extracapsular extension is thought to be present when the nodal margin appears irregular, without clear distinction with the surrounding fat or when there is thickening of surrounding fibroadipose tissue or muscle. Chest x-ray films should be routine. Bone scans should be requested only if bone involvement is suspected. X-ray films of the skeleton may be required in patients with positive findings on bone scans or clinical suspicion of bony lesions.

Follow-Up

Patients with oropharyngeal cancer usually are followed up with careful physical and indirect laryngoscopic examination as well as thorough cervical lymph node evaluation on a monthly basis for the first 6 months after therapy, every 3 months in years 2 and 3, every 6 months from year 3 to 5, and yearly thereafter. A recent report on 46

patients treated with irradiation showed that postirradiation CT scans may not add incremental information to the clinical examination for predicting local tumor control. Diffuse and symmetric changes of the soft tissue or asymmetry without detectable mass or less than 10 mm was associated with primary tumor control [174].

Staging

In staging oropharyngeal tumors, it is extremely important to include both the ulcerated and infiltrating components of the tumor and all of its submucosal extensions. Because of a tendency to overestimate the size of oropharyngeal tumors, a ruler or caliper must be used to measure the diameter of the lesion [160]. Visual, palpatory, and radiographic findings are critical in accurate staging. The usual staging classification for carcinoma of the oropharynx, including lymph node involvement, is that of the International Union Against Cancer or the American Joint Committee on Cancer (Table 1) [6]. A criticism of this staging system is that it is largely two-dimensional and does not take into account the third dimension, which determines tumor bulk and morphology (e.g., endophytic or exophytic lesions of similar size, which respond differently to similar treatment) [232].

Pathologic Classification

These tumors have characteristic features, including keratin in many cases, although some are nonkeratinizing; the tumors are graded I to IV, depending on the degree of differentiation. Carcinomas that arise in the faucial arch, usually of the squamous cell type, tend to be keratinizing and more differentiated than tumors that arise from the TF. SCCs, often poorly differentiated, account for more than 90% of cancers of the BOT. Although it has been suggested that keratinizing, more differentiated tumors have a somewhat better prognosis than others, no definite correlation between histologic type and pattern of behavior or response to therapy has been reported [232]. Lymphoepithelioma is much rarer in the tonsil or BOT (less than 1.5%) than in the nasopharynx. Most pathologists agree that lymphoepithelioma represents a poorly differentiated, nonkeratinizing SCC with a profuse lymphoid infiltration [232]. Other cell types include mucoepidermoid, adenocarcinoma, and adenoid cystic, which appear to behave more like salivary gland tumors of similar histology in other sites rather than like SCCs of similar size. Tumors of the salivary gland type are uncommon in the tonsil or faucial arch. Malignant melanomas of the TF are also rare [232]. Primary small cell carcinoma of the tonsil, with neurosecretory granules demonstrated by electron microscopy, have been infrequently described. As in other locations, this tumor has a high propensity for regional, nodal, and distant metastatic spread with a very poor prognosis. Malignant lymphomas, usually non-Hodgkin's type, constitute 10% to 15% of malignant tumors of the tonsil and 1% to 2% of the BOT. They tend to grow submucosally and may reach large size without significant mucosal ulceration. The surface of the tumor is covered by the same mucous membrane that covers the soft palate. Primary Hodgkin's disease in the tonsil is extremely rare. Metastatic carcinoma to the tonsil is rare, with only 92 cases reported in the world literature [232].

Prognostic Factors

Host and tumor factors have been correlated with survival but not consistently with primary, nodal, and distant relapses. Age and gender are host characteristics that

may have prognostic significance [232]. In some reports, women have shown a better prognosis than men, possibly because of earlier detection of tumors in women although other authors observed no significant survival difference between the genders. Significant differences in survival based on age (e.g., patients younger or older than 40 years) have not been established in sufficiently large and uniform patient cohorts and need to be stratified by disease stage and performance status [232]. Tumor characteristics that have prognostic significance include tumor size and extension (stage); presence of palpable lymph nodes; and location, number, and size of involved lymph nodes. Tumor regression during radiation therapy and histologic differentiation are additional prognostic factors reported. P53 and epidermal growth factor receptor overexpression has been associated with increased survival [232]. A significant correlation has been found between the stage of the primary tumor, the presence of involved cervical lymph nodes, and 5-year survival [234]. Tonsil tumor extension into the base of the tongue is associated with decreased survival [232]. There is no definite correlation between histologic type or degree of tumor differentiation and patient survival. In patients treated surgically after irradiation, more than 90% with negative histologic specimens survived for 5 years compared with only 30% of patients with persistent tumor [232]. Overall, BOT cancers have a worse prognosis than do their oral tongue or tonsil counterparts because of greater size at diagnosis, more frequent spread to adjacent structures, and higher rates of lymphatic spread. However, stage for stage, they may have similar prognoses as oral tongue cancers. Small exophytic tumors (i.e., superficial surface lesions) have higher rates of local tumor control by surgery or irradiation and a better prognosis than infiltrating or large tumors. Patients with tumors confined to the BOT survive longer than those with tumors that extend to the faucial arch, oral cavity, or larynx and hypopharynx [232]. The prognosis is better for patients without palpable lymph nodes (N0) and for those with small, ipsilateral, mobile lymph nodes rather than those with large, fixed, contralateral, or bilateral nodes [234].

Management Strategies, Results, and Outcomes

Lymphoepithelioma, representing a poorly differentiated, nonkeratinizing SCC with a profuse lymphoid infiltration, is rare (less than 1.5%) in the TF/SP and BOT. Mucoepidermoid, adenocarcinoma, and adenocystic carcinomas behave more or less like “salivary gland type of tumors” of similar histology in other sites of the head and neck, rather than like SCC. Moreover, these salivary glandlike tumors are particularly uncommon in the faucial arch and TF [287]. Koss et al. [159] and Abedi and Sismanis [1] found only a few cases of small cell carcinomas of the tonsil. Malignant lymphomas, mostly of the non-Hodgkin's type, constitute 10% to 15% of the TF and 1% to 2% of the BOT tumors. In contrast to non-Hodgkin's lymphoma, primary Hodgkin's disease in the oropharynx is extremely rare [14]. Metastatic lesions to the TF/SP and BOT are exceptionally rare as well. Oreggia et al. [224] found women to have a better prognosis than men (at 5-year overall survival [OS], 40% vs. 9%). In contrast, Vallis et al. [301] observed no significant difference between genders. Similarly, young age has not proven to be of prognostic significance [150]. Tumor characteristics like tumor size, stage, lymph nodal status, and tumor regression during therapy have been found to be of some prognostic significance. No definite correlation has been observed between histologic type, tumor differentiation, and patient survival [250,301]. In contrast, p53

overexpression and targeting the epidermal growth factor receptor family do seem to be of prognostic value [267]. For the more advanced tumors, there is a need for improvement, and the jury is still out on which treatment approach offers better tumor control and fewer side effects at the same time. One approach addressing the problem of improving the locoregional control in advanced tumors is reported by Hoogsteen et al. [136]. They tried to modify the response of malignant cells to radiation by overcoming tumor hypoxia. The Head and Neck Oncology group of the department of Radiotherapy of the St. Radbond University Hospital in Nijmegen argued that this can be done in several ways, including, for example, hyperbaric oxygen, carbogen breathing combined with nicotinamide, hypoxic cell sensitizers, and erythropoietin. There is now compelling evidence that shows that low hemoglobin levels before and during treatment are associated with reduced tumor control and decreased survival. The authors investigated the impact of low haemoglobin levels on locoregional control in patients who have been treated with accelerated radiotherapy with carbogen and nicotinamide. This is another example of good local tumor control and survival by modulating tumor cell biology (e.g., hypoxia) (Tables 7 and 8). For BOT tumors treated with accelerated radiotherapy with carbogen and nicotinamide, Kaanders et al. [153] showed an actuarial local control (LC) rate of 84% and actuarial OS rate of 50%. Similar findings were observed for TF/SP tumors at 5 years: LC rate of 86% and OS rate of 33%. Hyperbaric oxygen as adjunctive therapy, although never proven in a randomized setting, is another effective way of modulating the oxygen status of normal tissues beneficially [92]. In Erasmus MC, such a trial is currently ongoing. To measure the oxygen status of the tissues of these patients, a novel optical spectroscopic technique is used; this so called differential path-length spectroscopy allows for the in vivo measurement of hypoxia-related parameters such as blood oxygenation, blood content, and microvessel size in the most superficial layer of tissue [5]. For the advanced oropharyngeal tumors, there are many more innovative approaches feasible. For example, Suntharalingam [292] reviewed the beneficial effect of systemic and/or intra-arterial CHT as organ-preservation therapy. The author argued that the real focus in the treatment approach of the tumor, however, should be on newer biologic agents targeting cellular protein receptors. For more details one is referred to XII.

	Therapy	T1 # of pat (%)	T2 # of pat (%)	T3 # of pat (%)	T4 # of pat (%)
MD Anderson [1]					
TF/SP	Concomitant Boost	5	29 (96%)	41 (78%)	4 (50%)
BOT	Concomitant Boost	4	27 (96%)	22 (67%)	1 (NE)
Erasmus MC [2]					
TF/SP	EBRT 6 fr./week + HDR/IRT	13 (100%)	65 (89%)	24 (91%)	1 (100%)
TF/SP	EBRT 6 fr./week + S+PORT	5 (100%)	22 (95%)	58 (85%)	8 (69%)
BOT	EBRT 6 fr./week + HDR/IRT	9 (100%)	13 (84%)	9 (56%)	10 (89%)
BOT	EBRT 6 fr./week + S+PORT	0	1 (100%)	10 (100%)	6 (100%)
KUN [3]					
TF/SP	ARCON	0	3 (100%)	17 (100%)	8 (53%)
BOT	ARCON	1 (100%)	4 (100%)	4 (100%)	15 (76%)

Table 7: Comparison of radiation therapy schedules for treatment of carcinoma of the tonsillar fossa/soft palate and base of tongue: 5 years actuarial local control. Data obtained from [1] Gwozdz et al. and Mak et al., [2] Levendag et al., [3] Kaanders et al. See also bibliography.

	Therapy	T1 # of pat (%)	T2 # of pat (%)	T3 # of pat (%)	T4 # of pat (%)
MD Anderson [1]					
TF/SP	Concomitant Boost	5 (100%)	29 (64%)	41 (63%)	4 (58%)
BOT	Concomitant Boost	4 (100%)	27 (80%)	22 (57%)	1 (55%)
Erasmus MC [2]					
TF/SP	EBRT 6 fr./week + HDR/IRT	13 (77%)	65 (68%)	24 (66%)	1 (100%)
TF/SP	EBRT 6 fr./week + S+PORT	5 (67%)	22 (72%)	58 (50%)	8 (38%)
BOT	EBRT 6 fr./week + HDR/IRT	9 (67%)	13 (54%)	9 (53%)	10 (40%)
BOT	EBRT 6 fr./week + S+PORT	0	1 (0%)	10 (27%)	6 (67%)
KUN [3]					
TF/SP	ARCON	0	3 (33%)	17 (38%)	8 (25%)
BOT	ARCON	1 (100%)	4 (50%)	4 (50%)	15 (47%)

Table 8: Comparison of radiation therapy schedules for treatment of carcinoma of the tonsillar fossa & soft palate and base of tongue: 5 years actuarial overall survival. Data obtained from references [1] Gwozdz et al. and Mak et al., [2] Levendag et al., [3] Kaanders et al. See also bibliography.

Tumors of the Tonsillar Fossa and/or Soft Palate

For general reading on TF and/or SP tumors treated by external beam RT (EBRT) and/or surgery, one is referred to the literature search as referenced in this section [3,7,14,15,18,51,66,70,87,96,97,101,102,138,145,164,170,175,189,190,193,196,203,209,225,226]. The TF and/or SP tumors are also typically tumor sites very suitable for BT. For an overview on the techniques and results obtained with BT, see the following references for example [71,80,81,176,178,199,200,201,202,230,236,237,246,327]. Perez et al. [234] addressed the important issue of ipsilateral and/or contralateral neck failure in a series of 384 patients treated in a single institution (Washington University, St. Louis, MO) (Fig. 17). A similar type of analysis was done for the 254 patients with TF and/or SP tumors treated at Erasmus MC, Rotterdam (Fig. 18). Interestingly, in the Erasmus MC series, 37 patients received no treatment to the contralateral clinically N0 neck; only 1 patient (3%) had a recurrence in the neck. Based on these findings, in recent years one has become more selective in treating the contralateral neck. That is, according to treatment protocol in Erasmus MC, the contralateral neck is only treated if the CTV is crossing the midline, or when dealing with N2c,3 disease, or if the TF tumor is infiltrating the glossopalatine sulcus and/or the BOT [175].

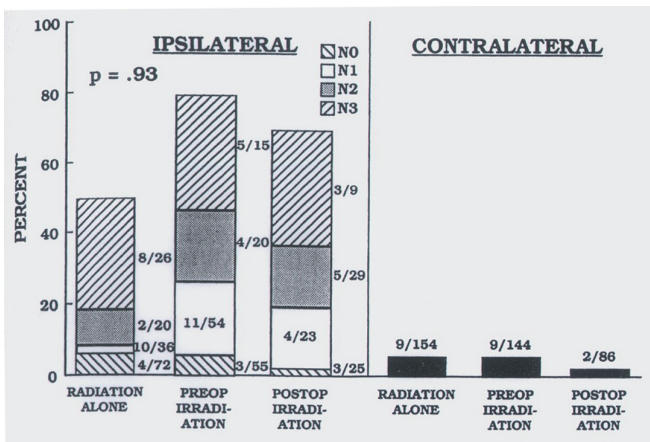

Figure 17: Carcinoma of the tonsil. Incidence of ipsilateral and contralateral neck recurrence in 384 patients treated with irradiation alone or combined with surgery at Mallinckrodt institute of Radiology, Washington University. Book: Principles and Practice of Radiation Oncology 2004. (Perez CA, Brady LW, Halperon EG, Schmidt-Ullrich RK. Lippincott Williams & Wilkins, chapter 38 page 1031).

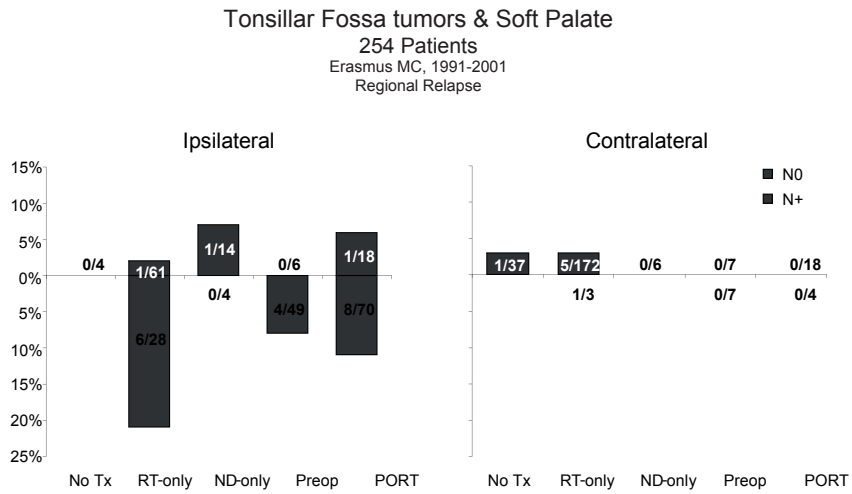

Figure 18: No Tx: no treatment. RT-only: radiation therapy as a single modality.ND-only: neck was treated by neck dissection alone. Preop: neck treated by neck dissection and preoperative irradiation 46 Gy. PORT: ND and postoperative radiation therapy.

Treatment Results

T1 lesions less than 1 cm can be treated with surgical resection or irradiation to the primary only to a dose of 65 to 70 Gy in 7 weeks. The majority of T1 or T2 tumors of the TF and/or SP are treated by irradiation, the ipsilateral neck inclusive, be it electively or because of N+ disease (see previous section). For T3 and T4 tumors, surgery of the primary is often advocated; it can require removal of the primary tumor, partial removal of the mandible in combination with an ipsilateral neck dissection (combined resection). Because of the high incidence of a recurrence with surgery as a single modality [86], surgery is to be followed by PORT [23]. Recent insights have demonstrated the potential beneficial effect of PORT combined with CHT [56]. Because of the particular location of some of these tumors (e.g., tumor growth in the midline of the SP), surgical resection of advanced tumors can lead to a permanent functional defect (e.g., in the SP). This then needs to be repaired by reconstructive surgery; otherwise the patient is left with open nasal speech. For reasons of organ preservation, T1-T3 TF/SP tumors are therefore frequently treated by RT, albeit by EBRT alone (70 to 75 Gy) to the neck and primary or EBRT (40 to 50 Gy) to the primary and neck, followed by a boost to the primary tumor by means of low-dose-rate (LDR; total dose, 20 to 30 Gy) or high-doserate (fractionated HDR; total dose, 20 to 25 Gy) BT (for details on BT, see Clinical Section on Tonsillar Fossa and/or Soft Palate and Tumors of the Base of Tongue). For the advanced cases, EBRT is combined with concomitant CHT [22]. Data from the literature on the surgical, EBRT only, and EBRT plus IRT results with regard to LC and survival are summarized in Tables 9-11, respectively.

First Author	N	T1/T2, %	T3/T4, %	LC T1/T2, 5-Yrs %	LC T3/T4, 5-Yrs %	DFS, 5-Yrs %	OS, 5-Yrs %
Mizono, 1986	40			LRC: 73			
Parsons, 2002	406		12 (T4)	76		CSS: 57	47
Perez, 1991	127		69	41 3-yrs			39
Perez, 1998	230		14	T1: 80, T2: 71	T3: 65, T4: 58		
Foote, 1994	72		3	T1: 78, T2: 76	T3: 4, T4: 0/2		
				LRC Stage I: 73	LRC Stage III: 53		
				LRC Stage II: 69	LRC Stage IV: 56		
Schuller, 1979	20		Stage IV: 20			CSS: 20	
Rabuzzi, 1982	47		Stage IV: 45			CSS: 57	
Givens, 1981	37		Stage IV: 51			CSS: 54	
Gluckman, 1985	82		Stage IV: 39			CSS: 56	

Table 9: Tonsillar fossa / soft palate: local control and survival according to stage, surgery and PORT. LC: local control. LRC: local regional control. CSS: cause specific survival.

Tumors of the Base of Tongue

SCCs, often poorly differentiated, account for more than 90% of cancers of the BOT. It is often difficult to estimate exact tumor extension by clinical examination. Fullness in the soft tissue around the hyoid bone may be a sign of inferior penetration through the valleculae (the transition zone between the BOT and the epiglottis). Tumors in the valleculae tend to be exophytic; they frequently encroach on the lingual aspect of the epiglottis. Rarely do these tumors infiltrate the palatine tonsils. Bilateral and contralateral lymphatic spread is common; retrograde spread to retropharyngeal lymph nodes has been reported in advanced cases. Overall, patients with BOT cancers present with lymphatic metastasis in 50% to 80%, with the jugulodigastric and parapharyngeal nodes most commonly involved. Bilateral spread is observed in 37% to 5 5% [179,227].

The incidence of pathologic lymph nodes (pN+) in the ipsilateral clinical N0 neck is estimated to be 22% to 33%. Contralateral lymphatic metastasis at presentation is observed in 37%, albeit by RT or surgery. These data testify to the fact that in BOT cancer, the neck should be treated electively bilaterally (N0; levels II-IV), or therapeutically (N+; levels I-V). An overview of the pertinent literature on BOT cancer can be obtained from references [15,44,66,87,101,119,123,124,127,128,129,135,136,141,143,148,155,163,168,169,184,189,192,193].

First Author	N	T1/T2, %	T3/T4, %	LC T1/T2, 5-Yrs %	LC T3/T4, 5-Yrs %	DFS, 5-Yrs %	OS, 5-Yrs %
Jackosn, 1999	170		63	DSS: 76.2		DSS: 61	55.7
Marcial, 1993	137		92	32 3-yrs			24
Horiot, 1992	325		56	47		35	
O'Sullivan, 1997	229			76			
Bataini, 1989	465		35	T1: 90, T2: 84	T3: 64, T4: 47		
Selek, 2004	60	100		82.6		74.3	
Mak-Kregar, 1993	68		76				75 3-yrs
Di Marco, 1990	183		75				28
Withers, 1995	676		75				
Mendelhall, 2000	400			T1: 83, T2: 81	T3: 74, T4: 60	CSS: 70	49
Wong, 1989	150		5	T1: 94, T2: 81	T3: 67, t4: 47	CSS: 70	
Perez, 1998	154		23	T1: 76, T2: 63	T3: 59, T4: 33	CSS: 70	
Erkal, 2001	107	61	49	T1: 86, T2: 91	T3: 67, T4: 19	CSS: 70	42
Chao, 2004	56			TF: 85 4-Yrs		TF: 79 4-Yrs	
				SP: 100 4-Yrs		SP: 100 4-Yrs	

Table 10: Tonsillar fossa /soft palate: local control and survival according to stage external beam radiotherapy. LC: local control. LRC: local regional control. CSS: cause specific survival. DFS: disease free survival TF: tonsillar fossa. SP: soft palate.

First Author	N	T1/T2, %	T3/T4, %	LC T1/T2, 5-Yrs %	LC T3/T4, 5-Yrs %	DFS, 5-Yrs %	OS, 5-Yrs %
Pernot, 1992	277		57	76 5-yrs			51
Puthawala, 1985	80		24	84			
				LRC Stage I:3/3	LRC Stage III:85		
				LRC Stage II:100	LRC Stage IV:56		
Pernot, 1994	361		1	T1:80, T2:71	T3:65, T4:58	CSS: 63	53
				LRC: 75			
Levendag, 2004	104	77		T1-T3: 88		57	67
Esche, 1988	43	T1: 34/43		92		CSS: 64	37
Mazeron, 1993		100		94		71	53
Peiffert, 1994	73	65/73	2/73	T1: 80, T2: 67		CSS: 64	30

Table 11: Tonsillar fossa / soft palate: local control and survival according to stage, brachytherapy boost. LC: local control. LRC: local regional control. CSS: cause specific survival. DFS: disease free survival.

Treatment Results

With regard to the management of BOT tumors, in short, the primary tumor in earlystage oropharyngeal cancers can be treated by either EBRT or IRT or surgery, whereas more advanced lesions often are treated by surgery plus PORT. Also EBRT, followed by a boost by IRT or intraoral cone and/or concomitant CHT for the more advanced cases, is frequently used. In the majority of institutions, however, RT is the preferred definitive treatment mode for T1, T2, and some of the exophytic T3, N0, N1 cancers. In general, a neck dissection is warranted only in these early cancer stages in patients treated by RT and experiencing a residual regional mass 6 weeks after completion of the therapy. In this respect, Doweck et al. [71] discussed the controversial role of selective neck dissection after definitive RT. For N1–3 disease, some protocols have successfully used routine neck dissections after preoperative RT (46 Gy), with excellent control rates. For the more advanced (endophytic) T3 lesions, as well as for the T4 tumors with significant extension into normal surrounding tissues, organ/normal tissue deformities are frequently the cause of clinical problems, for example, resulting in swallowing disability and trismus. For this category of patients, the treatment is frequently "tailor made" and surgery followed by PORT might sometimes be a more sensible option [299]. Reviewing the literature, however, the implementation of concomitant CHT has also been shown to be a highly effective treatment combination. BOT tumors may be resected transorally or via mandibulotomy; the last approach is frequently combined with reconstruction by tissue grafting [272]. Patients with advanced tumors may require a glossectomy. In these cases, a tracheotomy (to avoid aspiration) with placement of a speech button and a percutaneous endoscopic gastrostomy to circumvent swallowing dysfunction (thus to secure adequate food intake during treatment and immediate follow-up) is often performed at the time of surgery. The relevant data taken from the literature with regard to locoregional tumor control and survival has been summarized in Table 12 (for surgery), 13 (for EBRT), and 14 (for EBRT combined with a BT boost). Finally, two typical protocols, exemplified by Figures 19 and 20, illustrate different treatment approaches, but similar (good) LC and survival for oropharyngeal tumors. Figure 19 represents the oropharynx protocol of Erasmus MC, with emphasis on organ function-preserving properties by using accelerated fractionation during the first series of IMRT (6 fractions per week) and HDR-BT, or Cyber Knife as a boost technique. Figure 20 illustrates the protocol of the M.D. Anderson Cancer Center, with the main focus on the concomitant boost (altered fractionation) technique.

Tumors of the Lateral and Posterior Pharyngeal Walls

These tumors are less frequently reported in the literature and generally do not do so well with either RT or surgery as opposed to the TF and/or SP tumors or the tumors of the BOT. For a short bibliography see references [53,59,63,83,144,152,191,206,208,242,285,293,295,326].

First Author	N	T1/T2, %	T3/T4, %	N0, %	LC T1/T2, 5-Yrs %	LC T3/T4, 5-Yrs %	DFS, 5-Yrs %	OS, 5-Yrs %
Pol, 2004	58		26 (T4)	18	91		55	
Foote, 1993	55			49	LRC: 48			
Kraus, 1993	100			38	LRC: 72		DSS: 61	55
Malone, 2004	40		70	25	LRC: 100 2-Yrs		DSS: 93.6	74.7
Parsons, 2002	390		13 (T4)		76		CSS: 62	49
Sessions, 2003	262		19	45		LRC: 74	CSS: 49.6	42.4

Table 12: Base of tongue: local control and survival according to stage, surgery and PORT. LC: local control. LRC: local regional control. CSS: cause specific survival.

First Author	N	T1/T2, %	T3/T4, %	N0, %	LC T1/T2, 5-Yrs %	LC T3/T4, 5-Yrs %	DFS, 5-Yrs %	OS, 5-Yrs %
Selek, 2004	40	100		100			76	83
Spanos, 1976	174		37		T1: 91, T2 : 71	T3: 78, T4: 52		
Jaulerry, 1991	166		59	30	69	32		27
Mendenhall, 2000	217		19 (T4)		T1: 96, T2: 91	T3: 81, T4: 38	CSS: 50	64
Mak, 1995	54			17	LRC T1/T2: 85			59
					LRC T3: 67			
Hinerman, 1994	47 qd			18	LRC: 70			44
	90 bid							
Marcial, 1983	141			25	LRC: 31			15
Housset, 1987	29	100	0		T1: 100, T2: 74			52
Wang, 1991	79 qd	T1-T3 Conventional			T1/T2: 79	T3: 24		T1/T2: 65, T3: 14
	90 bid	T1-T3 bid			T1/T2: 85			T1/T2: 76, T3: 53
Chao, 2004	18				LRC: 88		80 4-Yrs	

Table 13: Base of tongue: local control and survival according to stage, external beam radiotherapy. LC: local control. LRC: local regional control. CSS: cause specific survival. DFS: disease free survival. bid: twice daily. qd: one fraction per day.

First Author	N	T1/T2, %	T3/T4, %	N0, %	LC T1/T2, 5-Yrs %	LC T3/ T4, 5-Yrs %	DFS, 5-Yrs %	OS, 5-Yrs %
Harrison, 1997	68		3 (T4)		T1: 87, T2: 93	T3: 82, T4: 100	T1: 88, T2: 93, T3: 82	87
Puthawala, 1988	70		17 (T4)		T1: 100, T2: 88	T3: 75, T4: 67	67	35
Barrett, 2004	20		35	10	2-Yrs		33	
Takacsi-Nagy, 2004	37		81	19	100	60	52	46
Karakoyun-Celik, 2005	40		54	30	LC: T1-4: 78		54	62
Pol, 2004	30		67 (T4)	30		63	45	40
Gibs, 2003	41		49	32	14	20	79	66
Brunin, 1999	216		61	30	T1: 93, T2: 66	T3: 45, T4: 18	CSS I-IV: 63-23	27
Crook, 1988	48	100			T1: 85, T2: 71		50	
Hoffstetter, 1996	136	55/136		N0/N1: 81	T1: 86, T2: 69	T3: 64		
Horwitz, 1996	20	11/20	9/20			10/11	T4: 8/9	72
Housset, 1987	29	100			T1: 6/6, T2: 74			30.5
Lusinchi, 1989	108	57/108	T3: 51/108		T1: 85, T2: 50	T3: 69		26

Table 14: Base of tongue: local control and survival according to stage, brachytherapy boost. LC: local control. CSS: cause specific survival. DFS: disease free survival.

Treatment Results

Guillamondequi et al. [112] found 28% recurrences after surgery, with salvage in less than one third of the patients. Fein et al. [81] at the University of Florida compared retrospectively once-daily versus twice-daily fractionation. The observed LC rates were 100% versus 100% for the T1 category, 67% versus 92% for the T2 tumors, 43% versus 80% for T3 tumors, and 17% versus 50% for T4 tumors. Meoz-Mendez et al. [207] reported on a mixed group of patients with hypopharyngeal and pharyngeal wall carcinomas treated in the M.D. Anderson Cancer Center: the LC for T1 was 91%; for T2, 73%; for T3, 61%; and for T4, 37%. Those treated with surgery and PORT or preoperative RT fared better (LC, 75%) as opposed to RT alone (LC, 51%). A study by Marks et al. [194,195] compared preoperative RT with definitive RT. There was no difference in LC, but significantly more grade III/IV complications in the surgery group. Spiro et al. [286], from Memorial Sloan Kettering Cancer Center in New York, reported on 78 patients with posterior wall carcinomas. The cumulative 5-year survival was poor: 32%. Good results, albeit in a small selected series of patients, were

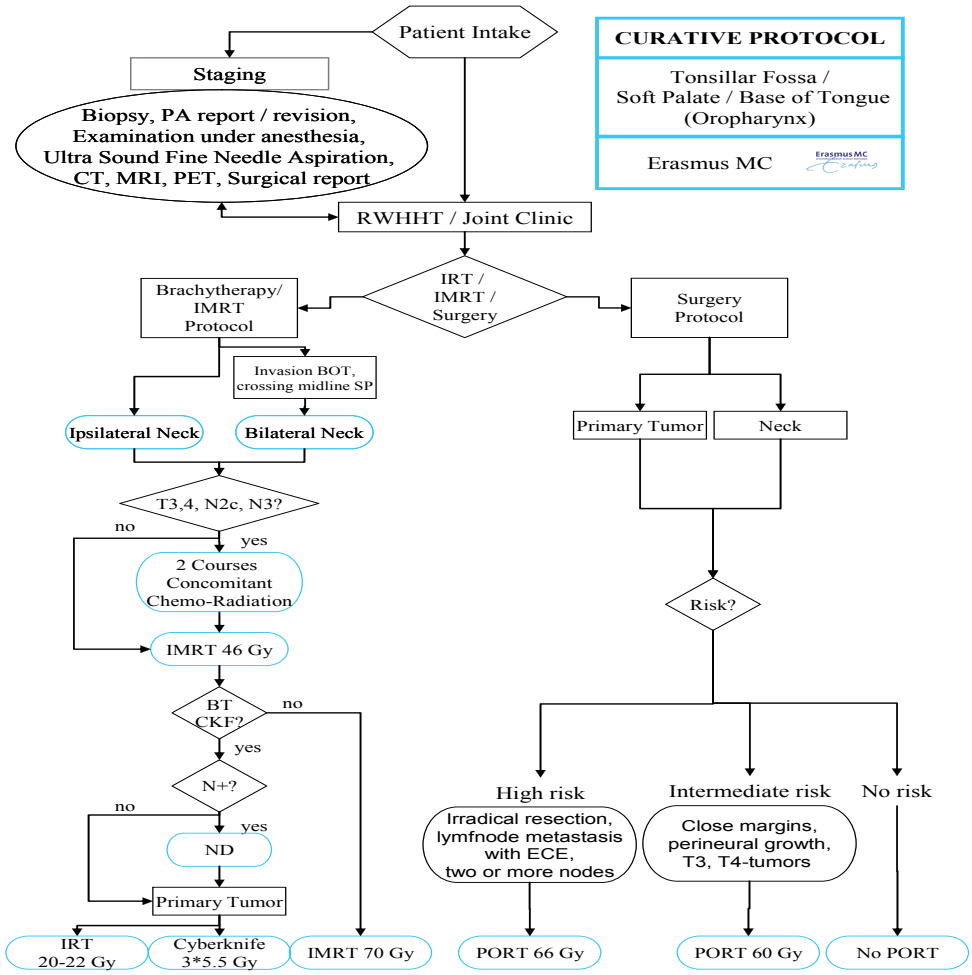

Figure 19: All curative cases are treated by 6 fractions per week.

obtained with an I125 or Ir192 implant; there was an LC rate of 82% at 5 years [284]. In general, the locoregional outcome and survival is significantly better for the early T1, T2, and T3N0,1 carcinomas as opposed to the (endophytic) T3,T4 and N2,3 tumors. Although RT alone most likely confers less functional impairment than is the case with surgery, surgery followed by PORT remains a valuable treatment option for advanced tumors. Different surgical approaches have been proposed for the primary tumor (see Chapter 17 in Harrison et al. [126]). A (bilateral) modified neck dissection is also included in the treatment approach of these difficult-to-manage malignant tumors. Posterior pharyngeal wall tumors in particular pose a technical problem when one needs to deliver high doses of definitive radiation to the primary tumor because of the proximity of the spinal cord. Grimard et al. [111] described an elegant technique for radiating these tumors without compromising the spinal cord tolerance by using two posterior arcs with closure of one jaw beyond the central axis. The initial target volume encompasses the primary tumor and the bilateral neck levels II-V, with the

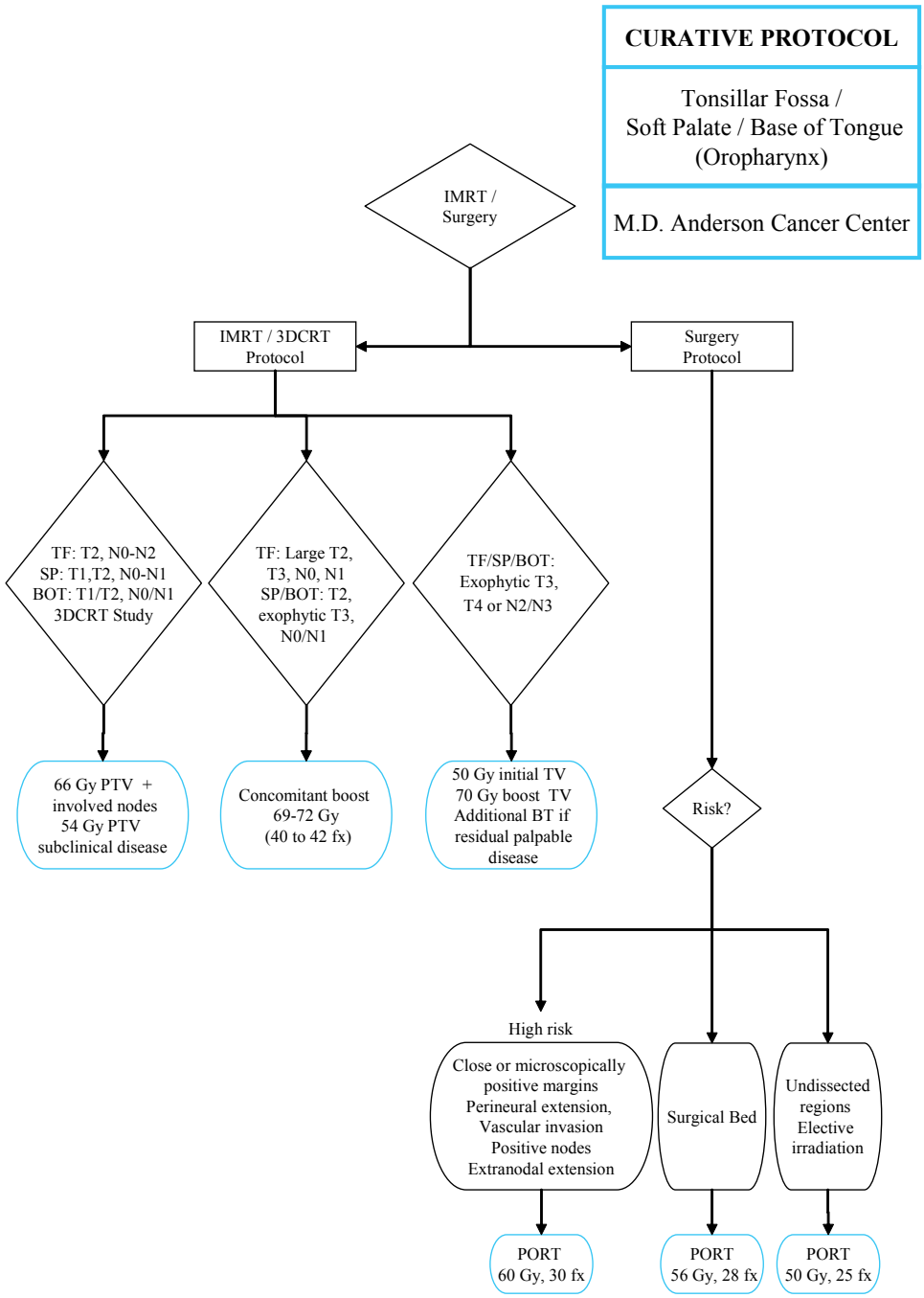

Figure 20: All curative cases are treated by 6 fractions per week.

parapharyngeal and retropharyngeal lymphatics inclusive. Finally, results in terms of tumor control, survival, and (severe) complications are summarized in Table 15.

Recurrent Disease and Salvage

The management of a locoregional failure in the head and neck remains a formidable challenge. Most recurrences (80%) manifest in the first 2 years following primary treatment. At least 50% of patients who die from uncontrolled disease have local and/or regional disease as their sole site of failure. Moreover, the majority (80%) of those who develop distant metastases also have local and /or regional failure. Another, related clinical entity is the management of second primary tumors (about 3% per year [161,220]) occurring in previously irradiated regions. Selected patients with locoregional recurrences can be successfully salvaged with surgery and/or RT. Treatment options are more limited if initial treatment consists of surgery combined with RT or high-dose RT. The average cure rate of these patients has been reported to vary between 30% and 40%, and most failures are due to locoregional relapses. The use of surgery alone as a salvage procedure in case of recurrent BOT cancer was reported by Pradhan et al. [242]. In approximately one third of the patients, LC was achieved for the duration of 1 year. Thirty-five patients required a total glossectomy. The role of RT is not widely appreciated as yet, mainly because of concerns about the tolerance of local tissues to reirradiation. In this regard, BT plays a crucial role (high-dose, small volume, rapid dose fall -off) [140,165,197]. An equivalent EBRT dose of 60/2 Gy by five fractions per week is being applied mostly as the reirradiation dose schedule. An important prognostic factor favoring long-term LC is an interval of more than 1 year between the radiation courses. Langlois et al. [165], for example, report on 123 patients treated for recurrent cancer or a new cancer of the tongue or oropharynx, arising in previously irradiated volumes.The actuarial LC rate was 67% at 2 years and 59% at 5 years. Levendag et al. [176] analyzed a 13-year experience with reirradiation. An improvement in LC was observed (50% vs. 29%) for the EBRT plus IRT as opposed to the EBRTalone series. The improvement in LC was typically not reflected in a survival benefit; that is, an actuarial OS of 20% at 5 years was observed in both series. Mazeron et al. [200] had similar results: actuarial LC was 72% at 2 years and 69% at 4 years. Although LC of the tumor was achieved in the majority of these patients, only 14% remained alive at 5 years. Best results were achieved in lesions of the faucial arch and posterior pharyngeal wall (LC, 100%). Other ways of applying reirradiation is in an intraoperative setting for residual microscopic disease by means of a silicone flexible intraoperative template (Fig. 21). After the dose of 10 Gy (prescribed mostly at 1 cm from the afterloading catheter in the flexible intraoperative template) has been delivered, the surgical defect can be closed by a reconstructive procedure using “fresh,” that is, donor tissue (e.g., deltopectoral flap) that has not been previously irradiated. The dose is mostly prescribed to a distance of 1 cm [157]; subsequently, a course of fractionated EBRT is applied as an outpatient procedure (e.g., 26 × 1.8 Gy). As with any retreatment situation, the complication rate is substantially higher than with primary therapy.

First Author	N	Modality	T1/ T2, %	T3/ T4, %	N0, %	LC T1/T2, 5-Yrs %	LC T3/T4, 5-Yrs %	DFS , 5-Yrs %	OS, 5-Yrs %	SC
Pommier, 1997	14	BT						37	21	None
Chenal, 1996	55	RT/ Surgery	55			67			38, mean 23 months	
Fein, 1993	9	RT				T1:100, T2:92	T3:80, T4:50			
						2 daily fx, 2-yrs				
Mak-Kregar, 1994	8	RT/ Surgery		100		50			38	
Spiro, 1990	78	RT/ Surgery							32	
Menden-hall, 1988	75	RT/ BT				T1: 75, T2: 57	T3: 44, T4: 20		II: 44, III:19	I: 0/2, II:1/16, III:2/22,
									IVA: 0, IVB: 8	IVA: 2/14, IVB: 3/20
Hull, 2003	148	RT/ Surgery	40	59	36	T1:93 T2: 82	T3: 59, T4: 50	I: 89, II:88,	I: 56, II: 52	16
								III: 44, IV: 34	III: 24, IV: 22	
Julieron, 2001	77	Sur-gery+ PORT				Local failure: 11			35	GPO: 22
Chang, 1996	74	RT				2-yrs; T1:100, T2: 55	2-yrs; T3:31, T4:29	2-yrs; I: 100, II: 85,	2-yrs; I: 75, II: 67,	
								III: 58, IV: 40	III: 33, IV: 30	
Cooper, 2000	22	RT				3-yrs; 73			3-yrs: 5	
Yoshida, 2004	51	RT/ Surgery				56		CSS: 48		

First Author	N	Modality	T1/ T2, %	T3/ T4, %	N0, %	LC T1/T2, 5-Yrs %	LC T3/ T4, 5-Yrs %	DFS , 5-Yrs %	OS, 5-Yrs %	SC
Meoz-Mendez, 1978	164	RT	13/ 56	53/ 108	69/ 164	1-yrs; T1: 91, T2: 73	1-yrs; T3: 61, T4: 37			I: 0, II:7, III:15, IV:17

Table 15: Local control for posterior pharyngeal wall tumors after treatment by radiation therapy and/or surgery. SC: Severe Complicatoins, GPO: General postoperative

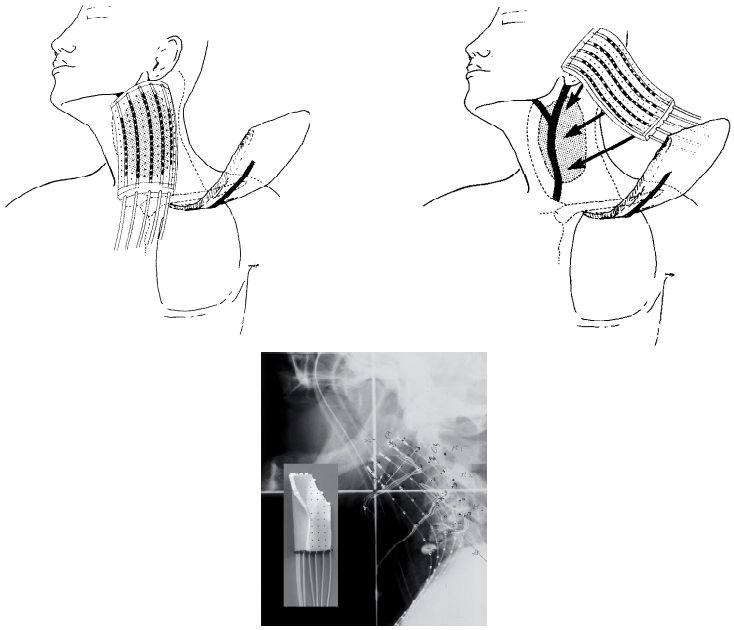

Figure 21: A: flexible intra-operative template (FIT) positioned on the tumor bed and a delto-pectoral flap is used to close the skin defect. B: the simulation radiograph of the FIT in situ (neck).

Radiation Therapy Techniques

Conventional Radiation Therapy

Irradiation portals for oropharyngeal cancers should encompass the primary tumor and its local and regional “extensions,” with a margin for the CTV (approximately 0.7 cm) and for the PTV (approximately 0.5 cm). The concept of regional coverage has been eluded to before extensively. Patients are generally treated in the supine position with bite-block and thermoplastic mask immobilization, with daily treatment of all fields. Neck portals should extend superiorly until C1 for N0, and the base of

skull (retrostyloid space) in case of N+ disease. Patient examples (T2N2b BOT tumor and T2N2b TF/SP tumor) with regard to the geometry of portals, treatment techniques used, and dose distributions are shown in Figures 22-33. In the examples presented in Figures 22-26, the primary tumor and both sides of the upper neck are irradiated using a conventional lateral parallel -opposed technique for the upper neck in case of a T2N2b BOT tumor. Both sides of the lower neck are generally irradiated through a single anteroposterior field, sometimes with a midline block. In order to p revent overdose at the junction line, a junction zone of 1 cm between the lateral fields and the anteroposterior portals is treated daily in Erasmus MC with maximum or minimum field sizes (the so called slip zone). If appropriate, the midline block shields the larynx and spinal cord. The spinal cord is shielded after administration of 46/2 to 50/2 Gy and if indicated, the posterior cervical triangles are boosted with 10-MeV electrons, therewith sparing the spinal cord. Tissue compensators (wedges) are used to ensure dose homogeneity in the lateral portals and to prevent excessive dose to the supraglottic larynx. After 46/2 Gy with 4- to 6-MV photon beams has been applied, the remaining dose can be delivered with high-energy photons (15 to 18 MV) in order to reduce the dose to the parotids, the mandible, and/or the temporomandibular joints (buildup). The middle ear and inner ear should be carefully shielded posteriorly. Small tumors of the TF, anterior tonsillar pillar, and retromolar trigone can be treated by ipsilateral wedged anterior and posterior fields or with BT. With the wedge technique, the dose to the mandible is high, and a greater incidence of complications (e.g., soft tissue necrosis and osteonecrosis of the mandible) can be anticipated. Limiting irradiation to the ipsilateral neck reduces the probability of xerostomia [18]. This approach was confirmed by O'Sullivan and Grice [225], who reported a 3-year tumor control rate of 77% and cause-specific survival rate of 76% in 228 patients with carcinoma of the tonsillar region treated with ipsilateral -only RT techniques (oblique wedge pair arrangement). Contralateral neck failure was observed in only eight patients (3.5%). Levendag et al. had similar observations (Fig. 18). Contralateral failure in the untreated neck was only 3% [175]. The intraoral cone technique, using orthovoltage or electrons, has been used selectively in the treatment of patients with small lesions. Adequate tumor coverage is aided by CT-based treatment planning (with or without MRI fusion); moreover, at the present time it is reasonable to consider CT-based treatment planning for head and neck cancer more or less obligatory. Many of the previously described techniques have therefore substantially changed since the introduction of new and innovative technology, such as IMRT, three-dimensional conformal radiation therapy, and cone beam CT (see also dedicated section XIII on IMRT). Figures 27-33 represent a TF and SP tumor treated by IMRT techniques. The figures depict adequate target coverage and maximum effort to spare major salivary glands. We have compared, for bilateral irradiation, bilateral sparing of parotid glands (Fig. 27), as opposed to maximum sparing of contralateral parotid glands (Fig. 28), or reducing CTV contralateral side (Fig. 29). The corresponding dose-volume histograms are depicted in Figures 30,31 and 32. Also, using this technology, new concepts can be incorporated in future treatment protocols. For example, Thorstad et al. [298] from M.D. Anderson Cancer Center, report favorable results for SCC of the oropharynx treated with IMRT. Multivariate analysis showed that the GTV (primary tumor ± nodes) became an independent risk factor determining locoregional control (GTV <50 mL LC ± 90% vs. GTV >50 mL LC

± 20%; p <.0001). From this type of data, the authors concluded that selecting “high-volume” patients for aggressive treatment protocls might be warranted. For more details, see IMRT section.

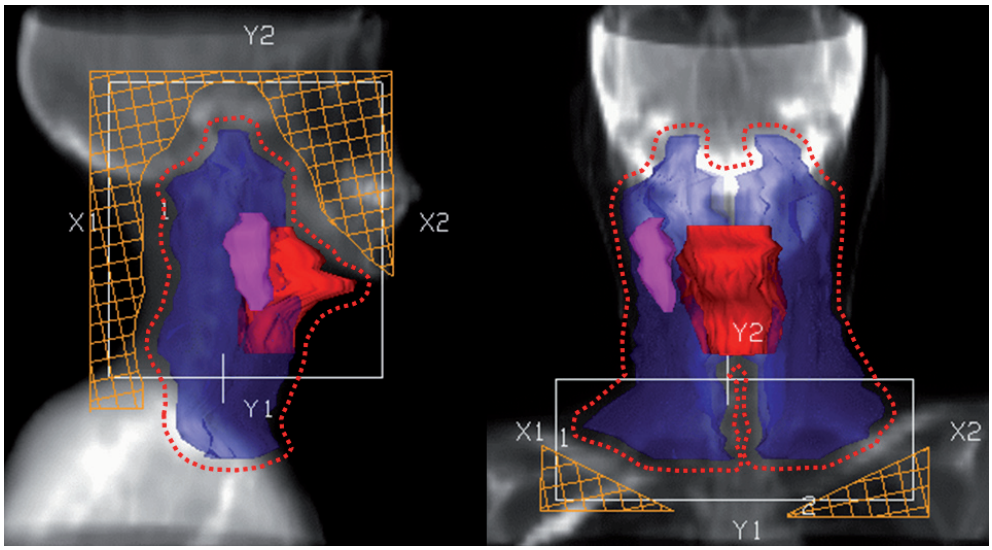

Figure 22: BOT tumor, staged T2N2b. Beams Eye View conventional parallel opposed fields upper neck. Red dotted line: PTV. Blue volume: CTV neck. Red volume: primary tumor. Magenta volume: lymphnodal volume levels II and III.

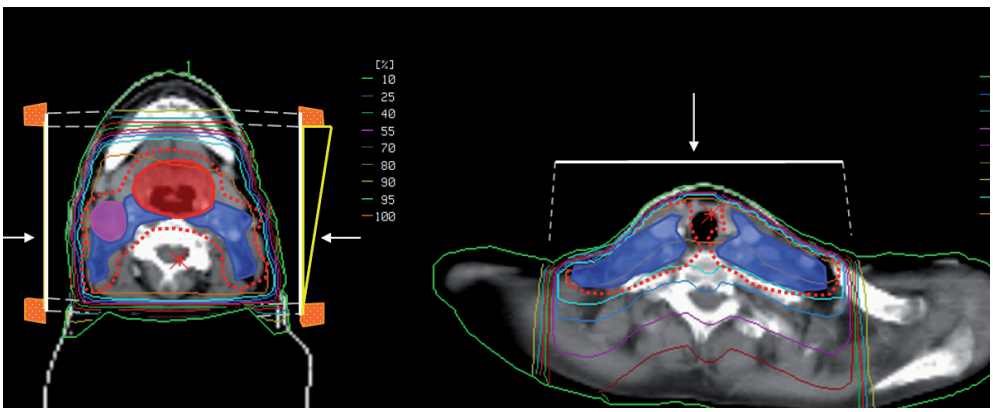

Figure 23: See legend figure 20. Dose (46/2 Gy) distribution axial CT slice upper neck and low anterior neck. Dose generally prescribed at 3cm depth or at a particular point of interest (e.g. in case of lymphnodes in lower neck). Note: no midline block because of potential shielding of tumor extensions.

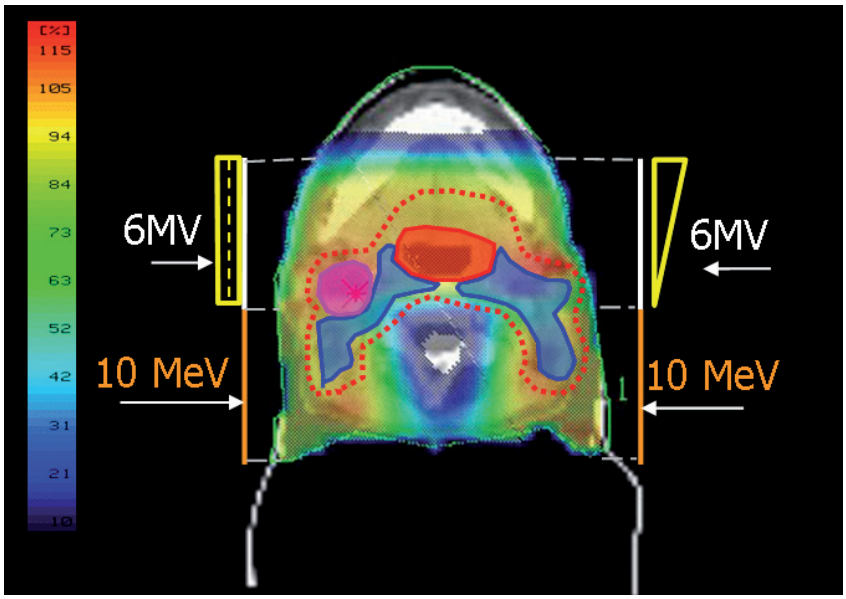

Figure 24: See legend figure 20. Field configuration and doe distribution boost to primary tumor to total dose of 24/2 Gy using parallel-opposed fields. Note shielding posterior neck (cord); dose shielded area supplemented by abutted high energy electron fields (10 MeV).

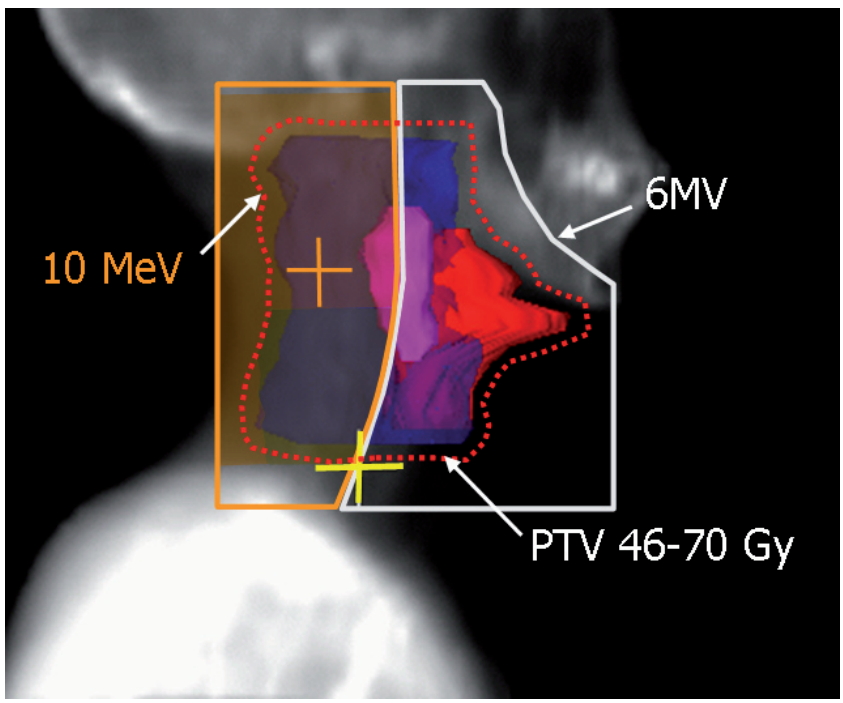

Figure 25: See legend figure 20. Beams Eye View treatment primary tumor and neck node levels II and III (boost).

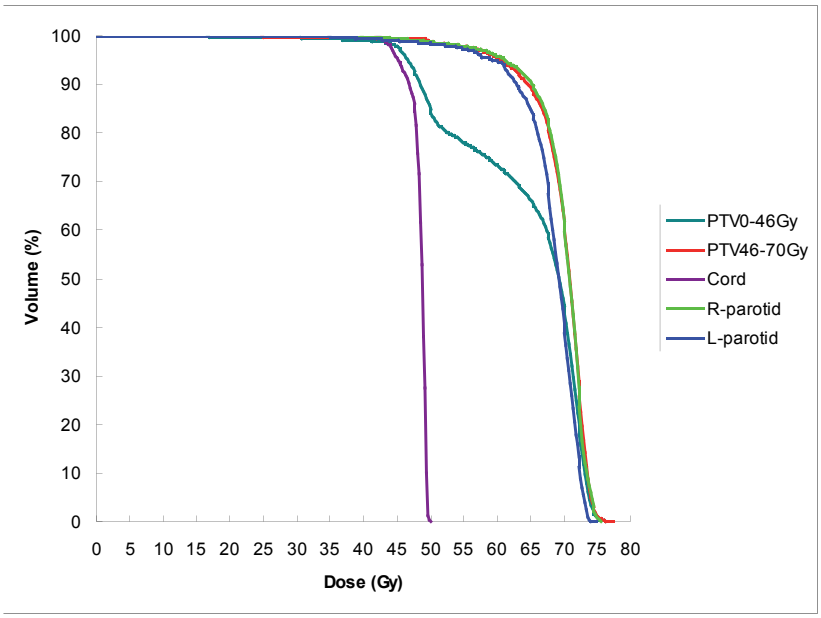

Figure 26: Cumulative Dose Volume Histogram BOT tumor treated to a cumulative dose of 70 /2 Gy. See also legend figure 20 and figure 23.

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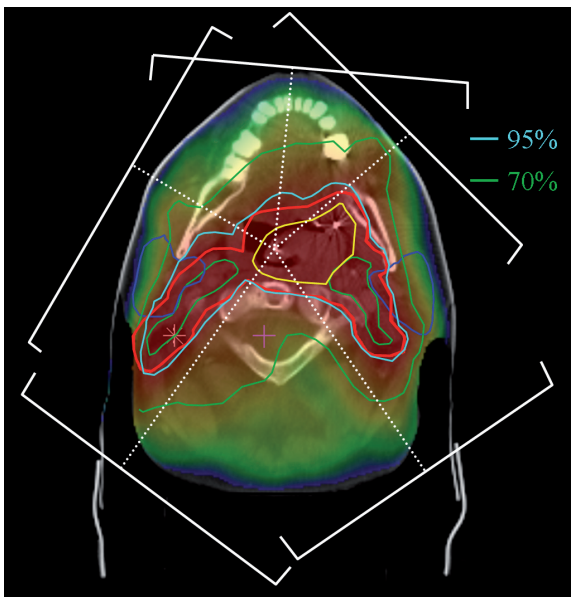


Figure 27: Dose distribution (color wash) TF and SP tumor, staged to T2N2b for first series of RT (46/2 Gy). Upper neck and primary tumor irradiated using a 5-field IMRT technique. CTV consists of primary tumor and neck levels I-V (ipsilateral, left) and neck levels II-IV (contralateral, right). Dose prescribed according ICRU 50 guidelines. Field configuration: Upper neck IMRT (this figure), lower neck A-P portal (figure 31). Equal sparing of both parotid glands was achieved. For abutted low anterior neck portal, see figure 31.

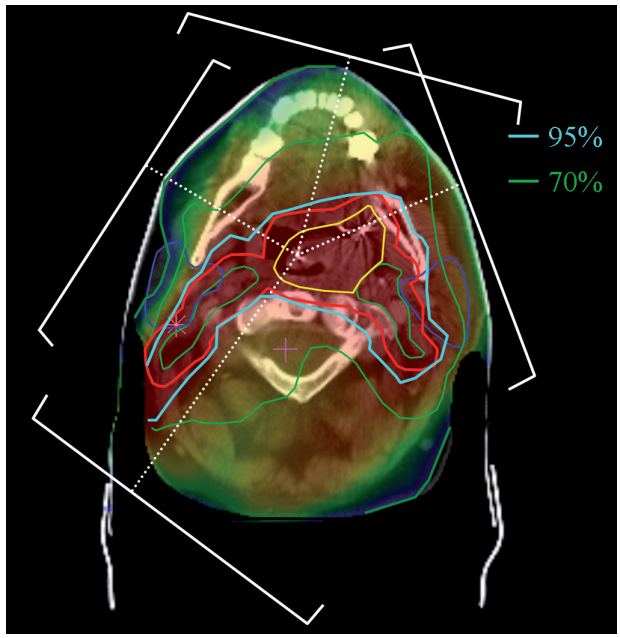


Figure 28: See legend figure 25. In order to better spare the contralateral parotid gland, relaxation of the ipsilateral parotid constraint is pursued and a asymmetric 4-field IMRT technique was implemented. Dose is prescribed to ICRU 50 guidelines. For abutted low anterior neck portal, see figure 31.

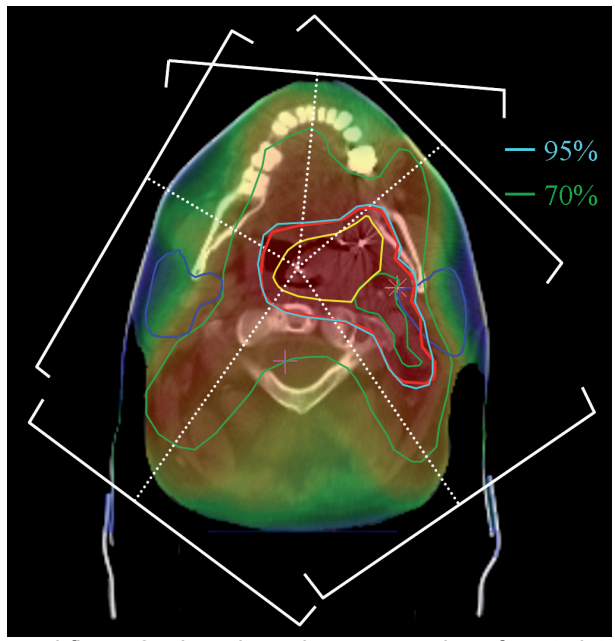


Figure 29: See legend figure 25. In order to improve sparing of contralateral parotid gland, contralateral cranial border of upper neck (level II) is lowered by 1 cm. A 5-field IMRT technique was used. For abutted low anterior neck portal, see figure 31.

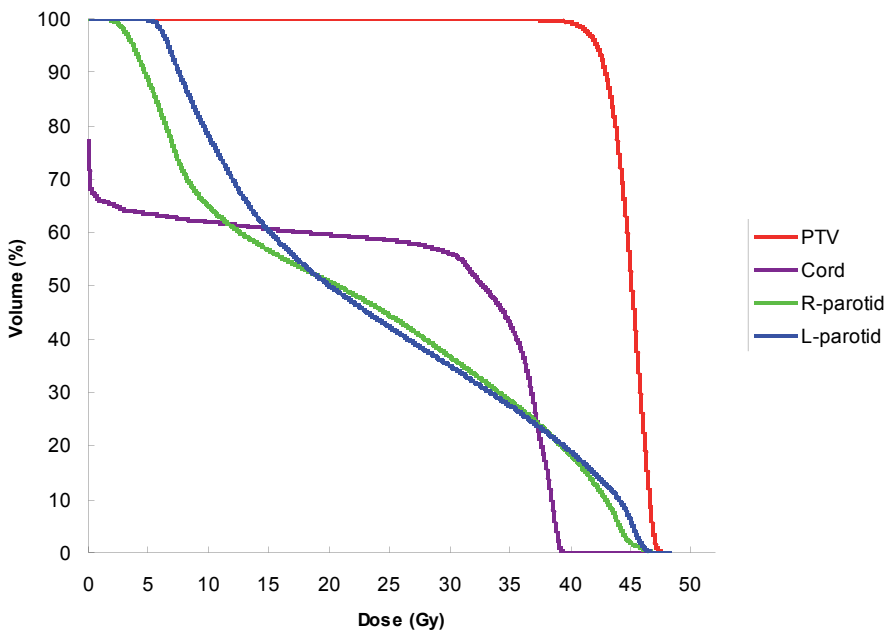


Figure 30: Dose Volume Histogram (DVH) corresponding to figure 25. Note:mean dose left parotid gland 23.2 Gy, mean dose right parotid gland 22.0 Gy.

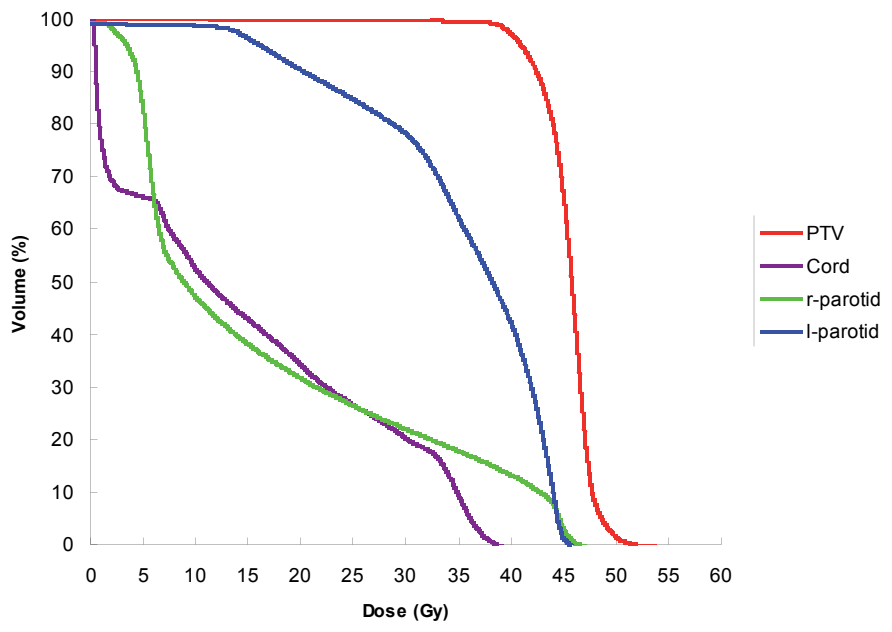


Figure 31: DVH corresponding to figure 26. Note: mean dose left parotid gland 34.8 Gy; however, mean dose right (= contralateral) parotid gland (16.9 Gy) improved by about 5 Gy.

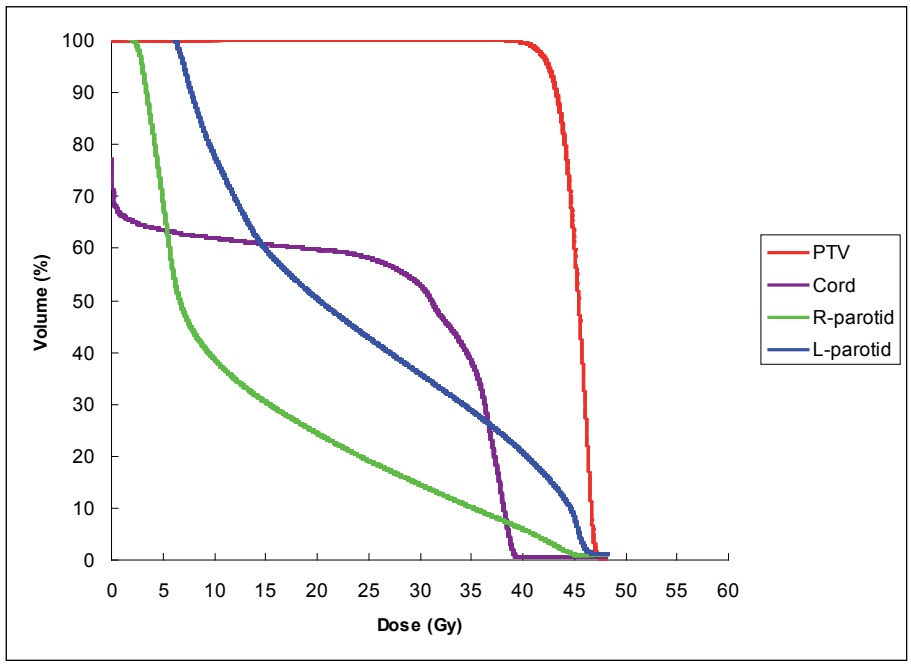


Figure 32: DVH corresponding to figure 27. Note: mean dose left parotid gland 23.0 Gy, mean dose right (= contralateral) parotid gland 12.7 Gy. That is, a significant amount of sparing was obtained due to lowering the cranial border of the right neck.

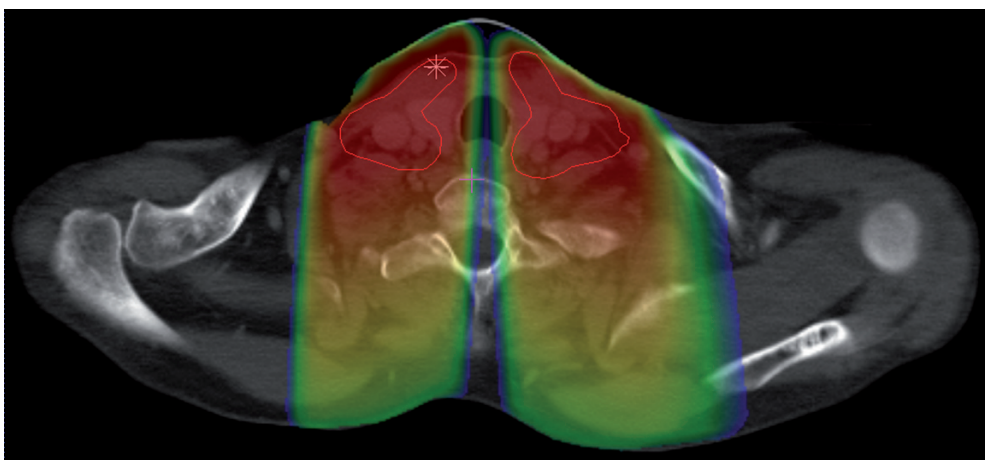


Figure 33: Low anterior neck dose distribution; dose generally prescribed at 3cm depth or at a particular point of interest in the neck (e.g. in case of lymphnodes in lower neck). Note: midline block sparing e.g. larynx.

Dose and Fractionation Primary Sites in Oropharynx

In general for T1–2 lesions, doses of 66 to 70 Gy in 6.5 to 7 weeks with conventional fractionation (1.8 to 2.0 Gy per fraction daily, six fractions per week) are recommended for definitive radiotherapy. However, for T3–4 oropharyngeal cancers, several studies have demonstrated better locoregional control when either accelerated or hyperfractionated regimens are used with concurrent CHT [41,88,91,155]. (For details on altered fractionation, see section Chemotherapy, Targeted Therapy, and Altered Fractionation Regimens). For locally advanced lesions in the head and neck, in recent years the addition of concurrent CHT to either conventional or altered fractionated radiation has shown to be beneficial compared to radiation therapy alone.

Side Effects of Conventional Treatment Techniques

Normal Tissue Toxicity Profile—Acute Effects

The major sequelae of RT can be divided into acute and chronic side effects. They are multifactorial. The potential acute effects on the oral cavity and pharynx after approximately 1 to 3 weeks of RT include mucositis (ulcer), sore throat, loss of taste, and xerostomia (if any of the major salivary glands are in the treatment portal). Approximately 5% of patients develop sialadenitis within 24 hours of the first irradiation treatment, but this usually resolves within 24 to 48 hours. The skin experiences erythema, peeling, and pigmentation. If the capacity of the basal cell layer to repopulate the epidermis is overwhelmed, the result is moist desquamation. Likewise, epilation of hair-bearing areas with accompanying loss of sweat and sebaceous gland function occurs.

Normal Tissue Toxicity Profile— Late Effects

The late effects after definitive RT can include xerostomia, dental caries, altered sense of taste, swallowing problems, dysphagia, altered quality of voice, lymphedema, hypothyroidism, epilation, trismus, cervical fibrosis, atrophy of the mucosa and skin, as well as soft tissue and bone necrosis. In a Rotterdam series on oropharyngeal tumors 25% grade III/IV mucositis (“pinpoint ulcer,” 47/190) and 10% trismus (19/190) were reported. In the process of osteoradionecrosis, radiation is believed to exert an avascular effect on tissues and epithelia that are thinner and more susceptible to injury. The process usually starts with ulceration of soft tissues, which can progress to bone exposure. For refractory cases, hyperbaric oxygen treatment has been advocated. Factors that can influence osteoradionecrosis include elective dental extraction after RT and treatment of tumors near bone. In the modern era, osteonecrosis should be an uncommon event (<5%) [17]. Technique could also play a role, the BT nonlooping technique being associated with a higher reported injury rate than the looping technique [124,191]. Of these late side effects, xerostomia is the most prominent [317], and will be discussed in more detail in the next paragraph. Dysphagia and trismus, although clinically important to prevent, are still somewhat underscored. These are given a prominent place in the discussion involving quality of life (QOL) in the section Performance Status Scale, Socioeconomic Outcomes, and Quality of Life. Finally, clinical reports on late side effects are summarized data in Table 16 [9,99,121,145,175,184,203,226,227,234,285,320].

Xerostomia

Given the way most patients were treated in the (recent) past, frequently using nonsparing parallel -opposed techniques, xerostomia seems to be the overriding side effect. Roesink, et al. from the Utrecht Medical Center reported important observations on the dry mouth syndrome, in particular related to the dose-effect relationship of the major salivary glands (Fig. 34). Irradiation of the salivary glands is obviously associated with loss of function, quantitatively and qualitatively, thus among other things resulting in a reduction in salivary flow and consequently dryness of the mouth. Moderate-to-severe xerostomia occurs in more than 75% of patients treated with conventional lateral beam arrangements. The best definition for objective parotid gland toxicity appeared to be reduction of stimulated output to <25% of the pre-radiotherapy output [260]. Two dose-response curves for stimulated parotid saliva flow rates obtained from relatively large patient groups are available [76,259] (Fig. 34). Both studies conclude that the mean dose to the parotid gland best predicts its function after radiotherapy. The steepness of the dose-response curve and the TD50 value at 1 year after irradiation differHowever, we can conclude from these studies that it is rather safe, in terms of preservation of stimulated parotid gland function, to have a mean parotid gland dose of less than 25 Gy.

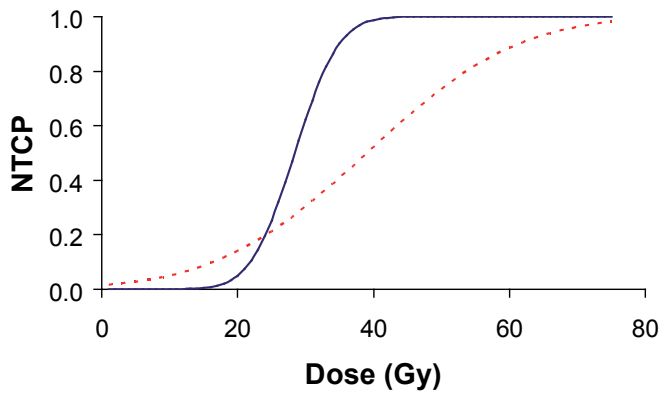


Figure 34: Dose effect relationship xerostomia from Roesink et al. (for explanation see text). NTCP: normal tissue control probability.

When a mean dose is reached above 50 Gy, nearly all patients will have a severe decrease in parotid flow rate. It is generally accepted that IMRT is a valuable tool for reducing the dose to the parotid gland. Several studies report on salivary flow after IMRT for oropharyngeal tumors. However, clinical studies that objectively demonstrate and quantify the advantages of IMRT compared with conventional beam arrangements are scarce. Chao et al. [49] found a correlation of the parotid flow ratio with the mean parotid dose, and a lower mean parotid dose in 27 IMRT patients compared with 14 patients treated conventionally. IMRT versus conventional treatment, however, did not independently influence the functional outcome of the salivary glands in this study. Roesink [259,260] and Terhaard et al. [297] prospectively evaluated a total of 56 patients with oropharyngeal cancer. Of these, 26 received conventional radiotherapy and 30 patients were treated with IMRT. The mean dose to the parotid

	N	First Author	Site		Incidence	%	Incidence	%
EBRT	2308	Parsons, 2002	TF	Servere complications Fatal complications		60.8		
	154	Perez, 1998	TF	Fatal complications Nonfatal complications	2/154 30/154	1 19		
	178	Jackson, 1999	TF	Osteoradionecrosis		3.5		
	676	Withers, 1995	TF	Severe late complications, grade 3/4 (mucossa, bone and muscle)				
	217	Mendenhall, 2000	BOT	Insufficient ability to swallow, osteonecrosis, chondronecrosis, fatal radiation-induced sarcoma	8/217	3.7		
	91	Spanos, 1976	BOT	Bone Necrosis	15/91	16		
	842	Parsons, 2002	BOT	Servere complications Fatal complications		3.8 0.4		
Surgery + PORT	151	Ang et al, 2001	All	Ulcer/soft tissue necrosis	2/76 (63 Gy/5 wk)	3	2/75 (63 Gy/7 wk)	3
				Fibrosis	19/76 (63 Gy/5 wk)	25	13/75 (63 Gy/7 wk)	17
				Dysphagia	16/76 (63 Gy/5 wk),	21	13/75 (63 Gy/7 wk)	17
				Fistula	2/76 (63 Gy/5 wk)	3	5/75 (63 Gy/7 wk)	7
				Osteonecrosis requiring surgery	1/76 (63 Gy/5 wk)	1	2/75 (63 Gy/7 wk)	3
				Chondritis	0/76 (63 Gy/5 wk)	0	1/75 (63 Gy/7 wk)	1
	86	Levendag, 2004	All	Late effect: Mucosa Late effect: Salivary glands Late effect: Dysphagia Late effect: Pain Late effect: Trismus	6/86 2/86 14/86 9/86 18/86	7 2 16 10 21		
	616	Parsons, 2002	TF	Servere complications Fatal complications		23 3.2		
	86	Perez, 1998	TF	Fatal complications Nonfatal complications	2/86 46/86	2 53		
	17	Machtay, 1997	BOT	Gastrostomy and/or tracheostomy	5/17	29.4		
				Osteoradionerosis/soft-tissue necrosis	0/17	0		
				Grade 3 trismus	1/17	5.9		
				Facial edema	1/17	5.9		
	407	Parsons, 2002	BOT	Severe complications Fatal complications		32 3.5		

	N	First Author	Site		Incidence	%	Incidence	%
BT	104	Levendag, 2004	All	Late effect: Mucosa Late effect: Salivary glands Late effect: Dysphagia Late effect: Pain Late effect: Trismus	41/104 6/104 21/104 21/104 1/104	39 6 20 20 1		
	68	Harrison, 1998	BOT	Fatal complications		3		
	41	Gibbs, 2003	BOT	Soft-tissue necrosis/ ulceration Osteoradionecrosis Gastrosstomy Sarcoma	3/41 2/41 1/41 1/41	7.3 4.8 2.4 2.4		

Table 16: Late complications after oropharyngeal cancer radiation treatment

glands was 48.1 Gy for the conventional treatment and 33.7 Gy for IMRT. As a result, 6 weeks after treatment the number of parotid complications was significantly lowerafter IMRT (55%) than after conventional radiotherapy (87%). There are several studies using toxicity scoring systems instead of saliva measurements. Eisbruch et al. report on parotid function after conformal radiotherapy and IMRT [76]. In a matched case control study with a low number of patients treated with standard radiotherapy, the QOL scores of patients treated with IMRT improved over time after irradiation, and no improvement was seen in patients treated with standard radiotherapy [144]. In the studies of Chao et al. [50], the dosimetric advantage of IMRT compared with conventional techniques did translate into a significant reduction of late salivary toxicity in patients with oropharyngeal carcinoma. One has to keep in mind that the submandibular glands also play a major role in producing saliva: in resting state, 70% of the saliva production is believed to be generated by the submandibular glands. The submandibular glands as well as the minor salivary glands are given more attention in clinical research at the present time, but much research on role of these structures still has to be performed. However, sparing of the submandibular gland in oropharyngeal cancer is extremely difficult in case of bilateral treatment of the neck. One possible future avenue is to routinely transfer the submandibular gland ventrally in the contralateral node-negative neck.

Performance Scale Status, Socioeconomic Outcomes, and Quality of Life

Performance Status Scale and Socioeconomic Outcome

A great deal of clinical interest and research is devoted at the present time to (functional) QOL issues, in particular after treatment with interstitial RT [237,258]. This seems relevant, in particular because of the great variation in treatment modalities and treatment schemes used in head and neck cancer with otherwise similar tumor control and survival outcome [253]. The acute toxicity of concurrent chemoradiation is signifi-

cant. However, because of organ preservation, according to an article by Nguyen et al. [217], patients may achieve a better QOL after chemoradiation compared with conventional use of surgery and PORT. Measurement instruments, such as validated questionnaires for QOL, are still evolving but are becoming a routine part of (clinical) research protocols. One such set of evaluation tools frequently used in head and neck cancer is the Performance Status Scale (PSS), as designed by List et al. [179,180]. The system yields scores reflecting patients' ability to eat in public, understandability of patient's speech, and normalcy of diet. The scale has been validated; the best possible score is 100 (normal). Harrison et al. [125] retrospectively examined patients with SCC of the BOT who were treated with RT or surgery, comparing QOL and functional outcome using PSS. Patients treated with RT had consistently better performance status and QOL scores and no difference was observed in all three functional PSS (eat in public, understandability of patient's speech, and normalcy of diet) scores, for early and for the more locally advanced tumors (p = .84). For surgery, the PSS deteriorated significantly when comparing T1 and T2 versus T3 and T4 (p = 0.0014). Pol et al. [240] studied retrospectively similar type of patients; that is, locally advanced T3/T4 BOT cancer treated by surgery plus PORT or EBRT plus HDR-IRT. The authors concluded that for all PSS, the patients scored better in functional QOL when treated by RT as opposed to surgery (p = N.S.). The difference in functional outcome could help clinical investigators in the future as to which treatment is to be preferred per tumor site. In fact, the findings also illustrate the preference of patients for organ-preservation therapy in general. Harrison et al. [123] also reported that at a median follow-up of 5 years, patients' annual incomes were similar to those at presentation, and the great majority of patients were still in full-time work. Nijdam and Levendag [218] studied the total hospital costs of TF and/or SP tumors treated by either IMRT plus BT boost with or without neck dissection versus surgery plus PORT (IMRT). Excellent locoregional tumor control (at 5 years, ±85%) was observed for either combined modality approach. Of particular interest is that the weighted mean cost for BT was significantly less as opposed to surgery: 18,001 versus 28,130. The main denominator in the excessive costs for surgery in this protocol is the number of days of clinical admission to the hospital. Table 17 summarizes the costs for the different treatment options in the current Erasmus MC protocol.

	Mea costs BT (weighted # patients)	Mean costs S (weighted # patients)	Mean costs EBRT (weighted # patients)
Treatment	€ 13.466	€ 24.219	€ 12.502
Folow-up	€ 649	€ 607	€ 482
(Treatment of) relapse	€ 2.848	€ 1.897	€ 4.577
and/or metastases			
Mean costs total group	€ 1.038	€ 1.407	€ 3.582*
Mean costs total group	€ 18.001	€ 28.130	€ 21.143

*Only two patients with significant late side-effects needing long lasting treatments

Table 17: Costs of different treatment modalities used according to Erasmus MC protocol for oropharyngeal cancer.

Health-Related Quality of Life

Several questionnaires have been developed to assess health-related quality of life (HRQOL) for head and neck cancer patients [27,30,46,314]. Each of the side effects can have a different impact on the HRQOL [28,29,105,106,115,116], varying from changes of speech and voice quality to impact on well-being and HRQOL in a broader sense. Interestingly, Nordgren et al. [220,221] evaluated the HRQOL of patients with pharyngeal carcinoma at diagnosis and after 1 and 5 years in a prospective multicenter study. Again, the HRQOL at diagnosis seems to be an important factor for the prognosis of both HRQOL over time and survival.

Trismus and Quality of Life

Trismus, severely restricted mouth opening, is a common problem in head and neck oncology. According to Dijkstra et al. [67,68], it is present at the time of diagnosis in approximately 2% of patients due to tumor growth; in tumors originating from or in the parapharyngeal space it is even more frequent (55%). Additionally, another 8% increase in trismus is due to treatment per se, be it surgery or RT [312]. One of the reasons for this variation in reporting is the lack of uniform criteria. Dijkstra et al. proposed to use as a cut-off point for mouth opening 35 mm, irrespective of dental status, but they acknowledge that differences per subgroup may exist. The paired mastication apparatus facilitates opening of the mouth; it consists of the processes coronoideus and the condyle of the mandible, as well as the muscles responsible for jaw movement. The functionality of this muscular compartment [95] can be summarized as follows: depression (lateral pterygoid, gravity), elevation (temporalis, masseter and medial pterygoid), protrusion (lateral pterygoid, masseter, temporalis), retraction (posterior fibers temporalis, deep fibers masseter), and lateral movement (contralateral lateral pterygoid, bilateral temporalis). Surgery and RT may induce trismus by causing fibrosis of one of the aforementioned muscles. Fibrosis might significantly impact QOL of the patient as it can affect the phonation, nutritional status, and dental hygiene of the patient [248]. The development of some of these late effects typically depend on factors like previous treatment, total dose, fractionation, irradiated volume, and treatment techniques. Dijkstra reported mandibular function impairments in 18% of 89 patients with cancers in the oral cavity and oropharynx. In the Rotterdam series, the incidence was only 1% for the treatment group EBRT plus BT; for the surgery plus PORT series it amounted to 21% [67]. Ways to counteract this often long-lasting problem of trismus are mechanical appliances to reduce the severity of fibrosis [161], hyperbaric oxygen [156], pentoxifylline [54,312], surgical corrective measures [48], and IMRT. Figure 35 depicts an axial CT slice on which the relevant muscles for jaw movement are delineated, the processes coronoideus and condyle of the mandible inclusive. One may decrease the dose to the masseter muscle significantly with IMRT by putting a constraint on the masseter muscle (Fig. 36).

Speech and Quality of Life

For technical treatment planning reasons, voice, and speech can be affected at the time of the actual treatment of cancers in the oropharynx and during the follow-up period. In a recent article by van Gogh et al. [104], the authors also concluded that deviant voice quality can also lead to limitations in social life [302,303]. A robust, short, five-item questionnaire was suggested to be able to detect voice deterioration and differentiate this in a busy outward clinic from a cancer in the larynx [104,152].

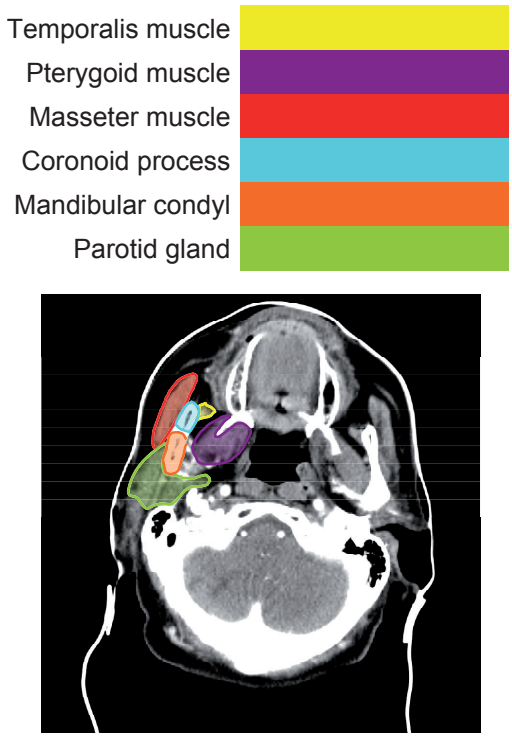


Figure 35: Paired mastication apparatus with structures of relevance depicted on axial CT slice.

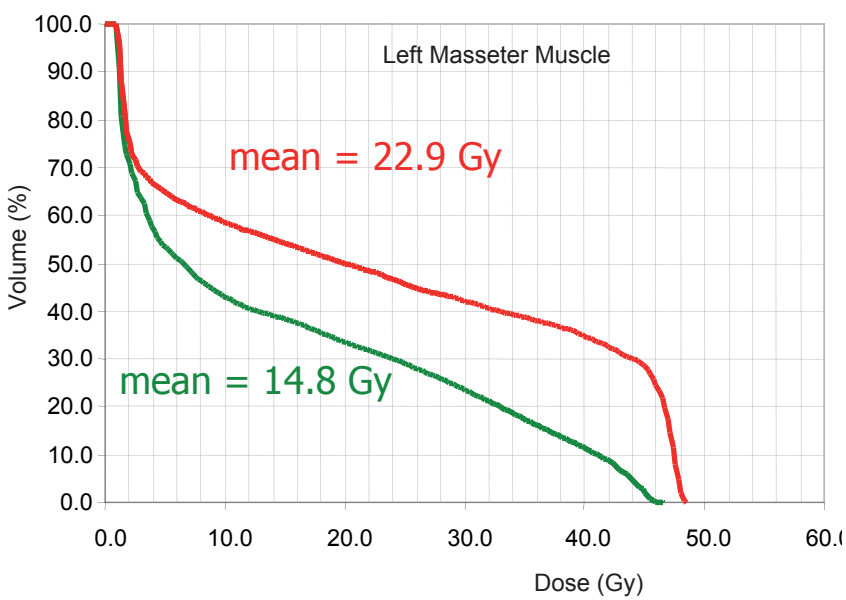


Figure 36: Dose volume histogram showing reduction in mean dose to masseter muscle with or without constraint (in masseter muscle) when using IMRT techniques.

Dysphagia and Quality of Life

Swallowing function may be affected adversely by surgical and nonsurgical tre atment of advanced oropharyngeal cancer [281]. Gastrotomy tube (G-tube) dependence 6 to12 months after surgical management varies in the literature between 6% and 39% [75,280]. Rates of swallowing dysfunction after chemoradiation are less well defined; G-tube dependence varies between 13% and 64% at short-term follow-up and between 13% and 33% at long-term follow-up [94,107,185,215,216,221,265]. In general, after long-term follow-up (>1 year), one third of patients were reported to be G-tube– dependent (BOT 67% vs. TF/SP 25%; p = .049). The swallowing apparatus, being the wall of the pharynx (Fig. 37), is composed of two layers of muscles: the external three constrictor muscles (superior, middle, and inferior constrictor [with its cricopharyngeal and thyropharyngeal part]), the circular fibers of esophagus inlet, and the internal longitudinal levator muscles (stylopharyngeus and palatopharyngeus muscles). Deglutition or swallowing is a complex act of these seven muscular structures. A study was recently initiated in Erasmus MC to get more insight in the problem of dysphagia. First, the components of the swallowing apparatus were determined and delineated on CT. After delineation, dose-volume histograms were constructed and mean doses calculated for every muscular structure. Fifty-five patients with cancer in the oropharynx who were treated between 2000 and 2005 in Erasmus MC were used to study the problem of dysphagia in more detail. All patients were asked to respond to validated questionnaires PSS, EORTC H&N35, and the M.D. Anderson Dysphagia Inventory (Fig. 38). Using a univariate ordered logistic regression analysis technique, it was found that the probability for having serious complaints with swallowing increases significantly with dose (Fig. 39), but interestingly, this was significant for the superior and middle constrictor muscles. A multivariate analysis showed that the only significant factor was BT (dose). However, given the tight enveloping nature of the deglutition musculature, it needs very sophisticated three-dimensional treatment planning to spare the constrictor muscles without compromising on the dose to the primary tumor.

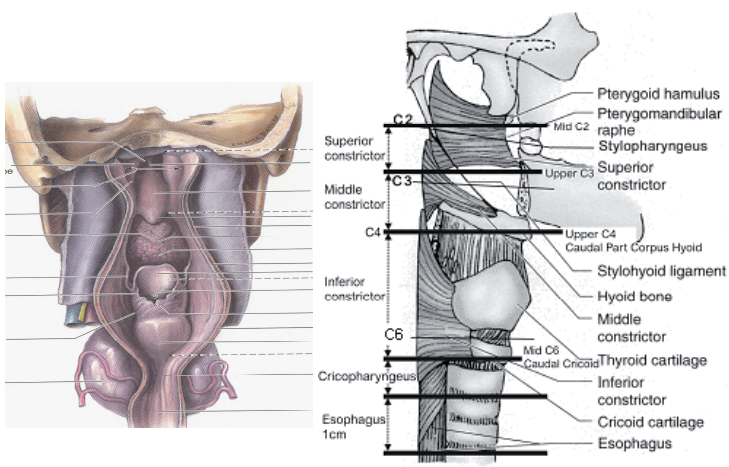
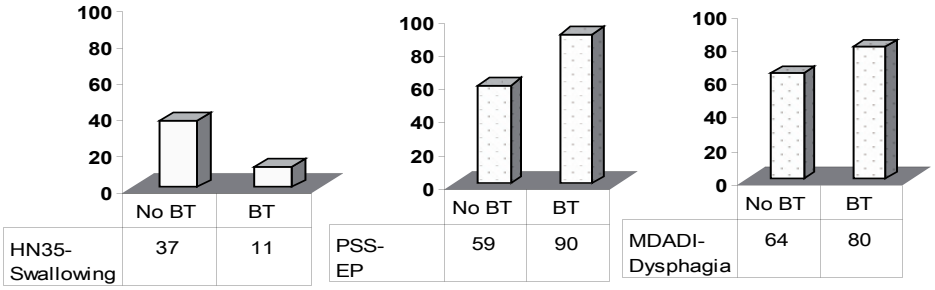


Figure 37: Anatomy swallowing apparatus; see for details text on dysphagia. Photograph from Moore KL, Dalley AF. Clinically Oriented Anatomy 4th Edition, 1999 p.1051, Lippincott Williams & Wilkins, Philadelphia.



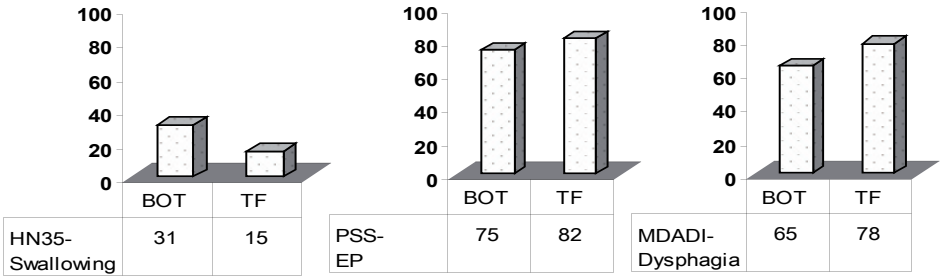


Figure 38: Examples of responses of patients to validated questionnaires HN 35, PSS and MDADI (for abbreviations, see text) the swallowing (HN35), eating in public (PSS) and dysphagia (MDADI) were studied for brachytherapy vs no brachytherapy as well as for BOT vs TF/SP.

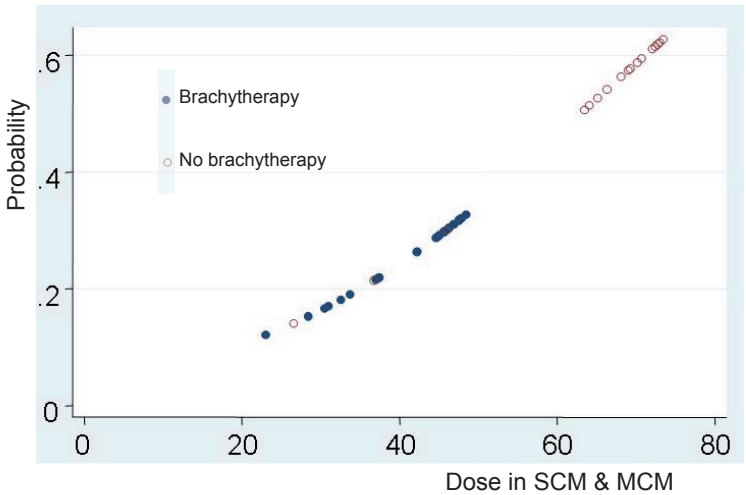


Figure 39: Dose effect relationship for dysphagia. From the figure it seems apparent that with higher doses more dysphagia problems can be expected; moreover the problem of dysphagia seems less with the use of brachytherapy as a boost technique (less dose to the superior- and middle constrictor muscle). SCM: Superior constrictor muscle; MCM: Middle constrictor muscle.

Brachytherapy

The history of BT dates back to the beginning of the 20th century, when the first BT procedures were performed using Radium-226 needles. Brachytherapy ("brachy" = Greek for "short") is a treatment modality in which the tumor is irradiated by positioning the radioactive sources very close to (mould or endocavitary techniques) or even inside the tumor volume (interstitial implant), either by permanent (seed) implant or by temporarily inserted applicators or afterloading catheters. In principle, BT is a conformal type of radiation therapy technique. In recent years, artificial radionuclides such as Cs137, Co60, I125, and Ir192 have become available. Manual afterloading of the sources into applicators or afterloading tubes replaced direct loading of sources into the patient. The French developed the so-called "Paris system" for low-dose-rate dosimetry purposes; that is, for parallel -equidistant sources, the system suggests specifying the dose of the implant as being 85% of the average dose in the basal dose points (local minima). A similar type of dose prescription is used for HDR BT (Figs. 40 and 41).

Also, computer-controlled afterloading devices, supported by sophisticated treatment planning software with optimization capabilities, became available. The BOT implant consists of afterloading catheters after the percutaneous introduction of trocars in a submental or submandibular approach (Fig. 42) [103]. For patients with disease extension toward the pharyngoepiglottic fold, lateral loops are added. The spacing between each end of the "looping" cathe-

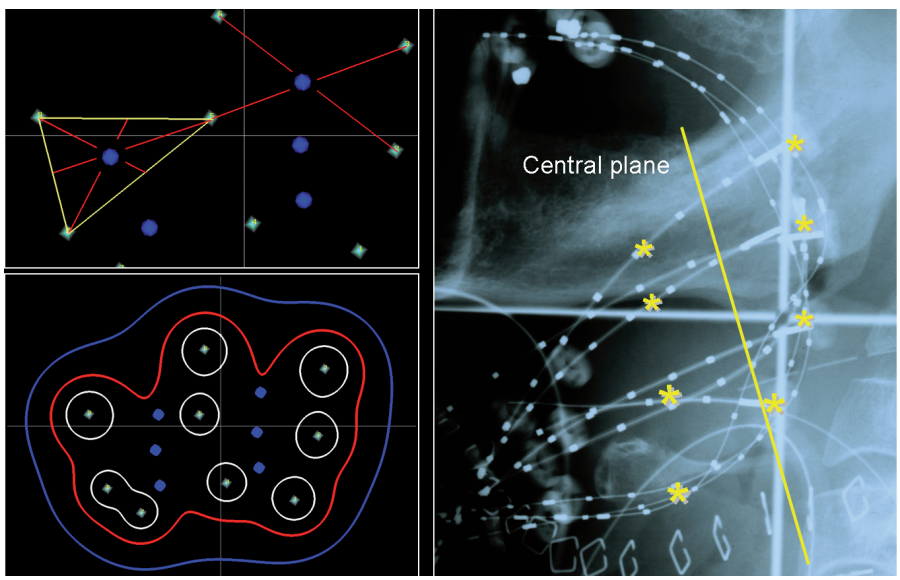


Figure 40: Patient with BOT implant. Sagittal view X-ray film of catheters with dummy sources in situ (right panel). Yellow line depicts central calculation plane. Also shown is cross section of tumor in central plane (left panel). Blue dots are basal dose points ("centers of gravity"). White dots represent "sources". Dose is prescribed to 85% of mean central dose (= average of doses calculated in centers of gravity of all triangles).

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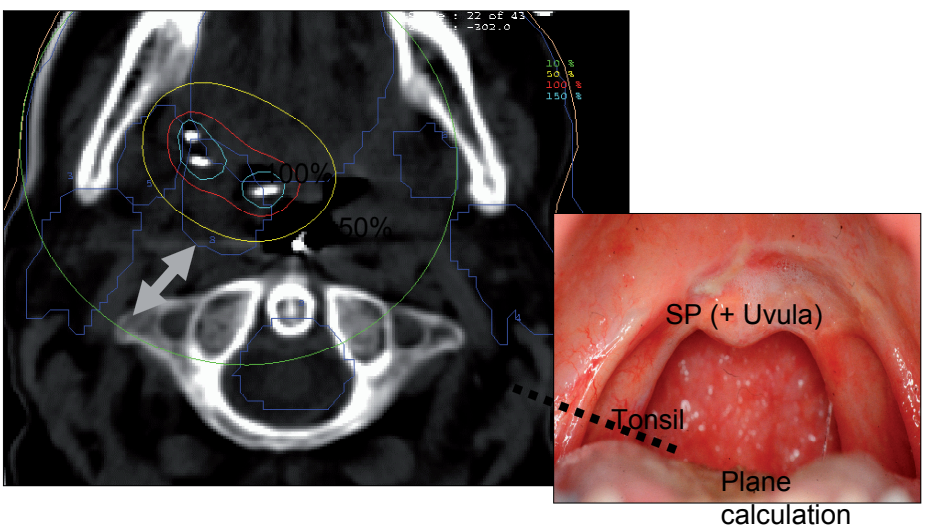

Figure 41: TF and SP implant. Dose distribution central plane. Dose prescribed to 0.5 cm after geometrical optimization.

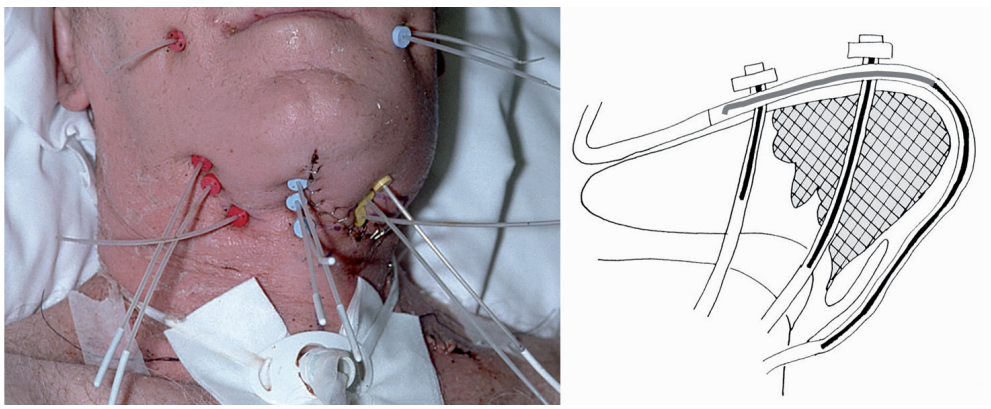

Figure 42: Patient with catheter configuration for BOT implant.

ters running over the dorsum of the tongue is ±1 cm. As a safety precaution, when removing the implant, a temporary tracheostomy is sometimes performed in patients immediately before the implantation. A typical case for fractionated HDR TF and SP implant is depicted in Figure 41. In the majority of cases, two to three catheters are implanted in TF and faucial arches (Fig. 41, inset). A temporary nasogastric feeding tube is placed at the completion of most of our BT procedures. The development of radiobiologic models enables one to predict to a certain extent the tumor control probability and normal tissue complication probability after the application of BT, much depending on factors such as fraction size, dose rate, the tumor, and the normal

tissues one is dealing with. Temporary BT has been used with several dose-rate categories. The French have published extensively on interstitial radiation therapy of TF and/or SP tumors, as well as on cancers of the BOT [32,60,69,79,86,98,139,175,201,229,235,236,249,274,327]; most of these data regard LDR implants. For example, Mazeron et al. [199] report on a subset of patients with early-stage (T1, T2) tumors of the TF and/or SP, with a LC rate of approximately 85%, that is, a regional control rate of 97% for N0, and 88% N1–3 disease. Patients were typically treated by 45 Gy EBRT and a 30 Gy LDR Ir192 boost. Soft tissue ulceration occurred in 17 patients. Similar locoregional control rates were reported by Pernot et al. [235,236] (LC LDR boost TF/SP T1, T2N0 tumors 90% vs. T1, T2N1–3 86%) and Levendag et al. [175,177] (TF and/or SP tumors LRC 87% at 5 years). The series of patients in Rotterdam were treated by fractionated HDR BT (daytime regimen) or PDR (24 hours regime) (Table 18). Esche et al. [79] described 43 patients with carcinoma of the SP and uvula with LC rate of 92%. Overall survival was 60% at 3 years and 37% at 5 years. The cause-specific survivals were 81% and 64%, respectively. The leading cause of death was other aerodigestive cancers (these cancers occur with an actuarial rate of 3% per year posttreatment). The “BT school ” of Memorial Sloan Kettering Cancer Center in New York pioneered large-volume implants in particular for cancer of the BOT, a technique initially designed by Vikram and Hilaris [307] and Vikram et al. [308]. Harrison et al. [120,121,125,127] elaborated on cancer of the BOT and also related outcomes to QOL. Some of the control rates with IRT can be taken from Table 42.11 (TF/SP) and Table 42.14 (BOT). In skillful, well-trained, hands, BT remains an extremely gratifying technique for applying high doses of radiation for small –volume disease located in the midline (e.g., SP tumors) with (in case of fractionated HDR) highly conformal and accelerated properties. Finally, IRT can also be a very rewarding technique, given the high doses in smallvolume disease and the rapid dose falloff in the treatment of recurrent cancers and/or in case of reirradiation [58].

For the future, image-guided BT will become routine; summation of dose distributions of BT and EBRT will become mandatory (Fig. 43). Moreover, by the development of soft x-ray sources and afterloading machines that carry multiple sources and have multiple drives, the flexibility of intraoperative BT has increased. One of these sources that is currently being tested is ytterbium [169].

Chemotherapy Targeted Therapy, and Altered Fractionation Regimes

Concurrent CHT and altered fractionated irradiation have shown independently to improve the outcome for head and neck cancer patients. The combination maximizes the chance for preservation of organ function and has the potential to improve the results even more by integration with new biologic agents [10,36,187,206,261,264,288]. Many of the hyperfractionated and/or accelerated schedules have resulted in improved locoregional control. Concomitant CHT appears to result in improved LRC and OS, in contrast to neoadjuvant CHT and maintenance CHT [22,42,217]. Not infrequently, these treatment regimes increase toxicity as well. Finally, the role of intra-arterial CHT [206,213,257] as well as the benefit of induction (neoadjuvant) and adjuvant CHT remains to be determined. In their concise review on randomized trials concerning multimoda lity treatment approaches, Bernier and Bentzen [22] emphasized that, to maximize outcome, each of the components of a particular treatment regime needs to be optimized separately. Importantly, Benasso et al. [20] and Taylor

Table of reference (Gy) for fractionated HDR (fr.HDR) and PDR brachytherapy as of 2001.

Tumor site	fr.HDR	PDR	SRT
BT as full course:			
Nasal vestibule, Skin, Lip	4+12x3+4		
One-plane implant: microscopic disease	4+12x3+4	2.5+29x1.5+2.5	
Any other site T1-4	4+16x3+4	2.5+38x1.5+2.5	6x6
Re-irradiation nasopharynx	15x3		
Re-irradiation other tumors	4+15x3+4	2.5+35x1.5+2.5 (preference)	
BT as boost:			
Nasopharynx			
After 60Gy EBRT	4+3x3+4		
After 70Gy EBRT	4+3+4		4x2.8
Re-irradiation after 46 Gy EBRT	6x3		
One-plane implant: microscopic disease			
After 46Gy EBRT	4+3+4	2+8x1+2	
Any other site T1-4			
After 46Gy EBRT	4+4x3+4	2+18x1+2	3x5.5

Total number of brachytherapy fracionts. Full course: radiation is only given by means of brachytherapy. In the case of booster doses, generally 46/2 Gy are given by means of external beam radiation therapy (EBRT). The booster dose for cancer in the nasopharynx is given after either 60/2 EBRT or 70/2 gy EBRT. SRT (stereotactic radiation therapy) means a booster dose by Cyberknife (as of 2005).

Table 18: Fractionation schedules for “fractionated HDR”, “PDR” and SRT (Cyberknife) used in the Erasmus MC-DDHCC.

et al. [295] conducted multivariate analyses of patients treated in chemoradiotherapy head and neck trials, and pointed out that the second most important prognostic factor is the experience of the Center. Regarding the effects on OS and locoregional control by altered fractionation and/or concomitant CHT, in 2004 Rosenthal and Kian [261] made some recommendations for treatment selection: conventional fractionation (and dose) for T1 and favorable T2N0,1 tumors, altered fractionation for unfavorable T2 or exophytic T3N0,1 (with or without neck dissection in case of N2,3 disease), and concurrent CHT for the more advanced cancers. Meanwhile, toxicity amelioration and identification of predictive biomarkers and effective molecularly targeted therapy should be pursued [261,292]. Salama et al. [264] published on aggressive trimodality treatment for the subset of patients with recurrent and/or second primary cancers in the head and neck. They evaluated 115 patients treated with a median lifetime radiation dose of 131 Gy. The locoregional control, OS, and freedom from distant metastasis rate at 3 years were 22%,

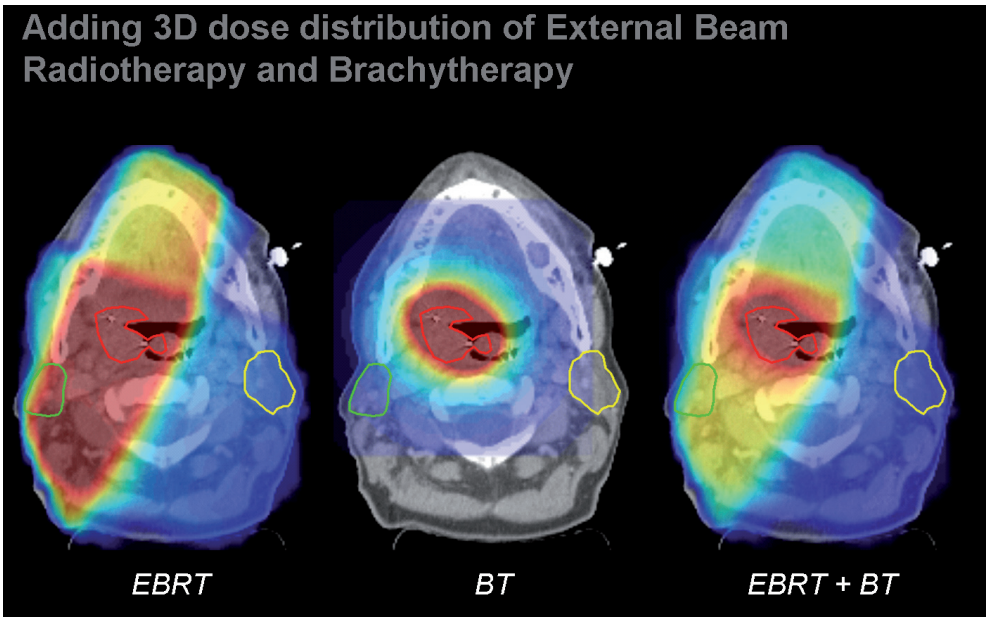

Figure 43: Treatment planning software is currently being developed in Erasmus MC to summate variable IMRT doses with BT doses, taking into account deformation of the target volume and normal tissues during treatment.

51%, and 61%, respectively. However, of note is that 19 patients died of treatment-related toxicity, 5 of these because of carotid blow-out. Suntharalingam [292] reviewed the early trials in 2003. Recognizing the mostly nonspecific nature of the toxicities of healthy tissues consequential to combined modality therapy, he argued that the real focus should be on researching newer biologic agents, targeting cellular protein receptors. Epidermal growth factor receptor is one of these receptors critical to cellular proliferation, differentiation, and survival. As it has been shown to be widely expressed in SCC cells of the head and neck, it was suggested that anti–epidermal growth factor receptor therapy could become a powerful agent in combined modality therapy in the future.

Nonrandomized Studies

Some of the studies reviewed in this section are designed to treat advanced cancers in the head and neck in general and not focused solely on tumors in the oropharynx. As has been shown by the meta-analyses, concomitant CHT and/or altered fractionation result in improved locoregional control and OS, but also a substantial amount of toxicity has been observed [35,238]. In fact, with regard to concomitant CHT, Pignon and Bourhis [238] showed at 5 years an 8% increase in OS and a hazard ratio of 2.17 for overall toxicity. Harrison [128] published the results of a phase II trial treating 82 patients with unresectable head and neck cancer using the delayed concomitant boost technique with concurrent cisplatin. The 3-year LC for oropharynx cancers was 64%. Twenty-four percent of patients required a treatment break. Two deaths due to sepsis occurred during treatment. Severe chronic toxicity occurred in three patients: one osteoradionecrosis, one frontal lobe necrosis, and one case of lung

toxicity secondary to adjuvant CHT. Bieri [25] reported on delayed concomitant boost radiation in which a planned total dose of 69.6 Gy was given in 5.5 weeks; one third of the patients received concurrent cisplatin-based CHT. Among the 55 patients with oropharynx carcinoma, LRC at 3 years was 69.5%. Eighty-two percent experienced grade 3 and 4 mucositis. Patients receiving CHT had more grade 3 dysphagia (68% vs. 25%; p = .003), hospitalization (37% vs. 14%; p = .08), and a need for nasogastric tube (68% vs. 22%; p = .001). Nathu [214] published the results of induction CHT followed by RT for patients with oropharyngeal carcinomas treated at the University of Florida. Neoadjuvant CHT consisted of cisplatinum (100 mg/m2) and 5-fluorouacil (1.0 mg/m2/day × 5 days) for three cycles, and was followed by definitive RT (83% received hyperfractionated RT from 74.4 to 81.75 Gy). Outcome was compared with oropharyngeal tumors treated with a similar radiation regimen, but without CHT. Multivariate analysis showed no difference in local failure or distant failure. However, disease-specific survival and OS were improved in those who received induction CHT (58% vs. 27% and 42% vs. 17%, respectively). Because of the nonrandomized nature of the study and the lack of statistically significant improvement in parameters of tumor control, the authors cautioned against any conclusions regarding the benefit of induction chemotherapy. A phase II study on 61 patients with advanced oropharyngeal carcinoma using induction chemotherapy followed by concurrent chemoradiation was reported by Vokes [309]. Neck dissections (n = 35) were performed for N2 to N3 disease. At a median follow-up of 39 months (68 months among survivors), LRC was 70%, distant metastasis-free survival was 89%, disease-free survival was 64%, and OS was 51%. Acute toxicity was substantial, with severe or life-threatening mucositis and leukopenia during the induction phase, whereas 81% had grade 3 or 4 mucositis during the concurrent chemoradiotherapy. The authors concluded that the treatment sequence of induction chemotherapy followed by concurrent chemoradiotherapy and optional organpreservation surgery is promising but that less toxic regimens need to be identified. Bensadoun [21] reported on 54 patients with unresectable oropharynx and hypopharynx carcinoma treated with concomitant hyperfractionated radiation (75.6 to 80.4 Gy) and three cycles of 5-FU/cisplatin in weeks 1, 4, and 7. Four percent mortality was observed from treatment related septicemia, 86% grade 3/4 mucositis but no patient required a treatment break greater than 4 days because of mucositis. Grade 2 xerostomia was observed in 70% of the patients and grade 2 cervical fibrosis in 45% of the patients. At a median follow-up of 16 months, diseasespecific survival was 72%. There are many other examples of chemoradiotherapy regimen for oropharyngeal carcinomas with encouraging LRC rates, but with short-term follow-up and/or too small patient numbers [10,100,187]. A promising approach was presented by the Memorial Sloan Kettering Cancer Center. Arruda et al. [62] studied 50 patients treated by IMRT in conjunction with concurrent CHT (86%). At 2 years, local progression-free OS and distant metastases-free survival is 98%, 98%, and 84%, respectively. Six of 42 patients remained with their percutaneous endoscopic gastrostomy until the time of analysis.

Randomized Trials

A prime example of a multinational, randomized trial of molecularly targeted therapy is the study by Bonner et al. [33] that was recently published in the New England Journal of Medicine. It compares patients with advanced cancers in the head and

neck treated with high-dose RT alone (n = 213) or with RT plus weekly cetuximab, a monoclonal antibody against epidermal growth factor. The outcome of the study showed a significant improvement of locoregional control (hazard ratio locoregional progression or death 0.68; p = .005) and OS (49 months for combined therapy vs. 29.3 months for RT alone [hazard ratio for death, 0.74; p = 0.03]). It reduced mortality without increasing the common side effects of radiation. Studies for future targeted therapies combining cetuximab with chemotherapeutic agents such as Taxotere, cisplatin, and 5FU are now underway. Concurrent CHT with hyperfractionated radiation was explored by Brizel [36] in a phase III randomized trial. One hundred sixteen patients with advanced head and neck cancer were randomized to hyperfractionated radiation alone treated with 1.25 Gy twice daily 5 days per week to 75 Gy during a 6-week period versus a concurrent CHT arm consisting of 5-FU/CDDP given on weeks 1 and 6 of splitcourse hyperfractionated radiation. Both groups received two adjuvant courses of 5-FU/CDDP after completion of radiation. At a median follow-up of 41 months, the concurrent CHT showed improved LRC (70% vs. 44%; p = .01) and a trend toward improved 3-year OS (55% vs. 34%; p = .07) and relapse-free survival (61% vs. 41%; p = .08). However, patients in the chemoradiotherapy arm developed more acute toxicity, including the requirement for more feeding tubes (44% vs. 29%) and worse hematologic suppression. Chronic toxicity was no different, with about a 10% incidence of necrosis of the skin or bone in both arms. The trial has been criticized, not only for the added toxicity, but also because of the imbalance in the proportion of advanced neck disease (44% vs. 63%) treated in the concurrent chemoradiotherapy, which may have accounted for the difference in LRC. Jeremic [148] reported a phase III randomized study testing whether daily low-dose cisplatin improved outcome for patients undergoing hyperfractionation radiation compared with those treated with the same hyperfractionated radiation alone in locally advanced head and neck cancers (37% were oropharynx). One hundred thirty patients with stage III or IV disease were randomized to 1.1 Gy twice daily to 77 Gy per 7 weeks with or without cisplatin (6 mg/m2/day). At a median follow-up of 79 months, the investigational arm showed improved LRC (50% vs. 36% at 5 years; p = .041), progression-free survival (46% vs. 25% at 5 years; p = .0068), and OS (46% vs. 25% at 5 years; p = .0075), and fewer distant metastases (14% vs. 43% at 5 years; p = .0013). Daily concurrent CHT was well tolerated, with no increase in acute grade 3 mucositis and esophagitis. There were no increases in late skin or severe effects to bone or salivary gland. A multicenter randomized trial reported by Staar [288] tested whether the combination of hyperfractionated accelerated radiation (69.9 Gy/5 × 5.5 weeks) with carboplatin (70 mg/m2) and 5-FU (600 mg/m2/day × 5 days) on weeks 1 and 5 of RT improved outcome compared with the same radiation regimen alone. At a median follow-up of 22 months, the 1- and 2-year respective rates of LRC were 69% and 52% after chemotherapy/RT compared with 58% and 45% after RT alone (p = .14). Patients with oropharyngeal carcinomas had a trend toward improved 2-year LRC with chemoradiotherapy compared with RT alone (51% vs. 42%; p = .07). Another German multicenter randomized trial compared hyperfractionated accelerated radiotherapy alone (77.6 Gy) with hyperfractionated accelerated radiochemotherapy (70.6 Gy) using mitomycin C and 5-FU (130). For patients treated inside the trial, no significant difference in survival was observed. A randomized phase II EORTC trial explored the feasibility of concomitant cisplatin and RT with conventional fractionation or mul-

tiple fractions per day (MFD). The MFD schedule was designed to achieve higher tumor concentrations of cisplatin at the time of irradiation by reducing the number of radiation treatment weeks from 7 to 3. No difference in acute and late side effects in both treatment arms while better tumor response was obtained with MFD. It is argued that the better tumor response in the MFD might be due to a (67%) higher daily dose of cisplatin concomitant with RT being given in a 3-week period [13]. Hao et al. [119] updated the meta-analyses outcome of concomitant CHT trials to date in SCC of the head and neck. They confirmed an 8% benefit in 5-year absolute survival. Toxicity in general seems to be more pronounced with combined modality regimens using hyperfractionated RT or when the concomitant CHT regimen included carboplatin plus 5-FU. Several other randomized studies (e.g., Horiot et al. [139] or Fu et al. [93]) have demonstrated the beneficial effect of hyperfractionation and/or accelerated fractionation over standard fractionation. Also, Calais [42,43] demonstrated better locoregional control when altered fractionation is used with concurrent CHT. According to Hao et al. [119], the current state of the evidence supports strongly to offer platinum-based concurrent CHT with conventional fractionated RT as a treatment option for patients with advanced head and neck cancers treated outside a clinical trial.

Three-Dimensional Conformal RT/IMRT

The introduction of the multileaf collimator and three-dimensional treatment planning systems (TPS) in the 1990s has been instrumental for the development and application of three-dimensional conformal radiation therapy and IMRT. The major advantages of IMRT for irradiation of the complex head and neck anatomy are now generally recognized. The possibility of tightly shaping the higher isodose surfaces around the often concave target volumes allows for substantial sparing of critical structures. The use of electrons for irradiating the posterior neck, without exceeding the cord dose, has become almost obsolete. In this section, procedures are described for a safe and beneficial application of this powerful tool with focus on the IMRT techniques as used in the Erasmus MC.

IMRT

Treatment Planning

In the Erasmus MC, in case of radical radiation therapy of oropharyngeal cancer, IMRT is used to deliver a total dose of 46 Gy, 2 Gy per fraction, 6 fractions per week, to the primary tumor and neck, generally followed by a BT- or CyberKnife boost (Fig. 19). In line with the International Commission on Radiation Units and Measurements criteria for dose homogeneity in the PTV, it is generally required that 100% of the PTV must obtain more than 95% of the prescribed dose [143], although small underdosages (e.g., around the salivary glands) are acceptable in specific cases. Tolerating minor PTV underdosages has also been described by Fogliata et al. [83] and Wu et al. [325]. Recently, we have studied this trade-off between full PTV coverage and sparing of the parotid glands, using a model for calculation of the subclinical disease control probability [163]. For the patients in the study, the mean parotid gland dose decreased by more than 10 Gy by allowing for a small underdosage in the PTV, corresponding with a reduction in the calculated subclinical disease control probability of typically 1% and a little higher. The applied planning constraints for the critical structures for IMRT as used in Erasmus MC are presented in Table 19 and

	ERASMUS MC	RTOG protocol H-0022
Spinal cord	Dmax < 50 Gy	Dmax < 45 Gy
Mandible		Dmax < 70 Gy
Glottic Larynx	#	2/3 below 50 Gy
Brainstem	Dmax < 50 Gy	Dmax < 54 Gy
Parotid gland	Dmean < 26 Gy	Dmean < 26 Gy *
Oral cavity	Dmean < 26 Gy	

Sparing of the larynx is described in detail in section IMRT, Treatment planning
* At least 50% of either parotid gland receives < 30 Gy, or at least 20 cc of the combined volume of both parotid glands receives < 20 Gy.

Table 19: Dose constraints for the critical stuctures according to the Radiation Therapy Oncology Group (RTOG) protocol H 0022, and as applied in IMRT techniques as used in the Erasmus MC. (1):2): At least 50 % of either parotid gland receives < 30 Gy, or at least 20 cc of the combined volume of both parotid glands receives < 20 Gy.

compared with the RTOG H-0022 protocol [247]. For plan design, the constraints for the cord and the PTV are overriding, and the criteria for the parotids and oral cavity are planning objectives rather than hard constraints. To create a safety margin, the cord constraint is set for the spinal canal, rather than for the cord per se. Depending on the patient geometry, different planning strategies are used. The most favorable strategy is to spare both parotid glands. This is done using a nonequiangular, five-field technique, with gantry angles of 0 degrees, ±60 degrees and ±140 degrees (optimized for each individual patient), using 6-MV beams. Especially when the boost is also delivered with IMRT, significant sparing of both parotids is frequently not feasible. It may then be decided to largely relax the constraint for the ipsilateral parotid gland and to focus on sparing of the contralateral gland. Generally, a non-symmetrical fourfield technique is then applied, with two parallel -opposed beams at gantry angles of around 350 degrees and 160 degrees (or 10 degrees and 200 degrees, depending on tumor position). With such an approach, that is, sparing of a single parotid gland structure Eisbruch et al. [73] observed a salivary flow increase after 2 years. In the absence of positive nodes, the lower neck region is treated with two non-IMRT anterior fields, positioned on either side of the cord with sparing of the larynx (midline block) (Fig. 33). The International Commission on Radiation Units and Measurements dose homogeneity criterion is then less strictly enforced. Another technique to cover the lower neck region is to extend the upper IMRT fields. Figures 27 and 30 show a five-field technique (0 to 46 Gy) for a patient with a TF tumor (T2N1) to be treated by RT to the primary and bilateral neck. For this bilateral parotid sparing treatment plan, mean doses to the parotids are 22 and 23 Gy, respectively. For comparison purposes, Figures 28 and 31 show a treatment plan with focus on maximum sparing of the contralateral parotid, yielding mean doses of 17 Gy (contralateral parotid gland) and 30 Gy (ipsilateral parotid gland).

Patient Setup Verification, Correction, and PTV-Margins
IMRT is most effective when used in combination with narrow PTV margins that have

to be in line with the geometrical uncertainties for the patient involved. This implies a proper knowledge of the setup variations. Each patient has a setup error that occurs during all fractions (the systematic or mean error) and day-to-day variations around this mean setup error (the random errors) [26,278]. By its nature, the systematic error of an individual patient can be obtained only from measurements during each fraction, and is therefore not known at the time of treatment planning. The setup uncertainties are generally quantified by three standard deviations Σ_x,Σ_y, and Σ_z, describing the distribution of systematic setup errors in the patient group, and the standard deviations σ_x, σ_y, and σ_z that represent the day-to-day variations. For head and neck cancer patients, these standard deviations are mostly derived from measurements with electronic portal imaging devices (EPIDs). Stroom et al. [289,290], from our institution, derived for each direction, i, the required PTV margin, M_i , given by: $M_i = 0.7 \cdot \sigma_i + 2 \cdot \Sigma_i$. In this approach, the PTV margin of each new patient is fully based on setup measurements performed for previously treated patients. The formula reflects the idea that systematic errors, potentially leading to an underdosage of a specific part of the tumor in all fractions, are more severe than random errors. The equation was confirmed by the work of van Herk et al. [132]. Setup errors can be minimized using EPID measurements and a correction protocol. Deviations in the patient setup are then quantified by comparison of the EPID images with digitally reconstructed radiographs derived from the planning CT scan. It is essential that the demarcations on the patient's skin or mask, used for setup at the linac, are in exact agreement with the isocenter of the planning CT scan. These demarcations should not be adjusted in a session at a conventional simulator, neither should verification be based on acquired simulator images [19]. In an online protocol, the patient setup error is assessed in each fraction using a few monitor units (MUs), followed by a subsequent correction and delivery of the remainder of the MUs. With such a protocol, both the systematic error and the random component can be substantially reduced. However, a disadvantage of online protocols is the involved workload at the treatment unit and the unavoidable increase of the fraction time. For this reason, so-called off-line protocols are more often applied than online protocols. In an off-line protocol, EPID images are only acquired in a limited number of fractions, and all image analyses are performed off-line, that is, not during the time of the delivery of the fractions. The latter excludes the possibility of reduction of random errors, which is of lesser relevance for the determination of the required margin (equation). Instead, the aim of an off-line protocol is to reduce the more important systematic patient setup errors by estimating the optimal a priori setup correction for subsequent fractions. In the Erasmus MC we have developed and implemented the no-action level (NAL) protocol for off-line corrections [63], which is now applied for most patient groups, including those with oropharyngeal cancer. For each patient, the protocol starts with acquisition of EPID images during the first Nm fractions (Erasmus MC Nm = 2 for head and neck sites), without applying any setup corrections. The involved systematic setup error for the complete fractionated treatment is then estimated by calculation of the mean setup error in these first Nm fractions. In the remainder of the fractions, the patient is first set up using the (original) marks on the patient mask. Then, prior to dose delivery, an a priori setup correction is performed as prescribed by minus the (estimated systematic error), followed by irradiation; no images are acquired. The first application of the NAL protocol for head and neck cancer was described by de

Boer et al. [65]. The patients in this study were treated with parallel -opposed laterals, and the NAL protocol was therefore only applied in two directions. Table 20 shows the setup errors for IMRT patients, as derived in a recent analysis (not published). As previously outlined, for each patient, the setup correction is based on an estimate of the systematic setup error, derived from measurements in only two fractions. As a consequence, application of the NAL protocol will diminish the systematic errors, but not cancel them out. In Table 20, both the distribution of the residual systematic errors, Σ_{NAL}, and the distribution of (calculated) initial systematic errors, Σ_{init}, that would have occurred without application of NAL, are presented. The presented margins are calculated with the equation provided. In clinical practice, margins of 5 mm are used for all directions, leaving some room for delineation uncertainty. Recently, the NAL protocol has been extended (eNAL) to systematically update setup corrections based on weekly follow-up measurements [64].

	LR	CC	AP
σ	1.6	1.6	1.4
Σ_{init}	2.3	1.6	2.1
M_{init}	6	5	6
Σ_{NAL}	0.9	0.9	0.8
M_{NAL}	3	3	3

Table 20: Set-up errors and calculated margins (in mm) for H&N cancer patients treated in the Erasmus MC with IMRT. Left-right (LR), cranio-caudal (CC), anterior-posterior (AP) directions. Standard deviations σ (distributions of random errors), Σ_{NAL} (residual systematic errors with the clinically applied NAL set-up correction protocol), Σ_{init} (systematic errors that would have occurred without NAL), M_{NAL}, and M_{init} are margins calculated with Equation (1) (see text).

Dosimetric Quality Assurance

In our institution, IMRT is delivered with dynamic multileaf collimation (DMLC), using the sliding window technique. Because of the complexity, a dedicated quality assurance (QA) protocol is instituted, supplementing the QA procedures for non-IMRT treatments. All involved dosimetric measurements for IMRT are performed with EPIDs (Fig. 44) [89,90,131]. For daily linac QA, the sliding-gap method as proposed by LoSasso et al. [181], measuring the leaf positioning accuracy with an ionization chamber for a single leaf pair, has been extended to two-dimensional, using the EPID [305]. The measurements take 3 minutes, including the analyses. Errors in leaf positioning as small as 0.1 to 0.2 mm can be detected. Apart from the daily verification of the leaf motions, QA procedures are performed for each individual IMRT patient [228,304,306,328,329]. These procedures aim at (a) verification of the final TPS dose calculation for the optimized treatment parameters such as the leaf trajectories, and (b) verification of the correct execution of the plan at the linac. Currently, the TPS dose is only verified by an independent dose calculation for a single or few points in the center of the tumor. A fully three-dimensional procedure is being developed. For verification of the correct fluence delivery at the linac, EPID dose

measurements are performed both prior to the first treatment fraction (pretreatment verification [229,306], and during treatment ("in vivo" verification [305]. For pretreatment verification, portal dose images (a two-dimensional dose distribution in the plane of the fluorescent screen of the EPID) measured with the EPID are compared with predictions. Differences point at errors in leaf sequencing, data transfer from the TPS to the linac, or to dosimetric/mechanical linac performance problems. Presently, portal dose image comparison (Fig. 45) has been fully integrated in the applied EPID software (Theraview NT, Cablon Medical, Heusden, The Netherlands); a method for automated image analysis also has been implemented.

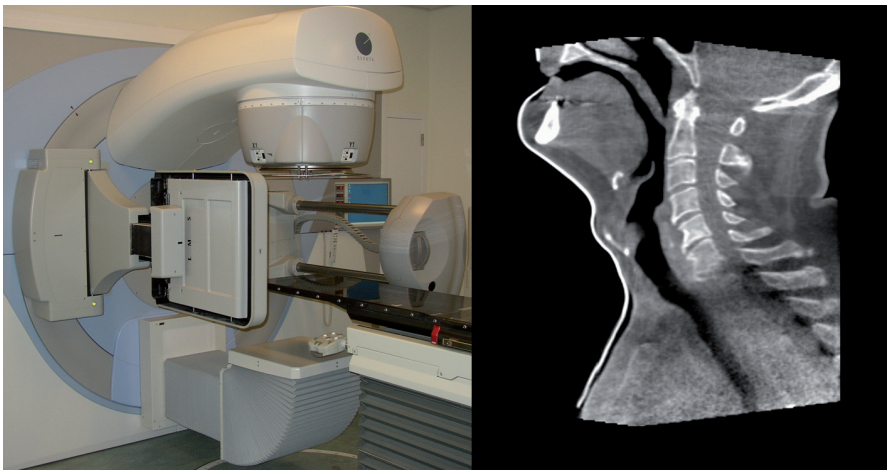

Figure 44: Left panel: the Elekta Synergy system with an additional kV tube and 2D detector for acquisition of cone-beam CT-scans and the Theraview NT EPID for set-up verification and dosimetric QA; Right panel: sagittal cone beam CT-slice for a H&N patient.

Images are only reviewed by a physicist in case of a failure to pass the automated test. Because of the high spatial resolution, EPIDs are suited for detection of tongue-and-groove underdosage effects. For a group of 270 IMRT patients, the pretreatment procedure has revealed four serious errors prior to the start of treatment [329]. Recently, methods have been developed for back-projection of fluence profiles, measured with the EPID, in the planning CT scan or in an in-room acquired cone beam CT scan, allowing full three-dimensional analyses [328]. Deviations in in vivo measured PDIs may be due to errors in fluence delivery, but may also be caused by changes in patient anatomy or variations in patient setup. To discriminate between the two, the split IMRT field technique [305] has been developed, which is now routinely applied for all head and neck cancer patients.

Alternative IMRT Approaches

Beam Orientations

Instead of dedicated orientations, often a relatively large number of equiangular beams are used. Whereas some articles report techniques with seven equiangular beams for oropharynx tumors [62,239], others advocate nine beams [324]. Generally, an odd number is used to avoid opposing beams.

Simultaneous Integrated Boost

For oropharyngeal cancer patients treated in the Erasmus MC, the boost is generally delivered with BT or the CyberKnife after 46 Gy. When using IMRT for full –dose delivery, a simultaneous integrated boost technique may be applied [166,247,325]. The involved simultaneous optimization of the large field and the boost technique does generally result in superior plans, compared with sequential optimization [211]. With the simultaneous integrated boost technique, an enhanced fraction dose may be selected for the primary tumor, yielding two simultaneous opportunities for biologic dose escalation: a shortening of the total treatment duration and an increased LC as a result of the higher daily tumor dose. However, the possibilities for application of escalated fraction doses are limited by the risk of increased toxicity [166,325]. Alternatively, to minimize complications, the fraction dose in the elective regions may be reduced. The current RTOG study H-0022 applies a simultaneous integrated boost technique, prescribing a GTV total dose of 66 Gy at 2.2 Gy / fraction, and a dose for the subclinical disease region of 54 Gy (1.8 Gy / fraction) [247].

Plan Optimization and Evaluation Using Radiobiologic Models

Instead of using dose- and dose-volume–based objectives and constraints, plan optimization and evaluation can, in principle, also be done using radiobiologic criteria such as the tumor control probability, normal tissue control probabilities, and the equivalent uniform dose for the tumor and organs at risk. For the head and neck region, several parameter sets for biologic models exist, derived from observed tumor

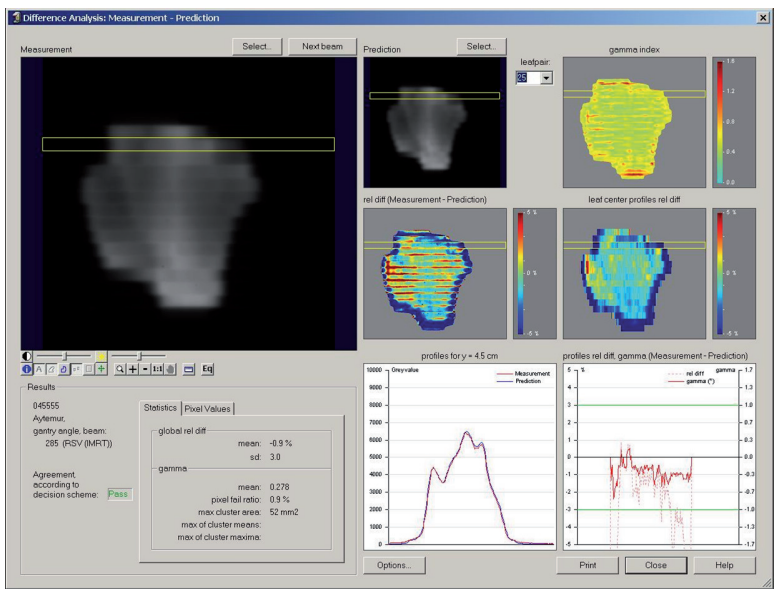

Figure 45: Screen-shot for dosimetric IMRT verification with an EPID. Portal dose images (PDI), measured prior to the start of the first treatment fraction, compared to predictions. measured PDI, (b) predicted PDI, (c) PDI comparison using the y- index, (d) PDI difference image, (e) PDI difference image, excluding the tongue-and-groove areas, (f) profile comparison for the leaf pair marked with a yellow line in (a)-(e), (g) dose and y-index differences for this leaf pair, (h) result of the automated test for 2D image comparison (Pass in this case).

control and toxicity data [76,77,259,269] (also used in tumor control probability/normal tissue control probabilities calculating modules [315]). Unfortunately, the results vary considerably with the applied parameter set: for a group of oropharynx cancer patients, van Vulpen et al. [310] reported predicted normal tissue control probabilities differences for the parotid glands ranging from -3% to +35% when applying different parameter sets. To our knowledge, articles describing a decisive role in clinical decision-making for the treatment of oropharyngeal cancer patients have not yet been published.

Step-and-Shoot or Segmental IMRT (SMLC)

Apart from the DMLC technique, intensity-modulated profiles can also be generated by sequential delivery of static field segments, with a variable shape and number of monitor units (SMLC). In the transition period from end of delivery of one segment to shaping of the next segment, the beam is switched off. DMLC allows for more precise realization of the optimized fluence profiles. However, some studies have concluded that the differences are of minor clinical importance [4,55,83]. It has also been reported that DMLC treatments require more MUs and SMLC treatments take more time. A leaf-sequencing algorithm for DMLC has been developed that fully prevents the occurrence of tongue-and-groove underdosage reported by van Santvoort et al. [266]. Currently, we use the Cadplan TPS (Varian Medical Systems, Espoo, Finland) for inverse planning and leaf sequencing. It was demonstrated that for extreme profiles, tongue-and-groove underdosage of up to 30% may occur with this TPS [80]. However, the protocol for pretreatment verification of the fluence profiles of each individual IMRT patient has never revealed a clinically relevant tongue-and-groove error. Also for SMLC, leaf-sequencing algorithms have been developed that reduce or prevent the occurrence of tongue-and-groove underdosage [61,182].

Study	N	Median FU	LRC	DFS	DMFS	OS	Acute Xerostomia ≥ gr 2	Acute Mucositis ≥ gr 3	Acute Xerostomia ≥ gr 2	Late Mucositis ≥ gr 3
		(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Chao, 2005	74	33 mo	78	66	84	87		41	12	
Garden, 2004	80	17 mo	94							
Huang, 2003	41	14 mo	89	91		89				
De Arruda, 2006	50	18 mo	86		84	98	60	38	33	
Yao, 2005	56	18 mo	98							
Chao, 2001	26	47 mo	88	80				42	30	10

Table 21: Overview of reported treatment results of oropharyngeal cancer using IMRT. Toxicity scored according to RTOG criteria. LRC: local-regional control. DFS: disease free survival. DMFS: distant metastases free survival. OS: overall survival.

Clinical Results

Some of the clinical results are presented in the section Xerostomia. Excellent reviews are presented by Puri et al. [243] and Lee et al. [168]. Table 21 summarizes the preliminary clinical results of several studies of IMRT treatment for oropharyngeal carcinoma. The studies confirm the high rates for (loco-) regional control, distant metastases-free survival, disease-free survival, and OS in combination with reduced toxicity in comparison to conventional radiotherapy. Finally the multi-institutional RTOG study (H-0022) using IMRT for early-stage oropharyngeal cancer has completed accrual, and final results are to be expected shortly [247]. IMRT allows dose to be concentrated in the tumor volume while sparing normal tissues. However, the downside to IMRT is the potential to increase the number of radiation-induced second cancers. The reasons for this potential are more MUs and, therefore, a larger total-body dose because of leakage radiation and, because IMRT involves more fields, a larger volume of normal tissue is exposed to lower radiation doses. In fact, Hall [114] calculated that IMRT may double the incidence of solid cancers in long-term survivals. In contrast to older patients, if balanced by an improvement of local tumor control, the use of IMRT might not be acceptable in children. An alternative might be to replace x-rays with protons in case of scanning pencil beams.

Alternative External Beam Approaches

Helical Tomotherapy

Apart from IMRT with linear accelerators, helical tomotherapy [186] (HiArt, TomoTherapy Inc., Madison, WI) can also be used for highly conformal dose delivery. Several articles report on dose distributions for head and neck cancer patients that might be superior to those obtained with linacs, regarding sparing of critical structures [82,230,310]. Long-term clinical evaluations are not available as yet. Compared to linac-based IMRT, tomotherapy requires more MUs to deliver the same target dose, because of the applied fan-beam [212]. This increases the whole-body dose equivalent, which may increase the risk for radiation-induced secondary malignancies [84]. The clinical implications of irradiating larger volumes to lower doses with tomotherapy, compared with smaller volumes with intermediate doses in linac IMRT, are unknown.

CyberKnife

The robotic CyberKnife system (Accuray Inc., Sunnyvale, CA) is another means of applying high dose of radiation with high accuracy [2]. Some preliminary experience with the CyberKnife is available from the Erasmus MC for cancer in the oropharynx (Fig. 19 shows the protocol). This regards the delivery of a boost treatment of three fractions of 5.5 Gy on each consecutive day, prescribed at the 80% isodose. Patients are immobilized with the regular thermoplastic mask with a three-point fixation. Highly conformal plans with steep dose gradients are generated using 100 to 200 noncoplanar and nonisocentric coned beams. Figure 46 shows a typical dose distribution for a CyberKnife boost with the applied beam orientations. The CyberKnife image-guidance system and the patient skull are used for frequent measurement of the patient setup during treatment. Observed translations and rotations are used for immediate correction of the position and direction of the next beams. Because of these continuous adjustments, a PTV margin of only 2 mm was applied originally.

Recently, the images obtained with the CyberKnife image-guidance system have been retrospectively analyzed, to quantify patient motion during delivery of a treatment fraction [135].
For head and neck cancer and brain cancer patients, the maximum observed displacement in a 2-minute period was 2.8 mm in a single direction; a maximum rotation of 2.3 degrees was observed after 3 minutes. The overall systematic and random threedimensional errors after 15 minutes are 1.3 and 1.2 mm (2 SD), respectively. With the CyberKnife image-guidance system, these in-fraction patient movements are automatically compensated using the robotic manipulator.

Cone-Beam CT

An important next step in image-guided RT for head and neck tumors may be the use of the recently introduced cone-beam CT scanners, integrated in linacs (Fig. 44) [146,172,202]. In contrast to EPIDs, these systems allow for visualization of soft tissues. So far, the image quality is not as good as for modern diagnostic scanners. During the fractionated head and neck treatment, various processes may result in a gradual change of the patient anatomy, such as postoperative changes/edema, weight loss, and shrinking of the primary tumor and/or nodal masses [11,118]. Large changes in the size of the GTV and the size and position of the parotid glands have been observed. These changes may result in suboptimal treatment as the dose delivery in all fractions is usually based on a treatment plan that is designed for the patient anatomy in the planning CT scan, which is acquired prior to the start of treatment. Studies have been performed to investigate the impact of replanning based on, or triggered by, anatomy changes observed in acquired cone beam CT scans [118,210]. A major clinical question to be answered is the target definition in case of a shrunken gross target volume. As part of the IMRT QA protocol, cone-beam CT scans may also be used to assess the “dose of the day” [328].

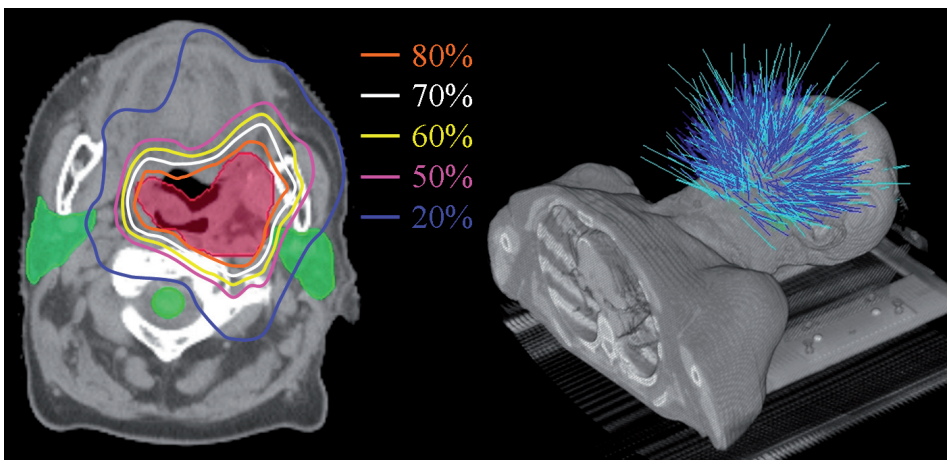

Figure 46: Left Panel: CyberKnife boost dose distribution of a patient with a tonsillar fossa tumor. Right panel: The applied beam setup. The light blue rods represent the beam directions that were actually used for treatment, with lengths proportional to the beam weight. The beams marked with the dark blue rods were available for treatment planning, but not selected in the final plan.

Future Technical Developments

Dose-Calculation Algorithms

It is well known that, especially in the presence of low-density inhomogeneities, significant dose-calculation errors may occur for single beams, even when using a modern commercial TPS. Such errors have also been observed for clinical, multibeam head and neck treatment plans [34,251,270]. Improved accuracies can be obtained with Monte Carlo dose-calculation algorithms, and vendors of TPSs have started to offer this tool [129,251]. However, to obtain clinically acceptable calculation times, approximations and simplifications are often used that could jeopardize the potential advantages of the full Monte Carlo technique. A comprehensive overview is provided by Reynaert et al. [252].

Paperless Electronic Records

In the previous section one is confronted with innovative, highly technological care, but also with clinical research regarding QOL issues. These processes will undoubtedly go on with virtually no limitations. From the organizational (data-retrieval) point of view, one could envisage that most departments of radiation oncology will eventually be structured as a “paperless office” (Fig. 47). Direct architecture changes the conventional workflow into a productive workspace environment; that is, with a click of a button it combines the ease of the use of Windows with access to all types of vendor applications, including record and verify, e-mail, IMRT-QA, and office applications. This server client architecture gives users the freedom to access their applications anywhere in the hospital or in the world for collaboration, consultation, or to access particular applications for personal use. Features like pen-enabled computing, centralized storage, and secure remote access of the applications via broadband are not new in the information technology arena, but definitely are not routine to radiation therapy. It is setting a stage for any type of new application to fit into the existing infrastructure without adding new workstations or PCs in the already fully taken workspace. The future generation of connectivity between radiotherapy applications is true flexibility at the physician’s desk, a solution without constraints.

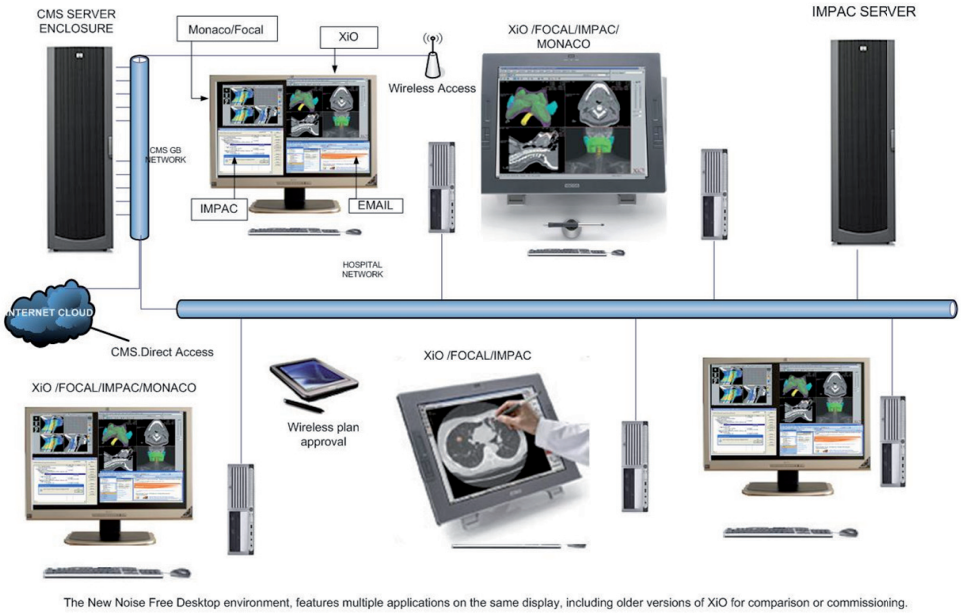

Figure 47: Various applications are consolidated in a vendor's independent workspace: flexibility and freedom of access to any application with a click of a button in a truly paperless office.

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3

Early Dysphagia Disorders in Patients with Cancer of the Oropharynx are Significantly Affected by the Radiation Therapy Dose to the Superior and Middle Constrictor Muscle: a Dose-Effect Relationship

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ABSTRACT

Purpose/Objective: To assess the relationship between the radiation therapy (RT) dose received by the muscular components of the swallowing (sw) apparatus and – dysphagia related - quality of life (QoL) in oropharyngeal cancer.

Materials/Methods: Between 2000-2005, 81 patients with SCC of the oropharynx were treated by 3DCRT or IMRT, with or without concomitant chemotherapy (CHT); 43 out of these 81 patients were boosted by brachytherapy (BT). Charts of 81 patients were reviewed with regard to late dysphagia complaints; 23% experienced severe dysphagia. Seventeen patients expired. Fifty-six out of 64 (88%) responded to Quality of Life (QoL) questionnaires; that is, the Performance Status Scales of List, EORTC H&N35, and the M.D. Anderson Dysphagia Inventory. The superior (scm), middle (mcm), and inferior constrictor muscle (icm), the cricopharyngeus muscle and the inlet of the esophagus, are considered of paramount importance for swallowing. The mean dose was calculated in the muscular structures. Univariate analyses and multivariate analysis were performed using the proportional odds model.

Results: Mean follow-up was 18 months (range 2-34) for IMRT, and 46 months for 3DCRT (range 2-72). At 3-years, a LRC of 84%, DFS of 78% and OS of 77% was observed. A significant correlation was observed between the mean dose in the scm and mcm, and severe dysphagia complaints (univariate analysis). A steep dose-effect relationship, with an increase of the probability of dysphagia of 19% with every additional 10 Gy, was established. In the multivariate analysis, BT (Dose) was the only significant factor.

Conclusion: A dose-effect relationship between dose and swallowing complaints was observed. One way to improve the QoL is to constraint the dose to be received by the swallowing muscles.

INTRODUCTION

In organ preservation therapy of head and neck cancer, over the years a number of investigators have noted a significant increase in dysphagia; this most likely relates to more aggressive treatment used in order to obtain better tumor control rates. The aggressive nature of the treatment modalities is exemplified by high doses of radiation, and/or (altered) fractionation regimen with or without (concomitant) chemotherapy [9]. Xerostomia has been well documented in patients treated with chemotherapy and / or radiation. It has been argued that the degree of xerostomia corresponds with dysphagia experienced by the patients [32,33]. At the present time we embarked on a study that relates these two factors in a retrospective and prospective fashion. This data analysis will be presented in a next paper. It is important to investigate the anatomical structures and functionality of the swallowing apparatus, in order to define potential rehabilitation strategies. Examples of preventative measures are the pre- and post treatment exercises and/or the introduction of Therabite [34,35]. Few studies have examined the association of dysphagia with the location of the primary tumor site [36,37].

This paper examines by chart review swallowing disorders in 81 patients with oropharyngeal cancers. All patients were treated by highly conformal radiation therapy techniques, which are 3D Conformal Radiotherapy (3DCRT) and Intensity Modulated Radiotherapy (IMRT), with or without concomitant chemotherapy. First, the anatomical structures involved in swallowing were defined. Subsequently the dose was computed in each - swallowing related - individual muscular structure. Finally severe late dysphagia disorders (grade 3 and 4), measured by quality of life instruments such as the performance status scale (PSS) [28], the EORTC Head and neck 35 (H&N35) [30], and the M.D. Anderson dysphagia inventory (MDADI) [38], were related to tumor site, treatment technique and dose. For this purpose one has to establish first the anatomical substrate of the swallowing mechanism. After reviewing the literature, five musculature structures were considered paramount in swallowing [39]. These muscular structures are the superior constrictor muscle (scm), the middle constrictor muscle (mcm), the inferior constrictor muscle (icm), the cricopharyngeus muscle (cphm) and the 1 cm of the muscular compartment of the esophageal inlet (eim). A previous study by Eisbruch et al. [16] showed that elevation of the larynx and pharynx during swallowing appeared to be essential for protection of the airway and propulsion of the bolus. This elevation is facilitated by the contraction of longitudinal constrictor muscles which are interspersed with the circular fibers of the scm, including the stylopharyngeus-, salpingopharyngues- and palatopharyngeus muscles. In fact, when the larynx and pharynx are elevated and pulled forward, they are also pushed away from the lower posterior pharyngeal wall, facilitating opening the esophageal inlet (cphm and eim).

	IMRT				3DCRT			
			Concomittant Chemotherapy				Concomittant Chemotherapy	
	TF / SP	BOT	TF / SP	BOT	TF / SP	BOT	TF / SP	BOT
2000-2002					9	0	15	10
2002-2005	22	5	4	4	10	1	0	1
Total	35				46			

Table 1: Eighty-one patients diagnosed with squamous cell carcinoma of the oropharynx and treated curatively between 2000-2005 by highly conformal radiation therapy techniques.

MATERIAL AND METHODS

This study is based on a cohort of 81 patients diagnosed with squamous cell carcinoma (SCC) of the oropharynx, treated with curative intent between 2000-2005 in a single institution by highly conformal radiation therapy techniques (Table 1). That is, 46 patients by 3DCRT and 35 patients by IMRT. The treatment of preference for Tonsillar Fossa / Soft Palate tumors, T1-T3 disease, or Base of Tongue tumors (T1-4 disease), consisted at the time of a first series of 46 Gy (2 Gy per fraction, 6 fractions per week) by IMRT or 3DCRT to the neck and primary tumor, followed by a boost of fractionated HDR or PDR BT (TD 20-22 Gy) to the primary tumor. In case of neck nodes, a neck dissection was executed. For those patients not eligible for BT (e.g. medically unfit, patient refusal, T4 tumors and advanced parapharyngeal extension), a combined resection, followed by IMRT or 3DCRT postoperative radiation therapy is performed. For details see Levendag et al. [9].

Patients were staged according to the TNM classification (UICC /AJCC Classification edition 2004) [11]. Of the current series, 28 patients had T3 and 4 patients had T4 disease; 50 patients had N+ neck disease (table 2). For this patient category the local relapse free survival (LRFS), the disease free survival (DFS) and overall survival (OS) were determined. During follow up 4 patients died because of intercurrent disease and 13 because of tumor relapse and/or regional metastases.Out of the 81 patients, according to the charts, 19 (23 %) experienced late dysphagia grade 3 or 4, that is dysphagia scored at the time-point more than 3 months after completion of the treatment. Dysphagia disorder grade 3 is defined as severe dysphagia or odynophagia with dehydration or weight loss (>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyper-alimentation. Dysphagia grade 4 is defined by complete obstruction, ulceration, perforation, and/or fistula. In order to evaluate dysphagia in more detail, the remaining 64 patients alive with no evidence of disease received in January 2006 four types of questionnaires: 1. The EORTC core Quality of Life (QoL) Questionnaire [QLQ]-C30 (30 items), 2. The EORTC QLQ-H&N35 swallowing scale, including four items (problems with swallowing of liquid [q.35], pureed food [q.36], solid food [q.37], or aspiration when swallowing [q.38]), 3. The Performance Status Scale (PSS) of List, with the functions eating in public, normalcy of diet and understandability of speech, and 4. the M.D. Anderson Dysphagia Inventory

(MDADI), consisting of 20 questions with global, emotional, functional, and physical subscales. Also, after the follow up of the present series of patients was completed (January 2006), all patients alive NED were seen once again at the outpatient clinic, with their complaints / wellbeing profile ultimately scored once again for the degree of xerostomia, pain, trismus, mucositis and swallowing.

A schematic diagram and the delineation of the swallowing muscles on CT are shown in figures 1a and 1b. Every 3DCRT and IMRT treatment plan of the previously irradiated 56 patients was retrieved; subsequently the muscular structures of the swallowing apparatus were delineated on the axial CT slices used at the time for the 3D treatment plan. Figure 2 typically shows a delineated muscle (scm) with the dose distribution of IMRT displayed on CT. The dose contribution by the 3DCRT or IMRT technique to the muscular structures (mean dose, maximum dose and minimum dose) was computed using original treatment plans [13]. In 14 out of 43 patients boosted by BT, a 3D conformal treatment plan was used for applying the BT. From these CT-based 3D dose distributions of the 14 patients, a mean BT dose contribution to the muscular structures was calculated (Table 3). This mean BT dose

	N0	N1	N2a	N2b	N2c	N3	Total
T1	1	3	2	5	1	1	13
T2	13	2	3	2	0	0	20
T3	9	4	3	4	1	0	21
T4a	1	1	0	0	0	0	2
Total	24	10	8	11	2	1	56

Table 2: TNM Classification UICC / AJCC, Geneva, 2004 edition.

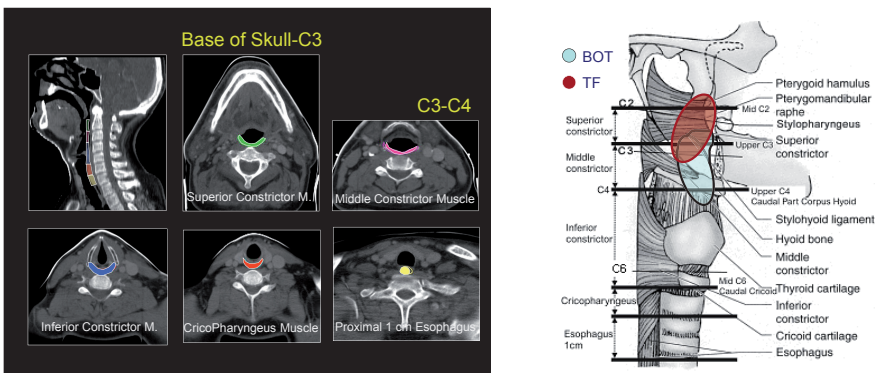

Figure 1 (a): Delineation of muscular structures of the swallowing apparatus on axial- and sagittal CT-slices. (b): Schematic diagram of the delineated five muscular structures considered of paramount importance in swallowing: the superior constrictor muscle (scm), the middle constrictor muscle (mcm), the inferior constrictor muscle (icm), the cricopharyngeal muscle (cphm) and the 1 cm of the muscular compartment of the esophagus inlet (eim). Also shown are the outlines of the projected Tonsillar Fossa / Soft Palate (red) as well as the Base of Tongue (cyan blue).

was also used for calculation of total dose for the remaining patients treated by a (non CT-based) BT boost. Finally, for the 43 patients treated by BT, the 3DCRT or IMRT dose and the BT dose were summated.

Statistical analyses

Prevalence of dysphagia: For chart review, PSS, H&N35, and MDADI, a moderate and severe degree of dysphagia is established by clustering, that is, for example for chart review the RTOG grades 3 and 4 were combined. Similarly, for H&N35 (q35, q36, q37 and q38) 'quite a bit' and 'very much' dysphagia was scored as grade 3 and 4, respectively. The PSS cut-off scores ≤ 50 and MDADI scores ≤ 50 were taken as the prevalence of a significant degree (equivalent to grade 3 or 4) of dysphagia.

Univariate dose-response relationship: For the scm, mcm, icm, cphm and eim, the correlations of dose in these muscular structures and the absence or presence of dysphagia grade 3 and 4 combined (binair) were calculated by the proportional odds model.

Dysphagia threshold values: A logistic model was used to calculate the probability of dysphagia complaints for a median dose in a particular muscular structure. This was done for every dysphagia related question of the different QoL questionnaires.

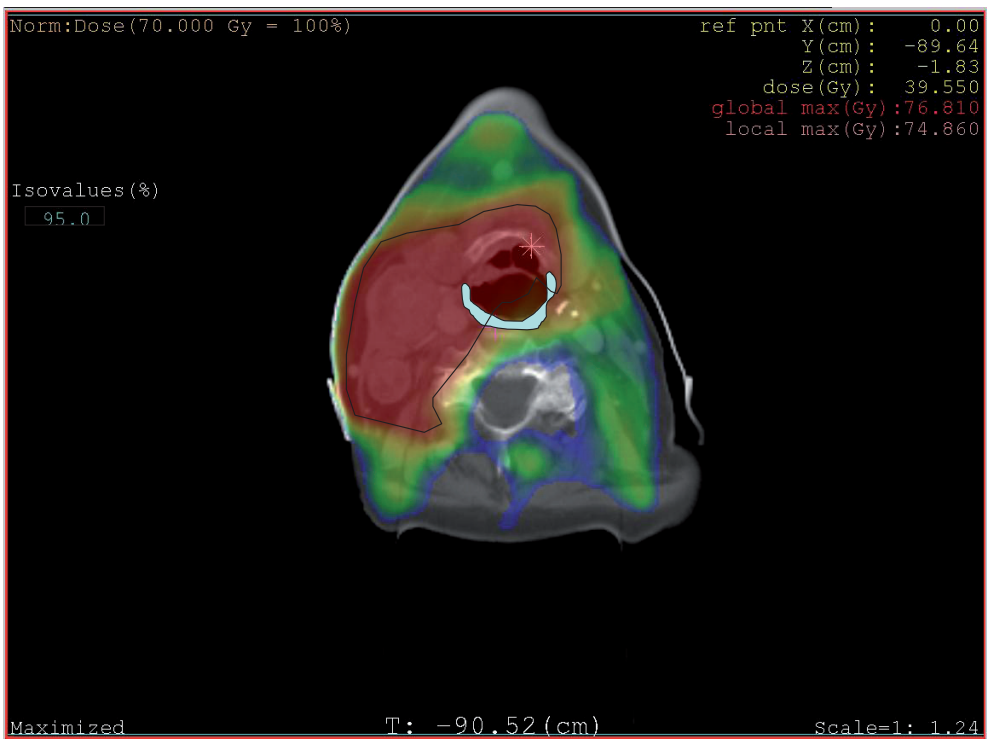

Figure 2: Taken at the level of the mid-tonsillar fossa, an axial CT-slice is shown with the delineated muscular structure involved in swallowing (i.e. at this level the scm). Also displayed is the dose distribution using an IMRT technique.

Using this model (p= 1 / (1 + exp (-(a+ b * dose)))) one can calculate the dose for the different probabilities of grade 3 and 4. As the distribution of scores of the questionnaires is highly 'non-normal', ordinal regression (presently used model) is more valid and more informative than ordinary least-squares regression [40].

Multivariate analysis

The following variables were used in the multivariate analysis: age, sex, site, T-stage, N-stage, dose, technique, surgery, chemotherapy and brachytherapy.

RESULTS

Prevalence of dysphagia: Eighty one patients with SCC of the TF/SP and BOT were analyzed for dysphagia (table 1). Advanced staged disease is present in 75% (14/56) of patients (table 2). The IMRT series of patients investigated has a mean follow up of 18 months (range 2-34) for IMRT as opposed to 46 months (range 2-72) for 3DCRT. Overall, the LRFS, DFS and OS at 3 years were 84%, 78% and 77%, respectively (figure 3).

	Mean dose by BT (Gy)	
	TF	BOT
Superior constrictor muscle	5.72	8.82
Middle constrictor muscle	2.81	7.14
Inferior constrictor muscle	0.93	2.84
Cricopharyngeus muscle	0.45	0.63
Oesophagus inlet	0.45	0.49

Table 3: Dose contribution (mean doses) to the scm, mcm, icm, cphm and eim of brachytherapy boost of Tonsillar Fossa / Soft Palate- or Base of Tongue. For abbreviations, see text.

	IMRT				3DCRT			
			Concomitant Chemotherapy				Concomitant Chemotherapy	
	TF / SP	BOT	TF / SP	BOT	TF / SP	BOT	TF / SP	BOT
2000-2002	0	0	0	0	6	0	10	7
2002-2005	16	4	3	4	6	0	0	0
Total	27				29			

Table 4: Breakdown of 56 patients treated by highly conformal radiation techniques (IMRT/3DCRT) and concomitant chemotherapy, responding to QoL questionnaires. Excluded: deaths due to intercurrent disease (4), deaths due to tumor (13), non-responders to QoL questionnaires (8).

Chart review revealed nineteen out of 81 patients (23 percent) experienced moderate to severe (RTOG grade 3 and 4) dysphagia. Out of the 64 patients, 56 (88%) responded to the QoL questionnaires. The characteristics of the patient subsites of the oropharynx, 41 TF/SP patients and 15 patients with BOT tumors, are listed in tables 4 & 5. The prevalence of grade 3 and 4 dysphagia (score ≥ 50) for patients studied by using the response to H&N35 (q.35, q.36, q.37 and q.38), was 18%, 11%, 20% and 7% respectively. With regard to PSS, a score ≤ 50 was seen in 19% of the patients eating in public, in 30% with respect to normalcy of diet and in 2% for difficulty in understandability of speech. Regarding the MDADI: a score ≤ 50 was found in 26% (total MDADI score) of the patients. Thus, 28% for the global subscale, 21% for the functional subscale, 21% for the emotional subscale and 32% for the physical subscale. For the analyses of this paper, all patients were seen in last follow-up at the outpatient clinic in January 2006. Relevant late side-effects were scored, such as VAS pain, VAS xerostomia, mucositis, trismus and dysphagia were observed in 16% (8/51), 59% (30/51), 24% (12/51), 6% (3/51) and 12% (6/51) respectively.

Univariate dose-response relationship

The doses given in patients with cancer in the oropharynx was applied by 3DCRT or IMRT or a combination of the previous with concomitant chemotherapy, to a total dose of 46 Gy; fractionated HDR or PDR BT was used as a preferential boost technique (Dose range boost 20-22 Gy). From table 3 one can appreciate the mean BT dose received by the different muscular swallowing structures in TF/SP and BOT tumors of 14 patients treated by 3D conformal CT-based BT. It is evident from figure 4 that patients treated with fractionated HDR

	TF/SP	BOT	All oropharynx
Number of patients	41	15	56
Male gender	27	10	37
Mean age (range) years	57 (40-73)	55 (44-68)	56 (40-73)
BT boost	34	9	43
IMRT (full course)	19	8	27
3D CRT (full course)	12	0	12
3D CRT + concomitant CHT	10	7	17
N0	22	2	24
N+	19	13	32
T1,2 vs. T3,3	28 vs. 13	5 vs. 0	33 vs. 23
IMRT / 3D CRT +CDDP	3	4	7
+Neck dissection	15	9	24

Table 5: Table displays the characteristics of the 56 patients alive NED with cancer of the oropharynx responding to the quality of life questionnaires.

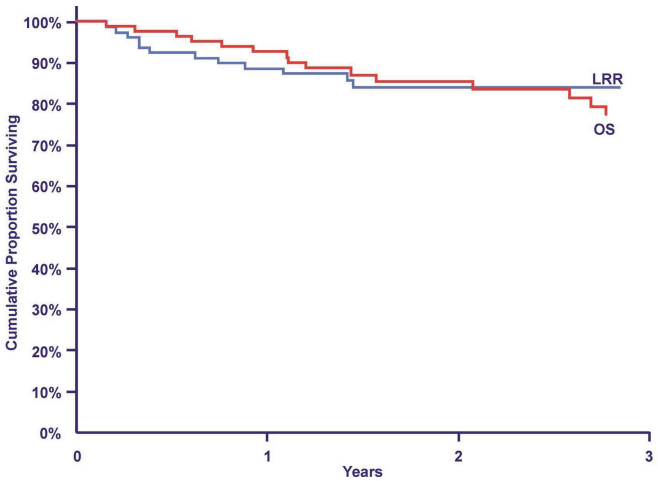

Figure 3: LRFS and OS at 3-years of 81 patients with cancer of the oropharynx treated with 3DCRT or IMRT between 2000-2005. For abbreviations see text.

Swallowing structure	Median dose	Range
Scm	51 Gy	22-73 Gy
Mcm	48 Gy	11-72 Gy
Icm	32 Gy	6-73 Gy
Cphm	23 Gy	4-73 Gy
Eim	18 Gy	3-64 Gy

Table 6: For the 5 muscular structures studied, the median dose and dose range are given.

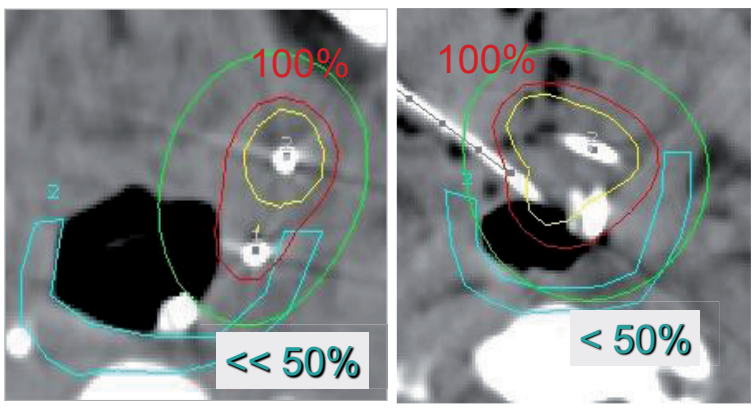

Figure 4: Dose distribution in superior constrictor muscle. Patient with tonsillar fossa / soft palate implant. Patients treated with fractionated HDR / PDR BT receive a substantially lower physical dose (and to a smaller volume) to the superior constrictor muscle as opposed to treatment with full course IMRT or 3DCRT.

/ PDR BT receive a substantially lower physical dose (Gy) and in a smaller volume of the scm / mcm, as opposed to when treated by IMRT or 3DCRT alone. Table 6 shows for the 5 muscular structures patients studied, the median dose and dose range.

The results of the dose-response relationships are exemplified by figures 5 and 6 and depicted per muscular structure in table 7. The dose in particular muscular structures were significantly associated with some of the items of the questionnaires. With regard to the QoL questionnaire H&N35, the dose in the scm, mcm & eim was significantly correlated with the item q.35 (see also page 8; 'liquid'). Similarly correlated is the dose in scm & mcm with item q.36, the dose in scm, mcm & icm with item q.37 (see also page 8; 'solid') and the dose in icm with item q.38 (see also page 8; 'aspiration'). Furthermore a significant effect was found for the dysphagia data obtained from the charts and the general MDADI score (see table 7). PSS scores were found not significant.

Dysphagia threshold values

A mean dose of 51 Gy, 48 Gy and 32 Gy was found in the scm, mcm and icm, respectively. With regard to the moderate and severe dysphagia complaints combined, an overall probability of 18%, 11%, 20% and 7% was observed for q35, q36, q37

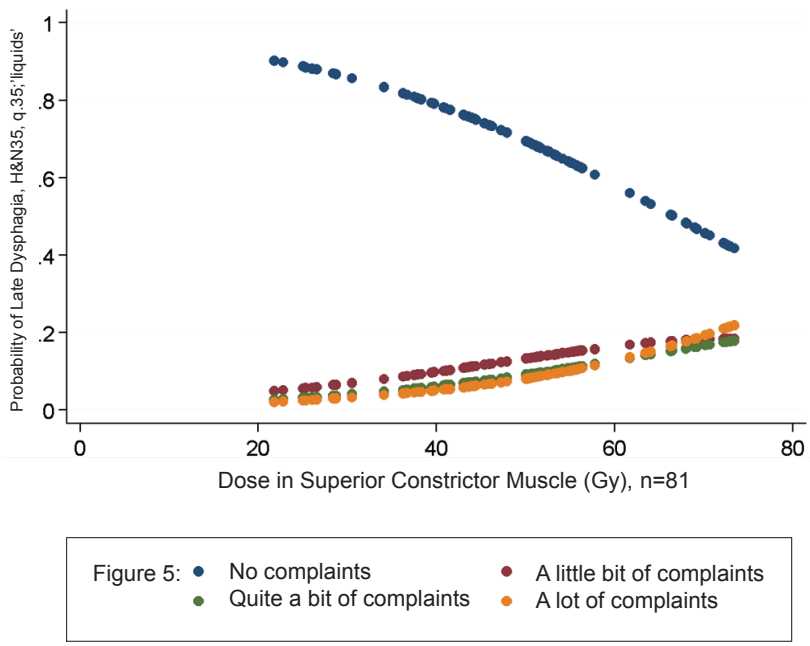

Figure 5: Using the quality of life questionnaire of the EORTC H&N35 (item q35; swallowing liquids), this figure shows a dose-effect relationship for the probability of having no - dysphagia related - complaints and the dose (Gy) in the superior constrictor muscle. For 'quite a bit, ' a little bit' and 'a lot of ' complaints, no significant relationship was found for dysphagia and dose to the scm.

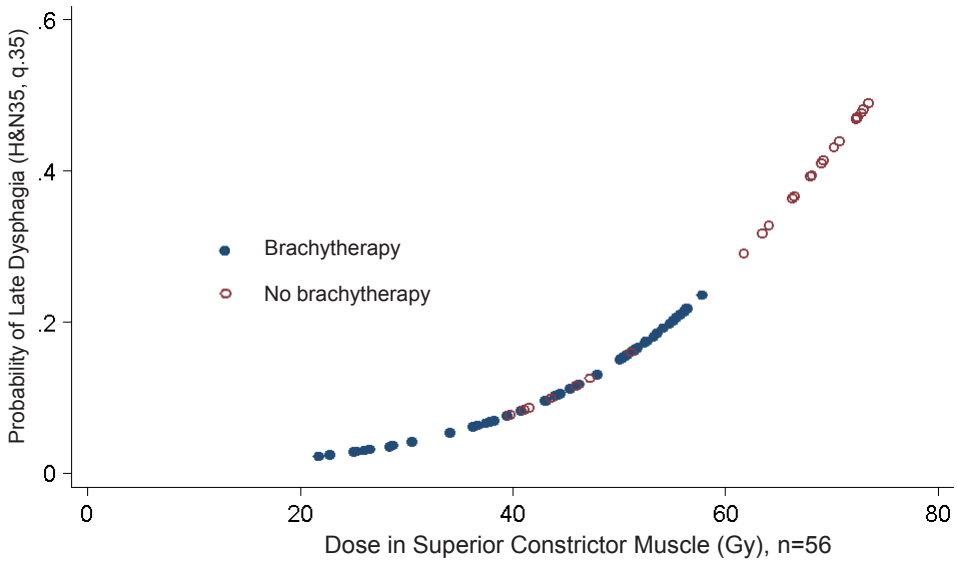

Figure 6: Significant dose-response relationship for dysphagia complaint category EORTC H&N35 item q.35 and dose in superior constrictor muscle. Patients can be subdivided in those treated by a brachytherapy boost (blue symbols) and those treated by 3DCRT or IMRT only (red symbols).

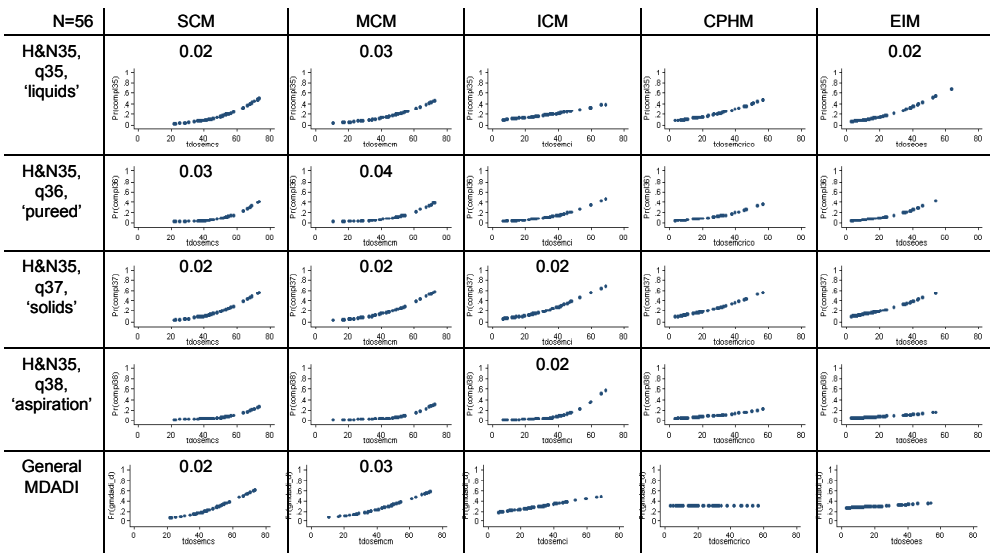

Table 7: Dose-response relationships are exemplified by figures 5 and 6. Table 7 shows the dose-response relationships in particular muscular structures relative to the items q.35-38 of the QoL questionnaire EORTC H&N35, "late dysphagia" (by chart review) and the general MDADI. In case of significance, p-values are given. For abbreviations, see text.

and q38 respectively. Using the logistic model for an overall probability of 2%, 10%, 20%, 30%, 40% and 50%, a dose in the scm of 22 Gy, 44 Gy, 55 Gy, 63 Gy, 69 Gy and 74 Gy was calculated. Same type of computations was done for the dysphagia disorders noted in the chart (see table 8).
In the multivariate analysis, if dose received by the scm and BT are entered simultaneously in the logistic regression analysis for H&N35 (q35-q38) and dysphagia established by chart review, only BT remains a significant factor (p=0.05; odds ratio 0.06).

DISCUSSION

It is evident from the current literature that the intensification of therapy for head and neck cancer in general, either by altered fractionation RT schemes (e.g. in case of accelerated RT) and/or by the addition of concomitant chemotherapy, results in improved local-regional tumor control [43]. Unfortunately, as shown by meta-analysis, the late sequelae also increase. Dysphagia is obviously correlated with the functionality of the swallowing mechanism. The functionality is based on a number of muscular structures that determine the transport of the bolus. For example, elevation of the larynx and pharynx during the swallow procedure is essential for protection of the airway and propulsion of the bolus. This elevation is facilitated by the contraction of longitudinal constrictor muscles which are interspersed with the circular fibers of the scm. Because of the limited availability and lack of awareness of objective measures to assess swallowing disorders, the incidence of this dysfunction seems also to be underreported [44]. Furthermore, swallowing related complaints have been shown to increase significantly in patients with reduced production of saliva after chemoradiation [33,45]. Swallowing disorders after surgery depend on the extent of the resection, the specific structures resected, and the nature of the reconstruction.

Probability	Dose q35			Dose q36			Dose q37			Dose q38			Chart review dysphagia		
2%	22	10		22	23	6	21	10							
10%	44	35	10	53	48	33	41	35	19	58	72	44	38	29	14
20%	55	51	37	62	61	47	52	47	33	69	69	50	50	43	30
30%	63	61	58	68	67	55	58	56	42		73	56	56	52	39
40%	69	69	72	73	73	64	65	62	50				62	58	47
50%						72	71	69	63				67	66	
60%														72	63
Overall	18%			11%			20%			7%			23%		
Median dose	51	48	32	51	48	32	51	48	32	51	48	32	51	48	32

Table 8: Numbers in table denote mean doses in Gy for the probabilities 2%, 10%, 20%, 30%, 40%, 50%, or 60%, of dysphagia disorders administered to swallowing muscles scm, mcm and icm. The dysphagia problems are defined by the QoL EORTC H&N35 q.35-38 questionnaire and the “late dysphagia” data obtained by chart review. For explanation of details of table and abbreviations, see text.

Patients undergoing postoperative RT experience radiation induced fibrosis, edema and necrosis of a number of normal tissues, for example, the muscles responsible for oropharyngeal sphincter. Eisbruch et al. reported on the toxic effects of concomitant chemotherapy and RT: several months after treatment, aspiration was experienced by 62% of patients [46]. Additionally, swallowing muscula ture weakness, pharyngeal residue, reduced hyoid/laryngeal movement, reduced epiglottic inversion, velopharyngeal incompetence, and upper esophageal strictures were found. These disorders are again likely the result of muscular fibrosis that causes incoordination of the swallowing process. It is thereby difficult to separate out the individual role of chemotherapy and RT in these swallowing disorders [17]. Nguyen et al. report that the severity of dysphagia isfrequently associated with a compromised QoL, anxiety, and depression [19].

This paper analyzes the dose-volume effect relationships for dysphagia of patients with oropharyngeal cancer treated by 3DCRT and IMRT. The majority of patients studied (78 % [63/81]), had stage 3 and 4 disease. This is also reflected in the frequent use of chemoradiation (42%) and the intermediate prognosis of this group. According to literature, the prevalence of dysphagia in organ preservation therapy is high. In some papers on head and neck cancer survivors, swallowing dysfunction is reported to be as high as 50% [5,17,18,22]. Chart review of the 81 patients showed that 19 (23 percent) experienced moderate to severe dysphagia (RTOG grade 3 and 4) during the course of their treatment. It is of importance to note that IMRT in our

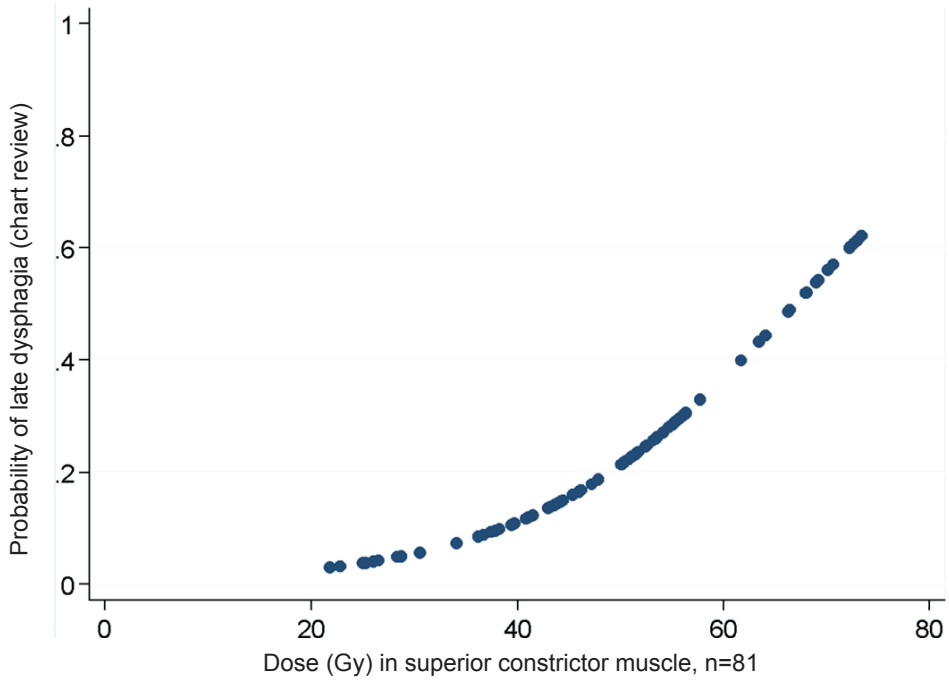

Figure 7: Significant dose-response relationship for dysphagia disorders (“late dysphagia”; data taken from chart review) and dose in superior constrictor muscle. The probability of swallowing problems increased significantly with dose (± 19% per 10 Gy after 55 Gy) for the scm (and mcm).

institution was initiated only as of 2000. With a mean follow up of 18 months (range 2-34) for IMRT, the prevalence of dysphagia might therefore be underreported and may be a confounding factor.
PSS and QoL instruments were used to objectivate the long-term effects of RT of the swallowing apparatus in oropharyngeal cancer patients in some detail. The prevalence of grade 3 and 4 dysphagia for the items of the H&N35 ranged from 7-18%; the RTOG grade 3 and 4 equivalent scores for the PSS varied from 2-30% and for the MDADI from 21-32%. So, dysphagia, as a late effect after radiation therapy, is indeed a significant problem in cancer of the oropharynx. When measured by the QoL questionnaires, dysphagia grade 3 and 4 was not very dissimilar to observations taken from chart review (23%). For the analyses of this paper, patients were additionally seen in last follow-up at the outpatient clinic in January 2006. The outcome of this "last" follow up clinic showed that severe xerostomia (VAS) and grade 3 and 4 dysphagia in long term follow-up were present in 59% (30/51) and 12% (6/51) respectively.
For the late dysphagia grade 3 and 4 (data taken from chart review) significant relationships were found with scm (p=0.002), mcm (p=0.003) and icm (0.006). Using the EORTC QoL questionnaire H&N35, the probability of having no complaints versus dose in the scm was found to be significant (p=0.02; odds-ratio 1.08, 95% confidence interval 1.01-1.14) for item 35 ('liquids') as displayed in figure 5. The significant dose-effect relationships of QoL questionnaire H&N35 (q.35-q.38 ('liquids, 'pureed', 'solids' and 'aspiration')), and the general MDADI, are summarized in table 7. In general, with lower doses to the muscular structures, which is particularly the case in patients treated with BT boost, less problems with dysphagia have been observed (figure 6). Again, using the H&N35 with the endpoint q.35 ('liquids'), the difference between BT vs. no BT was significant (p=0.001; odds ratio 0.06, 95% confidence interval 0.01-0.32). From figure 7 (dose-response relationship of late dysphagia), the steepness of the curve after a dose of 55 Gy, can be expressed by 19% per 10 Gy.
From table 8 one can appreciate the probabilities of severe dysphagia when applying a particular dose to the scm, mcm and icm. These computations were done for swallowing items of H&N35 and late dysphagia (chart review). Again it is demonstrated that severe dysphagia is not an uncommon co-morbidity. For example the probability is 40% for a median dose of about 70 Gy to the pharyngeal constrictors for item q.35 ('liquids'). For a median dose of 50 Gy there is a 20% chance of dysphagia but only in the scm and mcm. Almost absence (2%) of severe dysphagia is encountered for mean doses of 22 Gy (q.35; 'liquids'), 22 Gy (q.36: 'pureed') and 21 Gy (q.37: 'solids') for the scm. Finally in the multivariate analysis, if dose (received by the swallowing musculature) and BT are entered simultaneously in the logistic regression analysis for H&N35 (q.35-q.38), general MDADI and late dysphagia taken from chart review, only BT remains a significant factor (p=0.05). This can be explained by the high correlation of the dose in the swallowing musculature and BT: Brachytherapy patients got lower doses in smaller volumes in the swallowing musculature than no-BT patients. Actually, dose is interchangeable for BT in four cases.

CONCLUSIONS

We identified a subset of patients with oropharyngeal cancers with inability to swallow normally. Patients had been treated with highly conformal RT techniques, that is 3DCRT, IMRT and combinations of these with BT as a boost. Some of these patients were treated with concomitant chemotherapy as well. The dysphagia encountered in these patients is obviously multi-factorial. We were particularly interested in this paper whether the complaints were site and/or dose related. Patients were studied using QoL instruments. The responses of the QoL questionnaires, demonstrated that the probability of swallowing disorders increased significantly with dose (±19% per 10 Gy after 55 Gy) for the scm and mcm. In contrast to what is commonly reported, concomitant chemotherapy was not a significant factor in the multivariate analysis. However, this might be due to the small numbers. It is mandatory to investigate new techniques /modalities that can better spare the swallowing musculature.

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4

Treatment Techniques and Site Considerations regarding Dysphagia related Quality of Life in Cancer of the Oropharynx and Nasopharynx

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ABSTRACT

Purpose/Objective: To assess the relationship for oropharyngeal (OP) cancer and nasopharyngeal (NP) cancer, between the dose received by the swallowing structures and the dysphagia related quality of life (QoL).

Materials/Methods: Between 2000-2005, 85 OP- and 47 NP cancer patients were treated by radiation therapy. After 46 Gy, OP cancer is boosted by IMRT, brachytherapy (BT) or frameless stereotactic radiation / Cyberknife (CBK). After 46 Gy, the NP cancer was boosted with parallel-opposed (P-O) fields or IMRT to a total dose of 70 Gy; subsequently, a 2nd boost was given by either BT (11 Gy) or SRT/CBK (11.2 Gy). Sixty OP- and 21 NP cancer patients responded to functional and QoL questionnaires: i.e. the Performance Status Scales, EORTC H&N35, and M.D. Anderson Dysphagia Inventory. The swallowing muscles were delineated and the mean dose calculated using the original 3D CT-based treatment plans. Univariate analyses were performed using logistic regression analysis.

Results: Most dysphagia problems were observed in the BOT tumors. For OPC, boosting with IMRT resulted in more dysphagia as opposed to BT or SRT/CBK. For NPC patients in contrast to the first booster dose (46-70Gy), no additional increase of dysphagia by the 2nd boost was observed.

Conclusion: The lowest mean doses of radiation to the swallowing muscles were achieved when using BT as opposed to SRT/CBK or IMRT. For the 81 patients alive with no evidence of disease for at least one year, a dose-effect relationship was observed between the dose in the superior constrictor muscle and the 'normalcy of diet' (PSS) or 'swallowing scale' (H&N35) scores ($p<0.01$).

INTRODUCTION

In recent years, aggressive nature of the treatment modalities is seen after the introduction of high doses of radiation, and/or some of the (altered) fractionation regimen with or without (concomitant) chemotherapy (CHT). A frequently occurring but underreported serious late side-effect is dysphagia. Swallowing is a complex action requiring rapid and precise coordination between sensory input and motor function of the swallowing apparatus [1]. Tongue strength may play a role as well in oropharyngeal swallowing, particularly when related to the oral phase of the swallowing process [2,3]. Co-morbid conditions, large tumors (T3-T4 vs. T2), and resections e.g. of the base of tongue and soft palate can be associated with profound swallowing problems [4]. Several papers reported an aspiration rate of 21%-81% with chemoradiation treatment [4-11]. The types of impairments of the swallowing function after radiotherapy are described in literature as follows: poor pharyngeal motility, with subsequent pharyngeal residue, epiglottic immobility, reduced laryngeal excursion, poor closure of the laryngeal vestibule and aspiration [12-16]. Swallowing disorders are most likely caused by radiation-induced edema and neuromuscular fibrosis [17]. Impaired swallowing function may be dependent on both total dose and the treatment volume [18-21]. Patients are able to perceive decrements in their swallowing function and may have limited their oral intake in response to that perception [22]. For patients treated by chemoradiation some authors claim slowly (partly) recovering of the dysphagia after 6 to 12 months [4,23,24]. Examples of preventative measures for these swallowing problems are the pre- and post-treatment exercises and/or the introduction of Therabite [25-27]. Furthermore, it has been argued that the experienced dysphagia corresponds significantly with the degree of xerostomia [28]. This paper presents a detailed analysis of the relationship of the severity of dysphagia complaints and the dose delivered to the relevant muscular swallowing structures. The influence of the factors dose, treatment technique and site dependency will be assessed in some detail.

MATERIAL AND METHODS

Between 2000-2005 a cohort of 132 patients diagnosed with squamous cell carcinoma of the Tonsillar Fossa / Soft Palate (TF/SP) (n=63), Base of Tongue (BOT) (n=22) and Nasopharynx (NP) (n=47) were treated curatively in a single institution by various radiation therapy techniques (table 1). All patients were seen in joint consultation by the radiation-oncologist and H&N surgeon. Patients were assessed by clinical examination, panendoscopy, CT and/or MRI of the head and neck. In order to properly stage the disease, a biopsy of the primary tumor, and ultrasound-guided fine needle aspiration of suspicious regio nal lymph nodes, respectively, was performed. Finally patients were staged according to the TNM classification 2004 edition [29].

With regard to the nasopharynx: patients are treated routinely by EBRT: that is 46/2 Gy to the primary tumor and bilateral neck, and 24/2 Gy to the primary tumor (so-called 1st boost) and N+ neck (Figure 1). In case of T3-T4 tumors and/or N+ disease, the EBRT part of the treatment is preceded by 3 courses of neoadjuvant CHT. The external beam part of the treatment (up to a total dose of 70 Gy) is given by IMRT

	Tonsillar Fossa / Soft Palate	Base of Tongue	Nasopha-rynx
# patients	45	15	21
Male gender	30	10	15
Mean age	57	55	55
Brachytherapy	34	8	10
Stereotactic RT / Cyberknife boost	5	1	7
IMRT / 3DCRT (full course)	6	6	
No 2nd boost nasopharynx			4

Table 1: Characteristics of 81 patients with cancer of the tonsillar fossa / soft palate, base of tongue and nasopharynx and responding to the quality of life questionnaires.

techniques, if feasible; the daily fraction size is 2 Gy, a total of 6 fx/week is being applied. T1N0, and T2N0 nasopharyngeal cancers are given a so-called 2nd boost by fractionated endocavitary brachytherapy (ECBT; 11 Gy) [30]. The 2nd boost in advanced local disease (T3,T4) is given preferably by fractionated stereotactic radiation (SRT) or by frameless SRT (Cyberknife)(11.2 Gy). If BT was not feasible for whatever (medical) reason, or in case of T3,T4 N0,+ disease, the primary is boosted by means of stereotactic radiation or, currently, by the Cyberknife (4 times 2.8 Gy prescribed to the 80% iso-doseline to the residual GTV seen on an MRI scan taken at the 40-46 Gy level). Over the years, the treatment of preference for T1-T3 TF and/or SP tumors and T1-4 cancer of the BOT, consisted of a first series of 46 Gy (2 Gy per fraction, 6 fx/week by IMRT or 3DCRT to the neck and primary tumor, followed by a boost of fractionated High Dose Rate (Total Dose 20 Gy) / or Pulsed Dose Rate (Total Dose 22 Gy) to the primary tumor. In case of neck nodes, a neck dissection (ND) was executed before BT was applied. For those patients not eligible for BT (e.g. patients with TF/SP tumor but medically unfit, patient refusal, T4 tumors and/or extensive parapharyngeal extension), a combined resection followed by post-operative radiation therapy (IMRT or 3DCRT) is performed. For details see Levendag et al. [31].

The results of chart review for swallowing disorders grade 3 and 4 in 132 patients with OPC and NPC is presented. Dysphagia grade 3 is defined as severe dysphagia or odynophagia with dehydration or weight loss (>15% from pre-treatment baseline) requiring nasogastric feeding tube, I.V. fluids or hyper-alimentation; dysphagia grade 4 is defined by complete obstruction, ulceration, perforation, and/or fistula. From the 132 patients, 67 OPC and 28 NPC patients alive with no evidence of disease for at least one year received 4 types of questionnaires: 1. The EORTC core Quality of Life (QoL) Questionnaire [QLQ]-C30, 2. The EORTC QLQ-H&N35 [32], 3. The Performance Status Scale (PSS) of List et al. [33] and 4. the M.D. Anderson Dysphagia Inventory (MDADI) [34].

With regard to the swallowing mechanism, the following anatomical structures were

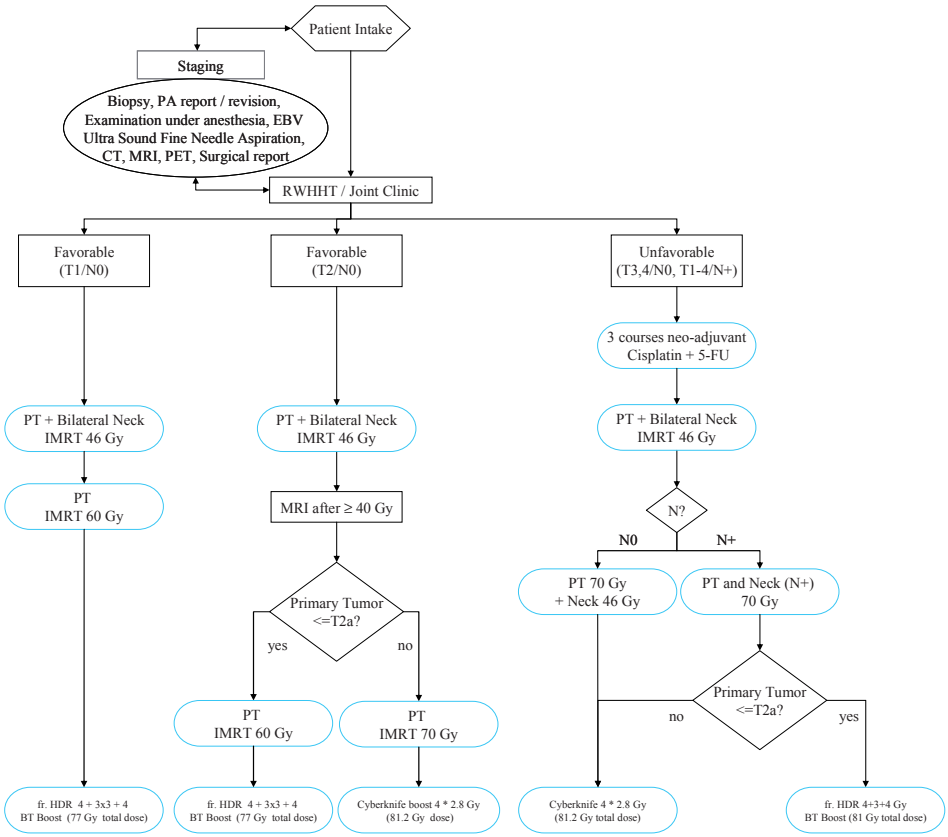


Figure 1: Flowchart of nasopharyngeal cancer treatment.

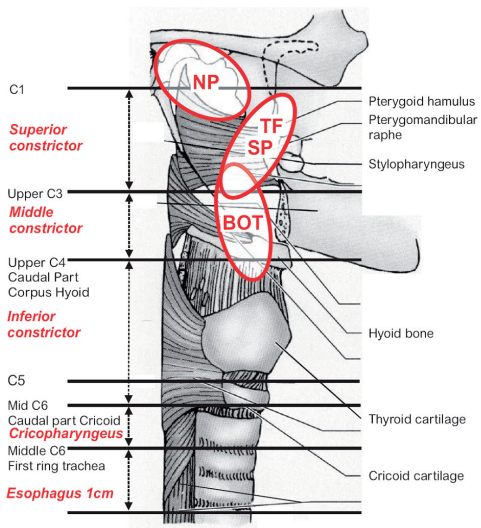


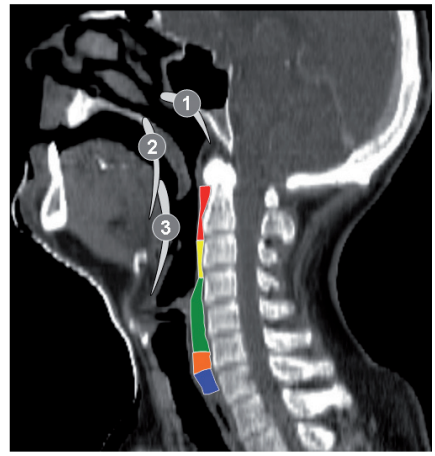
Figure 2: Schematic diagram of the delineated five muscular structures considered of paramount importance in swallowing.

Constrictor Muscles:

Superior: BOS - upper C3
Middle: Upper C3 - Hyoid (upper C4)
Inferior: Hyoid - Caudal Cricoid (upper C6)

Cricopharyngeal Muscle:
Caudal Cricoid (upper C6) - 1st Treacheal Ring

1 cm Esophageal Inlet:
Uppre part 2nd Tracheal Ring - Caudal part 3rd Tracheal Ring



1: Nasopharynx
2: Tonsillar Fossa / Soft Palate
3: Base of Tongue

Figure 3: Definitions and delineations of the swallowing muscles of the swallowing apparatus on a sagital CT-slice.

identified: the superior constrictor muscle (scm), the middle constrictor muscle (mcm), the inferior constrictor muscle (icm), the cricopharyngeal muscle (cphm) and the 1st cm of the muscular compartment of the esophagus inlet (eim) (Figure 2 & 3) [18,35]. Subsequently, every treatment plan of the previously irradiated patients was retrieved, now with the muscular structures of the swallowing apparatus being delineated on the axial CT slices. The mean dose contribution by the 3DCRT or IMRT technique to the muscular structures was computed using the original treatment plan. For the patients treated by parallel-opposed fields and from whom a CT-scan was available that was used at the time for treatment planning purposes, also the dose contribution to the swallowing muscles was calculated [36]. The mean BT dose was computed from the available CT-based 3D dose distributions. For those patients boosted by BT, SRT or Cyberknife, the 3DCRT, IMRT or parallel-opposed dose and the boost doses, respectively, were physically summated. Finally the relationship of the mean total dose received by each of the 5 swallowing muscles to the responses of the three - dysphagia related - QoL questionnaires (EORTC H&N35, PSS & MDADI), is established per tumor site and treatment technique. Also the possible relationship of dysphagia with xerostomia is assessed in some detail.
Prevalence of dysphagia: From chart review, EORTC H&N35 (swallowing scale), PSS (normalcy of diet) and the MDADI questionnaires, prevalence of dysphagia was scored. Also, a moderate and severe degree of dysphagia is established by clustering, that is, e.g. for chart review RTOG grade 3 and 4 were combined. Similarly, for H&N35 (swallowing) ‘quite a bit’ and ‘very much’ dysphagia was scored as grade 3 and 4, respectively. The PSS (normalcy diet) score ≤ 50 and total MDADI score ≤ 50 were taken as the prevalence of a significant degree (equivalent to grade 3 or 4) of dysphagia.

Univariate dose-response relationship: For the scm, mcm, icm, cphm and eim, the correlations of an independent continuous variable (dose) in these muscular structures and a dependent binary variable (that is the absence or presence of dysphagia grade 3 and 4 combined) were calculated using logistic regressions. For example:

$$\Pr\{\text{Normalcy of Diet} \leq 50 \mid \text{Dose in SCM}\} = 1 / (1 + \exp(-(\alpha + \beta * \text{Dose SCM})))$$

The unknown parameters alpha and beta are estimated with the maximum likelihood method. A test is also performed whether the hypthesis $\beta = 0$ can be rejected. A p-value of < 0.05 is interpreted as beta being statistically significant from zero. Thus, in the case $p < 0.05$ there is a significant relationship between probability P and dose in the muscles. Low dose means low probability and high dose means high probability.

RESULTS

Between 2000-2005, 132 OPC and NPC patients were treated by RT. The majority of these patients had advanced staged tumors (table 2a-c). The localregional control (LRC) for TF & SP, BOT and NPC patients at 5 years and the overall survival are shown in figures 4a-c. Sixty seven OPC patients and 28 NPC patients are included in this report (table 3). Sixty patients responded to all given Quality of life questionnaires in case of OPC (response rate: 60/67=90%) and 21 out of 28 in case of NPC (response rate: 75%).

According to the charts, 24 (18 %) patients experienced dysphagia grade 3 or 4 with a tumor located in the TF and/or SP in 22%, in the BOT in 32% and in the NP in 6%

The prevalence of grade 3 and 4 dysphagia was also studied using the response to the PSS (ND), H&N35 (swallowing) and MDADI (table 4). The OPC patients were also grouped according to the boost techniques used, that is BT, CBK or IMRT / 3DCRT. Results for PSS (Normalcy

of Diet), H&N35 (swallowing) and, MDADI are shown in table 5. For the NPC group, the reported number of patients with severe dysphagia was high

(Table 6). The results of the dose-response relationships are presented by table 7 and figure 5. Taken from the QoL questionnaire H&N35, the dose in the scm, mcm was significantly correlated with the swallowing scale. Similarly correlated is the dose in scm & mcm with PSS, (normalcy of diet).

Dysphagia and xerostomia related responses to questionnaires were also strongly associated. As can be seen in table 8, quite a number of these associations were highly significant. There was no significant influence of age, sex, nodal status, chemotherapy, brachytherapy, site, T-category and N-category found with univariate logistic regressions analysis.

(a)	T1	T2	T3	T4	
N0	2	16	10	0	
N1	4	5	4	0	
N2a	2	4	0	0	
N2b	4	5	1	0	
N2c	0	1	3	0	
N3	1	0	0	1	
(b)	T1	T2	T3	T4	
N0	0	0	1	2	
N1	0	2	2	1	
N2a	0	1	4	0	
N2b	2	1	3	0	
N2c	2	0	1	0	
(c)	T1	T2a	T2b	T3	T4
N0	1	3	1	2	4
N1	2	2	2	1	3
N2	3	0	0	4	10
N3a	4	1	1	0	2
N3b	1	0	0	0	0

Table 2: TNM Classification UICC / AJCC, 2004 edition. (a): Tonsillar fossa / soft palate (b): Base of tongue (c): Nasopharynx .

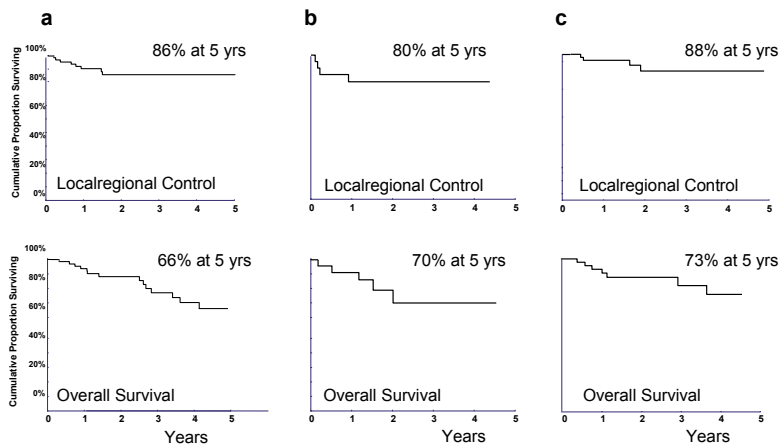


Figure 4a-c: Localregional control and overall survival at 5-years of patients with cancer of the tonsillar fossa / soft palate (a), the base of tongue (b) and the nasopharynx (c) treated between 2000-2005.

	Oropharynx	Nasopharynx
# patients	85	47
Deaths	17	8
Deaths of disease	8	7
Metastasis	-	3
2nd primary	1	1
Lost to Follow-up	-	7
Eligible questionnaires	67	28
No responses	7	6
No CT-scan	-	1
	60	21

Table 3: Breakdown of the exclusion criteria of the 132 oropharyngeal- and nasopharyngeal cancer patients. In total 81 patients remained eligible, that is patients without evidence of disease responding to the questionnaires.

	Dysphagia-related questionnaires		
	H&N35 (Swallowing)	PSS (Normalcy of Diet)	MDADI (Total)
TF / SP (n=45)	11%	27%	20%
BOT (n=15)	27%	27%	33%
NP (n=21)	20%	48%	5%

Table 4: Poor scores (%) of dysphagia for the questionnaires EORTC H&N35, PSS, and MDADI in the tonsillar fossa / soft palate (TF/SP), base of tongue (BOT) and nasopharynx (NP).

	Dysphagia-related questionnaires		
	H&N35 (Swallowing)	PSS (Normalcy of Diet)	MDADI (Total)
Brachytherapy (n=42)	7%	21%	14%
Cyberknife (n=6)	17%	33%	17%
Intensity-modulated radiation therapy / three-dimensional conformal radiation therapy n=12)	42%	58%	58%

Table 5: Poor scores (%) of dysphagia according to the questionnaires EORTC H&N35, PSS, and MDADI in oropharyngeal cancer patients when grouped by boost technique.

DISCUSSION

From the current literature we know that the intensification of therapy for head and neck cancer in general results in improved localregional tumor control [37-39]. However, late sequelae also increase, including swallowing disorder [40].
Limited data on swallowing problems is reported before 2005 [28]. Recently increased attention is given to the swallowing problem because of the ongoing randomized clinical trials in dysphagia [41]. The prevalence of dysphagia in organ preservation therapy is reported to be as high as 50% [7,17,42,43]. A study by Eisbruch et al. [35] showed that elevation of the larynx and pharynx during swallowing are essential for protection of the airway and propulsion of the bolus. After chemoradiation there is decreased base of tongue and/or posterior pharyngeal contraction and reduced pharyngeal contraction, resulting in impaired bolus transport through the pharynx [9]. Logemann et al. concludes that there is only little if any difference in frequency of swallowing problems across different disease sites af-

	Dysphagia-related questionnaires	
Boost Technique	H&N35 (Swallowing)	MDADI
(Total)		
No boost (n=4)	0%	0%
Brachytherapy (n=10)	10%	10%
SRT, CBK (n=7)	14%	0%

Table 6: Poor scores (%) regarding dysphagia according to the questionnaires EORTC H&N35 and MDADI in nasopharyngeal cancer patients when grouped by boost technique.

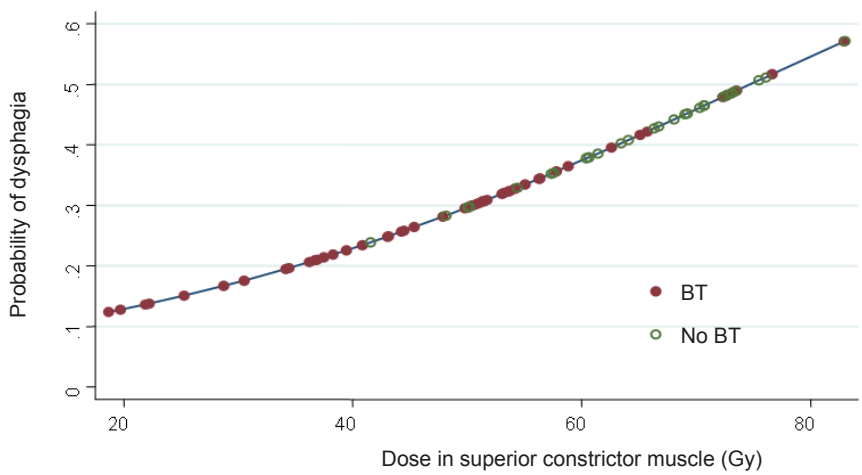


Figure 5: Dose-effect relationship for the probability of having dysphagia (PSS, normalcy of diet) and the dose (Gy) in the superior constrictor muscle. Curve of the estimated logistic regression is shown together with the estimated probabilities for each data point.

ter treatment and according to the same authors that the effects of the different chemotherapy agents were seemingly small [3]. Pre-treatment swallowing therapy may improve dysphagia and reduce the need for tube feedings [44]. Feng et al. demonstrated significant relationships between dose-volume parameters of structures and objective and subjective measurements of swallowing dysfunction[45]. Other groups also showed significant correlations of various dysphagia endpoints with dose; for the supraglottic lesions [46] and glottic cancers [20,46].

This paper analyzes the dose-volume relationships for dysphagia (and xerostomia). It particularly relates the side-effects (QoL) to different treatment techniques and to widely separated anatomical locations; that is the base of tongue, the tonsillar fossa and/or soft palate, and the nasopharynx. The treatment results for these intermediate prognostic groups are shown in figure 4a-c. From our series of 132 patients, chart review showed that 24 (18%) patients experienced moderate to severe dysphagia (RTOG grade 3 and 4) with more problems in patients with BOT (32%) cancer as opposed to patients with cancer of the TF/SP (22%) and NP (6%). As the prevention of dysphagia is of paramount importance in clinic and given the substantial amount of dysphagia in the present series, it was felt of interest to study this subject in detail by QoL instruments. Out of the 95 patients alive with no evidence of disease, 81

Coefficients	H&N35 (Swallo-wing)	PSS (Nomralcy of Diet)	MDADI (Total)	Global Dysphagia	Emotional Dysphagia	Physical Dysphagia	Functional Dysphagia
Dose scm	0.320*	0.310*	0.273†	0.252†	0.275†	0.247†	0.214†
Dose mcm	0.344*	0.258†	0.278†	0.266†	0.286†	0.247†	0.235†
Dose icm	0.198	0.007	0.105	0.202	0.105	0.066	0.095
Dose cphm	0.039	0.234	0.095	0.007	0.150	0.121	0.115
Dose eim	0.031	0.187	0.015	0.055	0.047	0.035	0.025

Table 7: Correlation coefficients for EORTC H&N35, PSS and MDADI and the dose in swallowing muscles. Swallowing muscles: the superior constrictor muscle (scm), the middle constrictor muscle (mcm), the inferior constrictor muscle (icm), the cricopharyngeus muscle (cphm) and the 1st cm of the muscular compartment of the esophagus inlet (eim). Note: With Bonferroni's correction only dose in scm and mcm vs. H&N35 (Swallowing) remain significance. Global, emotional, physical and functional dysphagia are distinct domains of the MDADI.

* Significant at the 0.01 level (2-tailed).

† Significant at the 0.05 level (2-tailed).

Dysphagia-related items	Xerostomia-related items		
p-values (Rho, 95% CI)	H&N35, dry mouth	H&N35, sticky saliva	VAS xerostomia
H&N35, swallowing	<0.001 (0.64, 0.49-0.76)	<0.001 (0.56, 0.38-0.70)	<0.001 (0.49, 0.30-0.64)
PSS, normalcy of diet	<0.001 (0.47, 0.27-0.63)	<0.001 (0.33, 011-0,52)	<0.001 (0.50, 0.31-0.65)
Total MDADI	<0.001 (0.58, 0.40-0.72)	<0.001 (0.47, 0.27-0.64)	<0.001 (0.60, 0.42-0.73)
Pain with swallowing	<0.01 (0.35, 0.14-0.54)	-	<0.01 (0.34, 0.12-0.53)

Table 8: Dysphagia related items correlated with xerostomia related items using Spearman's rank correlation. P-values are given when significant.

(85%) responded to the QoL questionnaires. According to the responses to the QoL questionnaires, swallowing problems are also most frequently encountered in patients with tumors of the BOT. Although correlations between the questionnaires were poor, almost a third of the patients' complain of swallowing disorders (table 4). Moreover, patients seem to experience more complaints of dysphagia with longer follow up (this finding is part of a separate paper in preparation). If grouped by treatment technique, most severe dysphagia was found in IMRT / 3DCRT, compared to BT group and SRT/CBK group (table 5). One explanation could be the cumulative dose in the swallowing structures. For example, if treated by EBRT techniques, the mean dose in the scm was 70 Gy in case of BOT tumors, 64 Gy in TF/SP and 67 Gy in NPC. If the booster is given by BT, the highest mean dose in scm is 52 Gy for BOT and 42 Gy for TF/SP (table 9). However, comparing dose distributions in TF/SP, BOT and NP, from tables 9 and figure 6 it can be seen that in the scm and mcm the highest dose was found in patients with NPC.

The NPC patient category is always treated (per protocol) by a large volume boost dose (so called first boost) of 24 Gy by EBRT techniques to a cumulative dose of 70 Gy to the primary tumor and positive neck nodes. It is at present unclear to us why the patients with NPC treated by a high dose to the upper swallowing muscles do not complain of dysphagia to the same extent compared to e.g. BOT cancer patients. One possible explanation could be the infiltrating nature of the disease itself in the case of BOT cancers. The BT or SRT / CBK booster dose in NPC is, however, of no relevance to the scm and other muscles given the very small volume and rapid dose fall-off.

Several dose-effect relationships between dysphagia problems and the dose received by the swallowing muscles were found to be significant (table 7). Most significant were the relationships between EORTC H&N35 and the dose in the scm / mcm and the association of the PSS (normalcy of diet) and the dose in the scm (p-values lower than 0.01). Figure 5 shows an example of the dose-effect relationship between PSS (normalcy of diet) and the dose in scm for all (81) patients. The higher the dose, the more chance of complaints of dysphagia. Xerostomia and dysphagia are strongly associated as depicted in table 8. Particularly highly correlated were the questions of the EORTC H&N35 questionnaire regarding swallowing, dry mouth and sticky saliva.

The previous findings suggest that BT dose distributions are more sparing to the swallowing musculature and salivary glands as opposed to the CBK/SRT and IMRT techniques. In order to differentiate between the intrinsic values of the irradiation techniques used, and whether it is simply due to margins, we computed for the 6 GTV's of clinical patients irradiated by CBK, the dose in the scm, mcm, left and right parotid, cord and CTV for PTV margins of 0, 2 and 5 mm, respectively. For each margin there is, approximately,little difference in dose if one compares the dose distribution in the various normal tissue structures. If one takes the clinical situation into account, that is com paring a PTV margin of 0 mm in case of BT vs. CBK with 2 mm margin and a 5 mm margin for IMRT an advantage can be observed for the BT and CBK with respect to the dose contributed to the normal tissues (table 10).

Moreover a higher dose is obtained in the CTV treated by the CBK compared to IMRT (18.3 Gy vs. 16.6 Gy). Margins do seem to have an substantial effect on the dose received by the swallowing muscles.

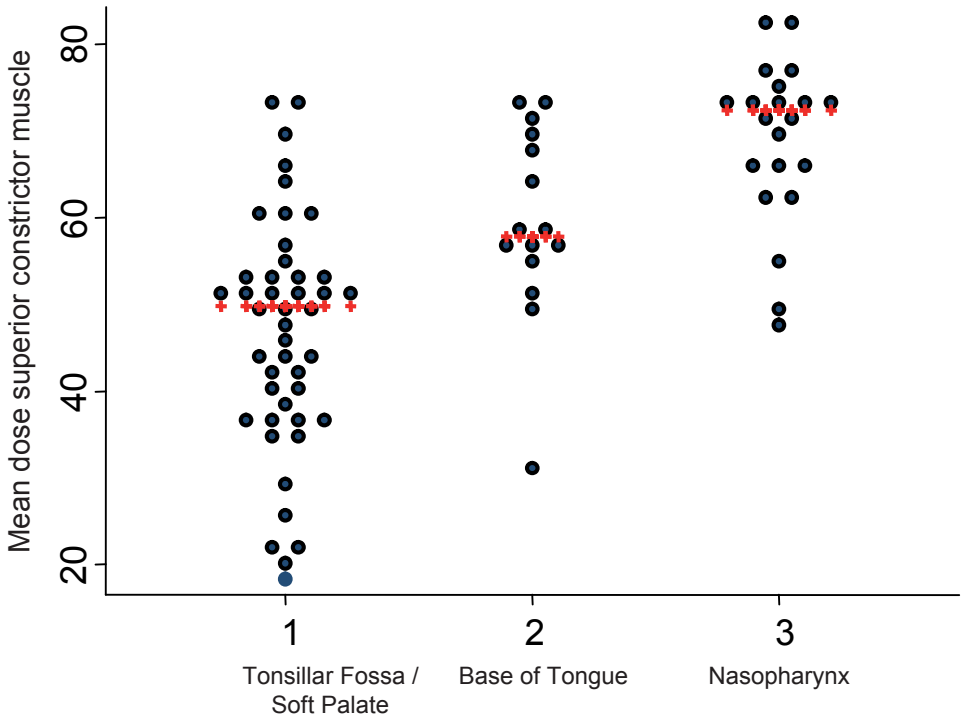


Figure 6: Plot of individual mean dose distribution of the superior constrictor muscle in the tonsillar fossa / soft palate, base of tongue and nasopharynx.

CONCLUSIONS

Patients treated with a variety of disease sites (TF / BOT / NPC) and treated by various RT techniques (IMRT / 3DCRT / BT / SRT / CBK) vary in their prevalence of severe dysphagia. Responses to QoL questionnaires in relation to the dose received by scm and mcm, demonstrated a dose-effect relationship. Dysphagia is also site (geographical position) dependant; most dysphagia problems are seen in BOT cancer patients. Although NPC patients receive the highest dose due to the treatment techniques used, dysphagia is still less as opposed to patients with cancer of the BOT. The explanation of this phenomenon remains somewhat unclear; it is speculated that this might have to do with the infiltrative (muscles) nature of the BOT cancers. Dysphagia is obviously multi-factorial. In particular, dysphagia is strongly correlated withxerostomia. From the findings of the present research, we would like to emphasize for the future to focus more on treatment planning research (constraints), especially for issues like this frequently underreported dysphagia problem.

Tonsillar Fossa / Soft Palate	IMRT / 3DCRT n=6	BT n=34	CBK n=5
(Gy)			
Scm	64	42	53
Mcm	61	36	47
Icm	45	24	29
Cphm	29	21	23
Eim	27	20	18
Base of Tongue	IMRT / 3DCRT n=6	BT n=34	CBK n=5
(Gy)			
Scm	70	52	(34)
Mcm	68	50	(39)
Icm	51	36	(35)
Cphm	38	26	(42)
Eim	36	20	(40)
All oropharynx	IMRT / 3DCRT n=12	BT n=34	CBK n=5
(Gy)			
Scm	67	44	50
Mcm	65	38	45
Icm	48	27	32
Cphm	34	22	25
Eim	32	20	23

Table 9: Mean dose to the superior-, middle- and inferior constrictor muscle, the cricopharyngeus muscle and the 1st cm of the muscular compartment of the esophagus inlet. Patients are grouped according to the boost-treatment technique used, that is IMRT / 3DCRT, brachytherapy (BT) and Cyberknife (CBK).

IMRT			
N=6	PTV_5mm	PTV_2mm	PTV_0mm
(Gy)			
Scm	13.3	12.0	11.1
Mcm	9.6	8.2	7.5
Left parotid	4.1	3.8	3.1
Right parotid	3.2	2.8	2.5
Cord	7.4	7.4	6.7
GTV	16.6	16.5	16.6
Cyberknife			
N=6	PTV_5mm	PTV_2mm	PTV_0mm
(Gy)			
Scm	14.3	12.7	10.8
Mcm	11.0	9.0	8.3
Left parotid	2.4	1.8	1.7
Right parotid	2.7	2.2	1.7
Cord	8.7	6.8	6.3
GTV	18.0	18.3	18.3

Table 10: Mean dose to the superior constrictor muscle (scm), middle constrictor muscle (mcm), left parotid, right parotid, cord and GTV with 0, 2 and 5 mm margins applied for the GTV, planned with IMRT 3D treatment planning system (XiO 4.3.3, CMS, USA) and Cyberknife plannings software (Multiplan 1.4.0, Accuray Inc., USA), respectively.

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Can IMRT or Brachytherapy Reduce Dysphagia Associated With Chemoradiotherapy of Head and Neck Cancer? The Michigan and Rotterdam Experiences

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ABSTRACT

Purpose/Objective: Dysphagia is a major late complication of intensive chemoradiotherapy of head and neck cancer. The initial clinical results of intensity-modulated radiotherapy (IMRT), or brachytherapy, planned specifically to reduce dysphagia are presented.

Patients and Methods: Previous research at Michigan University has suggested that the pharyngeal constrictors and glottic and supraglottic larynx are likely structures whose damage by chemo-RT causes dysphagia and aspiration. In a prospective Michigan trial, 36 patients with oropharyngeal (n = 31) or nasopharyngeal (n = 5) cancer underwent chemo-IMRT. IMRT cost functions included sparing noninvolved pharyngeal constrictors and the glottic and supraglottic larynx. After a review of published studies, the retropharyngeal nodes at risk were defined as the lateral, but not the medial, retropharyngeal nodes, which facilitated sparing of the swallowing structures. In Rotterdam, 77 patients with oropharyngeal cancer were treated with IMRT, three dimensional RT, or conventional RT; also one-half received brachytherapy. The dysphagia endpoints included videofluoroscopy and observer-assessed scores at Michigan and patient-reported quality-of-life instruments in both studies.

Results: In both studies, the doses to the upper and middle constrictors correlated highly with the dysphagia endpoints. In addition, doses to the glottic and supraglottic larynx were significant in the Michigan series. In the Rotterdam series, brachytherapy (which reduced the doses to the swallowing structures) was the only significant factor on multivariate analysis.

Conclusion:The dose–response relationships for the swallowing structures found in these studies suggest that reducing their doses, using either IMRT aimed at their sparing, or brachytherapy, might achieve clinical gains in dysphagia.

INTRODUCTION

Intensification of the therapy for head and neck cancer, by altered fractionated radiotherapy (RT) or the addition of concurrent chemotherapy, has resulted in improved tumor control rates. The main late sequela after treatment intensification has been increasing rates and severity of long-term dysphagia [1]. Dysphagia after chemo-RT of head-and-neck cancer is associated with aspiration, an underreported complication of therapy [2].

A previous study at the University of Michigan found that the pharyngeal constrictors (PCs) and the glottic and supraglottic larynx (GSL) changed anatomically after intensive chemo-RT, and their malfunction explained the post-therapy abnormalities observed in the objective assessments of swallowing [3]. Intensity-modulated RT (IMRT) plans whose cost function included sparing these structures without compromising target irradiation achieved significantly reduced doses to the swallowing structures compared with "standard" IMRT [3]. A prospective trial aiming to assess the clinical benefits gained by these strategies was subsequently initiated at Michigan.

At Erasmus MC in Rotterdam, brachytherapy (BT) has been used for many years as a tool to facilitate the delivery of a high tumor dose [4] and [5]. BT substantially reduces the doses delivered to neighboring tissues, specifically the neighboring swallowing structures, compared with conventional RT. Both IMRT aimed at the sparing of the swallowing structures at Michigan and BT at Rotterdam produced a wide dose range in these structures. This has allowed studies of dose–response relationships, whose initial results are summarized in this report.

PATIENTS AND METHODS

Patients and therapy

At Michigan, all 36 patients with oropharyngeal (n = 31) or nasopharyngeal (n = 5) cancer received IMRT, which included cost functions for sparing the PCs, GSL, and esophagus, without underdosing the targets, according to previously detailed methods [3]. Treatment was delivered in 35 fractions, with the gross disease (clinical target volume [CTV]1), high-risk (CTV2), and low-risk (CTV3) targets receiving 70, 63, and 59 Gy at 2.0, 1.8, and 1.7 Gy/fraction, respectively, concurrent with weekly carboplatin and Taxotere (oropharynx) or cisplatin (nasopharynx). At Rotterdam, 77 patients were treated with IMRT (n = 37), three-dimensional conformal RT (n = 22), or computed tomography-based parallel-opposed beam techniques. In 52% of the patients, BT was used according to previously detailed methods [4,5]. Additional details regarding the treatment methods used in Rotterdam have been previously published [6].

Target and structure delineation

Of particular importance to target delineation for IMRT at Michigan was the delineation of the retropharyngeal (RP) nodes. These nodes were defined as targets for all nasopharyngeal and almost all oropharyngeal cancers, particularly in patients with other clinically involved nodes. The RP nodes are divided into the lateral and medial RP nodal chains. The lateral RP nodes ("nodes of Rouviere") lie medial to the carotid

arteries and lateral to the longus coli and capitis muscles, and the medial RP nodes are intercalated along the lymphatics near the midline. Only the lateral RP nodes were defined as targets, and their CTVs were contoured in the spaces medial to the carotid arteries. The medial RP nodes were not defined as targets (unless radiologic evidence was present for gross lateral RP involvement), because they have been reported to be very rarely involved as metastatic sites [7,8]. Additional details regarding RP target delineation for this study, and its rationale, have been previously published [9]. The inclusion in the CTVs of only the lateral RP nodes, and the exclusion of the medial ones, facilitated the sparing of the swallowing structures.

Contouring of the swallowing structures, including the PCs and GSL, has been previously detailed [3]. In brief, the three parts of the PCs (upper, middle, and lower) were outlined as a single structure for which the cranial-most extent was the caudal tips of the pterygoid plates and the caudal-most extent was the inferior border of the cricoid cartilage. For the purposes of analysis, the PCs were considered as one structure and were also schematically divided into three parts: the superior PC was defined from the cranial-most extent through the upper edge of the hyoid bone, the middle PC was defined from the upper through the lower edge of the hyoid, and the inferior PC was defined from below the hyoid through the inferior edge of the cricoid cartilage. Caudal to the inferior border of the cricoid, the esophagus was contoured, and its caudal-most extent corresponded to the caudal-most extent of the low neck targets. The GSL was contoured as a single structure.

Evaluation of dysphagia

At Michigan, dysphagia was evaluated before and periodically after therapy with videofluoroscopy, quality-of life (QOL) instruments, including the HN-QOL questionnaire and the University of Washington HN-QOL Questionnaire, and the observer-rated Radiation Therapy Oncology Group late toxicity, scored by the treating physicians. At Rotterdam, dysphagia was assessed by three QOL instruments: the performance status questionnaire assessing “eating in public” and “normalcy of diet,” the European Organization for Research and Treatment of Cancer head-and-neck 35-item “swallowing” and “aspiration” questionnaire, and the M.D. Anderson dysphagia inventory–dysphagia-specific QOL questionnaire for head-and-neck cancer.

RESULTS

In the Michigan study, at 3 months after therapy, videofluoroscopy-based strictures were observed in 3 patients (8%) and aspirations (passage of barium past the vocal cords) in 16 (44%). The mean ± SD dose to the PC, GSL, and esophagus was 64 ± 5, 56 ± 10, and 41 ± 13 Gy, respectively. Significant correlations were observed between videofluoroscopy-based aspirations and the mean doses to the PC and GSL, as well as the partial volumes of these structures receiving 50–65 Gy. The greatest correlations were associated with doses to the superior PC ($p = 0.005$). All patients with aspirations had received a mean PC dose of >60 Gy or PC V65 >50%, and GSL V50 >50%. Reduced laryngeal elevation and epiglottic inversion correlated with the mean PC and GSL doses ($p < 0.01$). All 3 patients with strictures had received a PC V70 >50%. Worsening patient-reported liquid swallowing was correlated with the mean PC ($p = 0.05$) and esophageal ($p = 0.02$) doses. Only the mean PC doses

correlated with worsening patient-reported solid swallowing (p = 0.04) and observer-rated swallowing scores (p = 0.04). Of the individual PCs, the mean dose to the superior PC had the greatest correlation with the observer-rated and patient-reported dysphagia scores. Additional details of the results at Michigan have been previously published [9].

In the Rotterdam study, of 77 patients, 60 were alive and without evidence of disease. The locoregional relapse-free survival rate was 92% at a mean follow-up of 41 months (range 4–72). On univariate analysis, a significant correlation was observed between the doses delivered to the superior or middle PC, and the performance status scores, dysphagia scores of the European Organization for Research and Treatment of Cancer Head-and-Neck 35-item questionnaire, and M.D. Anderson dysphagia inventory–dysphagia-specific QOL questionnaire for head-and-neck cancer. In each QOL instrument, BT was associated with better outcome (p = 0.01). On multivariate analysis, BT was the predominant factor associated with reduced symptoms, because its use significantly reduced the doses to the superior and middle PCs. Additional details of the results at Rotterdam have been previously published [6].

DISCUSSION

In the Michigan and Rotterdam studies, statistically significant correlations were found between the dysphagia endpoints, including aspiration, and the dose–volume parameters for the superior and middle PCs. These relationships can be explained by several important details of the swallowing mechanism. Elevation of the larynx and pharynx during swallowing is essential for airway protection and bolus propulsion. This elevation is facilitated by contraction of the longitudinal muscles, which blend with the circular fibers of the superior PC, including the stylopharyngeus, salpingopharyngeus, and palatopharyngeus. As the larynx and pharynx are pulled up and forward by these muscles, they are pulled away from the lower posterior pharyngeal wall and facilitate opening of the upper esophageal sphincter at the cricopharyngeal level [3,10]. These mechanisms of swallowing and protection from aspiration, as well as our results, suggest that the benefits from efforts to spare the swallowing structures are likely to be maximized if they include the superior PCs, rather than being confined to the esophagus and its upper inlet (i.e., the caudal part of the inferior PCs).

The dose–effect relationships we have reported can now serve to define the optimization goals for IMRT. They should motivate efforts to reduce these doses as much as possible using either IMRT or BT, or both. Most importantly, care in the outlining of targets in the vicinity of these structures, avoiding target underdosing, and determining and reporting the locations of locoregional recurrences, are essential to ensure that the rates of local recurrences do not increase compared with the rates observed previously after IMRT or BT.

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Results of Fiberoptic Endoscopic Evaluation of Swallowing vs. Radiation Dose in the Swallowing Muscles after Radiotherapy of Cancer in the Oropharynx

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ABSTRACT

Background and purpose: Dysphagia is a serious complaint but frequently underreported. This paper assesses for oropharyngeal cancer (OPC) the relationship between the dose received by the swallowing structures, and the findings of a fiberoptic endoscopic evaluation of the swallowing process (FEES).

Materials and methods: Between 2000 and 2005, 60 out of 67 OPC patients local-regionally NED for at least one year following treatment responded to three types of QoL questionnaires; i.e. Performance Status Scales, EORTC H&N35, and M.D. Anderson Dysphagia Inventory. Twenty-four patients agreed to the FEES procedure. The main swallowing muscles were delineated, with the mean dose per muscle calculated using the original 3D CT-based treatment plans. Regression analysis was performed between FEES variables and the doses in the different swallowing muscles and the dysphagia related questionnaires.

Results: A significant relationship was found between the results of FEES and the mean dose in the superior constrictor muscle (SCM). Some of the subjective dysphagia complaints were significantly correlated with the FEES variables in this retrospectively study.

Conclusion: A higher dose in the SCM generally results in worsening of the findings obtained by the FEES examination.

INTRODUCTION

In recent years, chemoradiation protocols are becoming standard in the more advanced head and neck cancer patients because of their organ preservation properties. However a significant increase in side-effects, such as dysphagia, is also seen due to the use of more aggressive treatment modalities. Patients with complaints of dysphagia demonstrate significantly worse swallowing functions as indicated by lower oropharyngeal swallow efficiency (OPSE), increased pharyngeal transit times, larger residues, more swallows with aspiration [1], epiglottic immotility, pharyngeal dysmotility, limited laryngeal elevation and limited movement of the base of tongue [2]. Less tongue strength may play a role as well in oropharyngeal swallowing, particularly when related to the oral phase of the swallowing process [3,4]. Impaired swallowing function may be dependent on both the total dose received by the swallowing muscles and the treatment volume [5-8]. Furthermore, it has been argued that the experienced dysphagia corresponds significantly with the degree of xerostomia [9,10]. It is important to diagnose dysphagia early as it negatively affects the quality of life of head and neck cancer patients; moreover, nutritional surveillance needs to be provided to prevent malnutrion [11]. Examples of preventative measures for dysphagia are pre- and post-treatment exercises and/or the introduction of Therabite [12-16]. Pre-treatment swallowing therapy may improve dysphagia [17,18] and reduce the need for tube feedings. This paper will present regression analysis of fiberoptic endoscopic evaluation of swallowing (FEES) on the dose received by the swallowing structures. Also correlations will be calculated between the FEES variables and the swallowing related quality of life (QoL) questionnaires.

MATERIALS AND METHODS

Sixty-seven patients with oropharyngeal cancer were treated curatively in a single institution by radiation therapy (RT) techniques between 2000 and 2005, of the patients 60 NED oropharyngeal cancer patients responded to QoL questionnaires, i.e. Performance Status Scales, EORTC H&N35, and M.D. Anderson Dysphagia Inventory. Of these patients. The patients were seen in joint consultation by the radiation oncologist and H&N surgeon. Diagnosis was established by clinical examination, panendoscopy, CT and/or MRI of the head and neck. Biopsy of the primary tumor, and ultrasound-guided fine needle aspiration of suspicious regional lymph nodes were performed. Patients were staged according to the TNM classification 2002 edition [19], and patients staged before 2002 were restaged. Treatment protocol of the oropharyngeal patients had been detailed before [5]. In summary, as of 2000, a total dose of 46 Gy is given by IMRT. By an accelerated fractionation schedule (in our institution routinely used since 2000), six fractions of 2 Gy are delivered 5 days per week (once a week two fractions per day, administered with a minimum interval of 6 hours between fractions, the other 4 days one fraction of 2 Gy per day). For advanced T3/T4 tumors, in recent years the IMRT 0-46 Gy is frequently combined with two courses of chemotherapy (cisplatin 100 mg/m2). The IMRT is followed preferentially by a BT booster dose using a pulsed-dose-rate (PDR) or fractionated high-dose-rate fr. HDR BT schema, in conjunction with a neck dissection (ND) in case of positive neck nodes. If BT of the primary tumor is (technically) not feasible (e.g. in case of

parapharyngeal extension) or in case of patient refusal for whatever reason, from 2005, it is optional to use the Cyberknife to deliver the booster dose (3 x 5.5 Gy). For tumors of the tonsillar fossa and/or soft palate (TF/SP) to be boosted by brachytherapy (BT), fractionation schedules are similar. In case of fractionated HDR, after an initial fraction of 4 Gy, four additional fractions of 3 Gy, and a final fraction of 4 Gy (20 Gy total, two fractions per day, minimum 6 hour interval between fractions) is applied ("day-time" regimen). For PDR (pulsed-dose- rate): an initial fraction of 2 Gy followed by 18 x 1 Gy and a final fraction of 2 Gy (22 Gy total, 8 fraction per day, minimum 3 hours interval between fractions) are given ("day-and-night" schedule). These schedules are in accordance with our previously published BT protocol for the head and neck.

The 67 OPC patients alive and with no evidence of disease (NED) received four types of quality of life (QoL) questionnaires in 2007: 1. The EORTC core QoL Questionnaire [QLQ]-C30, 2. The EORTC QLQ-H&N35 with the swallowing scale, including four items (problems with swallowing of liquid, pureed food, or solid food, and aspiration when swallowing) and aspiration [20,3]. The Performance Status Scale (PSS) of List et al. with the item normalcy of diet [21,4]. The M.D. Anderson Dysphagia Inventory (MDADI), [22] consisting of 20 questions with global, emotional, functional, and physical subscales.
One objective of this paper is to analyze dysphagia measured according to the scoring parameter of the FEES procedure in relation to the dose received by the swallowing muscles. The muscular structures involved are the superior constrictor muscle (scm), the middle constrictor muscle (mcm), the inferior constrictor muscle (icm), the cricopharyngeal muscle (cphm) and the 1st cm of the muscular compartment of the esophagus inlet (eim) [5,23]. Subsequently, every treatment plan of the previously irradiated patients was retrieved, now with the muscular structures of the swallowing apparatus newly delineated on the axial CT slices. The mean dose contribution to the muscular components of the swallowing mechanism using parallel-opposed, 3DCRT or IMRT treatment plans was computed using the original treatment plan with the newly delineated swallowing muscles. From the available CT-based 3D dose distribution of patients boosted by means of BT, the mean BT dose was calculated. For those patients boosted by BT, SRT or Cyberknife, the 3DCRT, IMRT or parallel-opposed dose and the boost doses, respectively, were physically summated. Also dose-volume dependencies are calculated.
FEES was done according to the technique described by Langmore et al. [24]. The patient eats and drinks while the hypopharyngeal and laryngeal structures were kept in view with the fiberscope. Liquid (colored water), pureed food (yoghurt), and chewable food (cracker) were ingested. While one examiner passed the endoscope, another observed the patients' swallowing. Ten variables were scored: mucus stases and residue, penetration and aspiration of water, yoghurt and crackers, respectively (table 1). Prevalence of dysphagia: A moderate / severe degree of dysphagia is established by clustering the answers 'quite a bit' and 'very much' dysphagia of the EORTC H&N35 (swallowing and aspiration) [5]. The PSS (normalcy of diet) score ≤ 50 and total MDADI score ≤ 50 were taken as the prevalence of a significant degree (equivalent to grade 3 or 4) of Dysphagia. Also for the variables of the FEES, residue of water, yoghurt and crackers, respectively, were dichotomized, adding together

answers ‘absent’ and ‘little’ vs. ‘moderate’ and ‘severe’. Patients who cannott eat the cracker were dichotomized as severe. Mucus stases, aspiration and penetration of water, yoghurt and crackers score are already dichotomized during the scoring itself. Using the 10 dichotomized variables of the FEES procedure, a single score was calculated by summing up the individual scores of mucus stases and residues and twice the scores of aspiration and penetration of water, yoghurt and crackers, respectively. The aspiration and penetration scoring were doubled as these variables of the FEES do weigh more in the case of dysphagia.

Statistical considerations

Univariate logistic regression analysis was performed for the individual binary FEES variables on dose in five muscular structures: scm, mcm, icm, cphm and eim.
Correlations between FEES variables and QoL variables were assessed using Spearman rank correlation analysis. P-values ≤ 0.05 will be considered significant.

# patients	No	Yes	Little	Moderate	Severe	NA
Mucus Stases	17	7				0
Water residue	13		8	3	0	0
Water penetration	22	2				0
Water aspiration	24					0
Yoghurt residue	3		8	6	7	0
Yoghurt penetration	22	2				0
Yoghurt aspiration	23	1				0
Cracker residue	3		7	2	7	5
Cracker penetration	18	1				5
Cracker aspiration	19	0				5

Table 1: Fiberoptic endoscopic evaluation of swallowing (n = 24); Mucus stases/residue: no, little, moderate, severe, NA. Aspiration/penetration: no, yes, NA.

RESULTS

Twenty-four NED oropharyngeal cancer patients responded to QoL questionnaires, i.e. Performance Status Scales, EORTC H&N35, and M.D. Anderson Dysphagia Inventory and agreed to the FEES procedure. The FEES procedures were done after a minimal follow up of 1 year with no evidence of disease between November 2006 and March 2007. Mean follow up for FEES was three and half years (range 0,08-6,6 years). Patient characteristics are shown in table 2.
The prevalence of grade 3 and 4 dysphagia according to the H&N35 questionnaire (swallowing scale with a score ≥ 50), was 15% (9/60) for OPC. For PSS (Normalcy of diet) and total MDADI, values of 23% (14/60) and 27% (16/60), respectively, were obtained. These three questionnaires were used for analysis only as the EORTC-C30 did not contain swallowing related questions. The mean doses and the partial

	# patients
Tumor site	24
Tonsillar Fossa	16
Base of Tongue	8
Male	19
Age (mean/median)	58 / 60
Stage	
T1	3
T2	12
T3	8
T4a	1
N0	8
N1	4
N2a	6
N2b	3
N2c	2
N3	1
Chemotherapy	13
3DCRT	11
IMRT	13
Boost	
No	4
Brachytherapy	16
Cyberknife	4

Table 2: Patient characteristics.

volumes of the swallowing muscles received dose (VD) are summarized in table 3. Results of the FEES variables investigated are shown in table 1. With regard to the dose-effect relationship of the individual FEES variables (mucus stases and residual, penetration and aspiration with water, yoghurt and crackers), there is no significant relationship seen with the doses in the swallowing muscles (scm, mcm, icm, cphm and eim). However, a significant linear regression between the total FEES score (summation of the FEES variables) and the superior constrictor muscle was observed (figure 1); this was not the case for the other lower situated swallowing muscles. Significant correlations between FEES variables and answers to the swallowing related quality of life questionnaires were as seen in table 4. Mostly 'cracker penetration' and 'yoghurt' residue showed a relationship with the - dysphagia related - questionnaires. No relationships were found for the QoL question regarding 'pureed food' and 'aspiration' with the FEES variables. Also no correlati-

		Median	Range
SCM	Mean Dose (Gy)	53	(20-73)
	V20 (%)	100	(36-100)
	V40 (%)	100	(0-100)
	V50 (%)	0	(0-100)
	V60 (%)	0	(0-100)
MCM	Mean Dose (Gy)	50	(21-72)
	V20 (%)	100	(17-100)
	V40 (%)	93	(0-100)
	V50 (%)	0	(0-100)
	V60 (%)	0	(0-100)
ICM	Mean Dose (Gy)	34	(8-69)
	V20 (%)	73	(7-100)
	V40 (%)	45	(0-100)
	V50 (%)	0	(0-100)
	V60 (%)	0	(0-100)
CphM	Mean Dose (Gy)	23	(3-57)
	V20 (%)	43	(2-100)
	V40 (%)	13	(0-100)
	V50 (%)	0	(0-67)
	V60 (%)	0	(0-57)
EIM	Mean Dose (Gy)	17	(3-46)
	V20 (%)	32	(0-100)
	V40 (%)	2	(0-100)
	V50 (%)	0	(0-4)
	V60 (%)	0	(0)

Table 3: Mean doses of the swallowing structures and partial volumes receiving specified doses (VD).

ons were found for the FEES variables mucus stases, water penetration, water aspiration, yoghurt penetration and yoghurt aspiration with quality of life questionnaires. The total FEES score showed a significant relationship with QoL question regarding swallowing ‘pureed food’ ($p \leq 0.01$) and ‘solid food’ ($p \leq 0.05$) of the EORTC H&N35, and also with the ‘normalcy of diet’ ($p \leq 0.05$) question of the PSS and the total MDADI questionnaire ($p \leq 0.05$) No significant correlation was found regarding swallowing ‘liquids’ and aspiration questionnaires.

DISCUSSION

Swallowing is a complex action requiring rapid and precise coordination between sensory input and motor function of the swallowing apparatus [25]. Recently there is increased focus on dysphagia given the ongoing randomized clinical trials in dysphagia [26]. Reflexive cough while eating and drinking is important for the detection of oral pharyngeal dysphagia [27]. Swallowing is generally divided into phases that are modified during normal development due to anatomic and physiologic maturation [28]. The prevalence of dysphagia in organ preservation therapy is reported to be as high as 50% according to some papers on head and neck cancers [29-32] and an aspiration rate of 21-81% with chemoradiation [29,33-39] has been observed. However, its prevalence is probably being underreported because of its clinically silent nature. The following phases are identified in swallowing, i.e. an oral, oral propulsive, pharyngeal and esophageal phase. Swallowing disorders affect both oral and pharyngeal phases; they are most likely caused by radiation-induced edema and neuromuscular fibrosis [30]. The types of impairments of the swallowing function after radiotherapy are described in the literature as follows: poor pharyngeal motility, with subsequent pharyngeal residue, epiglottic immobility, reduced laryngeal excursion, poor closure of the laryngeal vestibule and aspiration [40-46]. A study by Eisbruch et al. [23] showed that elevation of the larynx and pharynx during swallowing is essential for protection of the airway and propulsion of the bolus. After chemoradiation there is decreased base of tongue and/or posterior pharyngeal contraction, resulting in impaired bolus transport through the pharynx [36]. Co-morbid conditions, T3-4 tumors (vs. T2), and resections of the base of tongue and soft palate (vs. defects of other dynamic structures) were associated with the most profound swallowing problems [39]. For patients treated by concomitant chemoradiation, some authors claim slow recovering of the dysphagia after 6-12 months [39,47,48], and patients have fewer functional swallows, i.e. swallows with longer pharyngeal delay, greater oral, and /or pharyngeal residue than normal swallows in patients with the same age and sex, than patients treated by radiation alone at 12 months post-treatment completion [49]. Logemann et al. conclude that there is only little if any difference in frequency of swallowing problems across different disease sites after treatment. Several groups showed significant relationships between dose-volume parameters of structures and mostly subjective measurements of swallowing dysfunction [5,50-52].

FEES and videofluoroscopy (modified barium swallow) for examining swallowing has some subjective nature. Kelly et al. investigated whether these types of dysphagia examinations influence the scoring of penetration and aspiration. Indeed penetration aspiration is perceived to be greater (more severe) from FEES than for the videofluoroscopy recordings [53]. This has to be taken into account when looking at the data. Whether patients have their dietary and behavioral management guided by the results of videofluoroscopy and / or FEES, their outcomes with respect to pneumonia incidence and pneumonia-free interval are essentially the same [54]. Although comparison of cost-effectiveness of videofluoroscopy via videofluoroscopy and videoendoscopy via FEES with sensory testing resulted in that FEES appears to be more cost-effective than videofluoroscopy [55].

In this paper, the severity of dysphagia was measured by the FEES procedure in tumors originating from the tonsillar fossa and / or soft palate or base of tongue. Subsequently, a relationship between dose and the outcome of the FEES procedure was established. It also describes the correlation of QoL (dysphagia) and the FEES outcome in patients for at least one year with no evidence of disease after treatment by radiation. In recent years intensification of therapy for head and neck cancers in general, either by altered fractionation RT schemes and/or by the addition of concomitant chemotherapy, results in improved local-regional tumor control [56-58]. It is of interest to note that in the analyzed patient subset of this paper, in 54% of the cases radiation was combined with concomitant cisplatin based chemotherapy. However, late sequelae have also increased [59], thereby modifying the quality of life of the patients in a negative fashion [33]. Given the significant impact of dysphagia on the QoL, prevention of this serious late side-effect is of paramount importance. We therefore studied this subject in more detail by performing the FEES procedure in patients radiated for the primary cancer located in the oropharynx. Placement of the flexible endoscope for FEES traverses partly the same path as a food bolus in the pharynx, and could therefore negatively influence safe and efficient swallowing. Suiter et al. determined if the presence of a flexible fiberoptic endoscope in the pharynx affects swallow physiology; this effect could not be established [60].

The QoL instruments used in our study were the questionnaires of the EORTC H&N35 (swallowing scale, aspiration), the MDADI and the PSS (normalcy of diet). Of the 67 patients alive with NED, 60 responded to the QoL questionnaires and 24 agreed to the FEES procedure. The BT dose was added to the EBRT by physical summation. BED was not calculated as it is of low relevance as the dose fall-off is very steep for BT. Even the BT dose contributing to the target is only maximally one-third of the total dose, so the contribution of the BT is even less. Moreover the dose rate is lower for the swallowing muscles than estimated compared to the target. Overall treatment for patients treated by external beam radiation only and external beam radiation + brachytherapy is the same: more or less 6 weeks. Calculating the BED is “technically” possible, however questionable as what the relevance is, also which values should be included in some of the parameters are still debatable. Of the five swallowing muscles studied, only for the superior constrictor muscle a dose-effect relationship for the total FEES score was found (figure 1). In line with our previous findings, indeed it is suggested that radiation to the superior constrictor muscles is extremely important for swallowing; dose in scm also correlates well with the answers to swallowing related QoL questionnaires [5]. Individual variables scored for FEES did not correlate significantly; this may be due to the small subgroups of patients investigated. In our previous paper we described a multivariate analysis on a greater group with the following variables used: age, sex, site, T-stage, N-stage, dose, technique, surgery, chemotherapy and brachytherapy. Brachytherapy seemed to be a significant factor, but chemotherapy and the other factors did not reach significance. The mean doses and the partial volumes of the swallowing muscles received dose (VD) are correlated very well as reported also by Feng et al, therefore no correlation analysis between (VD) with questionnaires was done [6].

Also is found that the total FEES score is correlated well with the capability of swallowing of pureed and solid foods, as formulated in the EORTC H&N35 questionnaire, and with the normalcy of diet item from the Performance Status scale and total mean

score of the MDADI. These findings show that the total FEES score of the variables is more sensitive to the patient findings than the individual FEES variables; this probably can be explained by the small number of patients who underwent the FEES procedure.

CONCLUSIONS

Oropharyngeal cancer patients frequently suffer from a significant degree of severe dysphagia. Total FEES score showed a dose-effect relationship for the dose received by the superior constrictor muscle, and correlates well with the responses to the QoL questionnaires. From the findings of the present clinical research, we would like to emphasize for the future to focus even more on constraints for the superior constrictor muscles and the dysphagia problem.

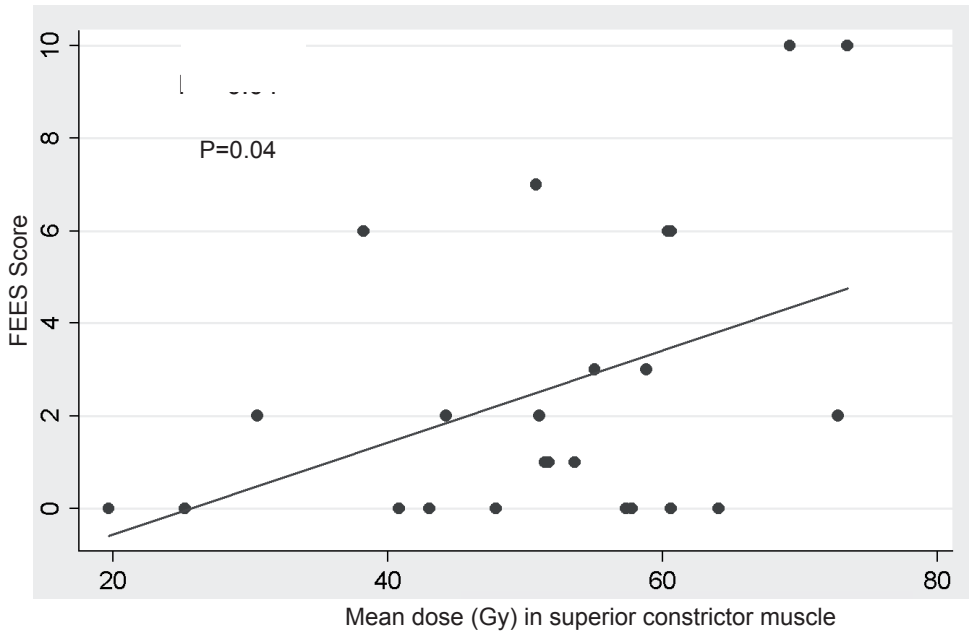

Figure 1: Dose vs. total FEES score relationship.

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Trismus in Patients with Oropharyngeal Cancer: Relationship with Dose in Structures of Mastication Apparatus

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ABSTRACT

Background: To assess the correlation between the radiation therapy (RT) dose to the mastication apparatus and trismus of oropharyngeal cancer patients.

Methods: 81 patients treated by RT were analyzed. The masseter, pterygoid and temporalis muscles and the coronoid and condyl were delineated on axial CT-slices. The mean dose in these structures was correlated with outcome of quality of life questionnaires.

Results: 56 (88%) patients responded; 16% of the patients scored grade 3/4 on the Head&Neck35 'opening mouth' question. A significant correlation was observed between dose in masseter and pterygoid muscles and trismus ($p = 0.02$).

Conclusion: Patients treated with brachytherapy received a lower dose in masticatory muscles. A steep dose-effect relationship between mean dose in masseter muscle and pterygoid muscles and the probability of having trismus complaints was observed; with every additional 10 Gy to the pterygoid muscle, an increase of the probability of trismus of 24% was observed.

INTRODUCTION

The wording 'trismus' has been coined in relation to a complication of the movement of the mandible following surgery and /or radiotherapy (RT) in head and neck cancer. It has been described as any type of restriction in opening of the mouth including radiation and conditions after trauma, surgery or tetanus [1-4]. The functionality of the 'trismus related' muscular compartment can be summarized as follows: Depression (lateral pterygoid muscles, gravity), Elevation (temporalis-, masseter- and medial pterygoid muscles), Protrusion (lateral pterygoid-, masseter-, temporalis muscles), Retraction (posterior fibers temporalis- and deep fibers masseter muscles), and Lateral movement (contralateral lateral pterygoid- and bilateral temporalis muscles). In radiation-induced fibrosis, there is presence of infiltrating inflammatory cells, atypical fibroblasts, and large amount of various extra-cellular matrix components. The result of this fibrosis limits the mouth opening, with major effects on nutrition, dental hygiene, swallowing and phonation. To alleviate the symptoms of trismus, an active mobilizing treatment is worth considering [5]. Usually trismus is investigated as a secondary outcome variable. Effects of therapeutic interventions are scarcely investigated [6]. Few publications yet discuss the prevention of trismus in the era of modern conformal radiation therapy techniques. Even more so, the definition and delineation of the normal tissue structures involved in trismus is to the great extent lacking. This paper was set out to define the precise location and role of the structures of the mastication apparatus. After identification of the structures, each of them was delineated on axial CT-slices of a consecutive series of patients with cancer of the Oropharynx, radiated by, highly conformal, Intensity Modulated Radiotherapy (IMRT)/3D Conformal Radiotherapy (3DCRT). In order to investigate a dose-effect relationship, the mean dose was computed for every structure and related to the responses to the Quality of Life (QoL) questionnaires.

MATERIAL AND METHODS

This study is based on a cohort of 81 patients diagnosed with scc of the oropharynx and treated curatively between 1999-2005 in a single institution by highly conformal radiation therapy techniques. That is, 46 patients by 3DCRT and 35 patients by IMRT. At the time, treatment of preference for T1-T3 disease consisted of 46/2 Gy external beam radiation therapy (EBRT) to the neck and primary tumor, followed by a boost by means of fractionated HDR (High Dose Rate) or PDR (Pulse Dose Rate) brachytherapy (BT) to the primary tumor. In case of neck nodes, a neck dissection was performed. For those patients not eligible for BT (e.g. medical unfit, patient refusal, T4 tumors and extensive parapharyngeal extension), a combined resection, followed by EBRT is performed. The clinical target volume for the N0, N+ neck is delineated according to the rulings of the international consensus [7,8]. External beam RT is prescribed according to International Commission on Radiation Units and Measurements 50 and 62 recommendations and generally delivered by a linear accelerator with a 6-10 MV (photon) beam. By an accelerated fractionation schedule, six fractions of 2 Gy are delivered 5 days per week (once a week two fractions per day, administered with a minimum interval of 6 hours between fractions) [9].

This accelerated conformal RT technique has been used routinely since 2000. For brachytherapy of the tonsillar fossa and / or soft palate, a split period of 1-2 weeks is allowed before implanting 2-3 catheters (single plane) in the CTV of the primary tumor. After optimization, the dose is prescribed at 0.5 – 0.75 cm of the central plane of implanted catheters. In case of a primary cancer in the base of tongue, a volume implant with afterloading catheters is performed, usually by implanting 3 sagital planes covering the whole of the BOT. Dose prescription for BOT implant is according to the Paris System rules; dose is prescribed at 85% of the mean basal dose. Fractionation schedules for tonsillar fossa and / or soft palate and BOT are similar. In case of fractionated HDR, after an initial fraction of 4 Gy, four additional fractions of 3 Gy, and a final fraction of 4 Gy (20 Gy total, two fractions per day, minimum 6 hour interval between fractions) is applied. For PDR (Pulsed Dose Rate): an initial fraction of 2 Gy followed by 18 x 1 Gy and a final fraction of 2 Gy (22 Gy total, 8 fraction per day, minimum 3 hours interval between fractions) are given. These schedules are in accordance with our previously published BT protocol for the head and neck [9]. Using this protocol, excellent loco-regional control has been obtained in T1-T3 tonsillar fossa and/or soft palate tumors and T1-4 tumors originating from the BOT. At 10 years the local control rate was approximately 80% [10].
Patients were staged according to the TNM classification (UICC /AJCC 2004)[11]. Thirty-two patients had T3/T4 disease, 50 patients had N+ disease. For this patient category the local relapse free survival (LRFS), the disease free survival (DFS) and overall survival (OS) were calculated. During follow up, 4 patients died because of intercurrent disease, 13 died because of tumor relapse and/or regional metastases. In order to evaluate trismus in more detail, the remaining 64 patients alive with no evidence of disease received 3 types of quality of life questionnaires: 1. The EORTC (European Organisation for Research and Treatment of Cancer) Core Quality-of-Life Questionnaire [QLQ]-C30 (30 items) 2. the EORTC Head and Neck cancer module QLQ-H&N35 with the items ‘opening mouth’ and ‘pain in jaw’ and scales ‘speech’ and ‘social eating’, the Performance Status Scale (PSS) of List with the functions: eating in public, normalcy of diet and understandability of speech. Given these items, albeit somewhat arbitrary, we thought it reasonable to define severe trismus (grade 3/4) to correspond with a PSS score ≤ 50, QLQ-C30 and H&N35 ≥ 50.

Questionnaires

The QLQ-C30 and QLQ-H&N35 QoL instruments, were developed and translated by the European Organization for Research and Treatment of Cancer (EORTC). The questionnaire has 2 parts. The core questionnaire (Quality-of-Life Questionnaire [QLQ]-C30) applies to all patients with cancers, and the disease-specific questionnaire (QLQ-H&N35) is designed for patients with cancer of the head and neck region. The raw scores obtained from the EORTC questionnaires were converted to scores ranging from 0 to 100 using linear transformation according to the scoring procedures [12]. The QLQ-C30 includes 30 questions comprising both multi-item scales and single-item measures. The 5 functional scales are physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. The 3 symptom scales are fatigue, nausea and vomiting, and pain.

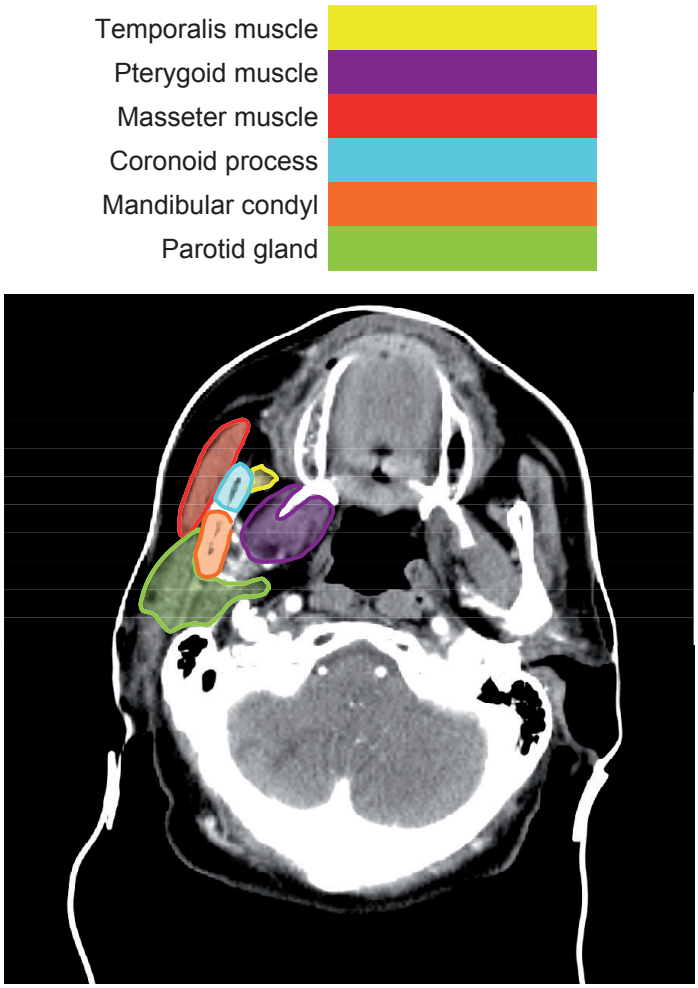

Figure 1: Schematic diagram of the delineated structures of the mastication apparatus.

There is also a global QOL scale. The 6 single-item measures are dyspnoe, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. A high score for a scale represents a higher response level. Thus, a high score for a functional scale represents a high or healthy level of functioning, a high score for the global QOL scale represents a high QOL, but a high score for a symptom scale or item represents a high level of symptoms (problems).
The comprises 35 questions incorporating 7 multi-item scales and 11 single items. The multi-item scales are pain, swallowing, senses, speech, social eating, social contact, and sexuality. The single items are teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain killers, nutritional supplements, feeding tube, weight loss, and weight gain. For all items and scales, high scores indicate more problems.
An important issue of this paper is to correlate dose with the trismus complaints. For this purpose we defined the relevant structures of the mastication apparatus. The relevant muscles for jaw movement (masseter-, temporalis- and pterygoid muscles)

are delineated, the processes coronoideus and condyl of the mandible inclusive. On the axial CT-slices of the treatment plans of every patient, the 5 bilateral structures of interest were delineated (figure 1).
Regarding the temporalis and pterygoid muscles, the most cranial slice was contoured 5 mm cranial to the coronoid process. The most caudal slice of the coronoid process and the condyl of the mandible are contoured at the level where the coronoid process and condyl of the mandible are not separately visible anymore. Both masseter muscles are contoured in all axial slices. The external beam dose contribution of the external beam part to the muscular structures was computed (mean doses) using the original treatment plan [13]. From a 3D dataset of 14 patients boosted by means of BT, the mean BT dose was calculated. For those patients treated by BT, the external beam dose and the BT dose were summated.

Statistical Analysis

Prevalence of trismus: As endpoints for trismus, data obtained by chart review for trismus related complaints and the QoL scores taken from the EORTC H&N35 and PSS of List questionnaires were obtained. For the H&N35 'opening mouth' item the gradings 'quite a bit' and 'very much' trismus were taken as grade 3 and 4, respectively. The PSS score ≤ 50 was taken as a significant degree (equivalent to grade 3 and 4) of trismus.
Univariate dose-response relationship: For the masseter-, pterygoid-, temporalis muscles and coronoid and condyl bony processus of the mandible, the correlations of dose in these structures and the absence or presence of trismus grade 3 and 4 combined were calculated by the proportional odds model.
Multivariate analysis: For the multivariate analysis the following variables were used: age, sex, site, T-classification, N-classification, dose, technique, unilateral /bilateral irradiation surgery, chemotherapy and brachytherapy.

RESULTS

At 5-years, for the 81 patients analyzed, a local regional control rate of 84% and an overall survival of 77% was observed. Sixty-four patients were alive with no evidence of disease at the censor date; 56 / 64 (88%) responded to the – trismus related – questions of the QoL questionnaires. The patient characteristics of the subsites of the oropharynx, being 41 patients with the tonsillar fossa /soft palate tumors and 15 patients with base of tongue (BOT) tumors, are lis ted in table 1. In 77% (43/56) brachytherapy (BT) was used; in 20% radiation was combined with concomitant chemotherapy (cCHT). Follow-up varied from 18 months (range 2-34) for IMRT to 46 months for 3DCRT (range 2-72).
According to the notes in the charts, 3 (4 %) patients experienced trismus. In contrast, in 15% of the IMRT group and in 20% of the 3DCRT group, the - trismus related - question of H&N35 ('opening mouth') was scored in category 3 or 4. Similarly, for tonsillar fossa and / or soft palate tumors categories 3 or 4 were observed in 12% vs. 27 % in BOT tumors. The cCHT group scored 25% vs. 9% in the non-cCHT patients. In the BT group in 12% of the cases category 3 and 4 was found vs. 31% in the non-BT patients (table 2).
Figure 2 shows the boxplot of the H&N35 question 'opening mouth' by BT vs. non-

BT. With regard to the PSS, 19% had difficulty with eating in public, 30% problems with normalcy of diet and in 2% difficulty with understandability of speech. Table 3

	TF / SP, no. of patients	BOT, no. of patients	All Oropharynx, no. of patients
Number of patients	41	15	56
Male gender	27	10	37
Mean age (range) years	57 (40-73)	55 (44-68)	56 (40-73)
BT Boost	34	9	43
IMRT + cCHT	3	4	7
IMRT - cCHT	16	4	20
3DCRT + cCHT	10	7	17
3DCRT - cCHT	12	0	12
+ Neck Dissection	15	9	24

Table 1: Patient characteristics of 56 patients with squamous cell carcinoma of the oropharynx. Abbreviations: TF: Tonsillar Fossa; BOT: Base of Tongue, cCHT: concurrent Chemotherapy; BT: Brachytherapy; IMRT: Intensity Modulated Radiotherapy; 3DCRT: 3D Conformal Radiotherapy.

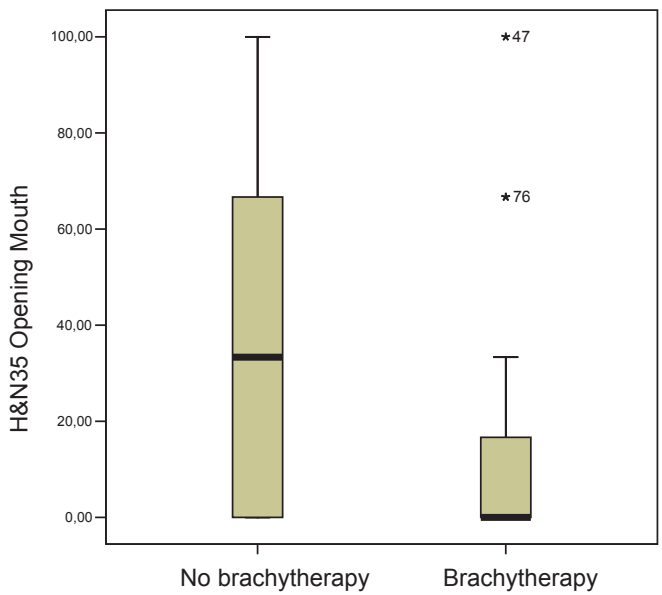

Figure 2: Boxplot of the EORTC H&N35 (European Organisation for Research and Treatment of Cancer Head & Neck cancer module) question 'opening mouth' grouped by Brachytherapy vs. No Brachytherapy cases.

Poor scores - trismus related - QoL	TF, No. of patients	BOT, %, No. of patients
H&N35* Opening Mouth	12% (5/41)	27% (4/15)
H&N35* Pain in Jaw	5% (2/41)	14% (2/14)
H&N35* Speech	2% (1/41)	13% (2/15)
H&N35* Social Eating	10% (4/40)	21% (3/14)
PSS† Understandability of Speech	2% (1/42)	0% (0/15)
Outpatient Clinic	5% (2/42)	7% (1/14)
	IMRT, %, No. of patients	3DCRT, %, No. of patients
H&N35* Opening Mouth	15% (4/27)	17% (5/29)
H&N35* Pain in Jaw	8% (2/26)	7% (2/29)
H&N35* Speech	7% (2/27)	3% (1/29)
H&N35 Social Eating	16% (4/25)	10% (3/29)
PSS† Understandability of Speech	0% (0/28)	3% (1/29)
Outpatient Clinic	4% (1/28)	18% (5/28)
	Non-CHT, %, No. of patients	CHT, %, No. of patients
H&N35* Opening Mouth	9% (3/32)	25% (6/24)
H&N35* Pain in Jaw	3% (1/31)	13% (3/24)
H&N35* Speech	6% (2/32)	4% (1/24)
H&N35* Social Eating	13% (4/31)	13% (3/23)
PSS† Understandability of Speech	0% (0/33)	4% (1/24)
Outpatient Clinic	3% (1/32)	8% (2/24)
	BT, %, No. of patients	Non-BT, %, No. of patients
H&N35* Opening Mouth	12% (5/43)	31% (4/13)
H&N35* Pain in Jaw	2% (3/13)	23% (1/42)
H&N35* Speech	2% (1/43)	15% (2/13)
H&N35* Social Eating	2% (1/43)	55% (6/11)
PSS† Understandability of Speech	2% (1/43)	0% (0/14)
Outpatient Clinic	5% (2/42)	7% (1/14)

Table 2: Percentage of patients scoring poor scores in Trismus related QoL questions between TF vs. BOT, non-CHT vs. CHT, BT vs. non-BT and IMRT vs. 3DCRT.
*EORTC (European Organisation for Research and Treatment of Cancer) Head & Neck cancer module.
†Performance Status Scale. Abbreviations: QoL: Quality of Life; TF: Tonsillar Fossa; BOT: Base of Tongue, CHT: Chemotherapy; BT: Brachytherapy; IMRT: Intensity Modulated Radiotherapy; 3DCRT: 3D Conformal Radiotherapy.

shows the distribution of poor scores for the H&N35 “opening mouth” and “pain in jaw” question. The percentages poor scores increased with T classification. All patients were ultimately seen at the outpatient clinic in December 2005 and categorized having limitations in opening mouth (6/56: 11%) or functionality within normal limits (89%: 50/56). The mean inter-incisal (id) distance measured approximately 39 mm (range 10 mm to 65 mm); the id of the patients scored as trismus (chart review) were 27 and 28 mm with 1 missing. Table 4 illustrates the id’s for patients scored having limitations ‘opening mouth’ at the time last follow-up, for patients with trismus according chart review and for those cases scoring category 3 or 4 of the - trismus related - QoL questionnaires vs. no limitations in mouth opening.

Univariate dose-response relationship: The results of the dose-response relationship stratified per muscular structure and complaint category of the different quality of life questionnaire are shown in table 5. In the univariate analysis a significant correlation was observed between the dose in the masseter-, pterygoid muscles, the coronoid and the trismus related question of the H&N 35 questionnaire. Further more a significant effect was found for trismus observed at the last follow-up visit of outpatient clinic correlating with dose in the masseter -, pterygoid muscles and the coronoid bone. In the multivariate analysis, BT was the only significant factor.

An overall probability of 5% and 10%, was observed for ‘opening mouth’ (H&N35) and speech (H&N35) respectively. Figure 3 shows the relationship between the probability of having complaints by increasing dose divided for BT and non-BT treatment. For every 10 Gy in the pterygoid muscle, after a dose of 40 Gy, an increase of probability of trismus of 24% was observed. For those patients of whom the trismus related muscles were irradiated bilaterally, a significant increase of the chance for trismus was observed with regard to the item ‘opening mouth’ (H&N35) (p=0,02) (table 6). All other items of the QoL were found not to differ significantly unilaterally and bilaterally.

DISCUSSION

In order to obtain better tumor control rates, in recent years more aggressive regimes have been implemented in the treatment of cancer of the head and neck. The aggressive nature of the treatment modalities is exemplified by using high doses of radiation per se, and /or (altered) fractionation regimen [9]. For example, Bourhis et al. showed in a meta-analyses an increase in local control of 6.4%, and an increase in OS of 3.4%, by using hyperfractionated or accelerated RT in the cancer of the head and neck [14]. At present, in organ preservation therapy, concomitant chemotherapy is also frequently used. The more recent data of Bonner et al. showed benefit of combining EGFR-targeted antibody cetuxi mab with radiation [15]. Future studies will focus on combining targeted antibody therapy with cCHT and radiation. However, one has to keep in mind that clinical investigators have frequently reported that combined treatment can be more expensive and /or results in excess of side-effects. Frequently encountered late side-effects are for example xerostomia, dysphagia and trismus [16]. Xerostomia has been well documented in patients treated with chemotherapy and / or RT [17]. Some studies have

Poor scores of trismus related QoL	T1	T2	T3	T4
H&N35* opening mouth	8% (1/13)	15% (3/20)	14% (3/21)	100% (2/2)
H&N35* pain in jaw	0% (0/12)	5% (1/19)	5% (1/21)	100% (2/2)

Table 3: Percentage of patients scoring poor scores in trismus related QoL questions between T classification. *EORTC (European Organisation for Research and Treatment of Cancer) Head & Neck cancer module.

reported on trismus [4,6,9,18]; however few studies examined trismus in relation to the location of the primary tumor site and dose, which is the purpose of the present analysis.

Traditionally, radiation-induced trismus is treated with mobilization exercises using mechanical appliances and/or by hyperbaric oxygen, or oral medications, such as pentoxifylline [1,19,20]. Sometimes fibrotic tissue is released by surgical excision to ease symptoms [21]. Buchbinder et al. compared three techniques of intervention on trismus [22,23]. The authors claim that TheraBite® (Atos Medical AB, Sweden) increases the

		Poor 50%			Good 50%		
Trismus related Qol	P-value	N	Mean id (mm)	Range	N	Mean id (mm)	Range
H&N35, opening mouth		7	32	10-45	35	40,6	25-65
H&N35, speech		3	40	35-45	39	39,1	10-65
H&N35, pain in jaw	0.03	2	26.5	25-28	39	39,8	10-65
H&N35, social eating		5	28.4	10-44	35	40,7	25-65
PSS, eating in public		10	33.3	10-45	33	41,0	25-65
PSS, understandability of speech		1	42	42	42	39,2	10-65
PSS, normalcy of diet		13	34.5	10-50	30	41,3	29-65
Chart	0.0001	2	27.5	27-28	41	39,8	10-65
Last follow-up		6	30.2	10-45	37	40,7	25-65
Total, mean			32.7			40,2	

Table 4: Inter-incisal distances (id) for patients having limitations 'opening mouth' at the time of last follow-up. This was measured in patients having trismus according chart review and for those patients scoring poor scores in trismus related QoL questions vs. good scores in 'opening mouth'.

Abbreviations: H&N35, EORTC (European Organisation for Research and Treatment of Cancer) Head & Neck cancer module; PSS, Performance Status Scale.

P-Values	Left masseter	Right masseter	Left pterygoid	Right pterygoid	Left coronoid	Right coronoid	Left mandibular condyl	Right mandibular condyl
Inter-incisal distance								
Follow-up clinic	0.04	0.02		0.03		0.03		
H&N35, opening mouth		0.02		0.02		0.03		0.03
H&N35, pain in jaw								
H&N35, speech				0.01		0.049		
H&N35, social eating								
PSS, Understandability of speech								

Table 5: P-values of dose-response relationships stratified per muscular sructure and complaint category of the different trismus related QoL questionnaires.

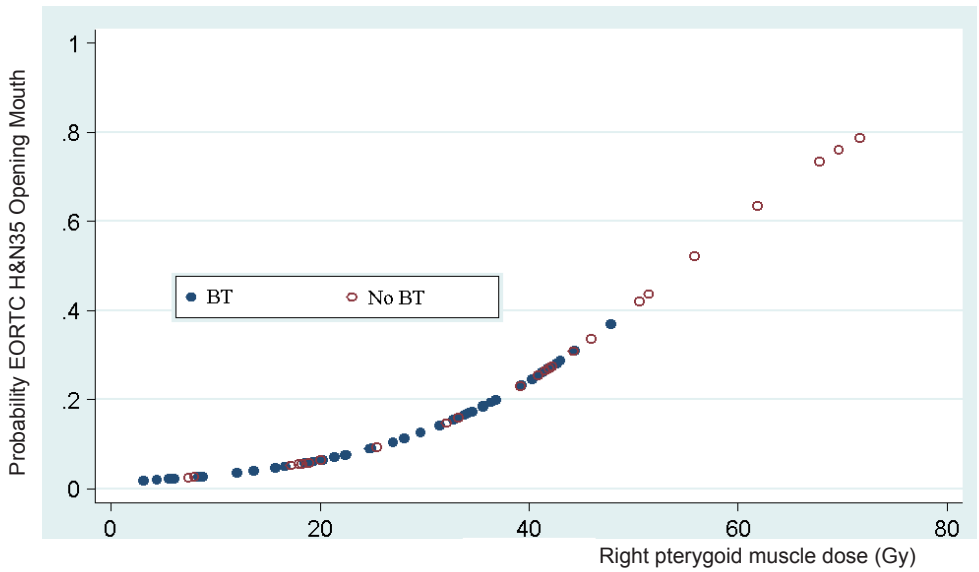

Figure 3: Relationship between the probability of having complaints of 'opening mouth' (European Organisation for Research and Treatment of Cancer Head & Neck cancer module) by increasing the dose, for Brachytherapy (BT) and No Brachytherapy (No BT) treatment, respectively.

'opening mouth' substantially more than exercises with wooden tongue blade or manual stretching. Trismus has a significant impact on the quality of life of head and neck cancer patients [1]. The incidence of radiation-induced trismus like other radiation-induced late complications, depends on factors such as the total dose of radiation, fractionation, overall treatment time and treatment techniques. By the group of Dijkstra et al., a reduced opening mouth of 18% (sd: 17%) was found in patients treated by RT involving the structures of the temporomandibular joint and / or pterygoid muscles [6]. The authors found a cut-off point of ≤ 35 mm for the inter-

incisal distance [24]. They concluded that the increase in opening mouth by exercise is substantially more in non-cancer patients as opposed to patients with trismus related to cancer of the head and neck. [25]. Kent et al. showed a high prevalence of trismus (47%) in cancer patients following > 55 Gy to the masseter and/or pterygoid muscles [26]. In a previously reported Rotterdam series, the incidence was only 1% for the treatment group EBRT + BT, but for the surgery + post-operative RT series it amounted to 21%, demonstrating substantial the interplay between surgery and radiation dose [9]. Finally, Jen et al. reported in nasopharyngeal carcinoma patients a trismus incidence of 14%-17% [27]. The population studied is based on 81 patients diagnosed with scc of the oropharynx and treated curatively between 1999-2005, in a single institution, by highly conformal radiation therapy techniques (3DCRT or IMRT). According to the notes in the charts, 3 (4%) patients experienced trismus. Anatomical structures involved in swallowing were defined (masseter-, temporalis-, pterygoid muscle, condyl- and coronoid processus), and the mean dose in each individual structure computed. Finally the probability of trismus measured by quality of life instruments, being performance status scale (PSS) scores according to List [28] and the EORTC Head and Neck 35 (H&N35) [29-31], was related to the mean dose in the masticatory structures. Based on the - trismus related - QoL questions, a number of parameters seemed to be more often associated with trismus. For example, the less favorable parameters in this regard were tumors located in the BOT, and treatment by 3DCRT, cCHT, non-BT and high dose raditaion. None of these factors, however, were found to be significant (table 3).
The mean measured inter-incisal distance was 39 mm (range 10 mm to 65 mm). In the group of patients with a poor - trismus related - QoL, being defined as having

Poor scores - trismus related - QoL	Unilateral, No. of patients, (%)	Bilateral, No. of patients, (%)	p-value
H&N35, Opening Mouth	0/18 (0%)	9/37 (24%)	0.02
H&N35, Pain in Jaw	0/18 (0%)	4/36 (11%)	
H&N35, Speech	0/18 (0%)	3/37 (8%)	
H&N35, Social Eating	0/18 (0%)	7/35 (20%)	
PSS, Eating in Public	1/18 (6%)	10/38 (26%)	
PSS, Understandability of Speech	0/18 (0%)	1/38 (3%)	
PSS, Normalcy of Diet	3/18 (17%)	14/38 (37%)	
Chart	1/26 (4%)	2/54 (4%)	
Last Follow-up	0/18 (0%)	6/37 (16%)	

Table 6: Percentages of poor score regarding trismus related QoL questionnaires between unilateral and bilateral irradiation.
Abbreviations: H&N35, EORTC (European Organisation for Research and Treatment of Cancer) Head & Neck cancer module; PSS, Performance Status Scale.

a score of less or equal than 50%, the mean id's were less (33 mm) as opposed to those patients with a good QoL score (40 mm) (table 4). However, only the H&N35 question 'pain in jaw' was significant. Similar conclusions about the id can be drawn from the chart review (and last follow-up clinic), with chart review showing a significant difference in id (28 vs. 40 mm) between patients having trismus or no trismus (p=0,0001) (table 4). Obviously the data set (including subgroups) contains only small numbers of patients and one therefore has to be prudent with drawing any conclusions. Table 5 illustrates for some of the structures of the mastication apparatus a significant relationship with a particular QoL question and dose. In this respect, by univariate analysis, a significant relationship was found between dose in the masseter muscles as well as the pterygoid muscles and coronoid bone and trismus complaints (table 5). In the multivariate analysis, BT was the only remaining significant factor. For those patients of whom the trismus related muscles were irradiated bilaterally, a significant increase of the probability of trismus was observed but only with regard to the item 'opening mouth' of the EORTC H&N35 questionnaire (p=0.02) (table 6).

CONCLUSIONS

This paper focuses on dose-effect relationships for trismus related structures of the mastication apparatus. Figure 3 shows the relationship between the probability of having complaints of trismus with dose for BT and non-BT treated patients, respectively. For example, for every additional 10 Gy in the pterygoid muscle, after a dose of 40 Gy, an increase of probability of trismus of 24% was observed. Given the retrospective nature of this study, we recognize the limitations of its findings. The small sample represents however a carefully selected group of patients with base of tongue and tonsillar fossa tumors treated by highly conformal RT techniques. Currently having the availability of IMRT techniques, one may decrease the dose received by putting constraints on masseter and pterygoid muscles. This is shown, for example, by figure 4 for the masseter muscle. Future studies should be designed in a prospective manner and focused on larger patient populations.

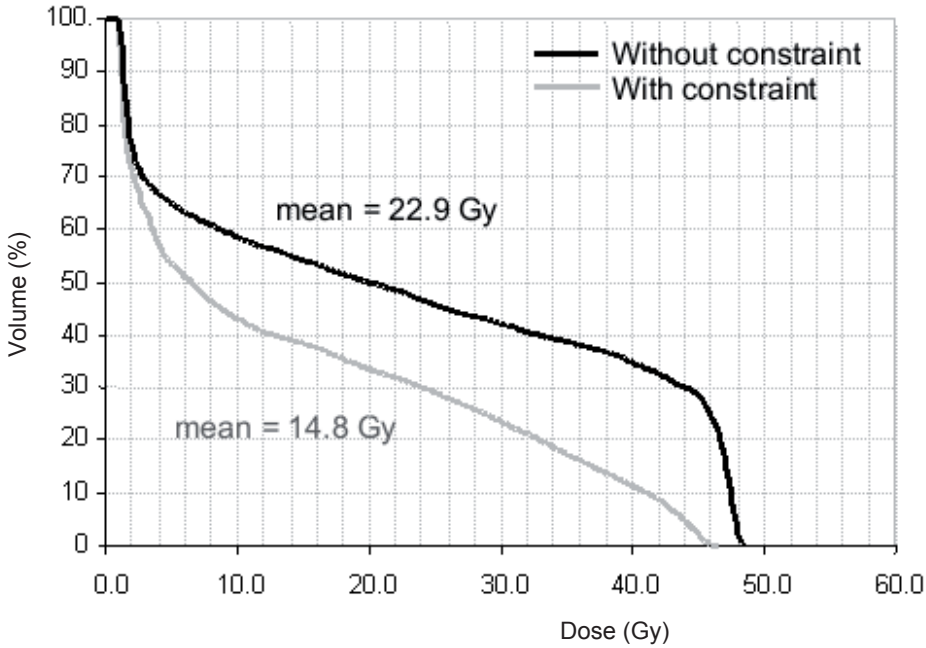

Figure 4: Dose volume histogram for the left masseter muscle with and without a constraint in the left masseter muscle.

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8

Interstitial Radiation Therapy in Cancer of the Oropharynx and Oral Cavity

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ABSTRACT

Background: Interstitial brachytherapy (IBT) is a highly conformal radiation therapy technique when treating cancer of the Head and Neck; it is used as a boost technique integrated in an organ function preservation protocol, with the oropharynx being a site of preference.

Material & Methods: The dose of radiation can be accurately delivered to the target by a radioactive source, dwelling in the implanted afterloading catheters connected to an afterloading machine. The prescribed dose (dwell times and source positions) is delivered after 3D dose calculation, using computerized (optimization) algorithms. Characteristics as steep dose fall-off and small margins make the dose distribution highly conformal and confine to the irradiated volume. Thus it allows for delivering high doses of radiation to the target (with intrinsic dose escalation), while at the same time sparing the critical surrounding normal tissues. Moreover, being able at present to sum the dose of the external beam (46/2 Gy) to the dose of the IBT, biological treatment planning is within reach.

Results & Conclusions: For oropharyngeal cancer boosted by IBT, at 10-years an excellent local control rate of 90% was observed. However, lack of training & clinical experience, only suitable for relatively small volume disease, invasiveness of the procedure and difficult logistics (operating room) can be, albeit rarely, conditionally limiting. Late side effects (e.g. soft tissue necrosis) are not totally negligible either, but if present in the great majority of cases spontaneously healing will occur. When comparing IBT to other forms of conformal radiation, such as stereotactic radiation therapy, Cyberknife and IMRT, the quality of life, as scored by the patient responses to the EORTC H&N35 questionnaires, in general speak in favor of IBT.

INTRODUCTION

Major improvements in surgical- and radiation therapy (RT) techniques have come about; overall survival (OS), however, showed little change. That is, typically patients with tumors of the head and neck present in more than 50% with locally advanced disease at the time of diagnosis, have local control rates of about 60-80% and a 5-years OS of approximately 30-50%, due to high incidence of secondary tumors originating from the aerodigestive tract (2nd tumors actuarial increase 3% annually). Substantially enhanced morbidity during and immediately after treatment, in particular in the fragile elderly, and less compliance due to excessive co-morbidity because of alcohol and tobacco abuse, might be reasons why some of these patients do not benefit (in terms of improvement of overall survival) from some of the proposed and promising new treatment approaches [1]. Also the late occurring side-effects, such as xerostomia, dysphagia, pain and fibrosis (e.g. trismus) give rise for concern. That is, some of these (interrelated) side effects can have a significant impact on the quality of life (QoL) [2]. This again might be a reason for being somewhat reluctant in enrolling patients in aggressive but promising protocols. In trying to improve one's result, that is in order to investigate new treatment strategies, a proper balance must exist between tumor response and treatment related acute- and late morbidity as opposed to the associated risk of non compliance.

We have opted over many years for IMRT with moderate acceleration, a treatment strategy which, according to a large meta-analysis, is very beneficial. In fact, it can be given without any enhancement of (late) side effects, and with only a minimally increased acute reaction [3]. For the external beam radiotherapy (EBRT) part (46/2 Gy) of the protocol, we have used as of the year 2000, IMRT as the treatment technique of preference. Boost doses to the primary tumor were given, if technically feasible, by means of high-dose-rate interstitial brachytherapy (IBT), thus like the EBRT in an accelerated fashion. As with IBT in general, only limited sized tumors (T1-3) are eligible for an IBT boost. If IBT is not feasible, IMRT and (in case of T3,T4 disease) concomitant chemotherapy is applied. In conclusion, this chapter is on dose acceleration (majority of patients receiving 6 fractions of IMRT / week; first series to a total dose of 46 Gy/2); dose escalation (majority treated by HDR-IBT), and on sparing (IMRT; HDR-IBT). It will focus on issues such as local & regional control, survival, early- and late side effects, and quality of life (QoL) after primary radiation therapy by EBRT and IRT (boost) treatment. To note is the significant role BT can play in case of persistent disease [4] with regard to local control and overall survival (80% complete response to brachytherapy) after previous definitive external beam radiotherapy or in case of a recurrence after previous RT [5,6,7]. Results are frequently reported dependent on volume of the (persistent, recurrent) disease, previously applied dose fractionation, interval between both treatment and site. For example, the most rewarding site seems to be cancer of the nasopharynx. Although it has been shown that BT can play substantial role in these cases, we will not discuss the literature on this subject in detail. Suffice to summarize in general variable response rates were observed (20-80%) with only limited or no survival benefit [5-7].

Historical Perspective Brachytherapy

In many of the classical handbooks on radiation therapy, as well as in the current literature, one can find excellent reviews on low- and high dose rate brachytherapy [8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24]. The history of BT dates back to the beginning of the 20th century, with the first BT procedures being performed using radium-226 needles. Alexander Graham Bell, the inventor of the telephone, suggested in 1901 to destroy a tumor "by inserting radioactive needles in the heart of the cancer", a first example of interstitial radiation therapy. Brachytherapy (brachy = Greek for short) is a treatment modality in which the tumor is irradiated by positioning the radioactive sources very close to the target surface (surface mould type), in naturally existing cavities of the body (endocavitary type) or in afterloading catheters implanted in the to be irradiated tissue (interstitial type). In recent times many artificial radionuclides such as I-125 and Ir-192 have become available and are used for example in the treatment of cancer of the head and neck. The French developed the so-called Paris system for LDR dosimetry purposes, that is, for parallel-equidistant sources the system recommends specifying the dose of the implant at 85% of the average dose in the basal dose points (local minima). Currently a similar type of dose prescription is used for high-dose rate (HDR) volume implants, such as the implant of the base of tongue (BOT), even though the sources may not be totally equidistant. Also computerized afterloading devices, supported by sophisticated 3D treatment-planning software with optimization capabilities became available. Finally, the concept of HDR versus pulsed-dose rate (PDR; in principle mimicking LDR by using many small fractions at small intervals) was launched (table 1). More recently a renewed interest has emerged in being able to sum the doses delivered by EBRT and BT (in this chapter an example will be presented). This way biological treatment planning comes within reach.

Dose Rate	Specifications
LDR	0.4 – 2 Gy / hour
MDR	2-12 Gy / hour
HDR	> 12 Gy / hour
Fractionated HDR	Erasmus MC day-time schedule. First and last fraction 4 Gy, in between 4 fractions of 3 Gy, maximum 2 fractions per day, interval 6 hours. No radiation in weekend.
Pulsed-Dose-Rate	Erasmus MC 24 hour schedule. First and last fraction 2 Gy, in between 18 fractions of 1 Gy, maximum 8 fractions of 1 Gy, interval 3 hours. Continuation of BT over the weekend.

Table 1: ose rate categories, taken from the literature and from the Erasmus MC protocols (PDR, fr.HDR). Fr.HDR: Fractionated HDR is given in fraction sizes of 3-4 Gy by connecting the afterloading tubes to microSelectron HDR (source strength 370 MBq). In case of PDR, fraction sizes of 1-2 Gy are being delivered by microSelectron PDR (source strength 37 MBq).

Brachytherapy Protocol Evolution

From the beginning it was realized that BT can be used routinely as a very conformal type of treatment, particularly for cancer located in the midline. Obvious examples are endocavitary boosts in cancers in the nasopharynx, IBT as a boost for cancer in the oropharynx, oral cavity, and in general for small volume disease in case of re-irradiation or in postoperative irradiation of the neck. In the Erasmus MC we initiated a treatment protocol implementing the use of IBT in 1991; Over the years a few changes were introduced because of important biological- and/or technical developments at the time, such as the introduction of IMRT, accelerated RT (6 fractions per week), and concomitant chemotherapy (for advanced T3,T4 tumors only) [25].

In the course of time, in the Erasmus MC, the preferred treatment for oral cavity tumors was argued to be surgery rather than IMRT [20,26]. This is partly due to the ease of surgical access and/or feasibility of reconstruction after resection of these tumors. Also in favor of surgery are the facts that this treatment is frequently a one-time type of treatment procedure (surgery) and the notion that IBT in the oral cavity is being associated a relatively high risk of serious complications (osteoradionecrosis) [27].

For oropharyngeal tumors, the principle therapy in the Erasmus MC is primary RT by IMRT to the neck and primary cancer to a dose of 46 Gy followed by a neck dissection in case of the neck containing positive lymph nodes and a boost to the primary by HDR-IBT. Finally, the principles underlying the BT protocol as designed in 1991 have been strictly adhered to in general.

However, at the time a number of patients were found to be non-eligible for IBT, due to e.g. medical reasons (medically unfit to undergo invasive procedures), or because of tumors with deep parapharyngeal extension, or (albeit rare) simply because of patient refusal. These patients would be offered surgery to the primary (and neck), or a boost to the primary tumor by IMRT. Currently, however, if brachytherapy is not feasible, they are offered as a second-line of boost treatment a Cyberknife (CBK) boost. The CBK, a non-invasive stereotactic - robotic - linear accelerator, was installed in 2005 in the department of RT in the Erasmus MC. The dose fractionation of the CBK boost protocol is 3 times 5.5 Gy, with the dose prescribed to the 80% isodose line. The boost volume is based on the original tumor mass, only with a PTV margin of 3 mm. Treatment policy regarding the neck remained the same, except that in N+ cases the proposed ND was planned after completion of the CBK boost (in order not to have too large a split between the IMRT series and the CBK boost) (figure 1).

Brachytherapy Techniques

All oropharyngeal tumors are jointly seen by the H&N surgeon and radiation oncologist with the patient under general anaesthesia. Using clinical information, panendoscopy, CT/MRI of the primary and neck, biopsy from the primary tumor and FNAC (fine needle aspiration cytology) of the node(s) and placing the radiopaque markers, patients are staged [28,29]. That is, at the time of the examination, markers are placed at the boundaries of what we believe to be the microscopic extensions (CTV) of the primary tumor. With the clinical information of the marker positions and on the images of the tumor (CT/MRI) combined, the primary tumor is delineated on a

treatment planning-CT. The BT techniques that are eluded to in this section in great detail, are the typical implants of primary cancers in the oropharynx, that is the single plane tonsillar fossa (TF) and/or soft palate (SP) implant, and the volume implant of the base of tongue (BOT) or combinations of these. IBT of oral cavity tumors (e.g. mouth, cheek, oral tongue etc.) are certainly feasible but in our institution (Erasmus MC) are in “competition” with surgery, and as a consequence less often executed.

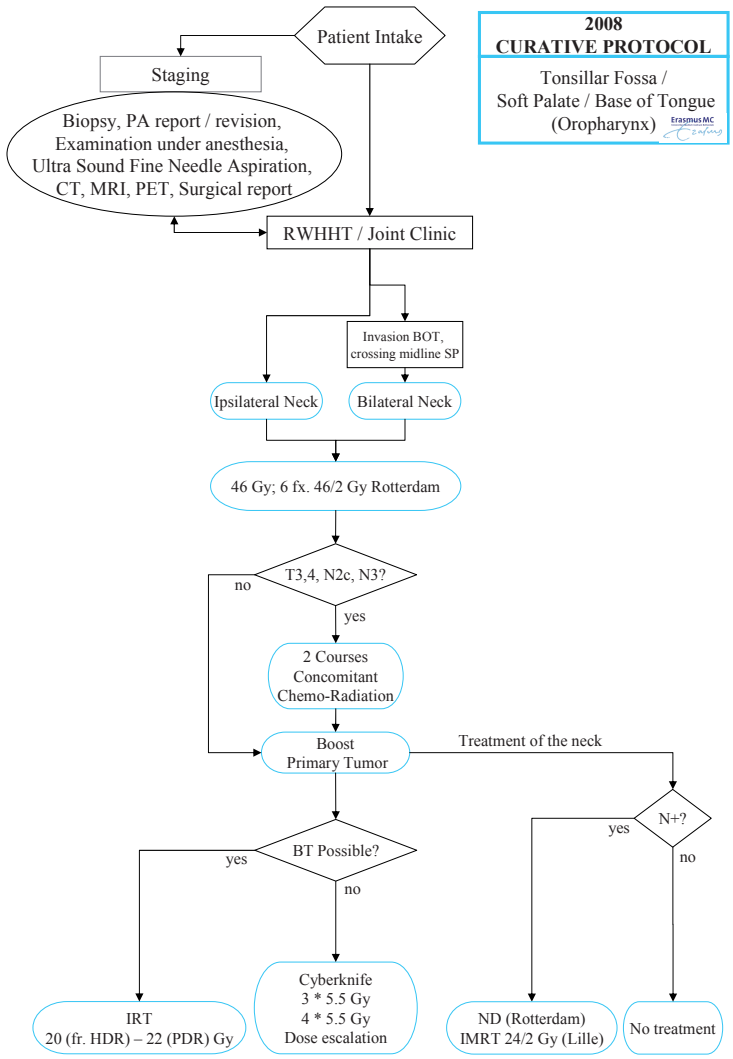


Figure 1: In the course of time changes have been introduced: First around 1996 accelerated fractionation to a total dose of 46 Gy was introduced (for details see legend of figure 2). As of 2000 all primary cancers were treated by IMRT. In later years, for some of the very advanced T3/T4 cancers, concomitant chemotherapy was added. Treatment policy regarding neck dissection and implant primary tumor remained the same. In 2008 the Cyberknife was used for boosting the primary tumor in case IBT was not feasible (see text).

Brachytherapy Techniques Oral Cavity

For IBT of cancer of the oral cavity, in general, one is introducing Ir-192 source "lines" in parallel-opposed looping catheters covering the CTV of the primary tumor. Besides this arching technique, single plane in practice are frequently used. Basically simple - straightforward - techniques. The preferred spacing between the source "lines" is approximately 0.5-0.7cm. Care should be taken to maintain strict parallelism of the sources and lead protection at the inner side mandible of at least one HVL (half value layer) should be provided at the time of the irradiation in order to prevent osteoradionecrosis (ORN) to occur. Because of easy access to surgery of these small oral cavity tumors, and still a relatively high risk of ORN when using IBT, implanting these cancers is not routinely being performed in Erasmus MC (anymore). Moreover, the necessary lead protection of the mandible per se leaves sometimes just too limited a space for the afterloading catheters (sources) to be implanted. With regard to the oral cavity, section V of this chapter will mainly focus on and illustrate some of the results as reported in the literature.

Brachytherapy Technique TF and/or SP

With regard to the TF and/or SP tumors: these sites are often difficult to accurately depict on CT or MRI images. At the time of the brachytherapy procedure, the (residual) tumor, as well as the boundaries of CTV can be clearly seen and thus accurately delineated. In general the implant, as opposed to IMRT, is thus more "on target", has smaller margins (no PTV margin) and as a consequence the irradiated volume is thus smaller and more conformal (see also figure 2)[16,29]. With regard to the protocol; first, an IMRT treatment plan of the primary tumor and neck is generated (CTV margin 5 mm, PTV margin 5 mm) and applied using an accelerated fractionation scheme to a total dose of 46/2 Gy. Afterloading tubes (2-3) are then implanted in the TF and SP approximately 1 (-2) week(s) after completion of the IMRT. Markers are implanted at the boundary of the CTV (CTV can sometimes be determined by the demarcating mucositis (after the first series of IMRT [46 Gy] has been applied). No PTV margin is needed in case of IBT, since the tumor is moving with the catheters in situ. The dose is prescribed at a distance of 5mm or 7.5mm of the central plane. The 3D dose distribution plan is generated using also dose point optimization. A neck dissection (ND) is performed in case of a N+ neck. Whether the contralateral neck is to be irradiated electively is still subject to debate. Our data suggest that this should only be done in case of infiltration of the primary tumor in the BOT or in case the SP tumor-infiltration extends over the midline 29 (figures 3-6).

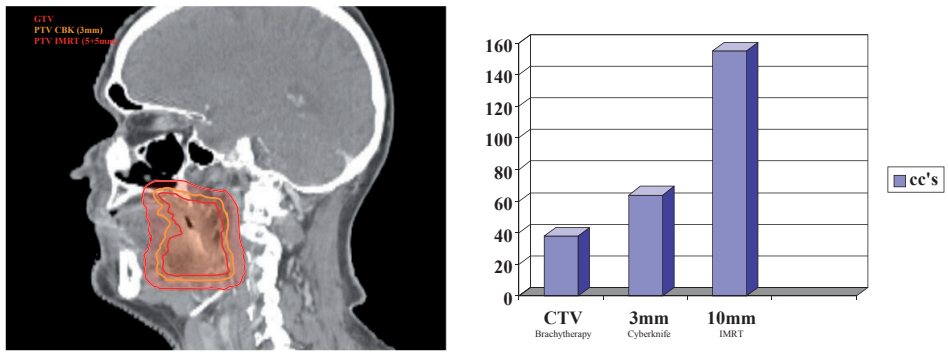


Figure 2: The treated volume of a tonsillar fossa and soft palate tumor with a delineated PTV using a margin of 3 mm in case of a Cyberknife treatment. For a similar tumor treated by brachytherapy or the IMRT, the margin for PTV is 0 mm or 5 mm, respectively. Using the different margins as discussed in the text, the right panel of this figure displays the consequences for the irradiated volume of a tonsillar fossa tumor radiated either by brachytherapy (CTV), Cyberknife (PTV) or IMRT (PTV).

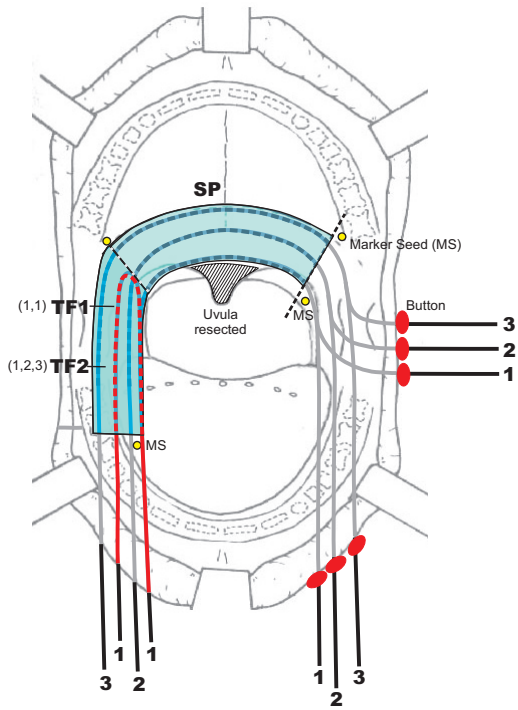


Figure 3: Schematic diagram of implant techniques (routes for the afterloading catheters to cover the target) in case of tumors sitting in the TF, SP, or both.

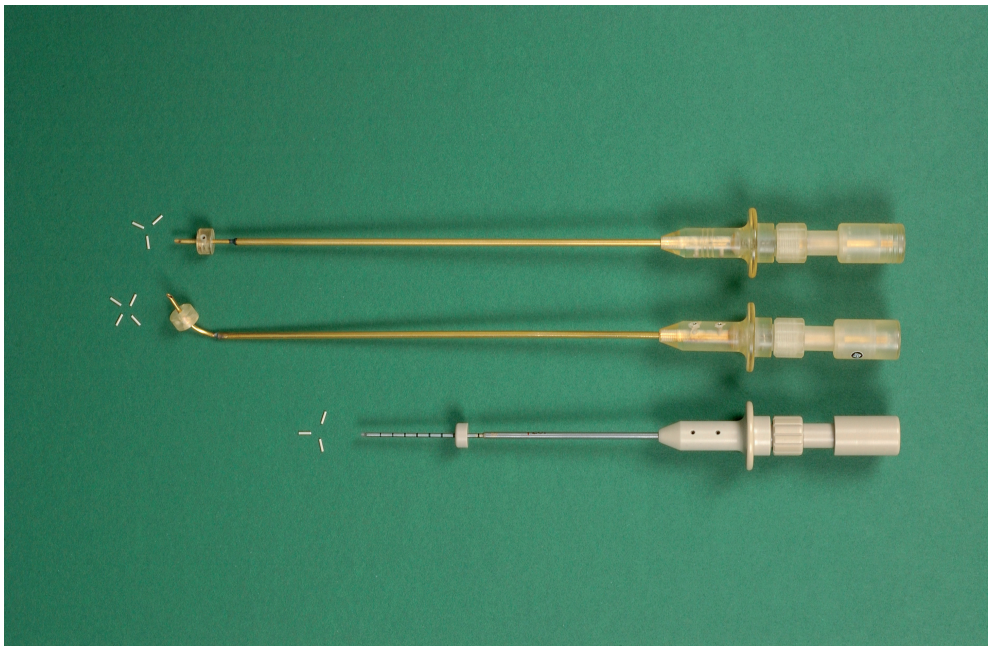
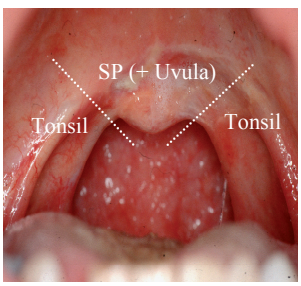
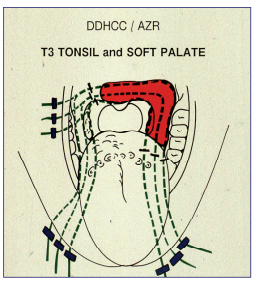


Figure 4: Home made instruments to inject marker seeds to demarcate the clinical target volume.





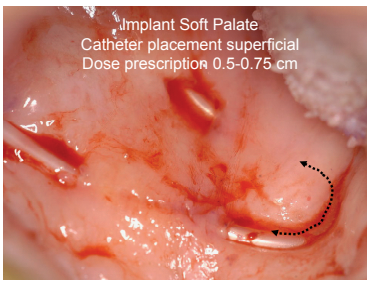


Figure 5: Afterloading catheters running submucosally after having been implanted according to one of the techniques shown in figure 4.

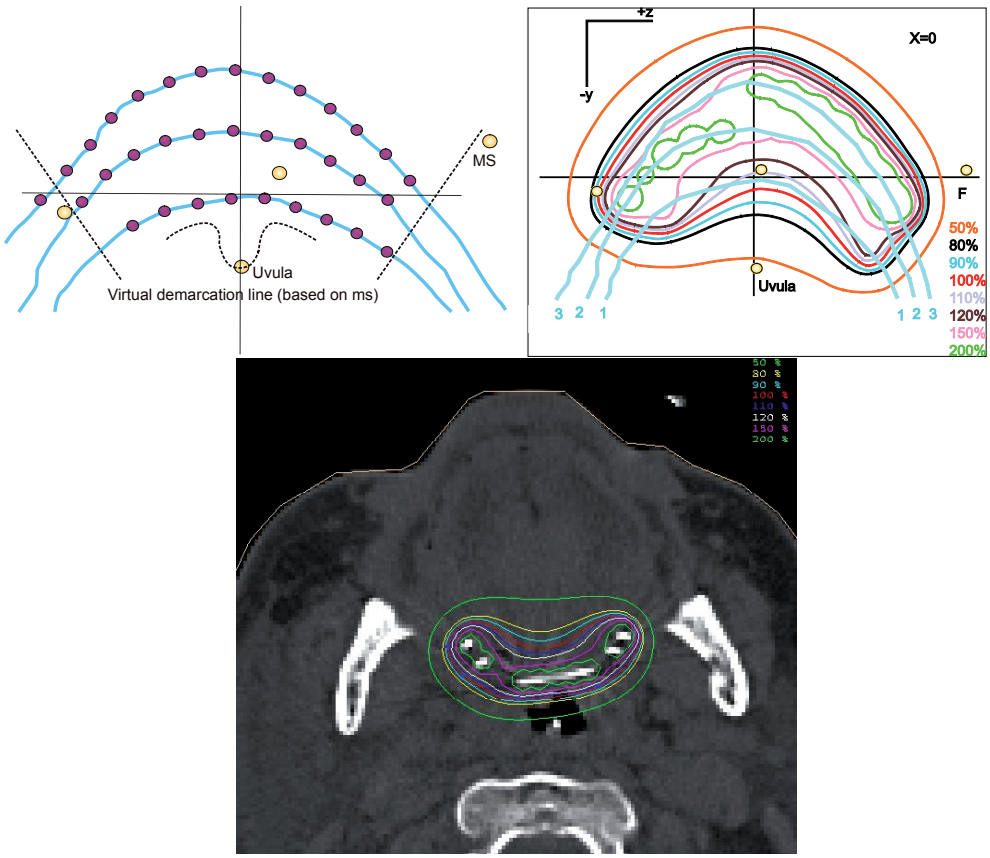


Figure 6: Dose distribution TF tumor with extension into the SP. Note marker seed position demarcating the boundary of the CTV.

Brachytherapy Technique BOT

Another frequently performed implant technique is the volume implant of the BOT originally described and pioneered as a LDR technique by Vikram in 1981 [30,31,15,13]. In general 3 afterloading catheters are implanted by introducing the afterloading (slightly curved) needles just above or beneath the hyoid bone (depending on the location of the primary tumor), therewith entering the oropharyngeal air cavity just posteriorly /caudal to the primary BOT tumor. These catheters run over the dorsum of the tongue and exit through the cheek (figures 7 & 8). Another 6 catheters are introduced somewhat more ventrally; each dorsum running catheter is then connected with specially designed sliding buttons to 2 of these vertical /ventral catheters, with 1 cm spacing between the sliding buttons. This way, three planes are constructed, each consisting of 3 catheters; that is, one central plane and two lateral sagital planes. After geometrical optimization a 3D dose plan is generated. The dose of the implant is specified at 85% of the average dose in the basal dose points (local minima), quite similar to the Paris system. For safety precautions (e.g. bleed at the time of removal of the implant), a tracheotomy is sometimes performed. In case of small, lateralized tumors in the BOT, we sometimes refrain from implant the whole of the

BOT (as was routinely done in the past), but in stead (boost) the residual or primary tumor mass only (CTV margin inclusive). Both necks are irradiated to 46/2 Gy in an accelerated fashion by means of IMRT. In case of N+ disease, a ND and an implant of the primary tumor is performed in the same session (figures 9&10).

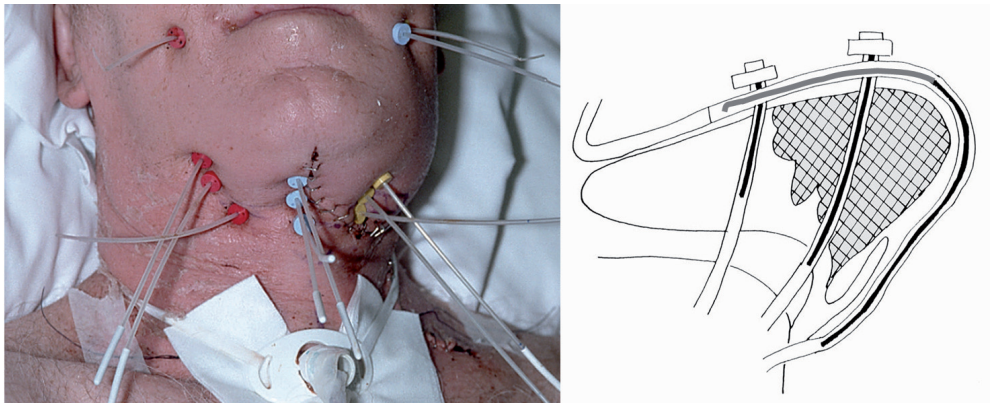


Figure 7: View of patient with BOT implant.

RESULTS

Results Cancer in the Oral Cavity

Many papers have been published on interstitial brachytherapy of primary can cers in the head and neck, the majority being classical papers from the LDR era on cancers in the oral cavity and oropharynx [32,33,34,35,19,26,36,37,38,39]. Some of the outcome data on local control have been summarized in table 2 (oral cavity tumors) and table 3 (oropharyngeal tumors). Furthermore, the references provided in this chapter enables one to get an in-depth view on the good results with IBT in terms of local- and regional control, disease free survival and overall survival. Given the reasons presented before (see section IV), the oral cavity experience as presented in the literature can summarized as follows: At 5-years the LC varies between 36% - 93%, and the OS from 8 - 69% (Table 2). Importantly, one of the few randomized studies in brachytherapy is on mobile tongue cancer and was published by the Japanese[36]; showed no significant difference for mobile tongue cancer treated with LDR versus fractionated HDR. This was true for LC (84% vs. 87%) and cause specific survival (CSS) (86% vs. 88%) [36].

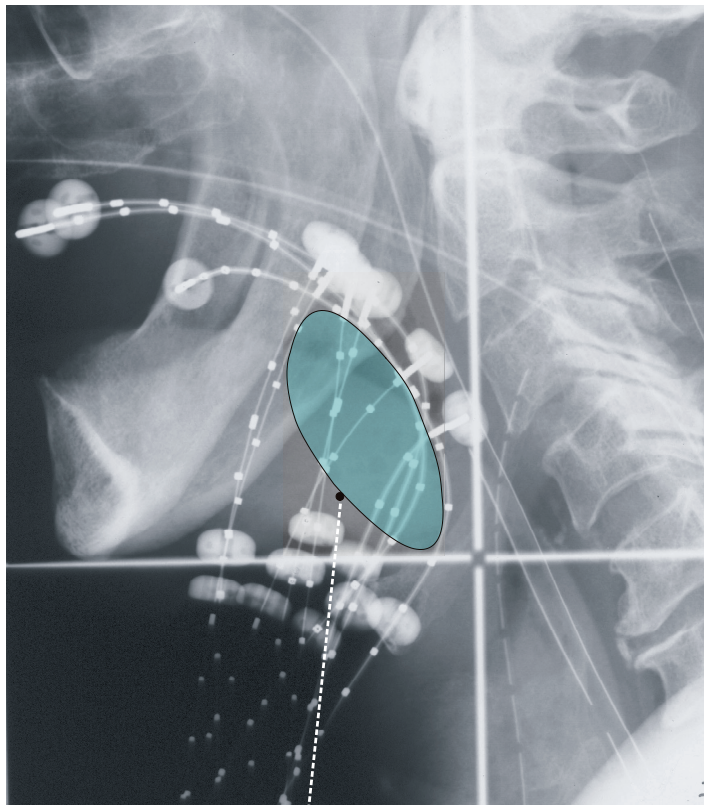


Figure 8: Dorsum of the tongue running afterloading catheter connected to two more ventrally positioned afterloading catheters in same sagital plane. Note specially constructed sliding (connecting) button.

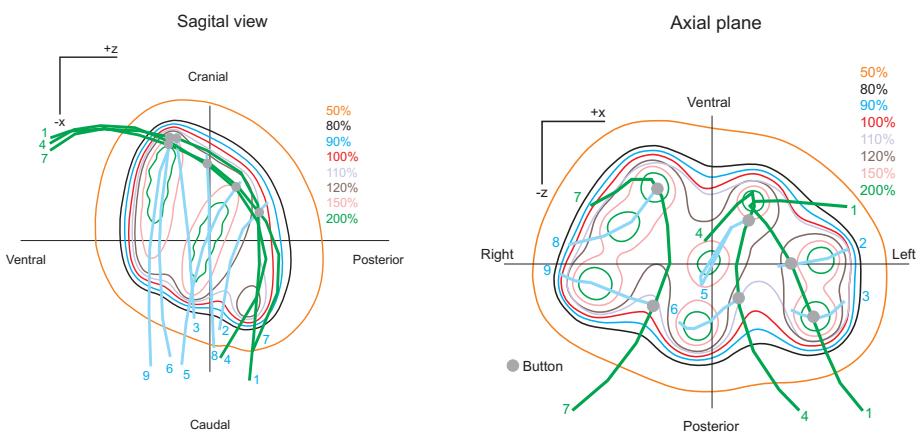


Figure 9: Dose distribution of BOT implant after geometrical optimization. Note marker seeds.

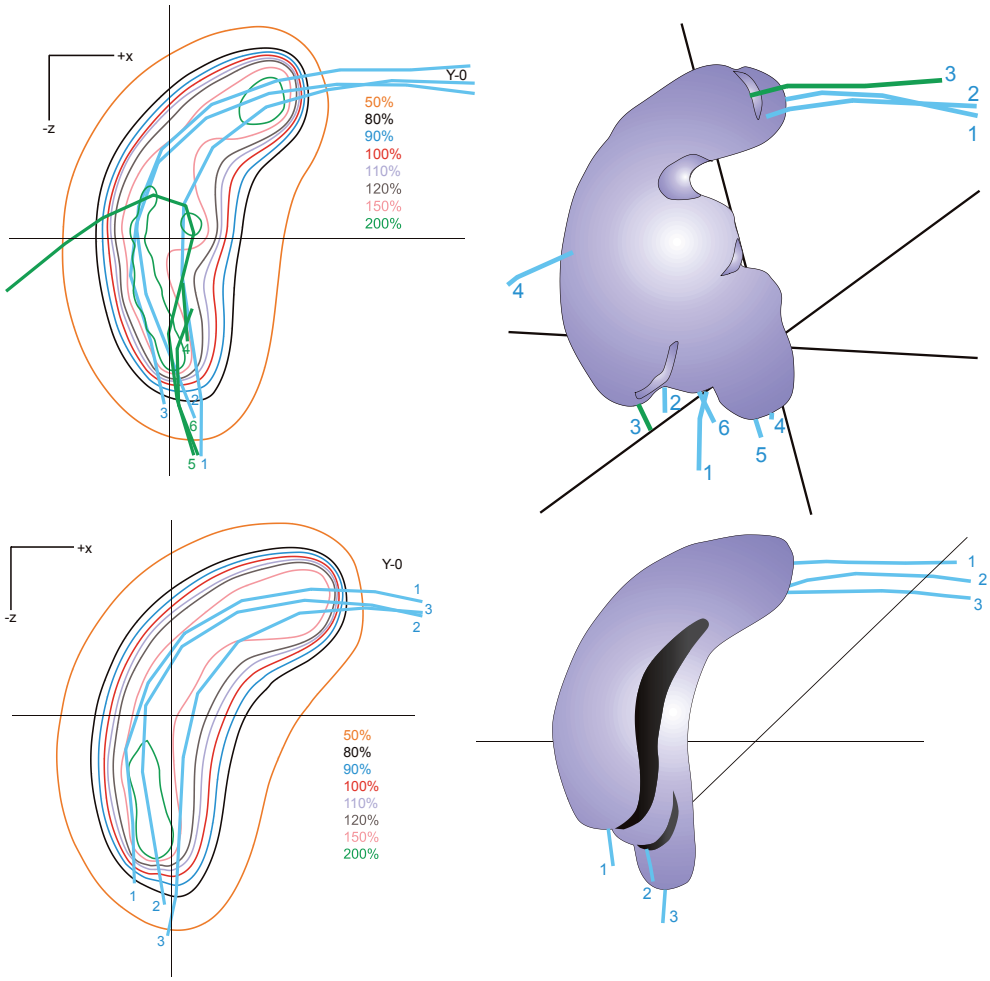


Figure 10: Tumor in BOT with extensions into TF and partially in SP. Basically it is a complex implant combining the dose distributions as shown in figure 6 & figure 9. This type of implant is preferably done under direct vision and would be difficult to perform by CT guidance.

Results Cancer in the Oropharynx

To investigate the results of using a combination of EBRT or IMRT (46/2 Gy) and LDR- or HDR-IBT (boost), we first analyzed the data of our institution. From 1991 to 2005, 336 oropharyngeal cancer patients were treated non-surgically for the primary cancer at the Erasmus MC, Rotterdam); at 5-years an actuarial LC rate for BT vs. non-BT was 84% vs. 60% (P< 0.05), DFS of 59% vs. 43% (P<0.05), and OS of 64% vs. 39% (P<0.05) was found. Apparently, the use of IBT seems to be of benefit, when considering LC, RC, DFS and OS [16]. From a multivariate analysis, it was found that BT and the time period (i.e. before or after the year 2000), are of significant influence on local control.

Piccirillo and Vlahiotis [40] reported on the co-morbidity being of significant influence

in outcome of treatment and prognosis. Similar experiences have been reported by others. Mazeron e.g. reported in 1988 and 1989 his LDR experience with IBT for T1,T2 cancers in the TF and/or SF; at 5 years a local control of 85%, regional control of 97% (88% for N1-3 disease) [41]. Also, Pernot et al. (1996) obtained 90% LC with T1T2N0 TF/SP tumors and 86% in case of T1T2N1-3 using an LDR-IBT boost [20]. Esche[9] reported on 43 patients with tumors in SP and uvula. LC was again high (92%) with OS of only 64% at 5-years, emphasizing in his paper the force of mortality of aerodigestive secondary tumors. Harrison reported excellent LC rates using HDR-IBT volume implants, a technique first pioneered by Vikram [30,31]. A 5-year LC, DFS and OS of 89%, 80% and 86% was published. Similar observations were made by van de Pol et al [21]; data were published in 2004 describing the Rotterdam results of T3/T4 BOT cancer treated by IBT as opposed to BOT cancer treated with surgery and PORT (VUmc, Amsterdam). The local failure at 5-years were 37% and 9%, for the IBT-series as opposed to the surgical series. The BT cases were non-selected; in fact some of these patients we would now even consider palliation. Thus, not unexpectedly, a lesser control for the IBT was found considering Rotterdam. However, analyzing the data in more detail, the overall survival was not significantly different (median 2.5 years vs. 2.9 years, respectively [p = 0.47]. Moreover, the quality of life was significantly better for the IBT patients (see next paragraph) treated in Rotterdam.

First Author	N	Primary, Boost or PO BT	LC 5-yrs %	DFS 5-yrs %	OS 5-yrs %
Lefebvre, 1994	429		53-91		
Wadsley, 2003	24	Primary BT	76	91 2-yrs	81 2-yrs
Mazeron, 1990	117	Primary BT	50-86		8.-52
Chu, 1973			83-94		
Wendt, 1995	103	Primary BT & Boost	65-92 2-yrs		
Mendenhall, 1989	31	Primary BT & Boost	40-75		
Inoue, 2001	51	Primary BT	84-87		
Benk, 1990	110	Primary BT & Boost	36-88	24-42	
Bailet,1982	966		53-91		
Decroix, 1981	602	Primary BT & Boost	76	48	36
Pernot, 1994	448	Primary BT & Boost	49-93		25-69

Table 2: Overview of some of the published data on local control (LC), disease free survival (DFS) and overall survival (OS) for cancer in the oral cavity.

A: Tonsillar Fossa / Soft Palate

First Author	N	T1/T2, %	T3/T4, %	LC T1/T2, 5-Yrs %	LC T3/T4, 5-Yrs %	DFS, 5-Yrs %	OS, 5-Yrs %
Pernot, 1992	277		57	76 5-yrs			51

Puthawala, 1985	80		24	84			
				LRC Stage I: 3/3	LRC Stage III: 85		
				LRC Stage II: 100	LRC Stage IV: 56		
Pernot, 1994	361		1	T1: 80, T2: 71	T3: 65, T4: 58	CSS: 63	53
				LRC: 75			
Levendag, 2004	104	77		T1-T3: 88		57	67
Esche, 1988	43	T1: 34/43		92		CSS: 64	37
Mazeron, 1993		100		94		71	53
Peiffert, 1994	73	65/73	2/73	T1: 80, T2: 67		CSS: 64	30

B: Base of Tongue

First Author	N	T1/T2, %	T3/T4, %	N0, %	LC T1/T2, 5-Yrs %	LC T3/T4, 5-Yrs %	DFS, 5-Yrs %	OS, 5-Yrs %
Harrison, 1997	68		3 (T4)		T1: 87, T2: 93	T3: 82, T4: 100	T1: 88, T2: 93, T3: 82	87
Puthawala, 1988	70		17 (T4)		T1: 100, T2: 88	T3: 75, T4: 67	67	35
Barrett, 2004	20		35	10	2-Yrs		33	
Takacsi-Nagy, 2004	37		81	19	100	60	52	46
Karakoyun-Celik, 2005	40		54	30	LC: T1-4: 78		54	62
Pol, 2004	30		67 (T4)	30		LC 63	45	40
Gibs, 2003	41		49	32	14	20	79	66
Brunin, 1999	216		61	30	T1: 93, T2: 66	T3: 45. T4: 18	CSS I-IV: 63-23	27
Crook, 1988	48	100			T1: 85, T2: 71		50	
Hoffstetter, 1996	136	55/136		N0/ N1:81	T1: 86, T2: 69	T3: 64		
Horwitz, 1996	20	11/20	9/20			10/11	T4: 8/9	72
Housset, 1987	29	100			T1: 6/6, T2: 74			30.5
Lusinchi, 1989	108	57/108	T3:51/108		T1: 85, T2: 50	T3: 69		26

Table 3: Overview of some of the published data on local control (LC), disease free survival (DFS) and overall survival (OS) for cancer in the Tonsillar Fossa and Soft Palate (SP and/or SP), and cancer in the Base of Tongue (BOT).

Side Effects and Quality of Life

Acute side-effects

It has been argued that many studies insufficiently address the enhanced toxicity and the compliance of patients during and immediately after treatment for some of the currently used aggressive treatment regimes. Although acute side-effects in cancer of the oral cavity are certainly not negligible, it appears hard to produce reliable data on this issue with respect to this type of cancer if solely based on the literature. This section therefore deals only with the acute side effects of patients with cancer in the oropharynx based on our own (peer reviewed) experience. It is evident from the charts that acute morbidity, leading to non-compliance, is extremely low. Obviously, this is due to the fact that the large irradiated volume is treated by a slightly accelerated fractionation schedule, and only taken to a dose of 46/2 Gy. Moreover, the implant is done after 1-2 weeks at the time when the side effects, experienced from the external beam irradiation (IMRT) part of the treatment, are already partly subdued. The acute side-effects typically seen in IBT patients are mucositis grade 3 (-4), maximally at the site of the implant during the time of irradiation, and xerostomia; soft tissue necrosis ("ulceration", grade 3 and 4) and pain, leading to swallowing problems, are typically in case of IBT experienced maximally between 3-6 months post treatment. Most frequently there is a good healing tendency, with spontaneous healing. If soft tissue necrosis and/or pain is persistent, patients are subjected to a course of hyperbaric oxygen (6 weeks; 30 sessions) with often good results [42].

Late side-effects

From the charts of 336 oropharyngeal cancer patients we found that patients treated according to our IBT-protocol, do experience late side-effects such as mucositis (32%), xerostomia (15%*), dysphagia (31%), pain (22%) and osteoradionecrosis (3%). Table 4 [43,13,16] summarizes some results published in the literature. Most of these typically radiation induced late side-effects, in particular the soft tissue necrosis or ulceration, are self-limiting, that is heal spontaneously over a period of a few months. As is suggested by the literature, several of these late occurring side-effects might not only be dose-related, but also associated with the quality of the implant [44,45,46,47,48]. For that purpose a number of physical parameters were analyzed in patients with large implants of the BOT; that is, 43 LDR- and 32 optimized fr.HDR/PDR volume implants. These 75 patients were considered to be a representative sample taken from the database of the "oropharyngeal cancer patients" (see section before). The physical pa rameters, being defined in table 5, were studied in these rather irregular large volume implants. Albeit may be somewhat preliminary, some conclusions can be drawn: 1. It seems relevant to study the maximum and minimum doses in the basal dose points. [2]. The UI and QI are strongly correlated. [3]. Probably due to the optimization of the 32

*: Unfortunately, not systemically scored/reported in charts

First Author	N	Site		Incidence	%
Levendag, 2004	104	All	Late effect: mucosa Late effect: salivary glands Late effect: dysphagia Late effect: pain Late effect: trismus	41/104 6/104 21/104 21/104 1/104	30 6 20 20 1
Harrison, 1998	68	BOT	Fatal complicatons		3
Gibbs, 2003	41	BOT	Soft-tissue necrosis/ulceeraton Osteoradionecrosi Gastrostomy	3/41 2/41 1/41	7.3 4.8 2.4

Table 4: Late complications after oropharyngeal cancer radiation treatment, BT Boost.

Definitions of physical parameters in the base-of-tongue study	
Parameter	Definition
Dbase85	85% of the average dose in all basal dose points [45]
Db_min	Lowest dose in any of the basal dose points
Db_max	Highest dose in any of the basal dose points
Sd_dbas	Standard deviation in the doses over all basal dose points; a measure of the (in)homogeneity of the dose over all basal dose points (and thus the implant)
Vdis100	Total volume (distributed, so not necessarily contiguous) receiving at least the prescribed dose; also called treated volume according to ICRU 58 [45]
Vdis150	Total volume (distributed, so not necessarily contiguous) receiving at least 150% of the prescribed dose
	The ratio Vdis150/ Vdis100 is a measure of the dose inhomogeneity (= DNR) [45].
UI	Uniformity index derived from natural DVH (according to Anderson [44]); a measure of the dose homogeneity taking into account the choice of reference isodose in relation to the relatively homogeneously irradiated volume
QI	Quality index derived from natural DVH (according to Anderson [44] and modified by R. van der Laarse); a measure of the dose homogeneity only, without taking into account the choice of the reference isodose in relation to the relatively homogeneously irradiated volume [48]

DNR—dose nonuniformity ratio; DVH—dose–volume histogram; ICRU—International Commission on Radiation Units and Measurements; QI—quality index.

Table 5: Physical parameters studied in 32 LDR- and 43 fr.HDR/PDR volume implants in sample of patients with cancer in the oropharynx.

fr.HDR/PDR implants, only relatively small differences between the UI, QI, DNR, and the sd of the basal dose of the LDR- as opposed to the same parameters of the fr.HDR/PDR base of tongue implants.
Most striking, no correlation was observed between the responses to the QoL questionnaires and any of the physical parameters (see next section). In conclusion, quality indices are not very useful in daily practice.

Quality of Life

Harrison et al.[49] published one of the first reports on QoL for IBT treatment of the BOT. It was stated that "most patients achieved excellent functional status and QoL". Moreover, patients in general had no problem with maintaining their employment status after primary radiation (fr.HDR boost) for advanced BOT cancer. According to Babin et al.[50], the "sociability" of individual patients has never been evaluated properly. He advocates studying QoL with emphasis in 3 domains: phsycial, psychological and social symptom domains.
On the other hand, Pourel et al.,[51] stated that although health-related QoL is significantly impaired in long-term survivors, the focus in treatment option comparisons should still be "survival" as being the most relevant endpoint. The group of Pourel et al., found no patient-, disease-, or treatment- related factors correlating with the swallowing scale and dry mouth items of the European Organization for Research and Treatment of Cancer EORTC - H&N35 questionnaire. Hammerlid et al. [52] reported on a prospective QoL study using the EORTC QLQ-C30 and EORTC H&N35 questionnaires for patients with oral and pharyngeal carcinoma treated with external beam irradiation with or without BT. Most symptoms were at their peak 2 or 3 months after the start of treatment. Nutrition and pain were found to be the major problems, and, of special interest, as many as 19% to 40% reported psychiatric distress.

Quality of life - Dysphagia

Dysphagia-related complaints have been the subject of a number of recent publications [53,54,55,56,57,58,59,60]. Poulsen et al. 58 found that a field length greater than 82 mm for the second phase of irradiation increased the probability of requiring intervention with percutaneous endoscopic gastrostomy or nasogastric tube feeding, that is, 36% (> 82 mm) versus 16% (< 82 mm). Manger et al.57 showed that prophylactic enteral feeding during RT minimizes average weight loss compared with reactive feeding. Caudell et al.[53] found a prevalence of 38% for dysphagia; by univariate analysis, the primary site, concurrent chemotherapy, RT schedule, and increasing age were significantly associated with development of long-term dysphagia. The use of concurrent chemotherapy, the primary site, and increasing age remained significant factors on multivariate analysis. The authors concluded that adding concurrent chemotherapy to RT for locally advanced head and neck cancer resulted in increased and long-time present dysphagia. Feng et al.[55], Jensen et al.[56], Teguh et al.[60,59] and Levendag et al.2, all were able to demonstrate the presence of significant relationships between the dose-volume parameters of structures and objective and subjective measurements of swallowing function and/or aspiration.

Rotterdam database patients with cancer of the oropharynx.
Between 1991 and 2005, 458 oropharyngeal cancer patients were treated in a single institution by RT (boost), 336 were available for analysis of side-effects. Chart review revealed 31% (103 of 336) of patient with 'severe' dysphagia (Research Therapy Oncology Group grade III and IV). Out of the 336 patients, 188 were treated with IBT as a boost. All patients alive and at least one year NED received three types of questionnaires: 1) the EORTC QLQ-C30 and EORTC QLQ-H&N35, which include a swallowing scale with four items (problems with swallowing liquid, pureed food, or solid food, and aspiration when swallowing) [61]; 2) the Performance Status Scale of List et al.[62], which includes a Normalcy of Diet item; and 3) the M.D. Anderson Dysphagia Inventory [63], which consists of 20 questions with global, emotional, functional, and physical subscales. By the censor date (January 1, 2006), 155 patients had responded to the QoL questionnaires. Of these 155 patients, 91 were male and 64 were female, and the mean age was 56 years (range, 35-78 years). Primary treatment sites were TF/SP (n = 108) and BOT (n = 47). Seventy-seven percent (119 of 155) had stage III or IV disease. Of the 155 patients, 107 received a BT boost (TF/SP, 83; BOT, 24) and 48 received a boost by non-BT techniques (TF/SP, 25; BOT, 23) and 59 of 155 (38%) received chemotherapy in a concomitant fashion. We focused the data analysis in this review on the late side effects: "swallowing problems" and "xerostomia."

QoL Responses (mean scores)	C30 QoL*	H&N35 Swallowing‡
Brachytherapy (n=111) Boost		
IMRT / 3DCRT (n=52) first series	75	14
Par-Opp (n=59) first series	72	25
Ccyberknife (n=12) Boost		
IMRT / 3DCRT (n=12) first series	73	15
Non-BT (n=49) Boost		
IMRT / 3DCRT (n=23) first series	71	32
Par-Opp (n=26) first series	60	46

Selected Groups	C30 QoL	H&N35 Swallowing	MDADI Physical	MDADI Functional	MDADI Emotional
All Patients, CBK excl. (n=160)					
BT (n=111)	74	20	68	78	77
vs. non-BT (n=49)	66	40	50	60	60
p-values	n.s.	< 0.001	< 0.001	< 0.001	< 0.001

Table 6: Quality of Life and Dysphagia (mean) scores compared byTechnique & Boost-Type.
‡ Problem scale: high score = severe problems.
* Function scale: high score = good functions.

Percentages of severe QoL scores for swallowing and dry mouth were lower for IBT patients than for non-BT patients (14-25% vs. 32-46% for H&N35 [swallowing] and 52% vs. 67% for H&N35 [xerostomia]); the outcome of the other questionnaires on "swallowing problems" (i.e. MDADI, List) are consistent for EORTC H&N 35 QoL questionnaires. For more detailed analyses see also table 6. From the univariate analysis, one can conclude that the following factors are significant for swallowing-related problems: IBT, T stage, boost treatment, neck surgery, and neck irradiation. In the multivariate analysis, IBT and the dose in the superior constrictor muscle remained the only two significant variables. Finally, xerostomia and dysphagia are strongly correlated ($P < 0.001$), as well as the mean dose in the superior and middle constrictor muscle with the dry mouth syndrome [60]. A steep dose-effect relationship was established (figure 11) [64]; for the way the calculation was performed in order to arrive at this D-E curve, the reader is referred to previous publications by Levendag 2 and Teguh 60. A 20% increase in complaints per 10 Gy was found after 60 Gy in the superior constrictor muscle.

The tolerance of the swallowing muscles depends to some extent on the treat ment modality used. In patients who receive BT as boost therapy, dysphagia is seen in 14% treated with an average dose of 53 Gy. In contrast, dysphagia was seen in 40% of patients treated with EBRT to a mean dose of 68 Gy (figure 11). We speculate that the increase in dysphagia is related to the increase in irradiated volume and radiation dose. Apparently, the IBT side-effects are not totally negligible; this could be due the high cumulative dose of radiation, that is the dose of IBT plus the dose of the first series of EBRT (IMRT) (46/2 Gy) being delivered to (a part of) the swallowing muscle and/or the combination with chemotherapy. However, from our data, it seems that patients treated with an IBT-boost still have a better

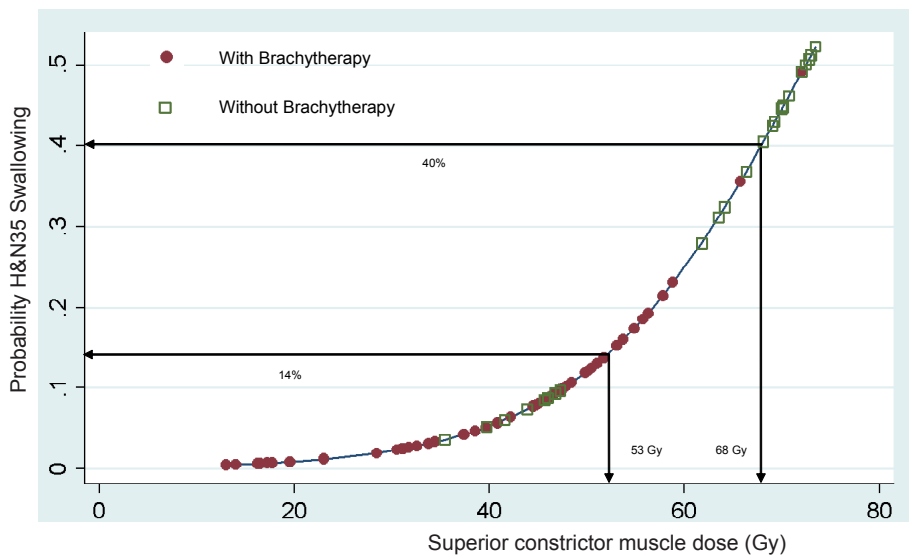


Figure 11: Dose-effect relationship swallowing problems measured by the scores obtained through responses to QoL questionnaires and the dose received by the swallowing muscles (as an example, this is dataset is relevant for the superior constrictor muscle).

swallowing-related QoL than those receiving IMRT only. This is probably because of the steep dose fall-off in case of IBT in part of the swallowing related structure(s). It would be of interest to do the same type of analysis in the future in a more precise way; that is, in stead of roughly summing physically “numbers of Grays”, it would be more appropriate to add real dose distributions in the total volume of interest (biological treatment planning). Because of the work on this issue at our department by Vásquez Osorio [65], it will now possible soon to do so in clinic. We expect this type of dose summing in combination with a process called auto-contouring [66], will further increase the accuracy of the treatment planning process and therewith hopefully allows for a further improvement of the QoL of our patients.

CONCLUSION

In conclusion, for oropharyngeal cancer boosted by IBT, at 10-years an excellent local control rate of 90% was observed. However lack of training, experience, small volume disease, invasiveness and logistics (operating room) can all be, albeit rarely, conditionally limiting. (Late) side effects (e.g. soft tissue necrosis) are not totally negligible, but if present, are in the great majority of cases spontaneously healing. When comparing IBT to other forms of conformal radiation, such as stereotactic radiation therapy, Cyberknife and IMRT, the quality of life, in particular regarding the clinically significant problem of dysphagia, speaks in favour of IBT.

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Quality of Life of Oropharyngeal Cancer Patients Treated with Brachytherapy - A Review

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ABSTRACT

Brachytherapy (BT) is a highly conformal (accurate clinical target volume delineation, no planning target volume margin) radiotherapy technique; the radioactive source, guided by afterloading catheters, is implanted into the heart of the tumor. The localized high dose of radiation enables high tumor control rates and, because of rapid dose fall-off, sparing of the adjacent normal tissues. At the Erasmus Medical Center, excellent results were observed: 5-year local regional control of 84%, 5-year disease-free survival of 59%, and 5-year overall survival of 64%. Therefore, in the case of moderately sized tumors, for well-trained, skillful physicians, BT is the therapy of choice (if technically feasible). However, side effects are not totally negligible, partly because of the cumulative dose of BT and the first series of 46/2 Gy. However, patients treated with BT still have a better swallowing-related quality of life, which might improve further if summation of BT and the first series of 46/2 Gy, as well as auto-contouring of the neck levels, are realized. So far, there is no significant relationship between the quality index of the BT implants and local control/overall survival and/or quality of life.

INTRODUCTION

Although major improvements in surgical and radiation therapy (RT) techniques have come about, overall survival (OS) has not changed significantly in the past decade [1]. Locally advanced disease in head and neck tumors is present in more than 50% of patients at diagnosis, with a 5-year survival rate of approximately 40% to 50% [1]. Side effects of RT for tumors of the head and neck are well known and extensively described in the literature. Moreover, in recent years, the late occurrence of dysphagia has been added to the list of side effects having a significant impact on patients' quality of life (QoL) [2]. Several papers on dose–effect (D-E) relationships for dysphagia and aspiration have been published recently [3–7]. From these papers, it has become evident that among the several causes of dysphagia, the dose delivered to the swallowing muscles is a key factor in its development. Therefore, it was thought of interest to study the role of brachytherapy (BT), which, given its conformality, may favorably influence the D-E relationship. Furthermore, prognostic factors for local control and side effects in association with BT also are detailed in this review.

BRACHYTHERAPY TECHNIQUES

The history of BT dates back to the beginning of the 20th century, with the first BT procedures being performed using radium-226 needles. Brachytherapy (brachy- = Greek for "short") is a treatment modality in which the tumor is irradiated by positioning the radioactive sources very close to the mold (endocavitary techniques) or even inside the tumor volume (interstitial implant) by permanent (seed) implant or by temporarily inserted seeds, applicators, or radioactive sources using afterloading catheters. In principle, BT is a conformal type of RT technique. In recent years, artificial radionuclides such as cesium-137, cobalt-60, iodine-125, and iridium-192 (IR-192) became available. Manual afterloading of the sources into applicators or afterloading tubes replaced direct loading of sources into the patient. The French developed the so-called Paris system for low–dose rate (LDR) dosimetry purposes; that is, for parallel-equidistant sources, the system recommends specifying the dose of the implant as 85% of the average dose in the basal dose points (local minima). A similar type of dose prescription is used for current high–dose rate (HDR) BT, even though the implanted sources (afterloading catheters) may not be totally equidistant. Also, computer-controlled afterloading devices, supported by sophisticated treatment-planning software with optimization capabilities, became available. The base-of-tongue (BOT) implant consists of afterloading catheters introduced in and surrounding the tumor volume after the percutaneous introduction of trocars in a submental or submandibular region is realized [8]. For patients with disease extension toward the pharyngo-epiglottic fold, lateral catheters are sometimes added. Mostly, however, the BOT implant consists of three planes of afterloading catheters (with three catheters per plane). The spacing between each end of the "looping" catheters running over the dorsum of the tongue is ± 0.75 to 1 cm. As a safety precaution, a temporary tracheotomy is sometimes indicated for implant removal and is executed immediately before the implantation per se and/or at the time of neck dissection. In most cases, two or three catheters are implanted in the tonsillar fossa (TF) and fau-

cial arches and/or soft palate (SP) tumors. A temporary nasogastric feeding tube is placed at the completion of most BT procedures. The development of radiobiologic models has enabled us to predict, to a certain extent, the tumor control probability and normal tissue complication probability after the application of BT, depending on factors such as fraction size, dose rate, the tumor, and the normal tissues one is dealing with. In general, BT can be divided into several dose rate categories:

- LDR: dose rate varies between 0.4 and 2 Gy/h
- Medium dose rate (MDR): dose rate varies between 2 and 12 Gy/h
- HDR: dose is delivered at a rate higher than 12 Gy/h
- Fractionated HDR (given at the Erasmus Medical Center [MC]): over many years, a fraction size of 3 to 4 Gy with a minimum fraction interval of 6 hours and a total fraction number of 6 to 7, for boost doses varying between 18 and 21 Gy after 46/2 Gy external beam irradiation has been applied.During the weekend, no BT is delivered by this “daytime” fractionating schedule.
- Pulsed–dose rate (PDR), LDR BT: regime simulates LDR by using many small fractions. At the Erasmus MC, time intervals of (less than) a few hours between fractions are used. This so-called PDR regime is defined as a booster dose of HDR-type radiation with a fraction size of 1 to 2 Gy and an interfraction time interval of 3 hours, with a total dose of 20 to 22 Gy. This PDR type of fractionation can be delivered over the weekend (automation: 24-hour regime).

In skillful, well-trained hands, BT remains an extremely gratifying technique for applying high doses of radiation for small-volume disease with highly conformal and accelerated properties. Through the development of soft x-ray sources and afterloading machines that carry multiple sources and have multiple drives, increases in dose rate flexibility and radiation protection have been obtained. One of these sources, ytterbium-169, currently is being tested. Finally, unless the tumor is very small, interstitial BT usually is used in conjunction with external beam irradiation.

LOCAL CONTROL AND SURVIVAL

The French school has published extensively on interstitial RT (IRT) of TF and/or SP tumors, as well as of BOT cancers [9–15]; most of these data regard LDR implants. For example, Mazeron et al. [16] reported on a subset of patients with early-stage (T1, T2) tumors of the TF and/or SP, with a local control rate (LCR) of approximately 85% and a regional control rate of 97% for N0 and 88% for N1-3 disease. Patients were typically treated with 45-Gy external beam RT (EBRT), conventional fractionation, followed by a 30-Gy LDR Ir-192 boost. Soft tissue ulceration occurred in 17 of the 127 patients (13%). Similar LRCs were reported by Pernot et al. [17] (90% in TF/SP T1,T2N0 tumors vs 86% in T1,T2N1-3 tumors, with LDR boost) and Levendag et al. [18,19] (87% in TF and/or SP tumors at 5 years).The series of patients in Rotterdam were treated by fractionated HDR BT (daytime regimen) or PDR (24-hour regime). Esche et al. [10] described 43 patients with carcinoma of the SP and uvula with an LCR of 92%. An overall- and cause-specific survival of 60% and 81% at 3 years and 37% and 64% at 5 years, respectively, was reported. The leading cause of death was other aerodigestive cancers; these cancers occur at an actuarial rate of 3% per

year post treatment. The “brachytherapy school” of Memorial Sloan-Kettering Cancer Center (MSKCC) in New York pioneered large-volume implants—a technique initially designed by Vikram [20,21]—particularly for cancer of the BOT. Harrison et al. [22] published extensively on the MSKCC experience with volume implants of the BOT. Five-year local control, disease-free survival (DFS), and OS rates of 89%, 80%, and 86%, respectively, were obtained. A classic paper published by Housset et al. [23] reported on local control for EBRT versus surgery plus postoperative RT (PORT) versus EBRT alone in patients with BOT cancer. In essence, the results were significantly worse for the EBRT-alone group, with local failure rates of 20.5% (EBRT + IRT), 18.5% (surgery + PORT), and 43% (EBRT alone). Most data in the literature concern the observation that BT with or without EBRT is associated with good LCRs, but the morbidity may be significant; therefore, these implantations should be performed at centers with adequate experience in three-dimensional planning and adequate management of complications. Regarding the complications, it is important to realize that in this day and age, advanced local disease frequently is treated with EBRT and concomitant chemotherapy, ultimately combined with BT. It is known from meta-analysis that concomitant chemotherapy does lead to better tumor control but is associated with greater morbidity [24].

From 1991 to 2005, 336 oropharyngeal cancer patients were treated nonsurgically at our institution, and the following results were observed with regard to actuarial local control, DFS, and OS rates when stratified by type of booster technique used, that is, BT versus no BT: the 5-year LCR was 84% versus 60% ($P < 0.05$), 5-year DFS was 59% versus 43% ($P < 0.05$), and 5-year OS was 64% versus 39% ($P < 0.05$). Outcomes for patients with cancer of the oropharynx depend on several well-known prognostic factors, such as weight loss, performance status, hemoglobin level, tumor (T) and nodal (N) stage, tumor sites, tumor differentiation, involvement of resection margins, extracapsular spread, perineural invasion, epidermal growth factor receptor inhibitors, presence of human papillomavirus, and previously used treatment modality [25].

From our multivariate analysis, we observed that BT and time period (< year 2000) are significant influences on local control. With regard to DFS and OS, BT’s influence disappears in multivariate analysis; sex, age, N stage, and head and neck surgery are prognostic factors instead. Piccirillo and Vlahiotis [26] described the prevalence of co-morbidity and its impact on treatment and prognosis in patients with cancer of the head and neck. The authors concluded that other diseases or conditions can affect treatment selection and prognosis. Failure to include an accurate description of comorbidities in hospital- and population-based registries may lead to misleading conclusions about treatment effectiveness, outcomes, and quality of cancer care.

QUALITY OF LIFE

Harrison et al. [27] published one of the earliest reports on QoL data for BT treatment. They stated that most patients achieved excellent functional status and QoL and could maintain their pre-diagnosis earning potential and employment status after primary radiation for advanced BOT cancer. Babin et al. [28] conducted a brief review of patient-reported outcome measures in head and neck cancer and differentiated the following symptom domains: physical symptoms linked to diet and feeding pat-

terns, communication disorders, pain, and the general state of health; psychological symptoms including depression, irritability, and loss of self-esteem; and social symptoms including relationship difficulties with a partner or other family members, loss of work, reduction in salary, and a sense of uselessness, resulting in a negative impact on daily life. According to Babin et al. [28], the "sociability" of individual patients was evaluated rarely until now. According to Pourel et al. [29], although health-related QoL is significantly impaired in long-term survivors of T1-T3 oropharyngeal carcinoma, the focus in treatment option comparisons should still be on survival as the most relevant end point; that is, QoL should be regarded as a secondary end point. This group found no patient-, disease-, or treatment-related factors related to the swallowing scale and dry mouth items on the European Organisation for Research and Treatment of Cancer (EORTC) H&N35 questionnaire, which is not in agreement with our findings (see next paragraph). Petruson et al. [30] reported that 80% of patients with tonsil and BOT cancer had problems with dry mouth and half the patients with tonsil and BOT cancer reported problems with swallowing solid food at 3-year follow-up. However, Pourel et al. [29] suggested that coping processes tend to "delete" any differences in symptom and functional scales among patients, regardless of the initial treatment. Hammerlid et al. [31] reported a prospective QoL study (EORTC QLQ-C30 and EORTC H&N35 questionnaires) of patients with oral and pharyngeal carcinoma treated with external beam irradiation with or without BT. Most symptoms were at their peak 2 or 3 months after the start of treatment. Nutrition and pain were found to be the major problems, and as many as 19% to 40% reported psychiatric distress. Patients who received additional BT did not report any increase in QoL problems (except for pain) compared with those who had external radiation only. QoL does not seem to be affected by the increased local radiation dose given when BT is included in the treatment regimen. In addition to better local control and sparing, Nijdam et al. [32] reported on the cost-effectiveness of this type of treatment; the mean total cost for patients treated with BT is lower compared with those treated with EBRT only or surgery.

DYSPHAGIA

Dysphagia-related complaints have been the subject of recent publications. Poulsen et al. [33] found that a field length greater than 82 mm for the second phase of irradiation increased the probability of requiring intervention with percutaneous endoscopic gastrostomy or nasogastric tube feeding, that is, 36% (> 82 mm) versus 16%. Mangar et al. showed that prophylactic enteral feeding during RT minimizes average weight loss compared with reactive feeding. Important clinical parameters associated with enteral nutrition include tumor site, World Health Organization (WHO) performance status of 2 to 3, increasing age, low body mass index, and serum albumin level. Patients with advanced-stage disease (III/IV) and a WHO performance status of 2 to 3 who smoke more than 20 cigarettes a day have a greater than 75% chance of needing enteral support during their treatment. Caudell et al. [35] found a prevalence of 38.5% for dysphagia; by univariate analysis, the primary site, concurrent chemotherapy, RT schedule, and increasing age were significantly associated with development of long-term dysphagia. The use of concurrent chemotherapy, the primary site, and increasing age remained significant factors on multivariate analy-

sis. The authors concluded that adding concurrent chemotherapy to RT for locally advanced head and neck cancer resulted in increased long-term dysphagia. Feng et al. [36] demonstrated significant relationships between the dose–volume parameters of structures and objective and subjective measurements of swallowing function. Other groups also showed significant correlations of various dysphagia end points with dose in supraglottic lesions [3] and glottic cancers [3,37].

ERASMUS MC EXPERIENCE

Between 1991 and 2005, 458 oropharyngeal cancer patients were treated with curative intent in a single institution by RT techniques. One hundred twenty-two patients were excluded from the present analysis because they had tumors of the non–squamous cell carcinoma type (n = 11), second primaries (n = 30), metastasis (n = 4), EBRT in a remote hospital (n = 12), LDR treatment (n = 2), death during treatment (n = 2), synchronous primary tumors (n = 16), or tumors treated with palliative intent (n = 39), or because of a protocol violation (n = 6). The remaining 336 patients form the basis of the analysis; of these, BT was used to treat 188 patients. Patients were seen in joint consultation by a radiation oncologist and head and neck surgeon. Diagnosis was established by clinical examination, panendoscopy, CT, and/or MRI of the head and neck. Biopsy of the primary tumor and ultrasound-guided fine-needle aspiration of the suspicious regional lymph nodes were performed [19]. Patients were classified according to the 2004 edition of the American Joint Committee on Cancer's staging manual [38]. A detailed treatment protocol was described in earlier papers [6,7,18,32,39].
The 336 patients with no evidence of disease (NED) received three types of questionnaires: 1) the EORTC core QoL (QLQ)-C30 and EORTC QLQ-H&N35, which include a swallowing scale with four items (problems with swallowing liquid, pureed food, or solid food, and aspiration when swallowing) [40]; 2) the Performance Status Scale of List et al. [41], which includes a Normalcy of Diet item [40,3] the M.D. Anderson Dysphagia Inventory [42], which consists of 20 questions with global, emotional, functional, and physical subscales. By the censor date (January 1, 2006), 155 patients had responded to the QoL questionnaires. Reviewing the charts of all the patients, we found that 31% (103 of 336) had dysphagia (Research Therapy Oncology Group grades III and IV). Thus, a cohort of 155 patients alive with NED after a minimum follow-1 year was available for analysis. Of these patients, 91 were male and 64 were female, and the mean age was 56 years (range, 35-78 years). Primary treatment sites were TF/SP (n=108) and BOT (n=47). Seventy-seven percent of the patients (119 of 155) had stage III or IV disease. Of these 155 patients, 107 received a BT boost (TF/SP, 83; BOT, 24) and 48 received a boost from non-BT techniques (TF/SP, 25; BOT, 23). We focused the data analysis in this review on late side effects: 'swallowing' and 'xerostomia'. Percentages of severe QoL scores for swallowing and dry mouth were lower for BT patients than for non-BT patients (14% vs. 34% for H&N35 [swallowing] and 52% vs. 67% for H&N35 [xerostomia]); the outcome data are consistent for all three QoL questionnaires. From the univariate analysis, one may conclude that the following factors are significant for swallowing-related questions: use of BT, T stage, boost treatment, neck surgery, and neck irradiation. In the multivariate analysis, BT and dose in the superior constrictor muscle remained significant. From Figure 1, one can appreciate a significant D-E relationship between the EORTC H&N35 swallowing scale and dose in the superior constrictor muscle ($P < 0.01$).

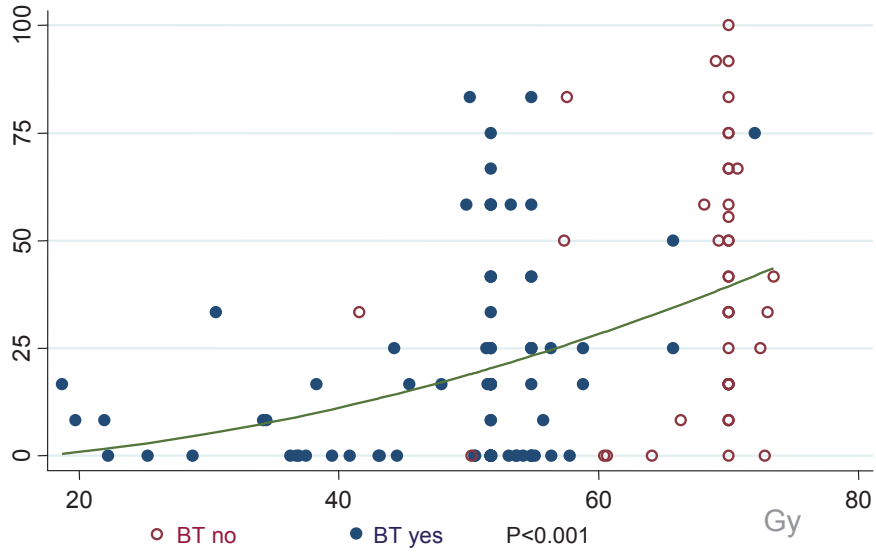

Figure 1: Correlation between the dose in constrictor superior muscle versus the swallowing item on the European Organisation for Research and Treatment of Cancer (EORTC) H&N35 questionnaire, 1991 to 2005.

A 20% increase in complaints per 10 Gy was found after 60 Gy in the superior constrictor muscle. We speculate that the increase in dysphagia is related to the increase in irradiated volume and radiation dose. Although the dose–volume data may prove a cause–effect relationship, clinical validation is needed to determine whether reducing the doses to the swallowing structures as much as possible is beneficial. Finally, xerostomia and dysphagia related structures also are strongly correlated ($P < 0.001$): for the mean dose in the superior and middle constrictor muscle versus dry mouth [7].

In conclusion, BT side effects are not totally negligible; this is partly the result of the cumulative dose of BT and the first series of EBRT (46/2 Gy). However, patients treated with BT still have a better swallowing-related QoL than those receiving EBRT only. Their QoL may improve even further if summation of BT and the first series of 46/2 Gy, as well as auto-contouring of the neck levels, are realized.

Brachytherapy quality indices for LDR and HDR/PDR interstitial volume implants

Various evaluation parameters are used to describe the quality of interstitial volume implants [43–45]. We analyzed these parameters for 75 representative volume BOT implants. Forty-three patients were treated with LDR BT using Ir-192 wires, and 32 were treated with fractionated HDR or PDR BT using a single stepping Ir-192 source. The main differences between LDR and HDR/PDR BT are the dose rate and the ability to optimize the dose distribution in HDR/PDR BT using dwell-time optimization, which results in nonuniform loading along the catheter [46]. Therefore, one would

Definitions of physical parameters in the base-of-tongue study	
Parameter	Definition
Dbase85	85% of the average dose in all basal dose points [46]
Db_min	Lowest dose in any of the basal dose points
Db_max	Highest dose in any of the basal dose points
Sd_dbas	Standard deviation in the doses over all basal dose points; a measure of the (in)homogeneity of the dose over all basal dose points (and thus the implant)
Vdis100	Total volume (distributed, so not necessarily contiguous) receiving at least the prescribed dose; also called treated volume according to ICRU 58 [46]
Vdis150	Total volume (distributed, so not necessarily contiguous) receiving at least 150% of the prescribed dose
	The ratio Vdis150/ Vdis100 is a measure of the dose inhomogeneity (= DNR) [46].
UI	Uniformity index derived from natural DVH (according to Anderson [44]); a measure of the dose homogeneity taking into account the choice of reference isodose in relation to the relatively homogeneously irradiated volume
QI	Quality index derived from natural DVH (according to Anderson [44] and modified by R. van der Laarse); a measure of the dose homogeneity only, without taking into account the choice of the reference isodose in relation to the relatively homogeneously irradiated volume [42]

DNR—dose nonuniformity ratio; DVH—dose–volume histogram; ICRU—International Commission on Radiation Units and Measurements; QI—quality index.

Table 1: Definitions of physical parameters in the base of tongue study.

expect significant differences in the BT quality indices when comparing LDR with HDR/PDR implants. For these 75 patients, we have studied the standard deviation of the dose in the basal dose points as a measure of dose homogeneity. From a “natural” dose–volume histogram, the uniformity index (UI) was derived [45]. The UI depends not only on the uniformity of the dose distribution, but also on the choice of reference isodose. Therefore, a quality index (QI) similar to the UI but independent of the choice of reference isodose also has been evaluated [43]. Other physical parameters investigated are Dbase85, Db_min, Db_max, Sd_dbas, Vdis100, and Vdis150. Definitions of these parameter are given in Table 1. We found that instead of evaluating the standard deviation of the dose in all basal dose points, it suffices to evaluate the maximum and minimum doses in these points for these rather irregular implants, as the standard deviation of the dose in all basal dose points was strongly correlated to the maximum and minimum dose in the basal dose points were strongly correlated. A correlation between UI and QI was found, probably because of the uniform method of defining the reference isodose, that is, at 85% of the dose (rate) in the basal dose points. However, a relationship between UI or QI and the

standard deviation of the dose in all basal points was not seen. The LDR and HDR/PDR implants differ with regard to the treatment volume and the fact that the dose distribution of the HDR/PDR implants was optimized. Therefore, it is surprising that the differences in UI, QI, dose nonuniformity ratio (DNR), and the standard deviation of the basal dose between LDR and HDR/PDR were relatively small (Table 2). A set of independent evaluation parameters can be defined with which the quality of interstitial volume implants can be characterized; this should include the maximum and minimum doses in the basal dose points and either the UI or DNR. These physical parameters were correlated with QoL questionnaire answers from the patients; however, no significant correlation could be established. Petruson et al. [30] also reported that there are no correlations between BT QIs and QoL scores.

BOT implant dose rate	Treatment volume (cm3)	Standard deviation basal dose (%)	UI	QI	DNR
LDR	89.7 ± 48.5	16.5 ± 7.7	1.43 ± 0.14	1.35 ± 0.11	0.33 ± 0.06
HDR/PDR	58.2 ± 21.7	11.3 ± 7.1	1.49 ± 0.11	1.42 ± 0.11	0.28 ± 0.04

Table2: Treatment volume and standard deviation of the dose in all basal dose points.
BOT: Base of tongue, DNR: dose nonuniformity ratio, HDR: high dose rate, LDR: low dose rate, PDR: pulsed dose rate, QI: quality index, UI: uniformity index.

CONCLUSIONS

BT is a specialized technique for applying high doses of radiation to small-volume disease with highly conformal and accelerated properties. Patients treated with BT have better local control, DFS, and OS than those treated with EBRT. At Erasmus MC, excellent results were observed: 5-year LRC of 84%, 5-year DFS of 59%, and 5-year OS of 64%. Selecting the right patients for BT, however, remains important. Using data from the Erasmus MC, we elected to report on a frequently underreported side effect: dysphagia. Swallowing problems were measured by three validated QoL questionnaires; the BT patients were found to have fewer swallowing problems compared with the non-BT group. Univariate analysis also demonstrated an advantage (ie, less dysphagia) related to T stage, boost treatment, neck surgery, and neck irradiation. The multivariate analysis showed a significant effect for BT (implicating fewer swallowing complaints because of the lower doses of radiation received by the superior swallowing constrictor muscles). To improve dysphagia-related QoL, the dose distribution should be optimized further. The tolerance of the swallowing muscles depends to some extent on the treatment modality used. In patients who receive BT as boost therapy, dysphagia is seen in 14% treated with an average dose of 53 Gy. In contrast, dysphagia was seen in 40% of patients treated with EBRT to a mean dose of 68 Gy (Fig. 2). So far, no significant relationship has been seen between the QI of the BT implants and local control/OS and / or QoL.

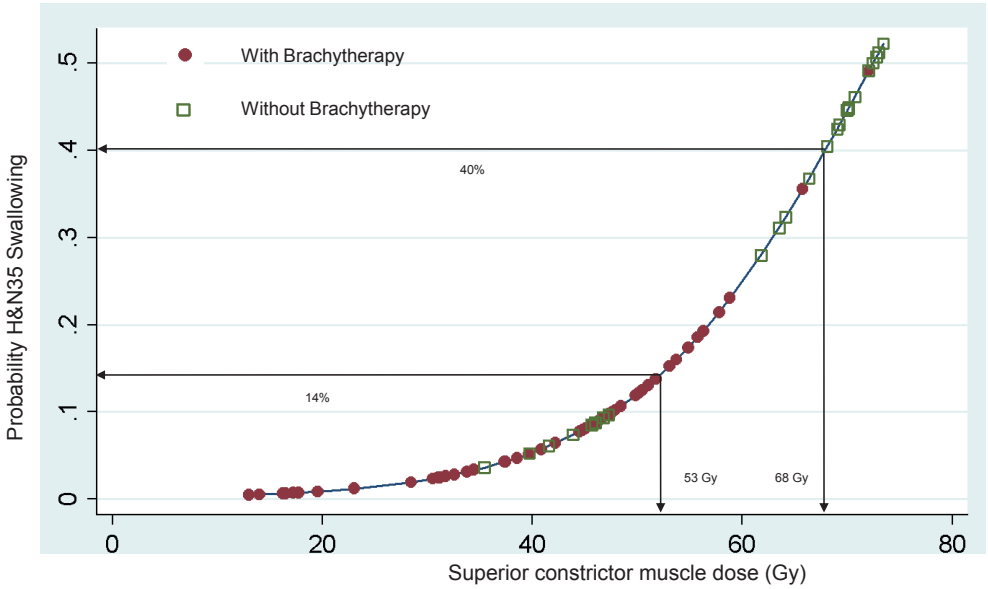

Figure 2. Probability for European Organisation for Research and Treatment of Cancer H&N35 questionnaire swallowing scale versus dose in superior constrictor muscle.

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10

Dysphagia-Related Quality of Life of Patients with Cancer in the Oropharynx: An Advantage for Brachytherapy?

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KEY POINTS

- Results of conventional head and neck radiotherapy by external beam radiotherapy, including a boost of external beam radiation, with or without concurrent chemotherapy, include a number of side effects among which are dysphagia and xerostomia.
- In addition to side effects, the quality of life is also negatively affected.
- In brachytherapy (BT), high doses are used in a short overall treatment time in relatively small volume disease (accelerated conformal treatment),with excellent tumor control rates.
- The current chapter describes the outcome in 155 patients with tonsillar fossa and/or soft palate tumors (n = 108) or cancers of the base of tongue (n = 47). Overall, according to chart review, a severe degree of dysphagia (RTOG grades III and IV) was experienced in 31% of the patients. Similarly, according to responses to the EORTC H&N35 QOL questionnaires, severe dysphagia was observed in about 20% of the BT group and about 38% in the non-BT group.
- Univariate analysis demonstrated less dysphagia for the following conditions: lower mean doses applied to swallowing muscles, BT treatment, single neck irradiation, and in case a neck dissection is performed. The multivariate analysis shows a signifi cant effect for BT (~ implicating less swallowing complaints due to the lower doses of radiation received by the swallowing muscles).
- For improvement of the dysphagia-related QOL, it is suggested to try and further optimize the dose distribution.

INTRODUCTION

In organ preservation therapy, for cancer in the head and neck, over the years a number of investigators have noted a signifi cant increase in dysphagia, defi ned as swallowing problems that most likely relate to more aggressive treatment regimes used in order to obtain better tumor control rates. The aggressive nature of the treatment modalities is exemplifi ed by high doses of radiation and/or (accelerated) fractionation regimens, with or without (concomitant) chemotherapy [12]. Xerostomia has been well documented in patients treated with chemotherapy (CHT) and/or radiation. It has been argued that the degree of xerostomia corresponds with the amount of dysphagia experienced by the patient [16,17]. To define potential rehabilitation strategies, it is important to investigate fi rst the anatomical structures and functionality of the swallowing apparatus. Examples of preventative measures are the pre- and posttreatment exercises and/or the introduction of Therabite [2,9]. Few studies have examined the association of dysphagia with the location of the primary tumor site [20,21]. This chapter analyses the response to validated QOL questionnaires in search of (severe) late side effects, such as swallowing disorders and xerostomia, in patients with oropharyngeal cancers treated between 1991 and 2005 in a single institution (Erasmus MC). The patient retrieval for the current analysis consisted of patients with tonsillar fossa and/or soft palate (TF and/or SP) or base-of-tongue (BOT) tumors treated by radiation therapy (RT). Over time the primary tumor was boosted by various RT techniques, that is, by either a parallel-opposed (P-O) fi eld confi guration, or by 3D conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), or brachytherapy (BT). A treatment regime using conventional 2 Gy/day fractionation, combined with a BT boost, has been applied in our institute by far the most over a great number of years (1991–2008) for various reasons: With regard to tumor control, HDR/PDR fractionation is given in an accelerated fashion with intrinsic dose escalation. A high conformality is obtained because of an accurate CTV delineation, no PTV margin (because catheters move with movement of target area), and rapid dose fall-off. The invasiveness of the procedure, the need for albeit some dexterity, the logistics in the OR, and patients being medically unfit for any type of surgical procedure are some of the disadvantages of BT. This chapter reports in particular those patients treated with BT.

PATIENTS AND METHODS

All patients with squamous cell carcinoma of the oropharynx were treated by RT in the Erasmus MC. Patients were seen in joint consultation by the radiation-oncologist and HN surgeon. Diagnosis was established by clinical examination, and preferentially by panendoscopy, CT, and/or MRI of the head and neck. Biopsy of the primary tumor and, in the majority of cases, ultrasound-guided fi ne-needle aspiration of the suspicious regional lymph nodes were performed. Staging was done according to the TNM classifi cation, 2002 edition [6]. The actuarial loco-regional control rate, diseasefree survival, and overall survival of the 336 patients, stratifi ed for type of booster technique (BT vs. non-BT), are depicted in Fig. 1 (LRC; 5 years 84 vs.60%), Fig. 2 (DFS; 5 years 59 vs. 43%), and Fig. 3, (OS;5 years 64 vs. 39%). Of the 336 patients treated, 155 were disease free with a minimum follow-up of 1 year and were

selected for the purpose of the present QOL analysis.
Ninety-one patients were male, and 64 female; mean age was 56 years (range, 35–78). Primary tumor sites were TF or SP (n = 108), or BOT (n = 47); 119/155 (77%) of patients were stages III and IV; for stage grouping, see also Tables 1 and 2. Over the years, the treatment of preference for T1–T3 TF and/or SP tumors and T1–T4 cancer of the BOT consisted of a first series of 46 Gy (2 Gy/fraction, five fractions/week; as of 2000, six fractions/week) by a P-O technique, 3DCRT, or IMRT to the neck and primary tumor, followed by a boost of fractionated high dose rate/or pulsed dose rate BT to the primary tumor. The doses of the external beam radiotherapy techniques are prescribed according to the International Commission on Radiation Units and Measurement 50 and 62 recommendations. In case of BT, the dose was prescribed to 0.5–0.75 cm of the catheter plane (TF and/or SP tumors; single plane implant), or to 85% of the mean central dose (BOT volume implant). The total dose of fractionated HDR was 20 Gy (4 Gy, 4 × 3 Gy, 4 Gy; two fractions/day 8-h interval minimum); in case of PDR, 22 Gy (2 Gy, 18 × 1 Gy, 2 Gy; interval 3 h) was given. In case of neck nodes, a neck dissection (ND) was executed in the same surgical session as BT was applied. All patients were treated preferably by a BT boost (BT group; n = 107; 83 TF/SP, 24 BOT); in case BT was not feasible, non-BT boost techniques were used (non-BT group; n = 48; 25 TF/SP, 23 BOT). The non-BT techniques used consisted of P-O techniques (P-O; n = 24), 3DCRT (n = 9), or IMRT (n = 15). For more details regarding the protocol, see [12,26]. All 155 patients without evidence of disease for a minimum of 1 year received three types of questionnaires: (1) The EORTC H&N35

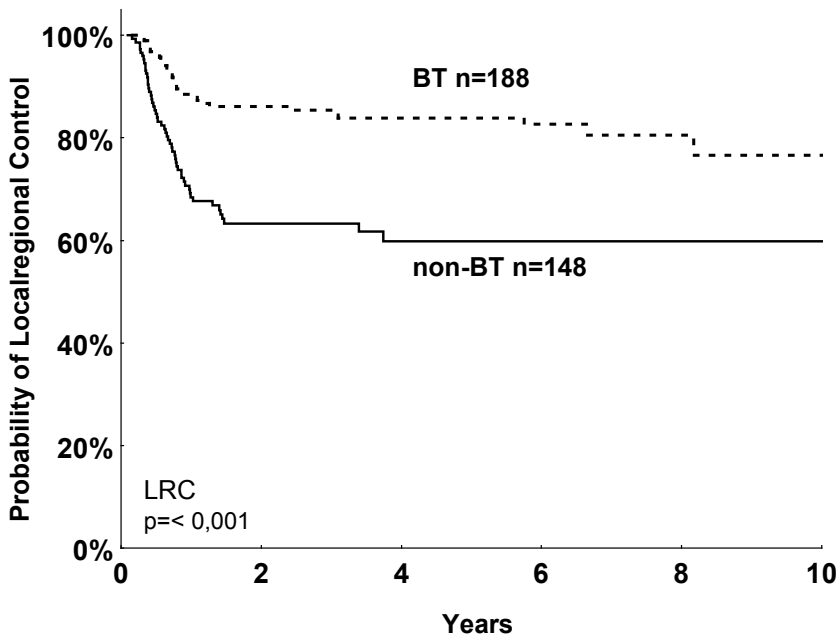

Figure 1: Loco-regional control of tumors in the oropharynx, treated between 1991 and 2005 in the Erasmus Medical Center – Daniel den Hoed Cancer Center. (BT, non-BT): primary tumors (tonsillar fossa and soft palate, base of tongue) were boosted by BT or by non-BT techniques.

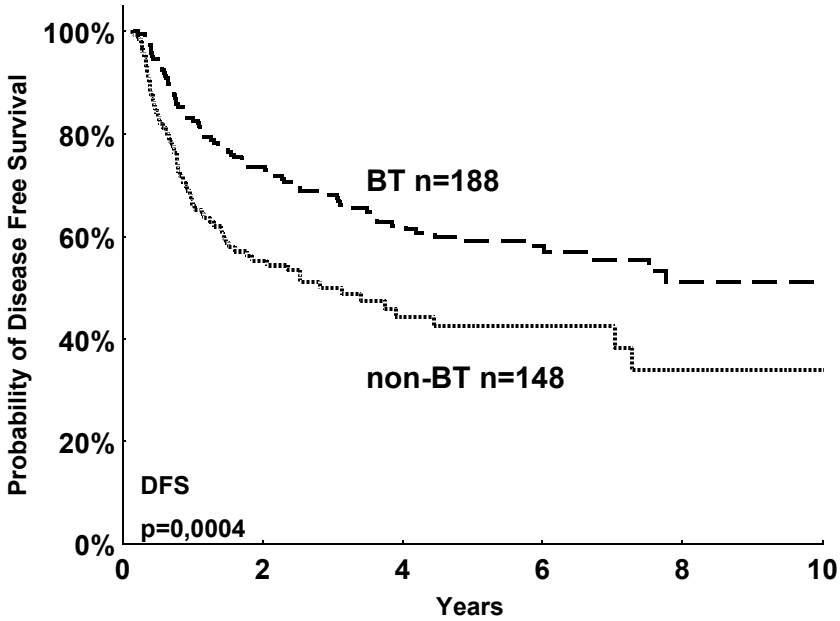

Figure 2: Disease-free survival of patients with tumors in the oropharynx, treated between 1991 and 2005 in the Erasmus Medical Center – Daniel den Hoed Cancer Center.

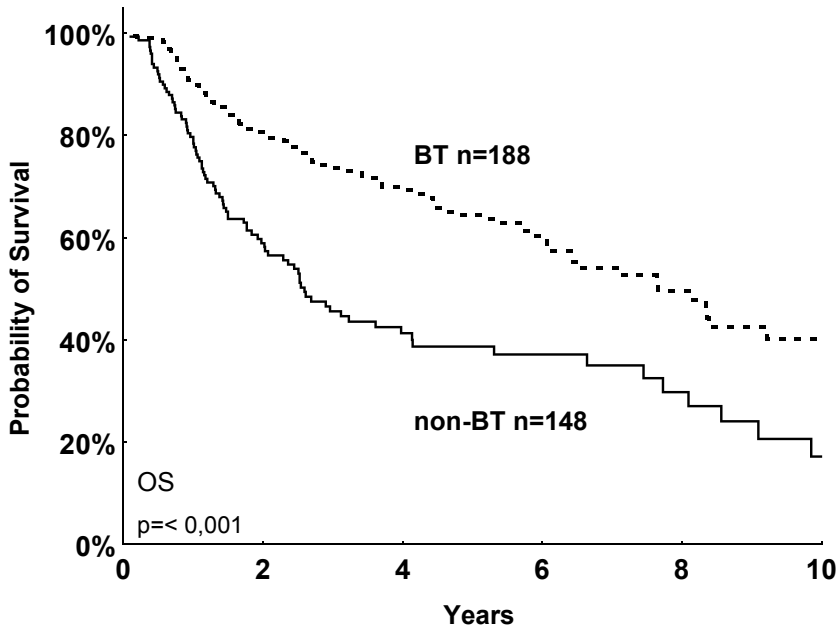

Figure 3: Overall survival of patients with tumors in the oropharynx, treated between 1991 and 2005 in the Erasmus Medical Center – Daniel den Hoed Cancer Center.

swallowing scale, including four items (problems with swallowing of liquid, pureed-food, or solid food, and aspiration when swallowing) [1], (2) The performance status scale (PSS) of List et al. (1996) with item normalcy of diet, and (3) The MD Anderson Dysphagia Inventory (MDADI) [3], consisting of 20 questions with global, emotional, functional, and physical subscales. Treatment plans of previously irradiated patients were retrieved, with the previously defi ned fi ve muscular structures of the swallowing apparatus delineated on the axial CT slices [13].Thus the mean dose contribution by the 3DCRT or IMRT technique to the muscular structures could be computed using the original treatment plan. From the patients treated by P-O fields and if a CT scan for treatment planning purposes was available, also the dose contribution to the swallowing muscles was calculated [7]. From the available CT-based 3D dose distributions of patients boosted by means of BT, the mean BT dose was calculated. For the patients boosted by BT, the 3DCRT, IMRT, or P-O dose and the boost doses were physically summated. Finally, the relationship of the mean total dose received by the five swallowing muscles to the responses of the three–dysphagia-related–QOL questionnaires (mean QOL scores; H&N35, PSS, and MDADI) is reported per tumor site (i.e., the TF and/or SP or BOT) and per treatment technique (BT vs. non-BT).

Dysphagia

From responses to the H&N35 (swallowing scale), PSS (normalcy diet), and to the MDADI questionnaires, prevalence of dysphagia was computed. Also, a moderate and severe degree of dysphagia is established by clustering, that is, e.g., regarding the charts, the RTOG grade 3 and 4 scores were combined. Similarly, for H&N35 (swallowing) “quite a bit” and “very much” dysphagia (score ≥ 50) was scored as grade 3 and 4, respectively, and clustered as “severe.” The PSS (normalcy diet) score ≤ 50 and total MDADI score ≤ 50 were taken as the prevalence of a significant degree (equivalent to RTOG grade 3 or 4) of dysphagia.

Xerostomia

Patients were also asked to respond to the dry mouth scale in the QOL questionnaire H&N35. The outcome was correlated to the dysphagia-related scale of the EORTC H&N35. A univariate and a multivariate analysis were performed for the parameters T-stage, N-stage, sex, age, dose in superior constrictor muscle (scm), dose in medial constrictor muscle (mcm), dose in inferior constrictor muscle (icm), dose in cricopharyngeal muscle (cphm), dose in fi rst centimeter of esophageal inlet (eim), site, neck irradiation unilateral, neck irradiation bilateral, neck irradiation plus ND, treatment before or after 2000 in relation to the QOL questionnaires.

Univariate Dose-Response Relationship

For the scm, mcm, icm, cphm and eim, the correlationsof dose in these muscular structures and the absence or presence of dysphagia grade 3 and 4 combined (dataset dichotomized) were calculated using logistic regressions. For example: Pr{H&N35 swallowing ≥ 50|Dose in scm} =1/(1 + exp (– (a + b *Dose scm))).We calculated coeffi cients for a and b and p-values for testing if b = 0.

Tonsillara Fossa / Soft Palate (n=108)														
	Brachytherapy (n=83)							Non-brachytherapy (n=25)						
	N0	N1	N2a	N2b	N2c	N3	To-tal	N0	N1	N2a	N2b	N2c	N3	To-tal
T1	2	4	3	5	0	2	16	0	0	0	1	0	0	1
T2	28	9	6	4	4	0	1	3	1	1	1	1	3	10
T3	9	1	3	2	0	0	15	3	5	0	0	2	0	10
T4a	0	0	0	0	0	0	0	2	1	0	0	0	0	3
T4b	1	0	0	0	0	0	1	1	0	0	0	0	0	1
Total	40	14	12	11	4	2	83	9	7	1	2	3	3	25

Table 1: UICC /AJCC 2002 edition TNM stage distribution for TF/SP tumors boosted by BT or non-BT techniques Tonsillar fossa/soft palate (n = 108) Brachytherapy (n = 83) Non-brachytherapy (n = 25).

Base of Tongue (n=47)														
	Brachytherapy (n=24)							Non-brachytherapy (n=23)						
	N0	N1	N2a	N2b	N2c	N3	To-tal	N0	N1	N2a	N2b	N2c	N3	To-tal
T1	1	0	3	3	2	0	9	0	0	0	0	0	1	1
T2	1	0	1	2	1	0	5	1	2	0	0	2	1	6
T3	1	1	3	1	0	1	7	2	0	0	2	1	0	5
T4a	3	0	0	0	0	0	3	4	1	0	4	1	0	10
T4b	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Total	6	1	7	6	3	1	24	7	3	0	6	5	2	23

Table 2: UICC /AJCC 2002 edition TNM stage distribution for BOT tumors boosted by BT or non-BT techniques.

RESULTS

Between 1991 and 2005, 155 oropharyngeal cancer patients were treated by RT; 107 were boosted by BT, and 48 boosted by non-BT techniques. At the censor date 1 January 2006, every patient without evidence of disease after a follow-up period of at least 1 year was asked to respond to three validated questionnaires, that is, the EORTC H&N35, PSS, and MDADI. Out of the patients alive NED, 93% responded. We have focused the data analysis in this chapter on calculating the mean number of patients with late side effects “dysphagia” (and “xerostomia”). Table 3 presents an overview of the boost techniques with the respective follow-up times.Tables 4 and 5 summarize the QOL scores of the EORTC H&N35 for the BT group and the non-BT group with regard to the scales “swallowing” and “dry mouth,” respectively. Table 6 presents QOL data with respect to the PSS scores, item “normalcy of diet.” Table 7 shows the QOL mean scores of the MDADI. From the Tables 4–7 one can appreciate differences in QOL outcome per validated questionnaire, per boost technique, and per tumor site. In short, the mean QOL scores for swallowing and dry mouth were

better for BT patients as opposed to non-BT patients, for TF and/or SP tumors as opposed to BOT tumors and for those patients treated with BT and CHT vs. patients treated with CHT in combination with non-BT boost techniques. Better QOL scores were also observed in patients radiated to a single neck as opposed to bilateral neck. The outcome data are consistent for all three QOL questionnaires and summarized in Table 8. From the univariate and multivariate analyses one can conclude that BT and boost treatment are signifi cant parameters ($p < 0.001$) (Table 9). Also from Fig. 4 one can appreciate a significant dose–effect relationship regarding swallowing; i.e., 20% increase points per 10 Gy was found (Fig. 4).

Boost Technique	# of Patients	Mean FU years	Range FU years
Brachytherapy	107	6.7	1.3-14.7
Non-Brachytherapy	48	3.7	1.0-10.5
IMRT	15	1.8	1.0-2.4
3DCRT	9	4.2	1.1-5.7
Parallel-Opposed	24	4.7	1.5-10.5

Table 3. Mean follow-up times for patients treated with different boost techniques: BT, IMRT, 3DCRT, P-O.

DISCUSSION

This chapter analyzes the dose–volume relationships for swallowing problems (dysphagia) in oropharyngeal cancer. It particularly focuses on the relationship of swallowing disorders caused by BT as opposed to other treatment techniques that have been used over the years to boost the primary tumor. Swallowing is a complex action requiring coordination between sensory input and motor function of the swallowing apparatus [24]. Intensifi cation of therapy for head and neck cancer in general, either by altered fractionation RT schemes and/or by the addition of concomitant chemo-

EORTC H&N35: Swallowing scale (mean scores)						
Quality of Life Categories	Brachytherapy			Non-Brachytherapy		
	TF/SP	BOT	Total	TF/SP	BOT	Total
All patients	19	22	19	30	47	38
Ipsilateral Neck RT	9	No data	9	17	No data	17
Bilateral Neck RT	24	22	23	31	47	39
Ipsilateral RT + ND	10	No data	10	0	No data	0
Bilateral Neck RT + ND	21	12	22	28	40	32
Chemotherapy	12	14	13	33	42	38

Table 4. Outcome QOL for oropharyngeal cancer patients treated between 1991 and 2005 in the Erasmus Medical Center-Daniel den Hoed Cancer Center: H&N35 swallowing scale: high scores, more problems.

EORTC H&N35: Dry mouth scale (mean scores)						
Quality of Life Categories	Brachytherapy			Non-Brachytherapy		
	TF/SP	BOT	Total	TF/SP	BOT	Total
All patients	49	54	50	71	71	71
Ipsilateral Neck RT	35	33	35	78	No data	78
Bilateral Neck RT	56	55	56	33	71	71
Ipsilateral RT + ND	35	No data	35	56	No data	33
Bilateral Neck RT + ND	49	50	49	49	58	57
Chemotherapy	40	41	40	72	70	71

Table 5: Outcome QOL for oropharyngeal cancer patients treated between 1991 and 2005 in the Erasmus Medical Center- Daniel den Hoed Cancer Center: H&N35, dry mouth scale.

therapy, results in improved loco-regional tumor control [5,11,23], and increase of late sequelae, such as dysphagia [22]. In general, the prevalence of dysphagia is probably being underreported because of its (sometimes) clinically silent nature, but can be as high as 50% according to some papers on head and neck cancer survivors [4,18,19,27]. Swallowing disorders are most likely caused by radiation induced edema and neuromuscular fibrosis [18]. Consequentially, a reduced pharyngeal contraction results in an impaired bolus transport through the pharynx [8]. Some controversy exists whether the various primary disease sites have a different impact on the severity and/or frequency of dysphagia. Pretreatment swallowing therapy may improve dysphagia and reduce the need for tube feedings [10,15]. The majority of our patients had stage III and IV disease (77%). After 2000, stage III and IV patients were offered more routinely concomitant CHT. In fact, before 2000 concomitant CHT was given to 11% of the advanced-staged patients, as opposed to 48% in advanced cases after 2000. Also, as of 2000, according to protocol, RT allowed for six fractions/week as opposed to (conventionally) five fractions. Between 1991 and 2005, 336 oropharyngeal cancers were treated. The LRC, DFS, and OS of the TF and/or SP and BOT tumors, boosted by BT or by non-BT techniques, are shown in Figs. 11.1–11.3. From this series of patients, chart review revealed that roughly 31% of patients experienced moderate to severe dysphagia (RTOG grade 3 and 4). Moreover, dysphagia was more of a problem in patients with BOT (40%) cancer as opposed to patients with cancer of the TF and/or SP (26%).

When grouped by the boost technique BT vs. non-BT, severe dysphagia (problem score of QOL H&N35 with swallowingitem ≥ 50) was observed in patients with TF and/or SP tumors in 19% and for BOT tumors in 22%. For the non-BT group, severe dysphagia was found in 30% of the TF/SP tumors and in 47% for the BOT tumors (see also Tables 4 and 5). A further break down of the non-BT group with respect to the booster technique used showed severe dysphagia in 42% for P-O, 25% for 3DCRT, and 25% for IMRT (data not shown in Tables 4 and 5). Also, more complaints were reported with higher doses, in particular with regard to the superior-and medial constrictor muscles.

Figure 11.4 shows an example of the dose–effect relationship computed by logistic

PSS: Normalcy of diet						
Quality of Life Categories	Brachytherapy			Non-Brachytherapy		
	TF/SP	BOT	Total	TF/SP	BOT	Total
All patients	75	78	75	64	51	58
Ipsilateral Neck RT	84	No data	84	75	No data	75
Bilateral Neck RT	70	78	73	63	51	57
Ipsilateral RT + ND	81	No data	81	100	No data	100
Bilateral Neck RT + ND	72	78	74	75	67	72
Chemotherapy	85	98	92	58	52	54

Table 11.6. Outcome QOL for oropharyngeal cancer patients treated between 1991 and 2005 in the Erasmus Medical Center-Daniel den Hoed Cancer Center: PSS (performance status scale), item “normalcy of diet”.

MDADI (Mean scres)						
Quality of Life Categories	Brachytherapy			Non-Brachytherapy		
	TF/SP	BOT	Total	TF/SP	BOT	Total
All patients	75	74	75	59	52	55
Ipsilateral Neck RT	80	No data	80	55	No data	55
Bilateral Neck RT	71	74	72	60	52	55
Ipsilateral RT + ND	82	No data	82	81	No data	81
Bilateral Neck RT + ND	66	78	69	63	52	58
Chemotherapy	78	80	79	61	50	54

Table 7: Outcome QOL for Oropharyngeal cancer patients treated between 1991 and 2005 in the Erasmus Medical Center: MDADI (MD Anderson Dysphagia Inventory), function scale. High scores better functions;

regression. The steepness of the curve from 60 Gy, can be expressed by 20% increase/10 Gy. Furthermore, next to dose being a significant factor, other variables of importance with respect to dysphagia are treatment of the unilateral (vs. bilateral neck), and ND (see also Table 8). We speculate that this increase in dysphagia (high dose, no BT, bilateral neck irradiation, no ND) has to do with the increase in irradiated volume and radiation dose. Finally, for the same reason, xerostomia and dysphagia are also strongly correlated; that is, $p \leq 0.001$ for the parameter dose in the scm/mcm vs. the parameter dry mouth [25].

CONCLUSIONS

Overall, according to chart review, a severe degree of dysphagia (RTOG grade III and IV) was experienced in 31% of the patients. Similarly, according to responses to the EORTC H&N35 QOL questionnaires, severe dysphagia was observed in about 20% of the BT group and about 38% in the non-BT group. Univariate analysis

Quality of Life Categories	H&N35 Swallowing	PSS Normalcy of diet	MDADI Dysphagia
BT all patients vs. non-BT all patients	BT >	BT >	No data
Ipsilateral Neck RT vs. Bilateral Neck RT	Ipsilateral >	Ipsilateral >	No data
Ipsilateral Neck RT + ND vs. Bilateral Neck RT	Ipsilateral >	Ipsilateral >	No data
Chemotherapy BT vs. Chemotherapy non-BT	CHT BT >	CHT BT >	No data
TF/SP BT vs. BOT BT	TF = BOT	TF = BOT	No data
TF/SP non-BT vs. BOT non-BT	TF > BOT	TF > BOT	TF > BOT

Table 8: For some of the relevant patient/tumor characteristics, comparison between the outcome of three QOL questionnaires used in the present chapter (i.e., EORTC H&N35, PSS, MDADI).
The compared outcome data were taken from Tables 4–7. That is, the differences in sparing capacity (e.g., less problems with swallowing, better functioning in general) is based on responses to the validated QOL questionnaires EORTC H&N35 (see Table 4 item “swallowing” and see Table 5 item “dry mouth”), PSS (see Table 11.6 item “normalcy of diet”), and MDADI (see Table 11.7 item “dysphagia”).
>: better; =: equivalent; ND: neck dissection; RT: radiation therapy.

Univariate/MultivariateAnalysis							
	T-stage	Brachy therapy	Boost Treat-ment	Surgery Neck	Neck Irradia-tion	Dose scm	Dose mcm
H&N 35 Swallowing	0,005	0,006	0,012	0,012	-	<0,001	<0,001
H&N 35 Dry mouth	-	-	0,003	0,01	0,006	<0,001	<0,001
MDADI	0,018	0,002	0,026	-	-	<0,001	0,001
PSS Normalcy of Diet	-	-	<0,001	-	0,02	<0,001	<0,001

Table 9: Univariate analysis: parameters found to be signifi cant in relation to outcome of QOL questionnaires H&N35 (swallowing, dry mouth), MDADI (dysphagia) and PSS (normalcy of diet).
Multivariate analysis: the parameters of the univariate analysis found to be significant for H&N35 (swallowing), H&N35 (dry mouth), MDADI (swallowing) and PSS (normalcy of diet).
scm: superior constrictor muscle; mcm: medial constrictor muscle.

demonstrated less dysphagia for the following conditions: lower mean doses applied to swallowing muscles, BT treatment, single neck irradiation, and in case a ND is performed. The multivariate analysis shows a signifi cant effect for BT (~implicating less swallowing complaints due to the lower doses of radiation received by the swallowing muscles). For improvement of the dysphagia-related QOL, it is suggested to try and further optimize the dose distribution.

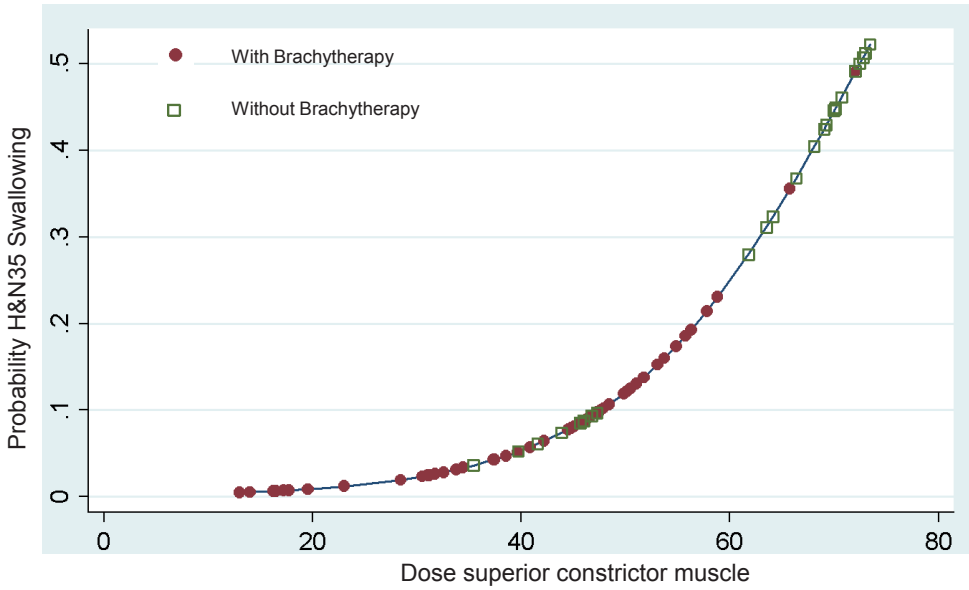

Fig. 4: Univariate dose–response relationship: for the scm, mcm, icm, cphm, and eim. The correlations of dose in these muscular structures and the absence or presence of dysphagia grade 3 and 4 combined (data set dichotomized) were calculated using logistic regressions. For example: Pr{H&N35 swallowing ≥ 50|Dose in scm} =1/(1+exp (– (a + b * Dose scm))). We calculated coefficients for a and b and p-values for testing if b = 0. This graph exemplifi es the D–E curve for the superior constrictor muscle (scm).

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11

Early Hyperbaric Oxygen Therapy for Reducing Radiotherapy Side Effects: Early Results of a Randomized Trial in Oropharyngeal and Nasopharyngeal Cancer

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ABSTRACT

Purpose: Comparison of quality of life (QoL) and side effects in a randomized trial for early hyperbaric oxygen therapy (HBOT) after radiotherapy (RT).

Methods and Materials: From 2006, 19 patients with tumor originating from the tonsillar fossa and/or soft palate (15), base of tongue (1), and nasopharynx (3) were randomized to receive HBOT or not. HBOT consisted of 30 sessions at 2.5 ATA (15 msw) with oxygen breathing for 90 min daily, 5 days per week, applied shortly after the RT treatment was completed. As of 2005, all patients received validated questionnaires (i.e., the European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30, EORTC QLQ Head and Neck Cancer Module (H&N35), Performance Status Scale): before treatment; at the start of RT treatment; after 46 Gy; at the end of RT treatment; and 2, 4, and 6 weeks and 3, 6, 12, and 18 months after follow-up.

Results: On all QoL items, better scores were obtained in patients treated with hyperbaric oxygen. The difference between HBOT vs. non-HBOT was significant for all parameters: EORTC H&N35 Swallowing ($p = 0.011$), EORTC H&N35 Dry Mouth ($p = 0.009$), EORTC H&N35, Sticky Saliva ($p = 0.01$), PSS Eating in Public ($p = 0.027$), and Pain in Mouth (visual analogue scale; $p < 0.0001$).

Conclusions: Patients randomized for receiving hyperbaric oxygen after the RT had better QoL scores for swallowing, sticky saliva, xerostomia, and pain in mouth.

INTRODUCTION

The goal of treating head and neck cancer patients with radiotherapy (RT) is to deliver high doses of ionizing radiation to the cancer (target) aiming for control of the disease and to maximally spare the surrounding normal tissues. The parotid glands are frequently protected from radiation by applying intensity-modulated radiation therapy (IMRT) techniques. The quality of life (QoL) of oropharyngeal or nasopharyngeal cancer patients treated with such high doses of RT is influenced by acute side effects, such as painful mucositis (e.g., leading to compromised food intake) and late sequelae, such as xerostomia, Grade 3/4 mucositis, trismus, and dysphagia. These non-life-threatening side effects frequently affect QoL. Recently, we have reported a dose–effect relationship for swallowing problems. Using the European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Module (H&N35) QoL questionnaire and fiberoptic endoscopic evaluation of swallowing (FEES), a significant increase in swallowing problems was reported with increasing dose [1]. Xerostomia or dry mouth syndrome results in medical and psychological problems and social distress. For example, the disorder can cause difficulties in speech, chewing, and swallowing, leading to social problems, nutritional problems, and potentially severe dental decay. Dry mouth syndrome is caused by a lack of saliva and a change in the quality of saliva by radiation damage to the major and minor salivary glands. Saliva is produced in both resting and under salivary glands stimulatory conditions. Eisbruch et al. [2], for example, have shown that limiting the mean parotid gland dose to approximately 26 Gy can preserve the parotid gland function. Although the parotid glands contribute significantly to the saliva production under stimulatory conditions, they contribute only 20% of the total volume of saliva under resting conditions, whereas submandibular salivary glands contribute 65% [3]. However, protecting the submandibular glands is far more difficult than protecting the parotid glands. Hyperbaric oxygen therapy (HBOT) is being used for treatment of late radiation tissue injury [4], but little is known whether HBOT shortly after radiotherapy can reduce radiation side effects. Recently Williamson [5] published an experimental study of the use of hyperbaric oxygen immediately after radiation treatment for malignant disease in a rat model. He reported that, in contrast to the non-HBOT rats, HBO-treated rats showed continued growth of teeth and maintenance of specialized tissues, such as salivary gland and bone in the histological sections. The potential benefit of HBOT in preventing and reducing side effects of RT or chemotherapy in oropharyngeal or nasopharyngeal cancers of the head and neck was the subject of this study. It focused on reduction of radiotherapy toxicity in treatment of oropharyngeal cancer patients with or without administration of HBOT after completion of a radiotherapy treatment schedule (table 1). Our primary study objective was to determine whether adjuvant hyperbaric oxygen would reduced RT-related side effects in primary oropharyngeal and nasopharyngeal cancer of the head and neck treated by radiation therapy. The primary endpoint was toxicity: xerostomia, dysphagia, trismus, and QoL.

METHODS AND MATERIALS

Patients

Patients presenting at the Erasmus Medical Center (Rotterdam, The Netherlands) with oropharyngeal or nasopharyngeal cancer were eligible for the trial. Patients aged > 18 with histological proof of squamous cell carcinoma of mucous membranes of the oropharynx and nasopharynx who were to be treated with curative intent and who had Karnofsky Performance Status score of ≥ 70 were included. All patients underwent dental examination before radiotherapy. The total prescribed dose of RT to the planning target volume ranged from 46 to 70 Gy. Prescribed brachythe rapy boost dose to the primary tumor ranged from 11 to 22 Gy, and prescribed Cyberknife boost dose ranged from 11.2 to 16.5 Gy. More detailed institutional treatment schedule has been described elsewhere [6,7]. The parotids received a mean dose of 6–67 Gy (median dose, 37 Gy). Written informed consent was obtained before the start of the treatment. The study was approved by the Erasmus Medical Center medical ethics board.

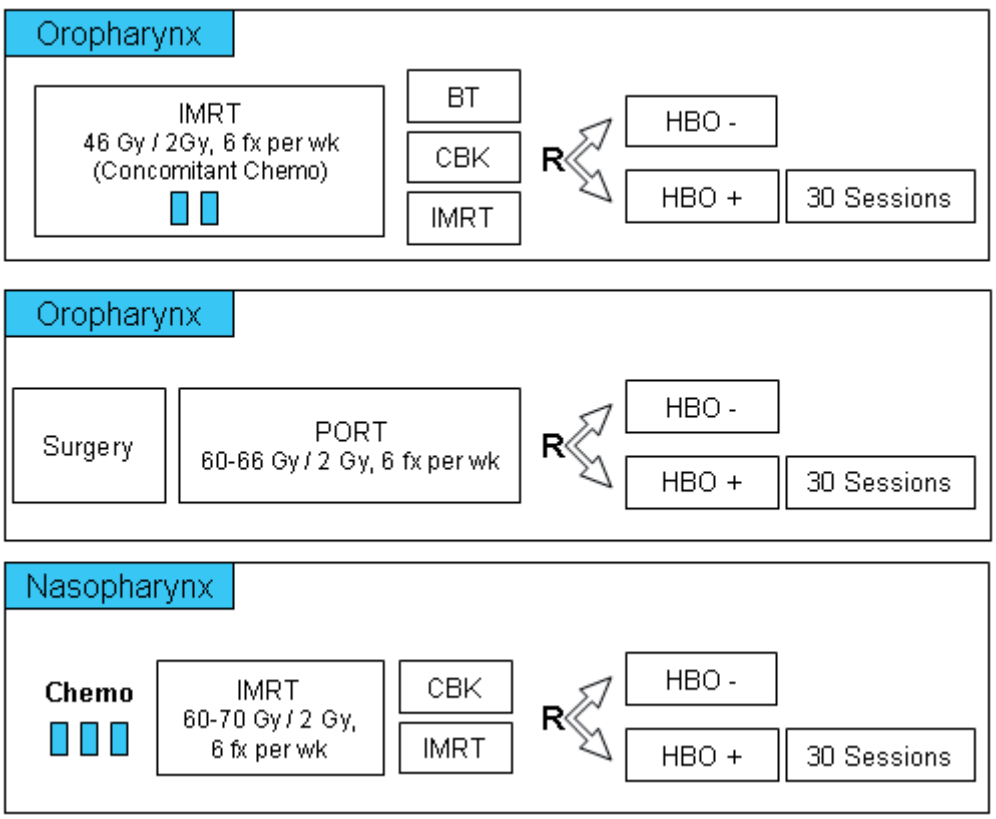

Table 1: Trial schema of the hyperbaric oxygen trial of oropharyngeal and nasopharyngeal cancer patients.
Abbreviations: IMRT = intensity-modulated radiotherapy; BT = brachytherapy; CBK = Cyberknife; HBO = hyperbaric oxygen; PORT = postoperative radiotherapy.

Hyperbaric treatment procedure

In patients randomized for HBOT, HBOT was started within 2 days after completion of radiotherapy (and chemotherapy if applicable). HBOT was given at the specialized Institute for Hyperbaric Medicine in Rotterdam in a multiplace hyperbaric chamber. The chamber was pressurized with air over 10 min to a treatment pressure of 2.5 atmospheres absolute (ATA). At this pressure, 100% oxygen was delivered by oronasal mask in three episodes of 25 min, interrupted by 5 min of air breathing, followed by a final 15-min block of oxygen. Depressurization was done on air over 10 min, resulting in an overall treatment duration of 125 min with a total of 90 min of hyperbaric oxygen breathing. This treatment schedule was followed 5 working days per week for the duration of 6 weeks, adding up to 30 total sessions. During pressure changes, great care was taken to avoid barotraumas, particularly of the middle ear, which is the most common side effect of hyperbaric treatment.

Randomization

Patients were randomized by the trial office. This randomization took place directly after inclusion of the patients in the study by use of a block of several randomized sizes. Patients were stratified by tumor site (i.e., oropharynx or nasopharynx) and treatment modality (i.e., IMRT or Cyberknife/Brachytherapy or postoperative radiotherapy).

Quality of life

For QoL investigation, all patients were given the following questionnaires: (1) The EORTC core QoL Questionnaire (QLQ)-C30, (2) The EORTC QLQ-H&N35 [8], and (3) the Performance Status Scale (PSS) of List et al. [9] with the normalcy of diet item. Patients also used a visual analogue scale (VAS; 0–10) to rate their dry mouth and pain. At the time points 0 (before treatment), 1 (start of treatment), 2 (46 Gy), 3 (end of treatment), 4 (2 weeks posttreatment, 5 (4 weeks posttreatment), 6 (6 weeks posttreatment), 7 (3 months posttreatment), 8 (6 months posttreatment), 9 (12 months posttreatment), and 10 (18 months posttreatment), questionnaires were sent to the patients by mail. After scoring, the questionnaires were returned to the data manager (table 2).

Statistical analysis

The sample size of this trial was based on a reduction of xerostomia of 50% to 25% at 1 year after starting treatment if HBOT was used, which meant that 2 × 66 patients (alpha = 0.05, two-sided; beta = 0.80) were needed to be included. A robust regression analysis was performed with the responses to the QoL questionnaires at the various time points (Table 2). Further, differences (p values) for the hyperbaric oxygen vs. control group were computed at time cohorts before radiotherapy (t = 0), at the end of radiotherapy and until 13 weeks posttreatment (t = 3 through t = 7), and during the time periods of 13 weeks until 78 weeks post treatment (t = 7 until t = 10). At t = 0, a Mann-Whitney U test was used. For the other two time cohorts, regression analysis for each complaint variable vs. time (coded with dummy variables) and treatment factor (yes/no hyperbaric oxygen) were performed with the program xtreg in Stata. This was a regression analysis based on maximum likelihood estimation

List number	Time point
0	Before treatment
1	Start treatment
2	Mid treatment (46 Gy)
3	End treatment
4	2 weeks post-treatment
5	4 weeks post-treatment
6	6 weeks post-treatment
7	3 months post-treatment
8	6 months post-treatment
9	12 months post-treatment
10	18 months post-treatment

Table 2: Time points corresponding to the quality of life list numbers.

and incorporating the longitudinal character of the data. Stata 9 software was used for the statistical analysis (Stata Statistical Software, Release 9; StataCorp, College Station, TX).

RESULTS

Because of slow accrual and lack of financial support, the trial was stopped at a premature time point, with only 19 patients eligible to be studied for the effect of hyperbaric oxygen. All patients included in the tri al were analyzed to this effect. Patient characteristics are shown in table 3. At the censor date of March 1, 2008, with first patient included at the beginning of 2006, maximum follow-up time was 78 weeks. Results regarding xerostomia-related questionnaires are shown in figure 1, figure 2 and figure 3. A significant difference in the HBOT group compared with the non-HBOT-treated control group was found for the sticky
saliva and dry mouth items of the EORTC H&N35 questionnaires and the VAS dry mouth item. The mean scores for the VAS dry mouth item per time point are given in Table 4. The p values were calculated by dividing the sequence of toxic events in an acute phase (end of radiation until 13 weeks posttreatment) and a late side effects phase (from 13 weeks until 78 weeks posttreatment). The differences in QoL scoring were not significant in the acute phase; however, late side effects were significantly reduced for the HBOT group (figure 1). For dysphagia-related questionnaires, there was also a significant difference in QoL between patients treated vs. not treated with hyperbaric oxygen (figure 4 and figure 5). The mean QoL scores for the EORTC H&N 35 swallowing item, per time point, are shown in table 5. The VAS score for pain in mouth between the with- and without-HBOT groups was also significantly different, as shown in figure 6. The following p values were established for EORTC

	HBO +	HBO -
Number	8	11
Tumor site		
Tonsillar Fossa	6	9
Base of Tongue	1	0
Nasopharynx	1	2
Male / Female	6 / 2	6 / 5
TNM stage		
T1	2	2
T2	5	3
T3	1	4
T4a	0	2
N0	3	3
N1	0	2
N2a	0	1
N2b	4	2
N2c	0	2
N3	1	1
Stage grouping		
I	0	1
II	3	2
III	4	6
IV	1	2
Chemotherapy	3	5
Boost		
No	3	6
Brachytherapy	4	2
Cyberknife	1	3
Bilateral Neck	1	1

Table 3: Patient characteristics tableAbbreviation: HBO = hyperbaric oxygen.

H&N35 sticky saliva ($p = 0.01$), EORTC H&N35 dry mouth ($p = 0.009$), EORTC H&N35 swallowing ($p = 0.011$), PSS eating in public ($p = 0.027$), and VAS Pain in mouth ($p < 0.0001$). HBOT side effects were limited in our patients. HBOT was well tolerated in this group of patients.

DISCUSSION

When radiation is used to treat cancer, it also (partly) affects a variety of critical

surrounding normal tissues, which can become hypocellular, hypovascular, and hypoxic, frequently eluded to as “3 H tissue.” The hypoxic status of tissues can be counteracted to some extent by oxygenation of normal cells with HBOT. The effects of hyperbaric oxygen can be briefly summarized as follows: short-term effects are enhanced by oxygen delivery, reduction of edema, and phagocytosis activation, as well as anti-inflammatory effects. Long-term effects are neovascularization, osteoneogenesis, and stimulation of collagen formation by fibroblasts [10]. It was recently found that a significant increase in mobilization of stem cells from the bone marrow occurs in the course of HBOT [4,11]. Wound healing and recovery of normal-tissue radiation injury are the end result [12-14]. It has been demonstrated that hyperbaric oxygen administration reaches its optimal effect after 24–30 sessions for neo-angiogenesis, and stem cell mobilization is particularly prominent after 20 treatments [11]. Therefore, in our study, we applied 30 sessions. It could be that 20 sessions are sufficient to reduce side effects. This remains to be elucidated in future studies.

Clinically, hyperbaric oxygen has shown beneficial effects, for example, in hypoxic ulcers that result in severe wound-healing problems and in osteoradionecrosis [4]. HBOT has been used for 40 years in combination with conservative treatment and radical surgery for necrotic soft tissues and bone that fail to heal.

Although there are some conflicting experimental results [15], it is now believed that HBOT does not promote cancer growth (primary or metastasis). Moreover, according to Feldmeier et al. [16], no evidence indicates that hyperbaric oxygen is an initiator or promotor of cancer de novo. According to Schonmeyr et al. [17], no difference of cellular proliferation of squamous cell cancer in vitro was observed comparing hyperbaric oxygen–treated cells with controls. In a study by Marx et al. [18], HBO induced significantly angiogenesis, measurable after eight HBOT sessions. Recently, Gerlach et al. [19] published a retrospective study on the use of HBOT in clinic; they described 21 patients who received radiotherapy for oral or oropharyngeal carcinoma in which swallowing-related problems significantly decreased with time. They also observed a subjective increase in saliva and an improvement in sense of taste. In a review by Bennett et al. [4], the authors concluded that there is some evidence that hyperbaric oxygen improves outcomes in late radiation tissue injury affecting bone and soft tissues of the head and neck, for proctitis, and to prevent the development of osteoradionecrosis following tooth extraction in an irradiated field. A large double-blind randomized study has shown the substantial benefit of HBOT on QoL in chronic refractory radiation proctitis [20]. In contrast to our study, these publications are concerned with the use of HBOT in late radiation tissue damage. The possible preventive action of HBOT immediately after radiotherapy has not been addressed, which was the purpose for our study.

We found a significant difference in several QoL aspects between patients in whom early hyperbaric oxygen was administered vs. a non-HBOT group. Five to 18 patients responded to the questionnaires at each time point. Although there was variation in response to the questionnaires at each time point, comparison of the groups at the various time points appeared to be nonsignificant (Mann-Whitney U test; $p = 0.84$). Clearly, the QoL of patients is similar until the end of radiation or in the 2

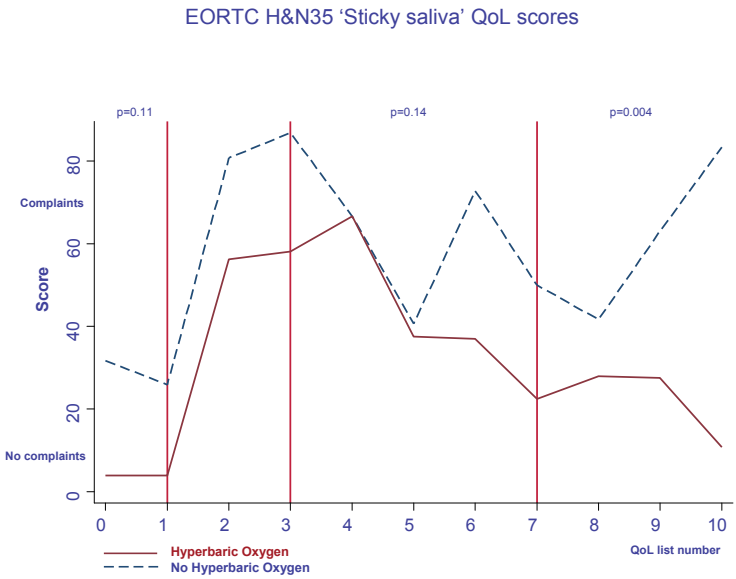

Figure 1: European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Module (H&N35) sticky saliva item scores between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

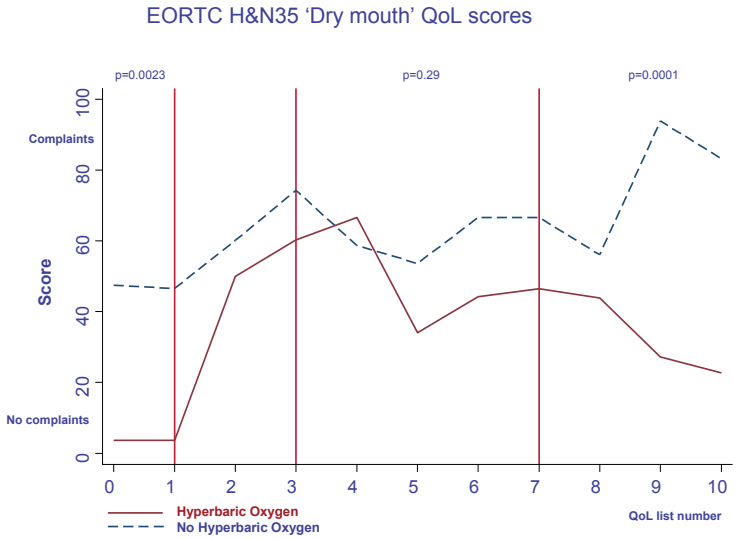

Figure 2: European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Module (H&N35) dry mouth item scores between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

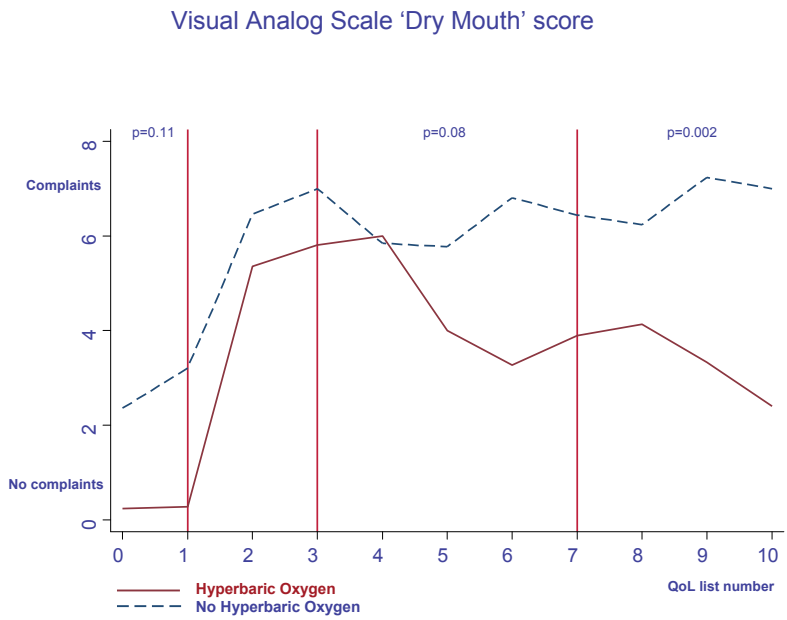

Figure 3: Visual analog scale of the dry mouth between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

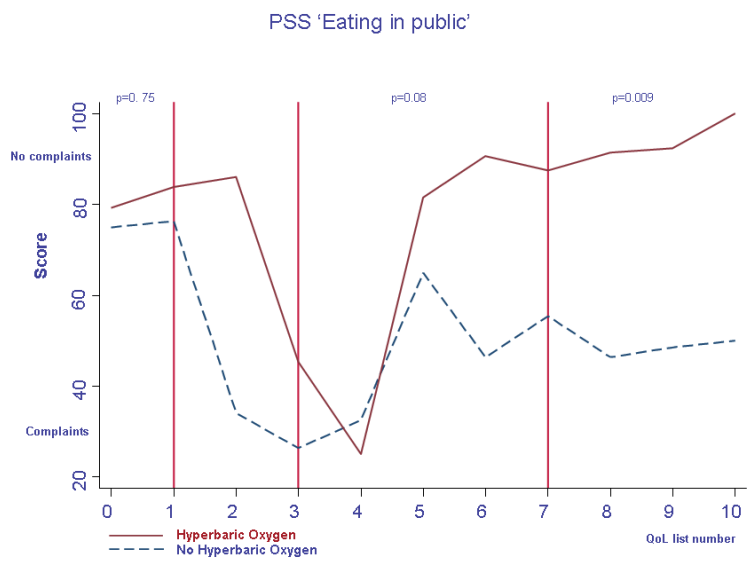

Figure 4: Performance status scale (PSS) eating in public item scores between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

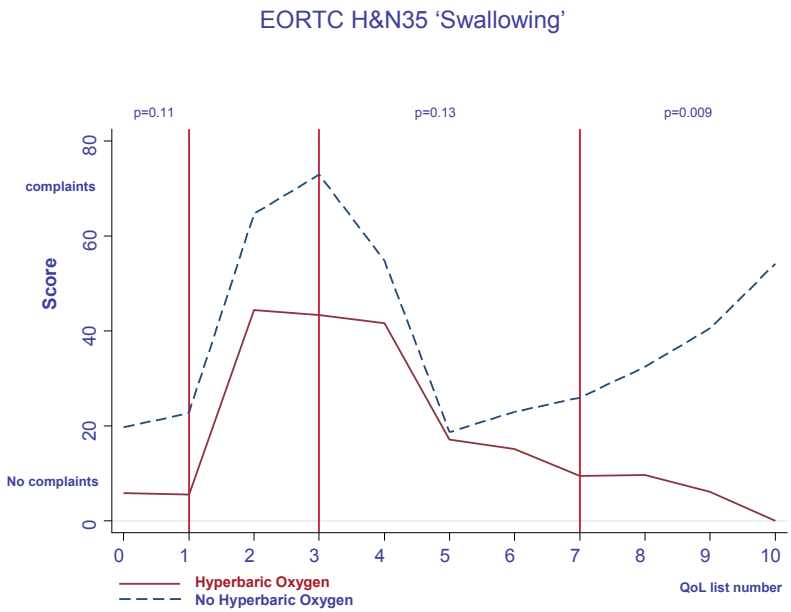

Figure 5: European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Module (H&N35) swallowing item scores between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

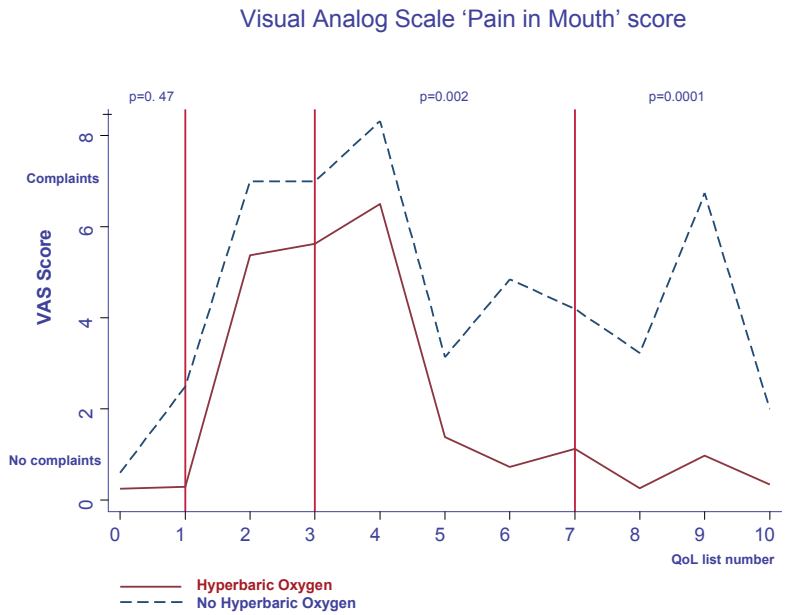

Figure 6: Visual analog scale of the pain in mouth question between the hyperbaric oxygen–administered group of patients and the group that was not administered hyperbaric oxygen over an 18-month period. QoL = quality of life.

List number	HBO	No HBO	Total group
0	0	3	2
1	0	3	2
2	5	6	6
3	6	7	6
4	6	6	5
5	5	6	6
6	4	7	5
7	4	6	5
8	4	6	5
9	4	7	4
10	3	7	5

Table 4: Mean quality of life score for visual analog scale dry mouth at the different time points. Abbreviation: HBO = hyperbaric oxygen.

List number	HBO	No HBO	Total group
0	7	25	17
1	6	28	18
2	45	59	53
3	42	56	48
4	42	52	48
5	19	19	19
6	15	33	27
7	10	30	21
8	12	33	24
9	7	40	20
10	0	54	22

Table 5: Mean quality of life score for EORTC H&N35 swallowing item at the various time points. Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; H&N35 = Head and Neck Cancer Module; HBO = hyperbaric oxygen.

period within 2 weeks after radiation. The worst scores on the QoL items (patient complaints) were found at the end of radiation or in the period within 2 weeks after completion of radiation. A significant difference was observed for the EORTC H&N35 dry mouth question (figure 2), that is, baseline values for the patients treated with HBO and those not treated. However, we could not identify confounding factors to explain this difference. One possible reason for this is that some patients who knew they were not going to receive HBOT after radiation could argue that they must have a dry mouth to some extent because the purpose of the investigation was to investigate potential successful treatment of xerostomia with HBOT. Increased QoL in patients treated with hyperbaric oxygen showed a steep improvement beginning 2

weeks after finishing RT. This was found to be particularly true for the data in our study regarding xerostomia and dysphagia. Pain (VAS score) was also almost totally eliminated (no pain 6 weeks posttreatment). Of interest is the fact that no significant effect of hyperbaric oxygen was shown for early side effects (see figure 1, figure 4 and figure 5; time cohort 3 until 7 (≤ 13 weeks) as opposed to the late side effects (≥ 13 weeks posttreatment). Patients undergoing HBOT are probably aware that the treatment under study consisted of hyperbaric oxygen, with the reverse being true for those not receiving HBOT; however, we do not believe that patients filling in the questionnaires after 18 months maximum follow-up are biased by the treatment. Nevertheless, a placebo effect could not totally be disproved.

CONCLUSIONS

A significant difference was observed between the non-HBOT vs. HBOT groups in almost every QoL issue studied. Although this study is limited by the small numbers of patients, we feel that the data are of interest because they emphasize the potential beneficial effect of early hyperbaric oxygen. Several issues remain to be explored. It is of interest to determine the optimal commencement of HBOT after radiation therapy as well as the necessary number of treatments. Also, the mechanisms through which HBOT shortly after radiotherapy cause the demonstrated beneficial effects on QoL should be further explored. Because questions remain regarding HBOT after radiotherapy, a bigger randomized trial should be conducted to answer the remaining questions.

Acknowledgments

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12

Local Anatomic Changes in Parotid and Submandibular Glands during Radiotherapy for Oropharynx Cancer and Correlation with Dose, Studied in Detail with Nonrigid Registration.

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ABSTRACT

Purpose: To quantify the anatomic changes caused by external beam radiotherapy in head-and-neck cancer patients in full three dimensions and to relate the local anatomic changes to the planned mean dose.

Methods and Materials: A nonrigid registration method was adapted for RT image registration. The method was applied in 10 head-and-neck cancer patients, who each underwent a planning and a repeat computed tomography scan. Contoured structures (parotid, submandibular glands, and tumor) were registered in a nonrigid manner. The accuracy of the transformation was determined. The transformation results were used to summarize the anatomic changes on a local scale for the irradiated and spared glands. The volume reduction of the glands was related to the planned mean dose.

Results: Transformation was accurate with a mean error of 0.6 ± 0.5 mm. The volume of all glands and the primary tumor decreased. The lateral regions of the irradiated parotid glands moved inward (average, 3 mm), and the medial regions tended to remain in the same position. The irradiated submandibular glands shrank and moved upward. The spared glands showed only a small deformation (not, vert, similar1 mm in most regions). Overall, the primary tumors shrank. The volume loss of the parotid glands correlated significantly with the planned mean dose ($p < 0.001$).

Conclusion: General shrinkage and deformation of irradiated glands was seen. The spared glands showed few changes. These changes were assessed by a nonrigid registration method, which effectively described the local changes occurring in the head-and-neck region after external beam radiotherapy.

INTRODUCTION

Technical improvements in dose delivery and verification of patient positioning have widened the therapeutic window for radiotherapy (RT) of head and neck cancer [1-6]. For example, intensity-modulated RT makes it possible to escalate the dose by conforming the high-dose region tightly to the target volume, thereby sparing adjacent normal tissue. In-room imaging devices, such as cone beam computed tomography (CT) scanners or CT on rails, allow for the assessment of nonrigid setup errors in head-and-neck cancer patients [7-10]. Currently, computer-aided dose optimization is determined from a single CT scan acquired before the start of treatment. During treatment, significant anatomic changes, including shrinkage of the primary tumor and nodal masses and changes in overall body habitus, have been observed [11-13]. These changes can cause deviations between the planned and delivered dose and might partly undo the benefits of intensity-modulated RT [14-16].

To date, mostly global measures, such as volume and position changes, have been used to quantify the anatomic changes [11,14]. Using a repeat CT study, Robar et al. [17] reported the systematic medial translation of the lateral regions of the parotid glands. This analysis was based on two selected points, one on the lateral and one on the medial border of the gland. In our study, a nonrigid registration method [18] was adapted and used to quantify local soft-tissue changes in 10 head-and-neck cancer patients using two CT scans: the planning CT scan and a repeat CT scan after 46 Gy of external beam radiotherapy (EBRT). This method allows for soft-tissue changes to be assessed in full three dimensions (3D). The shape and position changes of the primary tumor and the parotid and submandibular glands were quantified. After nonrigid registration, the glands were divided into irradiated glands, belonging to a treated neck, and spared glands, belonging to a nontreated neck. On the basis of these registrations, in both groups, the changes in shape and position during EBRT were summarized on a local scale by dividing each organ into six regions. Furthermore, the volume changes in the parotid and submandibular glands were related to the planned mean doses.

METHODS AND MATERIALS

Patient data

A total of 10 consecutive oropharyngeal patients, 5 men and 5 women, aged 48–83 years (mean, 60 years), who were treated between November 2004 and December 2005, were included in this study. The patient characteristic are listed in Table 1. The patients first underwent EBRT to a total dose of 46 Gy in 23 fractions (dynamic intensity-modulated RT), followed by a brachytherapy boost (20–22 Gy) [19-21]. Two intravenous contrast-enhanced CT scans were available for each patient, the planning CT scan and a repeat CT scan taken with the patient in the treatment setup position 2 weeks after the end of the EBRT (post-EBRT CT scan). A Posicast mask was used for immobilization during all CT scanning and treatment fractions. The slice spacing was 3 mm for the planning scan and 1.5 mm for the post-EBRT scan. Before the nonrigid registration, the CT scans were first rigidly matched using the bony anatomy

in the region of interest. The primary tumor and parotid and submandibular glands were manually contoured in both CT scans. For consistency, the post-EBRT CT scan was delineated, using the planning CT scan as a reference. All delineations were checked by a second observer. The delineated contours were used to create surfaces. These surfaces were defined by a set of triangles joining contours in the consecutive slices.

Bilateral neck treatment incded both necks; unilateral neck treatment included only ipsilateral neck, which was always located on right side; Patient 6 received concurrent chemotherapy.

Pt. no.	TNM classification	Neck treatment	Site
1	T1N2cM0	Bilateral	Base of tongue
2	T3N2aM0	Bilateral	Base of tongue
3	T2N1M0	Unilateral	Tonsillar fossa
4	T2N0M0	Unilateral	Tonsillar fossa
5	T2N0M0	Unilateral	Soft palate
6	T3N2aM0	Bilateral	Base of tongue
7	T2N0M0	Unilateral	Tonsillar fossa
8	T1N1M0	Unilateral	Tonsillar fossa
9	T3N3M0	Bilateral	Base of tongue
10	T1N2cM0	Bilateral	Base of tongue

Table 1: Patient characteristics. Abbreviation: Pt. no. = patient number.

Nonrigid registration method

A point-based method for nonrigid registration, known as Thin Plate Splines–Robust Point Matching or TPS-RPM, was modified [18,22]. This method handles the nonrigid registration as a nonrigid point matching problem on which the correspondence and the transformation between two points sets, called in this report the “reference” and “deforming” point sets, are optimized iteratively. We generated sets of points based on the 3D surface of each delineated structure (Fig. 1, Step 1, and Fig. 2a,b). These points defined the boundaries of the structures in the method, and they were distributed nearly homogeneously over the surface using a mean distance of 3 mm. The points were placed within the triangles that described the 3D surfaces. The distance was chosen so that the accuracy of the transformation was adequate to quantify the observed shape and position changes without exceeding the computational resources. Note, the generated points were not restricted to the axial planes of the CT scans.

The iterative process for generating the transformation function is driven by determi-

nistic annealing (Fig. 1, Step 2). This results first in a global and rough approximation and, later, in a local and detailed deformation.

Each cycle of the process consists of two steps: (1) fuzzy correspondence estimation based on the position of the points, and (2) transformation update based on the correspondence. At the end of each cycle, the positions of the deforming points are transformed by the newly found transformation. The annealing process controls the search range allowed to create the correspondence between the reference and the transformed deforming point sets (global-to-local strategy). At first, every deforming point is allowed to correspond to all reference points (global fuzzy correspondence). Gradually, the search range is decreased; as a consequence, only deforming and reference points in close proximity were allowed to correspond. Because the number and precise distribution of the points of the reference and deforming sets are, in general, different, no binary one-to-one correspondence is expected to exist between the points of both sets. The correspondence between points is therefore not forced to reach a one-to-one state but is limited by the mean distance between the nearest neighbors of the deforming points. A pseudoclustering was implemented to, up front, avoid the correspondence of points between different organs. The final transformation T transforms the deforming point set to resemble the shape of the reference point set (Fig. 1, Step 3). When the roles of the reference and deforming point sets are switched in the process, a back-transformation, BT, is generated.

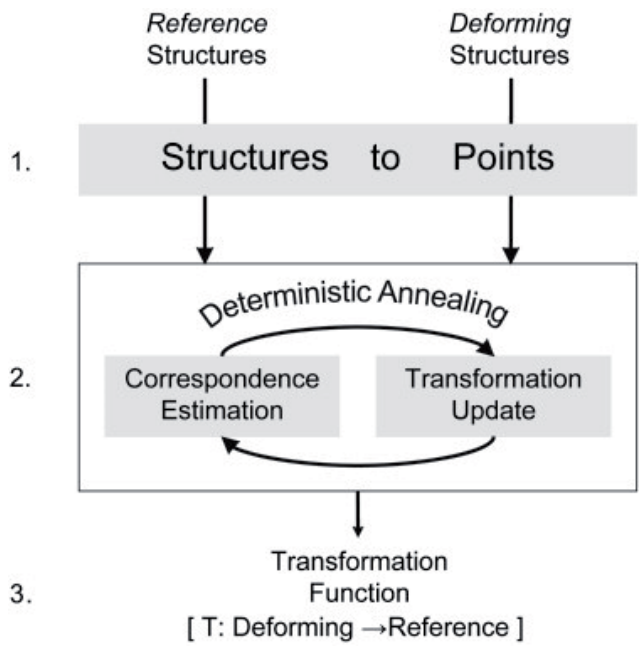

Fig. 1. Process workflow. Step 1: Generation of points based on input structures' surfaces. Step 2: Nonrigid registration for generating the transformation function. Step 3: Application of generated transformation T to align deforming and reference structures.

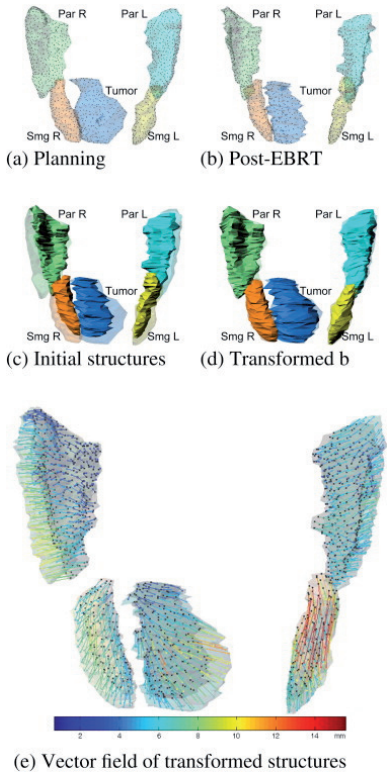

Fig. 2: Illustration of steps of transformation process for 1 patient (bilateral neck treatment). (a,b) Structures and control points. (c,d) Overlapping structures before and after transformation. Transparent colors, planning; solid colors, post-EBRT. (e) Transformed points (as vectors), organs are separated for visualization. Par R/L = parotid right/left; Smg R/L = submandibular right/left.

For the final analyses, we created refined surfaces based on the original surfaces. The triangles defining the surfaces were subdivided in smaller triangles, such that their edge length was, on average, 1.3 mm. Note, the refined surfaces were identical in shape to the original surfaces, but they contained more vertices, and these vertices distributed nearly homogeneously.

Patient data analyses

The parotid and submandibular glands were divided into two groups defined by the neck treatment: irradiated glands, belonging to treated neck, and spared glands, belonging to the nontreated neck. Note, for each gland type, the irradiated glands included five left and five right glands from the bilateral neck treatment and five right glands from the ipsilateral neck in the unilateral neck treatment. The spared glands included five left glands from the contralateral neck in the unilateral neck treatment. The volume changes after treatment were measured. In addition, the volume changes of the glands were related to the planned mean dose in the organs.

A transformation T (Fig. 2d,e), and back-transformation BT were generated for each patient. Note, T and BT were determined for the glands and tumor of each patient simul-

taneously, and not for each organ separately. To report the shape and position changes on a local scale, the refined surfaces of each organ were divided into six regions (Fig. 3). The vertices of the refined surfaces were transformed and back-transformed using the transformations obtained per patient. To compare and process the results of the transformation and back-transformation in the same frame of reference, the direction of the resulting displacements of one of the transformations must be inverted (back-transformation in this study). For each of the six regions of an organ surface, all displacements resulting from T and BT were collected, and for each directional component (right–left, anterior-posterior, and inferior-superior), the average displacement was calculated for each organ region per patient. The displacements per region were then averaged for the patient group, and standard deviations were calculated. Next, results of T and BT were averaged per region. Finally the length of the mean 3D displacement vector was calculated for each region on the basis of the average values of the directional components. These lengths and their corresponding standard deviations, describing interpatient variations, are reported. Note, the changes determined from the nonrigid registration account for the deformation and shifts of the glands.

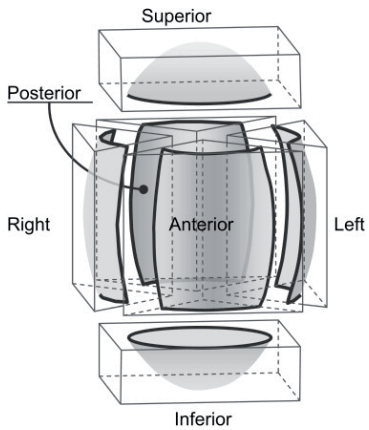

Fig. 3: Division in six regions for simple ellipsoid. Right, left, anterior, posterior, superior, and inferior subvolumes shown. Superior and inferior boxes contain 20% of total volume of bounding box. Four wedges define remaining (central) volumes. Each subvolume gathers approximately 17% of total number of organ surface vertices.

Accuracy of nonrigid registration

The transformation accuracy measures the misalignments between the transformed deforming surface and the reference surface (Fig. 2d). To quantify the transformation accuracy, the distance from each vertex of the transformed refined deforming surface to the closest triangle on the reference surface was measured, and its mean value is reported. There is no explicit drive in the method that makes the back-transformation BT to be the inverse of the original transformation T; however, because the input points are the same, this behavior can be expected. Equivalence, or near equivalence, of the back-projection and the inverse of the original transformation is a minimal condition for application. This equivalence was expressed by the distance between a point and the same point after it was transformed and back-transformed

(Fig. 4). In detail, a point P (on the surface) is transformed by the original transformation T(P) = PT. The transformed point PT is then back-transformed BT(PT) = P'. The distance equivalence d between P and P' was measured and reported. Note, the distance d also accounts for surface misalignments (because of transformation inaccuracy). When T and BT are inverse functions of each other and the misalignment is zero between the transformed and reference surface, P' and P are mapped to the same position, and d is zero.

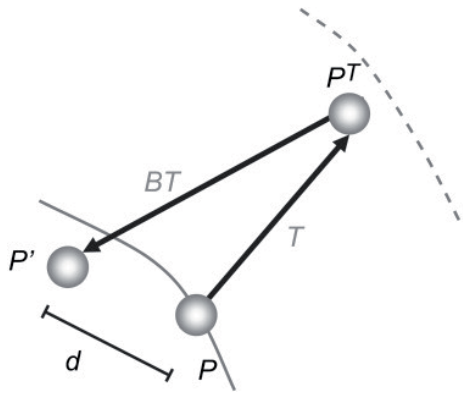

Fig. 4: Schematic drawing of transformation and back-transformation of point P. PT = T(P) is transformed P using transformation T; P' = BT(PT) is the back-transformed PT using back-transformation BT. d is distance between P and P'. Distance d is zero when T and BT are inverse function of each other, with no misalignment between transformed and reference surfaces. Solid line represents deforming surface and dashed line, reference surface.

RESULTS

Figure 5 shows the anatomic changes for one of the patients who underwent bilateral neck treatment after EBRT. The space between the skin and mask in Fig. 5b clearly shows anatomic changes possibly caused by weight loss. Also visible is the shrinkage and displacement of the contoured organs and tumor (Fig. 5b) compared with the planning CT scan (Fig. 5a). Fig. 5c shows the transformed contoured structures of the planning CT scan together with the post-EBRT structures. The transformed planning structures (red shadow) and the post-EBRT structures (yellow contours) overlapped accurately.

In all patients, the transformation accuracy (surface misalignment between the reference and transformed deforming surfaces) was small, with an average mean distance of 0.6 ± 0.5 mm. These values were independent of organ or direction of the transformation (planning as reference and post-EBRT as deforming surfaces or vice versa). The average equivalence distance d (Fig. 4) was also small (1.5 ± 0.7 mm).

Volume reduction

All glands and primary tumors showed a significant reduction in volume. In the primary tumors, the volume reduction was 25% ± 15% compared with its original volume ($p < 0.001$, t test). Volume reductions, as well as the average planned

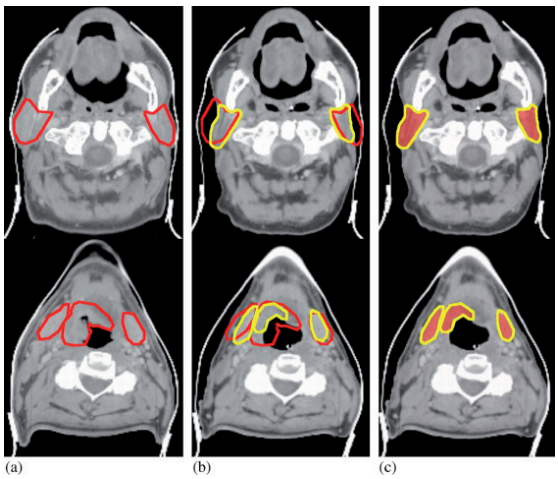

Fig. 5: Example of observed shape and position changes for head-and-neck patient (bilateral neck treatment). (Upper) Parotid glands and (Lower) submandibular glands and primary tumor. (a) Planning computed tomography (CT) scan and delineated structures in red. (b) Post-external beam radiotherapy (EBRT) CT scan with planning (red) and post-EBRT CT scan (yellow) delineations. (c) Post-EBRT CT scan with delineated structures (yellow) and transformed planning structures (red shadow).

mean doses, of the parotid and submandibular glands are summarized in Table 2. The volume reduction for irradiated glands was significantly larger than the volume reduction of the spared glands ($p < 0.001$ for the parotid and $p = 0.05$ for submandibular glands, t test). Also, in the unilateral patients only, the volume reduction of the irradiated, or ipsilateral, glands was significantly larger than the volume reduction of the spared, or contralateral, glands ($p = 0.02$ for parotid and $p = 0.001$ for submandibular glands, paired t test). No statistical difference was found in the volume reduction of the irradiated glands in patients with unilateral or bilateral neck treatment ($p = 0.6$, t test).

When correlating the volume changes with the planned mean doses, a significant relation was found for the parotid glands ($p < 0.001$, $r = 0.68$, linear regression ana-

Gland	Volume loss (%)	p-value	Planned mean dose (Gy)
Parotid glands			
Irradiated	17 ± 7	<0.001	25.15 ± 6.45
Spared	5 ± 4	0.04	6.97 ± 3.49
Submandibular glands			
Irradiated	20 ± 10	< 0.001	45.62 ± 1.87
Spared	11 ± 7	0.03	4.65 ± 2.49

Table 2: Volume reduction with respect to original volume and planned mean dose for irradiated and spared glands. Data presented as mean ± standard deviation.

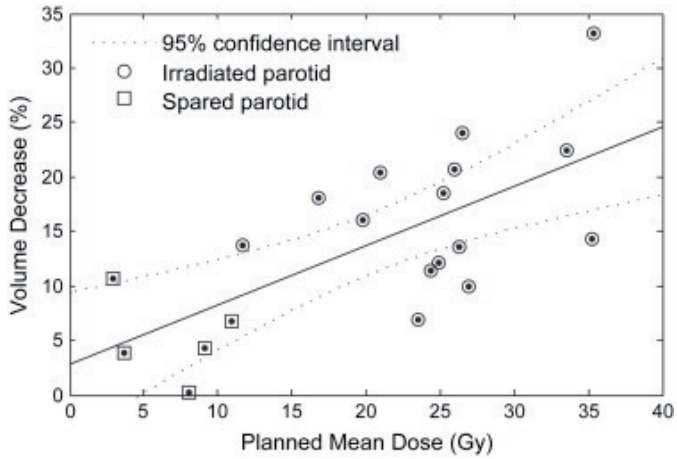

Fig. 6. Volume changes vs. planned mean dose for parotid glands. Solid line indicates linear regression ($p < 0.001$, $r = 0.68$).

lysis; Fig. 6). No significant relation was found for the submandibular glands ($p = 0.14$, $r = 0.35$).

Local shape and position changes

The measured average deformations and standard deviation for all 10 patients are shown schematically in Fig. 7. The left side of Fig. 7, the solid line, represents the irradiated glands; the contralateral glands belonging to the irradiated group were mapped on the left side of Fig. 7. The spared glands are represented on the right side with the dashed line. The front view (Fig. 7b) shows the four glands and the displacement of each visible region after EBRT. Figure 7a shows the right view (posterior-anterior and inferior-superior projection) of the irradiated glands. Figure 7c shows the left view (anteroposterior–inferosuperior projection) of the spared glands. The arrows represent the direction of the displacement of each region in each pro-

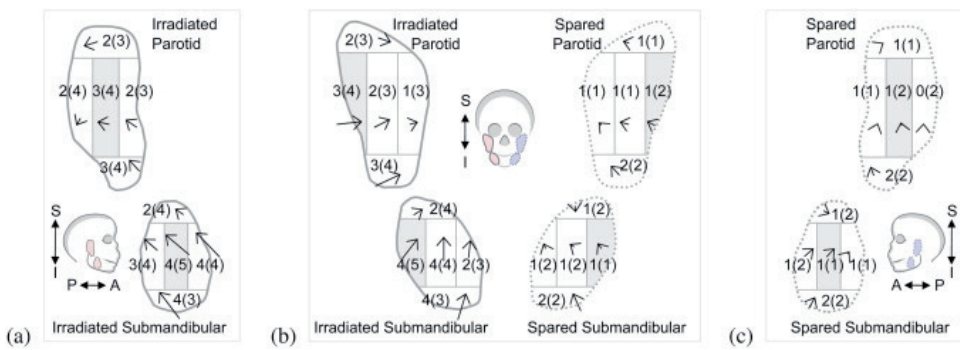

Fig. 7: Three-dimensional (3D) lengths of average 3D vectors and standard deviations for each region in millimeters. Arrows show projection of average 3D deformation vectors in (a) right, (b) frontal, and (c) left views. Solid lines represent irradiated glands (15 parotid and submandibular glands); dashed lines represent spared glands (5 parotid and submandibular glands). External lateral walls of glands represented with gray shadows.

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jection. The values are the average 3D displacements in millimeters with standard deviations, when the average was taken for the patient group. The gray areas represent the external lateral walls of the glands.

Shape and position changes of parotid glands

The shape and position changes in all six regions of the irradiated parotids were significantly larger than the changes in the spared parotids group (maximal $p = 0.02$, t test per region; Fig. 7). Within the unilateral group, the shape and position changes between the ipsilateral parotid glands were, on average, larger than the shape and position changes of the contralateral glands, but the differences were not statistically significant. In the irradiated group, the parotid glands shrank, keeping the regions nearby to bony anatomy as an anchor. All regions showed a tendency to move inward (right parotid leftward and left parotid rightward). The largest displacements were in the lateral and inferior regions. The region that moved the least was the medial region (partially adjacent to the bony structure). Spared parotid glands showed translations of about 1 mm for the superior, lateral, and anterior regions, all in a similar direction (inward and upward). The posterior region showed zero mean displacement, and the inferior region showed the largest displacement. Figure 8 shows the scans of a patient who underwent unilateral EBRT, on which the asymmetric shrinkage of the parotids is visible (Fig. 8b). The nonsymmetric change in the space between the skin and mask is clear.

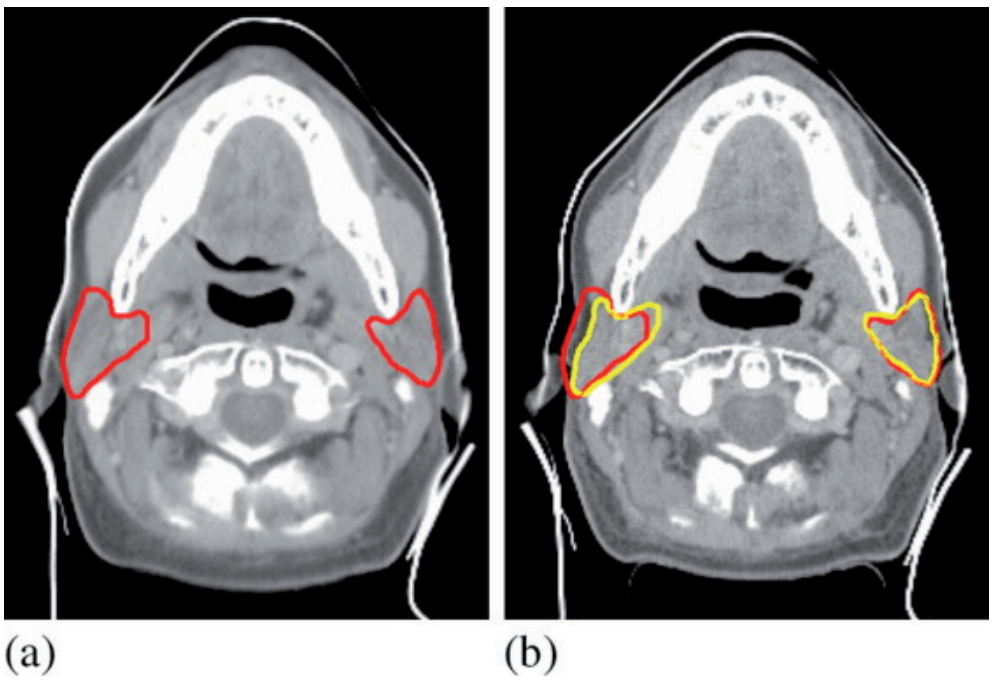

Fig. 8. Patient with unilateral irradiation (right neck). (a) Planning computed tomography scan. Red contours indicate parotid glands. (b) Computed tomography scan after external beam radiotherapy. Yellow contours indicate parotid glands after treament; red contours, parotid glands before treatment.

Shape and position changes of submandibular glands

The shape and position changes in most regions of the irradiated submandibular glands were significantly larger than the changes in the spared submandibular group (border line significance, $p = 0.06$ for the medial region, maximal $p = 0.05$, t test for other regions; Fig. 7). In the unilateral group, the shape and position changes between the ipsilateral and contralateral glands were not significantly different. In the irradiated group, the submandibular glands shrank and moved upward. The regional displacements in these structures were directed mostly superiorly and posteriorly. The superior and medial regions moved the least. The rest of the regions presented a displacement of between 3 and 4 mm. All regions of spared submandibular glands displaced approximately in the same direction as the irradiated glands. The magnitude, however, was much smaller: 1–2 mm.

Shape and position changes of primary tumor

The results for the clinical target volume should be interpreted with care owing to the uncertainty related to its localization and the variability of the tumor sites included in the study. The clinical target volume presented a general shrinkage with a pronounced reduction in the posterior region (4 ± 4 mm), mostly in the anterior direction. The displacements in the left region were 3 ± 4 mm rightward. The region that moved the least was the right region (1 ± 3 mm). The other regions moved about 2 mm.

DISCUSSION

The presented nonrigid registration method is a powerful tool to accurately assess local shape and position changes in head-and-neck patients. The measurement accuracy of such changes was determined by the inherent accuracy of the method, as well as the accuracy and precision of the contouring by the physician. The inherent accuracy was investigated by assessing the transformation accuracy, and the equivalence of the inverse transformation T^{-1}, with its corresponding back-transformation BT (expressed as the equivalence distance d). The transformation accuracy, defined as the mean distance between the reference surfaces and corresponding transformed deforming surfaces, was 0.6 ± 0.5 mm. The observed small values for d (1.5 ± 0.7 mm) confirmed that T^{-1} and BT are nearly equivalent, which is a minimal requirement for clinical application. The displacements found for the spared glands had magnitudes in the order of the error of the method.

In an attempt to keep the systematic component of the delineation error small, in this study, the same person delineated both CT scans. Moreover, the planning CT scan was always used as a reference for post-EBRT CT scan delineation. However, some random variations in the contouring of both CT scans were still present. The uncertainty related to contouring mainly affects the clinical target volume, because the contrast between the tumor and its surrounding tissues is very low.

When the found transformation was applied to CT scans, a good alignment between the transformed structures and original contours was found. One should note that the nonrigid registration was controlled by the point sets on the surfaces of the organs. Therefore, the accuracy of the transformation is decreased outside the region of interest, because the contribution of the nonrigid components of the transformation

decreases further away from the region of interest. Inside the structures only a small misalignment is expected, because the organs are totally enclosed by control points, and the volume is relatively small. Kaus et al. [23] showed that for liver, lung, and prostate cases, millimeter or even submillimeter accuracy was achieved, measured as the distance between the anatomic landmarks. Kaus et al. [23] tested three models, based on thin-plate splines (used in our method), Wendland function, and elastic body spline. None of the methods performed consistently better or worse.

The method aligns two sets of structures accurately. When larger areas outside the region of the structure set need to be aligned, more structures should be added to the nonrigid process. In theory, the method allows for the inclusion of more points, both for defining other organs (such as skin, bony anatomy) or including landmarks. However, the present method is limited by computational resources, such as memory and time, which now requires about 1.5 h/patient on a Pentium IV (2.8 GHz, with 2 GB RAM). Chui et al. [24] introduced a cluster strategy to increase the amount of information included in the registration without increasing computational requirements.

The local anatomic changes observed in this study were consistent with the global measurements reported in published studies [11,14,17,25]. Hansen et al. [14] reported a mean change in the volume of 21.5% and 15.6% for left and right parotid, respectively, between the planning and second CT scan used for replanning. Volumetric and positional changes for gross tumor volumes and normal tissues in relation to the C2 vertebra center of mass were reported by Barker et al. [11], who also found time trends in volume and position of parotid glands. When using the volume decrease rate found by Barker et al. [11] for 23 treatment days, a volume decrease of 13.8% is obtained. The average volume reduction for both parotids in our study was 14%. Barker et al. [11] found a median medial shift of 3.1 mm for the center of mass of the parotid glands. This medial shift of the center of mass might partly be explained by our observed asymmetric shifts in parotid gland surfaces, with average displacements of 1 ± 3 mm and 3 ± 3 mm for the medial and lateral regions of the irradiated glands, respectively (Fig. 7). The changes in the lateral regions of the parotid were also reported by Robar et al. [17], who found a systematic displacement of a selected point in the lateral region of the parotid glands in the medial direction of 2.6 ± 0.3 mm and −1.9 ± 0.2 mm, for the left and right parotid, respectively. A selected point in the medial region of the parotid did not show a systematic translation. However, the selection of the same lateral and medial point in a series of CT scans, relying on bony anatomy not fully in contact with the parotid gland, might include errors in the measured displacements. In addition, this approach assumes no changes in the inferior-superior or posterior-anterior direction of the parotid glands, which were observed in our patient group (Fig. 7). The full 3D approach used in our study is a more reliable strategy.

Barker et al. [11] found a significant correlation between weight loss and volume change in the parotid glands. Information about weight loss was not collected for our study. However, it is well known that, in general, patients lose weight during treatment. We also observed a significant volume loss for the spared glands. Our data showed that the planned mean dose is significantly related to the observed parotid gland volume

reduction ($p < 0.001$, $r = 0.68$; Fig. 6). Additional studies are needed to identify all variables leading to volume reduction.

As suggested by Barker et al. [11] and demonstrated by Hansen et al. [14] and Robar et al. [17], the observed anatomic changes might have a dosimetric effect when highly conformal treatment techniques are used. When comparing replanning with no-replanning treatments, Hansen et al. [14] found that the doses to target volumes decreased and the doses to normal structures increased. In the particular case of the parotid glands, all dosimetric endpoints (mean dose, dose to 50% of the volume, and volume receiving ≥26 Gy) to the right parotid gland significantly increased without repeat planning, although the changes for the left parotid gland were not significant. Robar et al. [17] reported an increase in the mean dose of 2.6% ± 4.3% and 0.2% ± 4.0% for the left and right parotid. The asymmetry in the results between the left and right parotid presented by Hansen et al. [14] and Robar et al. [17] show the need to classify the parotid in a manner other than left or right; it is possible that the patient groups (14 patients for Hansen et al. [14] and 15 patients for Robar et al. [17] were not balanced with respect to whether the left and right neck was treated. In our study, a different classification, determined by the treated or nontreated neck, was used. We have demonstrated that for irradiated parotid glands, the lateral regions (with the lower planning doses) displace inward (i.e., toward the higher doses, with the spared parotid glands presenting little and near homogeneous deformation).

CONCLUSION

The nonrigid registration method accurately described local changes occurring in the head-and-neck region after EBRT in full 3D. The classification of the glands into irradiated and spared groups revealed a significant difference in the volume reduction and shape and position changes between the groups. Glands belonging to nontreated necks showed few changes. Glands belonging to treated necks showed a general shrinkage and deformation. Nonrigid registration is an ideal tool with which to perform additional studies in larger patient series to investigate the relationship between the local dose and local shape and position changes in more detail.

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3D Dose Addition of External Beam Radiotherapy and Brachytherapy for Oropharyngeal Patients using Non-Rigid Registration

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ABSTRACT

Purpose: To develop and evaluate a method for adding dose distributions of combined external beam radiotherapy (EBRT) and brachytherapy (BT) for oropharyngeal patients.

Materials and Methods: Two CT scans were used for 5 patients: the EBRT CT, used for EBRT planning, and the BT CT, acquired after catheter implantation. For each scan, the salivary glands, chewing and swallowing muscles were contoured, and a dose distribution was calculated. A non-rigid transformation was obtained by registering the organs' surfaces. The transformation was then applied to the BT dose distribution, to map it onto the EBRT dose distribution. To account for differences in fractionation, the physical doses were converted to equivalent dose in 2Gy, and the total dose was found by adding dose voxel by voxel. The robustness of the method was investigated by varying delineations and input parameters of the registration method. The effect of the perturbations was quantified using Dose-Volume Histograms (DVH) and gamma analyses (Distance-To-Agreement=1mm/Dose-Difference=2Gy).

Results: The variations in input parameters and delineations caused only small perturbations in the DVH of the added dose distributions. The gamma index was low (median gamma index λ 0.4 for salivary glands and chewing muscles), and moderately elevated for organs lying in areas with a steep gradient (median gamma index λ 1.5 for constrictor muscles).

Conclusions: The presented method allows adding dose distributions of combined EBRT and BT for oropharyngeal patients. The method is reliable and robust with respect to uncertainty in organ delineation and perturbations in input parameters of the method.

INTRODUCTION

Combination of external beam radiotherapy (EBRT) and bra¬chy¬the¬ra¬py (BT) is commonly used in the treatment of head and neck cancer, cervical cancer and prostate cancer [1-3]. EBRT aims at treating the primary tumor and areas at risk for microscopic disease, while BT is used to boost the primary tumor. However, in current clinical practice, BT boost are optimized independently, without taking into account the dose already delivered. The reason is that addition of 3-dimensional (3D) dose distributions is challenging due to anatomical changes of the patient, e.g. caused by weight loss, tumor shrinkage, different patient set-ups, implantation of catheters, insertion of applicators or other surgical procedures (see figure 1). Furthermore, to establish dose-effect relationships for tumor control and side effects in combined modality treatments, simple approximations are often used [4-7]. Some studies use only part of the treatment to establish dose-effect relationships [6,7]. In other studies, the accumulated dose was approximated without taking patient deformations into account. For example, Levendag et al. [4] and Teguh et al. [5] related the probability of experiencing dysphagia to the dose to the swallowing muscles for oropharyngeal and nasopharyngeal patients. To account for the total dose received by the organs, the physical EBRT and BT mean doses were simply summated.

Rigid registration, including rotation and translation, followed by the linear addition of the dose matrices is not accurate to add dose. A rigid transformation does not align deforming anatomy adequately (see figure 1). Non-rigid registration, on the other hand, allows to better align the anatomy, enabling different dose distributions to be mapped to a common frame of reference. Another aspect is the dose addition itself. Different modalities often use different fractionation schemes. Therefore, dose distributions require a conversion to biological equivalent doses before adding the dose in each voxel [8].

In this paper we propose a method for adding 3D EBRT and BT dose distributions, using a non-rigid registration framework developed in-house based on Chui et. al. [9-11]. The method was tested for organs at risk (salivary glands, swallowing and chewing muscles) of 5 oropharyngeal patients treated with EBRT, followed by BT boost. Three of the patients underwent neck dissection before catheter insertion [1, 4, 5]. The biological effects of the different fractionation schemes were taken into account by converting the physical EBRT and BT dose to biologically equivalent dose for 2Gy fractions (EQD2, [8]) before adding each dose voxel. The robustness of the method was investigated by variations in input parameters of the registration method and simulating variations in organ delineations around the clinical contours (delineation uncertainty).

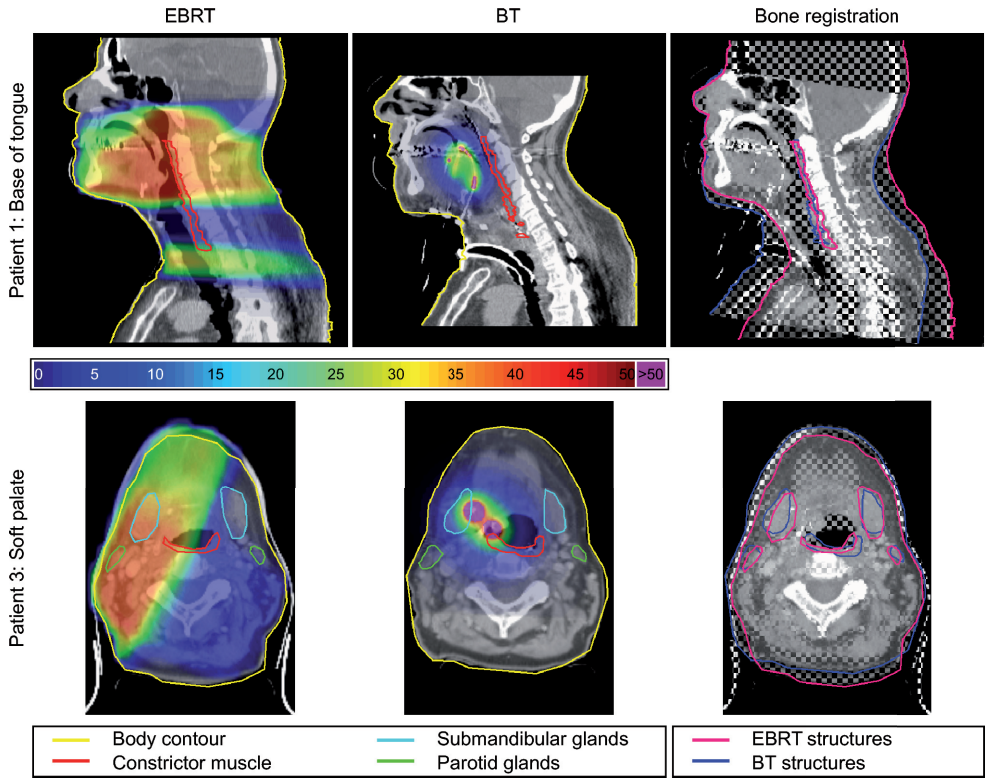

Figure 1: Anatomical changes between EBRT and BT for patient 1 and 3. The first row shows the sagittal planes of patient 1. Notice the large anatomical changes between the EBRT and BT CT scan, mostly caused by the neck dissection, catheter insertion and different patient positioning. The second row presents the axial planes of patient 3. The first column shows the CT scans used for EBRT planning, the second column the repeat CT scans taken after catheter implantation and just before BT and the last rigid registrations based on bone. Notice that rigid registration is not adequate to align both CT scans.

MATERIAL AND METHODS

Patient data

Five oropharyngeal cancer patients were included in this study (see table 1). These patients belonged to a larger group previously used for quantifying anatomical changes using non-rigid registration [12]. According to the protocol [1, 4, 5, 13], the patients first underwent EBRT to a total dose of 46Gy in 23 fractions (dynamic intensity-modulated RT), followed by a brachytherapy boost two weeks after the end of EBRT (PDR scheme 2Gy-18x1Gy-2Gy, biologically equivalent to HDR scheme 4Gy-4x3Gy-4Gy) [14]. Patients 2 and 3 received unilateral EBRT to the ipsilateral neck, while patients 1, 4 and 5 received bilateral EBRT. Just before catheter implantation, patients 1, 4 and 5 (node-positive) underwent neck dissection in which the neck lymph nodes and the submandibular glands, among other soft tissue, were removed.

Id.	Sex	Age	Site	TNM staging		
1	m	57	Base of tongue	T3	N2a	M0
2	m	48	Tonsillar fossa	T2	N0	M0
3	f	59	Soft palate	T2	N0	M0
4	m	58	Base of tongue	T3	N2a	M0
5	f	52	Base of tongue	T1	N2c	M0

Table 1: Patient characteristics.

Two intravenous contrast-enhanced CT scans were used for each patient: the CT scan used for planning EBRT (EBRT CT scan), and a repeat CT scan taken two weeks after the end of EBRT, after catheter implantation and just before BT dose delivery (BT CT scan). The slice spacing was 3mm for the EBRT scans and 1.5mm for the BT scans. The catheters were clearly visible in the BT CT since copper wires were inserted for the CT acquisition. The body contour, chewing muscles (masseter, pterygoid and temporalis muscles), swallowing muscles (superior, middle and inferior constrictor, cricopharyngeus, and esophagus inlet muscles) and major salivary glands (parotid and submandibular glands) were contoured in both CT scans. For consistency, the BT CT scan was delineated, using the EBRT CT scan as a reference. All delineations were checked by a second observer. Surfaces, defined by a set of triangles joining contours in the consecutive slices, were created from the delineated structures.
Dose distributions for the EBRT and BT treatments were calculated using the treatment planning system used clinically at the time: CadPlan version 6.4.7 (Varian Medical Systems, USA) and Plato BPS version 14.2 (Nucletron, The Netherlands) respectively. The BT dose distribution was originally calculated based on implant reconstruction from orthogonal X-rays. For this study, we reconstructed the BT dose distribution on the BT CT scan. The catheters were made visible on the BT CT scan using copper wires enabling reconstruction of the implant geometry and definition of active dwell positions. The corresponding dwell times were copied from the original plan. Finally the BT dose was calculated and the dose grid was exported. Both dose distributions were interpolated to a regular grid with resolution with resolution 1x1x1 mm^3.

Dose addition

Figure 2 illustrates the steps to add the EBRT and BT dose distributions taking into account anatomical changes. First, the triangulated surfaces generated from the delineated structures (above) were used to compute a non-rigid transformation using a non-rigid registration method developed in-house [10, 11]. The non-rigid registration framework was previously validated using anatomical landmarks [10] and was improved to reinforce inverse consistency [11]. The non-rigid transformation, modeled by a regularized thin plate spline [9, 15], implicitly comprises the changes between the two structures sets. Second, using the transformation ob-

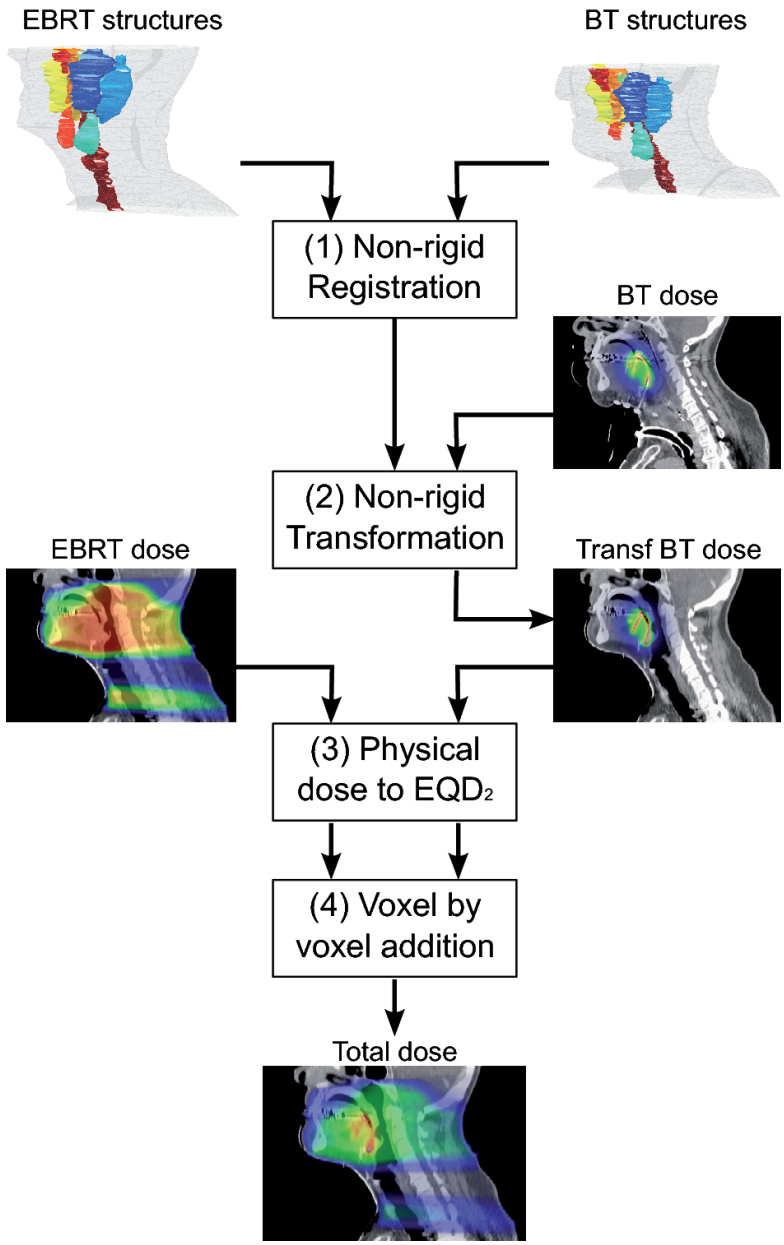

Figure 2: Schematic showing the steps for dose addition. In step 3 we used the linear quadratic model with α/β = 3Gy for healthy tissues to convert doses to biologically equivalent doses for 2Gy fractions.

tained, we computed the transformed BT dose by inverse mapping using the Insight Toolkit (ITK, [16]). Inverse mapping finds the transformed BT dose on the EBRT grid dose by transforming each EBRT grid position into the BT dose grid. Then the dose is interpolated at the mapped location using the doses of the closest neighboring grid

points. This procedure avoids the creation of empty areas in the transformed dose. Third, both physical doses, i.e. EBRT dose and transformed BT dose, were separately converted into biologically equivalent doses for 2Gy fractions (EQD2) using the linear quadratic model (α/β = 3Gy). Finally, the 3D total dose distribution was calculated by adding the converted EBRT doses and the transformed and converted BT dose voxel by voxel.

Robustness of dose addition

As in previous studies [10], each non-rigid registration produced a satisfactory non-rigid transformation in terms of the transformation error (below 1mm), defined as the mean distance between surfaces, and checked by visual inspection. Previously, we validated the anatomical correspondence of the non-rigid registration framework using identifiable landmarks in CT data sets [10]. However, the image sets currently used do not contain sufficient information to indistinguishably identify corresponding tissue elements on a functional subunit level. Alternatively, in this study we investigated the robustness of the dose addition method with respect to changes in 1) the parameters of the non-rigid registration framework, 2) control point distribution and 3) variations in organ delineation around the clinical contours. To assess the influence of each of these perturbations, we compared each total dose distribution resulting from a perturbation to the unperturbed reference total dose distribution using dose-volume histograms (DVH) and the gamma index method [17]. The gamma index combines the dose-difference (DD) and distance-to-agreement (DTA), to compare two dose distributions. Gamma index was evaluated in each voxel within the delineated structures using DD=2Gy and DTA=1mm. Perfect agreement between two voxels is represented by a gamma index equal to zero (same dose in the same spatial position). Two voxels that have the same dose and are separated by a distance of DTA, or that are in the same spatial position and which dose difference is DD, would score a gamma index equal to one. Figure 3 shows the gamma index between two voxels. We report distributions of gamma indices of all voxels inside the organs using box and whisker diagrams.

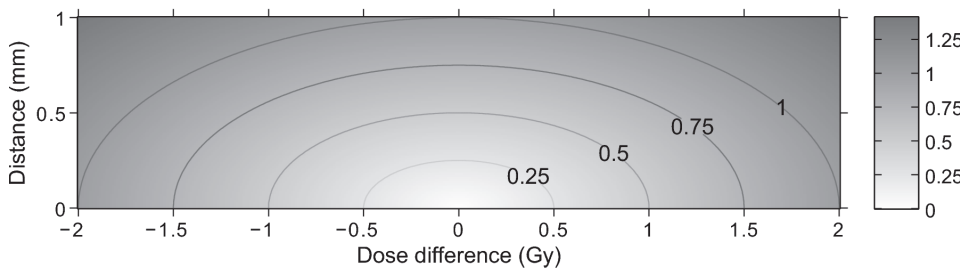

Figure 3: Gamma index as a function of distance and dose difference between two voxels using Dose-Difference=2Gy and Distance-To-Agreement=1mm.

Perturbations of framework parameters

The non-rigid registration framework uses points to represent the structures to be registered. The framework includes a procedure to generate points from surfaces which is controlled by the parameter r or density radius. The parameter r determines the density of control points, which affects the computational time and accuracy.

Small r means large number of points, longer computational time and, theoretically, more accurate results. Conversely, large r produces few points, shorter computational time and less accurate results. Based on previous experience, we tested r=5, 6 and 8mm (reference r=5mm).
The second framework parameter is λ. This weight parameter controls the degree of deformation of the transformation function by regulating the thin-plate spline used as transformation. Large λ restricts the transformation to be mostly affine, opposite to a small λ, which relaxes the restriction. We tested λ=0.5 and 5, which in combination with the chosen r produced transformation errors below 1mm in 10. We used λ = 5 as reference in this study.

Perturbations in control point distribution
We investigated the influence of using different control point distributions on the dose addition. As mentioned, the framework includes a procedure to generate control points, which spread pseudo-homogeneously on the surfaces of the delineated structures [10, 11]. In this procedure, a refined surface of the structures is generated by dividing iteratively the triangles that join contours of consecutive slices. The vertices of the triangles already spread pseudo-homogeneously, however registering such a large number of points is beyond the computational resources available. Then, the vertices of the refined triangles are grouped in spheres whose radius is the density radius (r), and the centroid is calculated. Last, the points are replaced by the closest point on the surface to the calculated centroid. We used this procedure to create four control point distributions with the same density radius (r=6mm). By randomly varying the position of the grouping spheres, different point distributions were generated.

Perturbations in structures delineations
To determine the influence of delineation variations on the non-rigid registration, and consequently on the dose addition, we simulated observer variations of 1, 3 and 5mm in the delineation of structures. To simulate the variations, random deformations were applied to the surfaces of the EBRT and BT structures. Figure 4 explains the procedure to create random deformations. First, one third of the contour points that constitute the surface of the structures was randomly selected. Only points that were not in close proximity to other organs were considered, in order to avoid overlapping of perturbed contours of neighboring organs. Second, random deformation vectors were generated. In order to simulate the real situation, the deformation vectors were limited to the axial planes where the contours were drawn, and their direction and length was random, to a maximum of the variation simulated (1, 3 or 5 mm). Third, the deformation was interpolated to the rest of the structure points using a thin-plate spline [15]. Finally, the deformed structures were used in the non-rigid registration framework to generate the non-rigid transformation. We calculated a total of 9 non-rigid transformations per patient, using three random deformations per simulated maximum variation of 1, 3 and 5 mm. Calculation of DVHs and gamma analyses were performed using the non-perturbed delineations in order to only assess the effects of the perturbations on the results of the dose addition.

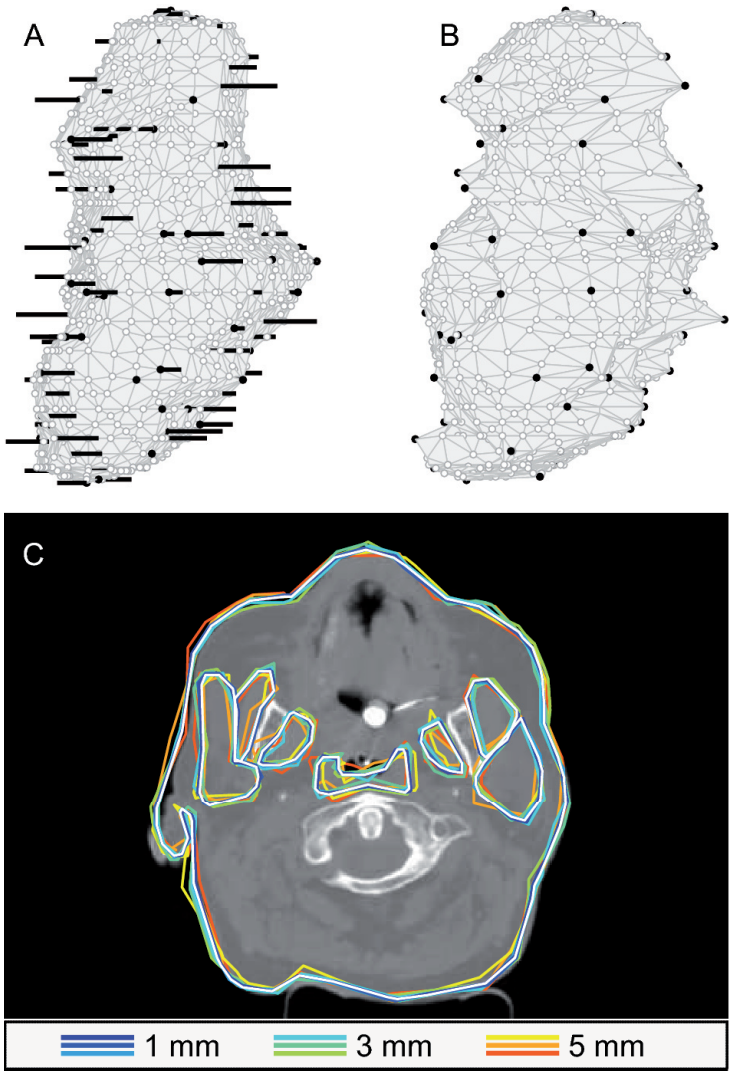

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Figure 4: Procedure to simulate delineation variations. A) A set of points is randomly selected (black dots) from the points in the original structure (light triangles). Then deforming vectors, restricted to the axial planes, are generated (thick lines) limiting their lengths to the delineation variation simulated (1, 3 or 5mm). B) The deformation is interpolated to the rest of the structure using a thin-plate spline. C) BT CT scan of patient 5 showing all 9 delineation variations simulated. The clinical delineation is shown in white.

Simple alternatives to full 3D non-rigid registration

We investigated the validity of approximating the mean dose, D99 and D1 by adding the separate mean dose, D99 and D1 for the EBRT and BT dose distributions without taking anatomical changes into account. We defined D99 and D1 as the dose received by the 99% and 1% of the organ's voxels respectively, as read from the DVH data. We compared these approximations converted to EQD2 to the values obtained by non-rigid registration.

RESULTS

Total dose

Figures 5, 6 and 7 show the DVHs for the EBRT, BT and total dose distributions for the salivary glands, the chewing muscles and the swallowing muscles, respectively. The largest total doses were found for the constrictor muscles for patients 3 and 4, and for the right submandibular gland for patient 3. For all patients, the largest contribution to the total dose came from the EBRT, and most organs at risk received low BT doses.

Perturbations analysis

Besides the DVHs for the reference EBRT, BT and total dose distributions, figures 5, 6 and 7 also show the total dose DVHs for the 19 perturbations. Most perturbations produced only minor deviations with respect to the reference DVHs, to the point that most total dose DVHs blend into one single curve. The largest variations were found in the superior, middle and inferior constrictor muscles. Figures 8 and 9 show distributions of gamma indices using box and whisker diagrams categorizing the data by perturbation type and per patient, respectively. In general, the perturbations in the control point distributions produced the lowest gamma indices. The largest gamma

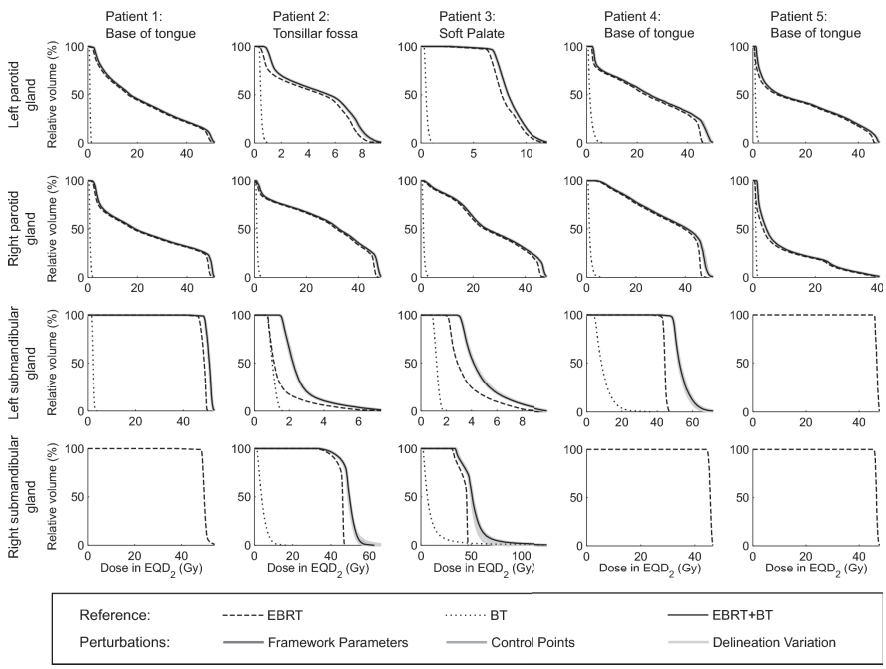

Figure 5: Dose volume histograms for the EBRT, BT and total dose distributions (reference and 19 perturbations) for the salivary glands. Perturbations on the total dose are shown in different shades of gray, and most of them blend with the reference DVH curve. All doses are biologically equivalent doses for 2Gy fractions (EQD2). Dose axes were cropped to the largest D1. The right submandibular glands for patient 1, 4 and 5, and the left submandibular gland for patient 4, were removed during neck dissection.

indices were found for the perturbations using λ = 0.5 and delineation variations of 5mm. Results varied among patients. Patient 4 presented the largest variations and patient 1 the smallest, while both were base of tongue cases. All chewing muscles, the parotid glands, the esophagus inlet and the cricopharyngeus muscles, presented small gamma indices for all patients (median ≤ 0.2). The organs that presented the most variation were the constrictor muscles and the submandibular glands (median ≤ 1.5). These organs were close to the target volume in all patients, and some submandibular glands were treated as part of the clinical target volume. One example is shown in the last row of figure 1. Particularly for BT, the proximity to the target volume means a steep gradient within the organs.

Simple alternatives to full 3D non-rigid registration

For the organs at risk considered, the differences between calculating the D1 of the total dose versus adding D1 of the EBRT and BT dose distributions were large (average, range: -0.9Gy, -14.5 to 25.6Gy), for example 25.6Gy for the middle constrictor muscle for patient 3 and 14.5Gy for the right submandibular gland (shown in the lower column in figure 1). The differences for the mean doses were moderately small (-0.1Gy, -2.6 to 0.4Gy), as well as for D99 (0.1Gy, -1.7 to 1.5Gy). None of the DVH parameters were systematically underestimated or overestimated by the approximation.

DISCUSSION

In this paper we present a method for adding dose distributions of different modalities taking into account anatomical changes and biological effects. The method was applied to organs at risk of 5 oropharyngeal patients. A robustness analysis was presented as an alternative to validation against ground truth. Overall, the method was robust against perturbations of the input parameters and delineation variations, as demonstrated by the overlapping total dose DVH curves in figures 5, 6 and 7. Robustness was also investigated by gamma analyses (figures 8 and 9), comparing perturbed and reference dose distributions using very strict criteria, i.e. DTA=1mm and DD=2Gy. Low gamma indices (median ≤ 0.2) for the esophagus inlet, cricopharyngeus and chewing muscles and the parotid glands indicate small deviations for the total doses resulting from the perturbations. Larger indices were found in the constrictor muscles and the submandibular glands (median ≤ 1.5). These last organs were located in areas with steep BT dose gradients, which explains the enhanced effect of the perturbations. When comparing the perturbation types (figure 8), larger gamma indices were found for λ=0.5 and for the largest delineation variations (5mm). The λ parameter controls the flexibility of the transformation, and a low λ produces a more flexible transformation. Compared to the reference dose distributions, total doses calculated by transformations using λ=0.5, showed larger local differences, resulting in larger gamma indices. The gamma indices were low for the perturbations in control point distributions, using λ=5 , and delineation variations below 5mm. Considering all analyses, we conclude that the presented method for adding EBRT and BT dose distributions is sufficiently insensitive to perturbations and renders reliable results.

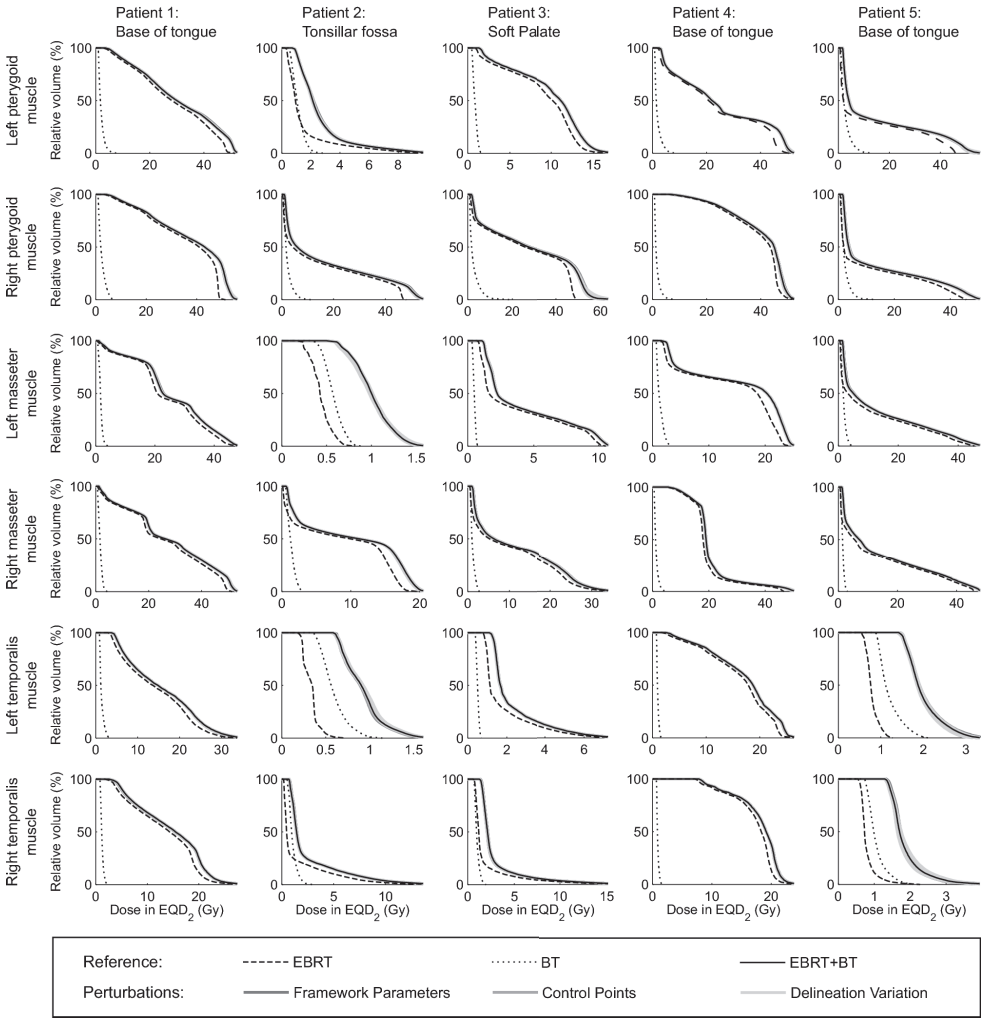

Figure 6: Dose volume histograms for the EBRT, BT and total dose distributions (reference and 19 perturbations) for the chewing muscles. Perturbations on the total dose are shown in different shades of gray, and most of them blend with the reference DVH curve. All doses are biologically equivalent doses for 2Gy fractions (EQD2). Dose axes were cropped to the largest D1.

The robustness of the method could be explained by the fact that the correspondence of each organ is optimized individually by correspondence filtering [10]. Here the correspondence problem is limited to each individual organ, and the global transformation is stable. In addition, correspondence filtering allows the inclusion of anatomical landmarks, which increases control in localized positions, and fine-tunes the transformation locally. Therefore, if subunit information is available, it can be included in the registration.

In the present study, the total dose to the tumor was not calculated. Besides the large changes happening to the target volume due to catheter implantation, several studies have found that target volumes may shrink during EBRT treatment [18,19].

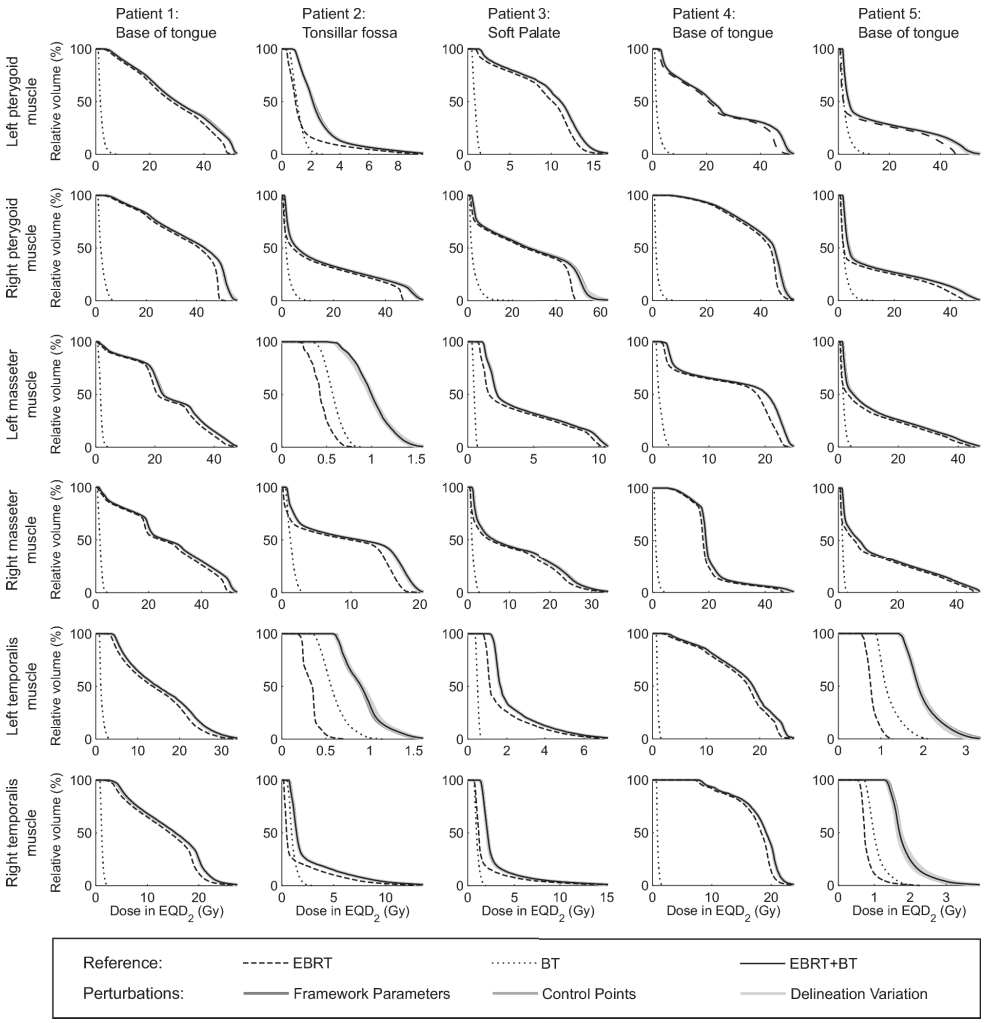

Figure 7: Dose volume histograms for the EBRT, BT and total dose distributions (reference and 19 perturbations) for the swallowing muscles. Perturbations on the total dose are shown in different shades of gray, and most of them blend with the reference DVH curve, except for the constrictor muscles where slightly larger variability can be seen. All doses are biologically equivalent doses for 2Gy fractions (EQD2). Dose axes were cropped to the largest D1.

Dose accumulation for a regressing mass requires further research to handle disappearing tissue properly.

To further improve the method, octant interpolation for the dose mapping can be implemented for organs that lie in areas with steep dose gradient, as suggested by Rosu et al. [20]. In their study, two interpolation approaches were investigated and compared: direct approximation, using one point to estimate the dose at each dose grid position, and octant interpolation, where the dose of each grid position wasestimated from 8 points. Rosu et al. concluded that octant interpolation is better suitable for areas with steep dose gradients.

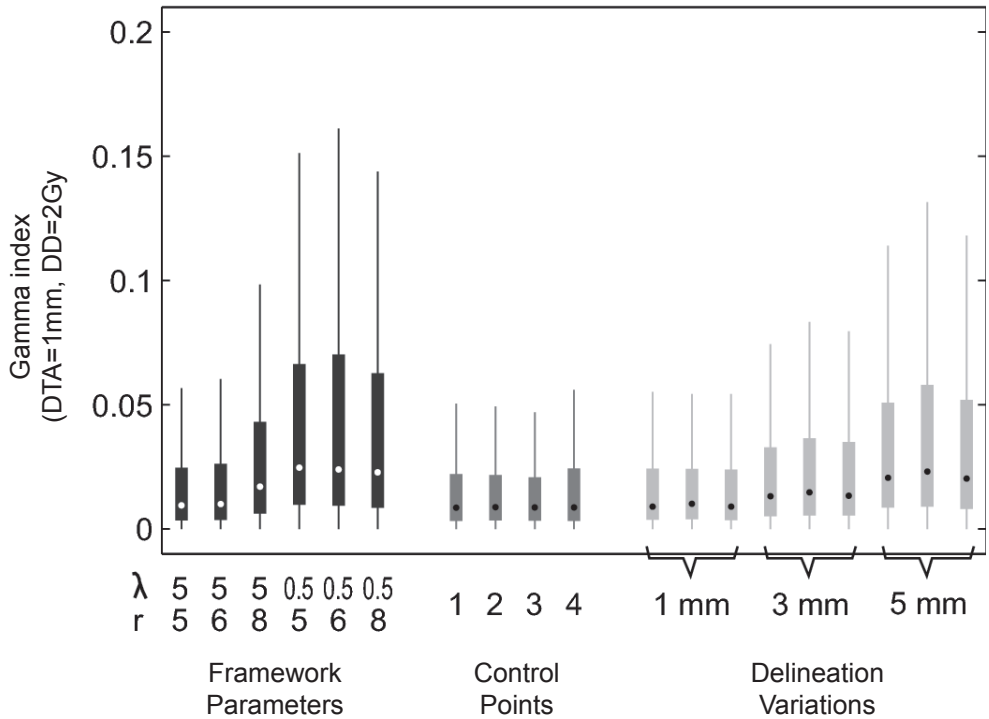

Figure 8: Distributions of gamma indices (DTA=1mm,DD=2Gy) for all organs and all patients, categorized by perturbation type. The dots represent the median, and the edges of each box are the 25th and 75th percentiles, the whiskers extend to the most extreme data points not considered outliers.

We investigated whether an addition without non-rigid registration of D1, D99 and mean EBRT and BT dose is a valid approximation for the corresponding parameters of the total dose. We found large differences ($\leq$ 25.6Gy) between this approximation and calculating D1 of the total dose. The differences were smaller for mean dose and D99 ($\leq$ 2.6 Gy and 1.7 Gy respectively). For large quality of life studies where mean doses are summed up, such as [5], differences of this scale of magnitude are probably negligible. However, this approximation assumes not large deformations and may not hold for other sites where deformations are more complex.

The concept of accumulating dose using non-rigid registration has been explored in the literature. However to our knowledge, there is no previous attempt to add 3D dose distributions of EBRT and BT taking anatomical changes into account. Few reports are available that address the anatomical validity of dose addition. Schaly et al [21] proposed to track tissue elements (voxels) between daily CT scans and accumulate their dose distributions using thin-plate spline. In a sensitivity analysis of control point placement, they found dose differences up to 37% for bladder and 27% for rectum. An alternative approach for dose accumulation uses finite element analysis [22, 23]. However, inclusion of anatomical landmarks inside or outside the surfaces is limited, and the mechanical properties for the tissue should be accurate [24].

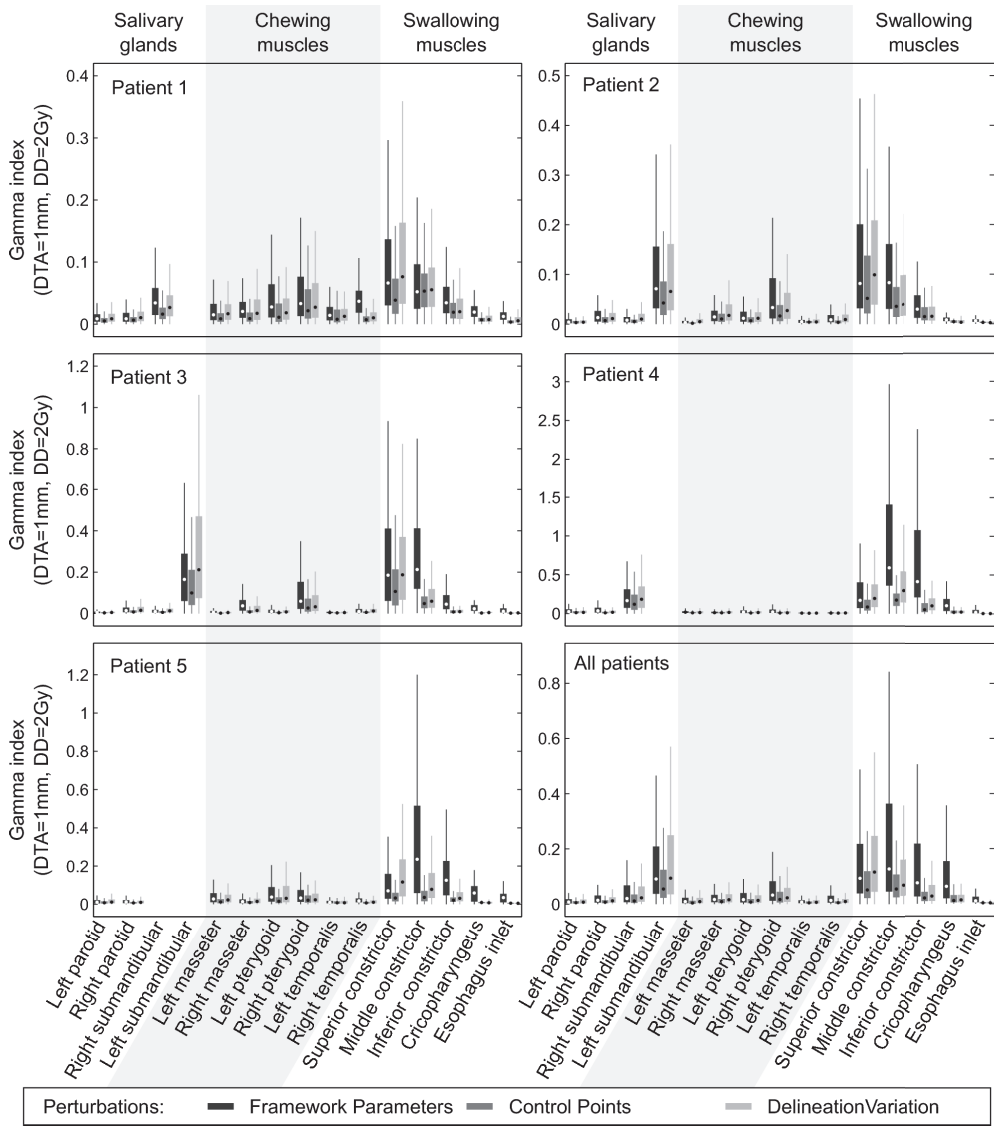

Figure 9: Distributions of gamma indices (DTA=1mm,DD=2Gy) categorized by organs and perturbation type per patient. The dots represent the median, and the edges of each box are the 25th and 75th percentiles, the whiskers extend to the most extreme data points not considered outliers.

Apart from head and neck cases [12], our non-rigid registration framework has been used in a previous study to analyze the deformation of the prostate and the seminal vesicles in prostate cancer patients [25] and it was used for cervix cancer patients experiencing extreme deformations as a result of bladder filling variations [26]. Based on this experience and the results described in this paper, we expect our method for dose addition to be applicable to other sites treated with combined modality treat-

ment, e.g. prostate and gynecological sites.
The method can also accumulate dose distributions from other radiation modalities. Dose accumulation can also be used to optimize radiation treatment plans considering dose previously delivered to the patient, e.g. optimizing BT plans taking the EBRT dose into account or for re-planning in adaptive strategies. Also, using a better approximation of the total dose, treatment related toxicity and dose-effect relationships can be determined more accurately.

CONCLUSION

The presented method allows adding 3D dose distributions of combined EBRT and BT for organs at risk in oropharyngeal patients. The method is reliable and robust with respect to placement of control points, choice of input parameters for the registration method and variations in organ delineation. Optimization of BT plans while taking into account the EBRT dose already delivered, and re-planning in adaptive strategies are promising new possibilities.

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Clinical Validation of Atlas-Based Auto-Segmentation of Multiple Target Volumes and Normal Tissue Structures in the Head & Neck

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ABSTRACT

Purpose: To validate and clinically evaluate autocontouring using atlas-based autosegmentation (ABAS) of computed tomography images.

Methods and Materials: The data from 10 head-and-neck patients were selected as input for ABAS, and neck levels I-V and 20 organs at risk were manually contoured according to published guidelines. The total contouring times were recorded. Two different ABAS strategies, multiple and single subject, were evaluated, and the similarity of the autocontours with the atlas contours was assessed using Dice coefficients and the mean distances, using the leave-one-out method. For 12 clinically treated patients, 5 experienced observers edited the autosegmented contours. The editing times were recorded. The Dice coefficients and mean distances were calculated among the clinically used contours, autocontours, and edited autocontours. Finally, an expert panel scored all autocontours and the edited autocontours regarding their adequacy relative to the published atlas.

Results: The time to autosegment all the structures using ABAS was 7 min/patient. No significant differences were observed in the autosegmentation accuracy for stage N0 and N+ patients. The multisubject atlas performed best, with a Dice coefficient and mean distance of 0.74 and 2 mm, 0.67 and 3 mm, 0.71 and 2 mm, 0.50 and 2 mm, and 0.78 and 2 mm for the salivary glands, neck levels, chewing muscles, swallowing muscles, and spinal cord-brainstem, respectively. The mean Dice coefficient and mean distance of the autocontours vs. the clinical contours was 0.8 and 2.4 mm for the neck levels and salivary glands, respectively. For the autocontours vs. the edited autocontours, the mean Dice coefficient and mean distance was 0.9 and 1.6 mm, respectively. The expert panel scored 100% of the autocontours as a “minor deviation, editable” or better. The expert panel scored 88% of the edited contours as good compared with 83% of the clinical contours. The total editing time was 66 min.

Conclusions: Multiple-subject ABAS of computed tomography images proved to be a useful novel tool in the rapid delineation of target and normal tissues. Although editing of the autocontours is inevitable, a substantial time reduction was achieved using editing, instead of manual contouring (180 vs. 66 min).

INTRODUCTION

The large numbers of target and normal tissue structures that require manual delineation in head-and-neck cancer patients has made contouring tedious and time consuming. In addition, optimal sparing conditions for head-and-neck intensity-modulated radiotherapy require accurate delineation of those structures. To ensure consistent delineation of the target volume, a computed tomography (CT)-based atlas of neck levels I–V and guidelines for critical organs at risk (OARs) were developed and are in use [1-4]. However, contouring still results in intra- and interobserver variations [5-7].

A promising new tool is auto-contouring using Atlas-Based Auto-Segmentation (ABAS) of CT-images [8,9,10]. This tool automatically creates the contours for the neck levels and OARs in the CT images of a new patient. ABAS has the potential to lower the contouring burden and thus allow more normal tissues to be included in inverse treatment planning for high-dose intensity-modulated radiotherapy to fully exploit our knowledge of dose–volume effects. ABAS also has the potential to reduce the intra and interobserver variability in contouring.

In the present study, we have quantified the accuracy of autocontouring using ABAS and assessed the clinical applicability of this tool. This is, to our knowledge, the first report describing the validation of an ABAS tool (Elekta-CMS Software) for contouring target tissues (including neck levels I–V) and all possible normal tissue structures (including the mastication and swallowing muscles) in the head and neck. We determined the accuracy and time reduction for contouring. The first part of the present study assessed the geometric accuracy of the ABAS. Two ABAS approaches were evaluated: (1) selection of the atlas patient with the greatest similarity metric; and (2) combining multiple segmentations of all atlas patients into one segmentation. The comparison of a multiple-subject atlas with a single-subject atlas was quantified. The second part of the present study addressed the clinical implementation. The differences among the clinically used contours, autocontours, and edited autocontours were quantified, and the quality of all contours was scored by an expert panel.

MATERIAL AND METHODS

Description of the ABAS tool

Atlas-based autosegmentation is the process of performing segmentation on novel data using the knowledge of a previous segmentation, a data set that has the structures of interest already labeled. The registration strategy incorporates the objects' shape information in the atlas to help improve the registration efficiency and robustness, while still accounting for large intersubject shape differences. The key component of ABAS is a database (i.e., the so-called atlas) containing image data (e.g., CT scan data) with delineated contours of the structures (organs) of interest. These atlas contours must be transferred to the image data of a new patient who undergoing radiotherapy planning. The transfer is accomplished by nonrigidly registering the image data of the atlas to the image data of the new subject. Having obtained the transformation vectors from the atlas image data to the new subject image data, it is possible to transform the atlas contours to the new patient. The implementa-

tion we tested used a hierarchical approach (ABAS, version 1.1) for the nonrigid registration. This approach makes the nonrigid registration procedure efficient and robust, while still able to register large shape differences present between different patients. Hierarchical atlas registration consists of three major steps: linear registration; object-driven “poly–smooth” nonlinear registration; and shape-constrained dense deformable registration [9,10].

Atlas patients

The CT data of 10 head-and-neck cancer patients (4 Stage N0 and 6 Stage N+) were used. An experienced staff member manually contoured the individual neck levels I–V (both necks) and 20 OARs (salivary glands, chewing and swallowing muscles, and spinal cord-brainstem) (table 1). First, the contouring was done by a research fellow and subsequently corrected by the supervisor. Contouring of the neck levels was done using the international consensus guidelines of Gregoire and Levendag [11], and contouring of the normal tissues was done according to our guidelines for delineating the OARs [2-4,12]. Those contours were used to construct the atlas and were regarded as the reference standard. The total contouring time needed to create the atlas was recorded. The contours of neck levels with invaded muscle in —N+ patients were not used for autosegmentation, because in our guideline, the anatomic border of those levels is defined differently than that for levels with noninvaded muscle. Other than the levels with invaded muscle, all other contours of Stage N+ patients were used by the ABAS tool.

Tissue	n
Submandibular glands	2
Parotid glands	2
Mastication muscles	5x2
Swallowing muscles	5
Spinal cord	1
Neck levels	5x2

Table 1: Tissues delineated for the atlas.

Atlas Selection

In theory, ABAS requires just one set of images from a patient as the atlas. In practice, however, the differences in the anatomy of patients merits the use of various atlas patients. In the present study, we evaluated two different atlas selection strategies to determine the best approach (figure 1). The first approach was selection of the atlas patient according to the greatest similarity metric among all the atlas patients and the new patient. The global mutual information similarity after global linear registration was used to choose the best atlas. The global correlation coefficient was only good for linear registration. The local correlation coefficient metric was

also evaluated. The local correlation coefficient is the usual correlation coefficient computed within a small neighborhood of each image voxel. The second approach for the atlas selection strategy was to apply multiple atlas data sets to the CT data of a new patient, thereby generating multiple autosegmentation sets. For the fusion of multiple single-atlas autosegmentation sets to one multiple-subject autosegmentation, the simultaneous truth and performance level evaluation (STAPLE) algorithm was used [13]. The STAPLE algorithm was introduced by Warfield et al. [13] and offers a more sophisticated strategy for multiple segmentation fusion in that it automatically estimates the segmentation quality of each classifier and also derives a weighted combination of the multiple classifiers according to their estimated segmentation quality. The STAPLE method was applied for each structure separately. For each structure, the STAPLE algorithm takes as input a collection of segmentation results, one for each atlas. It then simultaneously computes: a probabilistic estimate of the "true" segmentation and a measure of the performance level for each individual atlas result.

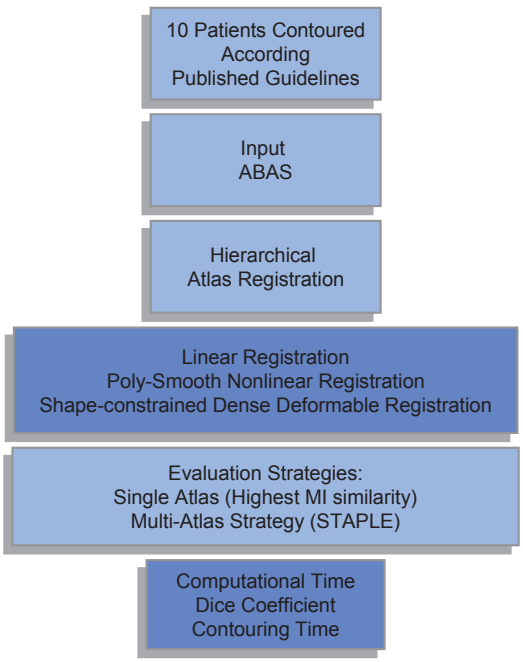

Figure 1: Flow chart input ABAS and strategy evaluation.

Atlas Evaluation

For evaluation, the mean distance and standard deviation around the mean distance between the autosegmented structure and the reference structure and the Dice coefficient were calculated. The mean distance measure was the mean distance between corresponding points on the surfaces of A, B. The surfaces were represented by triangular meshes consisting of sets of node points (triangle vertices) and edges (triangle sides) between the node points. Because the surfaces generally had different numbers of nodes, the distance d (A, B) was taken from the nodes on

one surface A to the nearest node on the other structure. The mean distance was defined as

$$M(A,B) = \frac{1}{N(A)} \sum_{i=0}^{N(A)} d(A,B)$$

where $d(A,B) = \sqrt{(a_1 - b_1)^2}$ is the Euclidean distance from the i-th point on A, a, to b, the point on B closest to a, and N(A) is the number of surface mesh nodes on structure A. The standard deviation of the distances d(A,B) was defined as

$$SD(d(A,B)) = \left[\frac{1}{N(A)-1} \sum_{i=0}^{N(A)} (d(A,B) - M(d(A,B))^2 \right]^{1/2}$$

This is a measure of the degree to which the distances are spread out over their range. If the structures are in good agreement, the mean and standard deviation will both be small. The Dice coefficient is defined as follows:

$$\text{Dice} = 2\,|A \cap B| \,/\, (|A|+|B|)$$

where A and B are the two structures evaluated. This formula represents the size of the union of two structures divided by the average size of the two sets. A value of 0 indicates no overlap; a value of 1 indicates perfect agreement. The leave-one-out cross-validation method was used to remove bias (i.e., the patient for whom the autocontours were generated was temporarily removed from the atlas). The levels with invaded muscle were excluded from the geometric validation, because the border of these levels differed, by definition, from the levels without invaded muscle. The levels with invaded muscle were evaluated in the clinical validation of ABAS (see the section “Clinical Validation of ABAS”).

Clinical Validation of ABAS

First, for 12 N0 and N+ patients who had undergone intensity-modulated radiotherapy by 10 experienced clinicians and residents, the clinically applied contours (levels and salivary glands) were evaluated by an expert panel and compared with the published atlases [2-4, 11,12] using the following scores: 0=poor, 1=moderate, 2=good (figure 2). Next, autocontours were generated for those patients using the multiple-subject ABAS tool. The accuracy of the autocontours relative to the published atlas was evaluated by the expert panel. For the autocontours, the following scoring system was used: 0, poor; 1, major deviation, editable; 2, minor deviation, editable; and 3, perfect. Generally, the expert panel scored the accuracy as a “minor deviation, editable” when the structures needed to be edited on a maximum of three CT slices, otherwise, it was scored as a “major deviation, editable.” Finally, for each patient, those autocontours were offered to 2 of a group of 5 experienced observers to edit, if needed, and the editing times were recorded. Contour editing was done using Focal, version 4.3.3 (Elekta - CMS Software, Maryland Heights, MO 63043). Those edited autocontours were also scored by the expert panel. The Dice coefficients and mean distance were calculated to quantify the differences among the clinical contours, autocontours, and edited autocontours of the observers (figure 2). In addition, other contours, i.e. mastication muscles, swallowing muscles, and spinal cord-brainstem) were autocontoured and edited, and the editing time was also recorded.

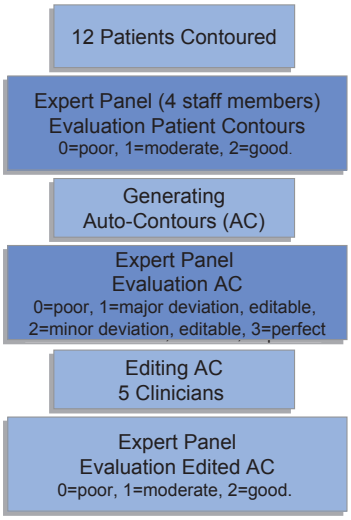

Figure 2: Flow chart clinical validation.

RESULTS

Geometrical validation of ABAS

The time needed to autocontour all the structures using ABAS was approximately 7 min/patient. The initial contouring time for the 30 structures delineated (Table 1) averaged 180 min/patient. Figure 3 shows an example of an autosegmentation of a neck level and swallowing muscle using a single-subject and multiple-subject atlas. In this example, the multiple-subject atlas contours were in better agreement with the reference contours than were the selected single-subject atlas contours. The comparison for all patients and structures is summarized in Fig. 4. Figure 4 shows the Dice coefficients and mean distances for the single-subject and multiple-subject approaches. The multiple-subject atlas method consistently performed superior to the selected single-subject atlas. These results and that the tested similarity metrics did not correlate, or moderately correlated, with the accuracy of the autosegmentation (median R^2, 0.2; range, 0.1–0.6) were in agreement. Excluding the levels with invaded muscle, no significant differences were observed in the autosegmentation accuracy for the N0 and N+ patients.

For all patients, the mean Dice coefficient and mean distance of the multiple-subject method are listed in Table 2. Other results of the multiple-subject autosegmentation are shown in [Fig. 5] and [Fig. 6] through 7. In Fig. 5, an example of the application of auto-ABAS for the contouring of the OARs (i.e., masseter muscles, pterygoid muscles, temporalis muscles, and parotid glands) is shown. Figure 6 shows a coronal view of the autocontours and reference contours of Levels II–IV. Figure 7 shows the autosegmentation of the levels vs. observer contouring. Figure 8 shows an autosegmentation example for a neck level with invaded muscle (reference contour in green and multiple-subject autocontour in yellow). The muscle was not included in the autocontour, because the algorithm used the level of N0 atlas patients to auto-

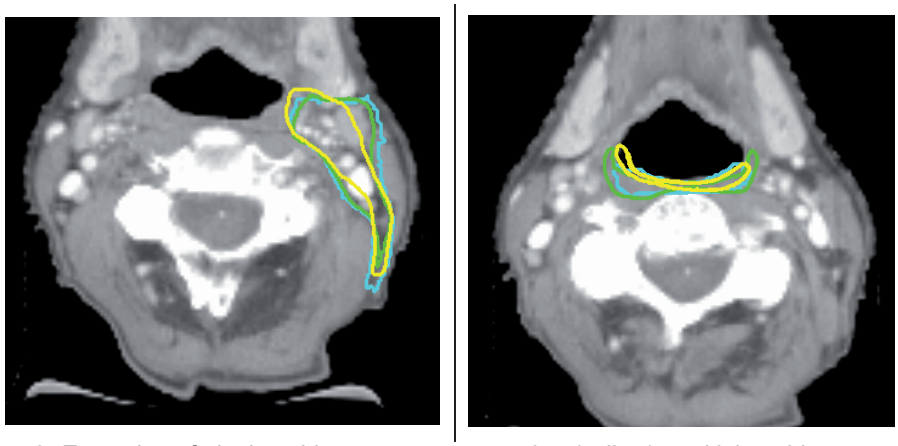

Figure 3: Examples of single-subject autosegementation (yellow), multiple-subject autosegmentation (turquoise), and reference contours (reference standard; green). (Left) level II; (Right) swallowing muscle.

segment the involved level of the N+ patient. At the medial site, some vessels were not encompassed. Both issues were quickly fixed by editing the autocontour.

Clinical validation

The mean editing time for the neck levels, parotid glands, submandibular glands, mastication muscles, swallowing muscles, and spinal cord-brainstem was 31, 7, 6, 14, 7, and 1 min, respectively. The Dice coefficient and the mean distance of the clinical contours vs. the autocontours, the autocontours vs. the edited autocontours, and the observer 1 contours vs. observer 2 contours are listed in Table 3.

The greatest variation was found for the neck levels, in particular, for the clinical contours and autocontours of the neck levels. All autocontours (100%) were scored as a “minor deviation, editable” or better by the expert panel. The expert panel scored 88% of the edited contours as good and 83% of the clinically used contours as good. The automatically generated contours still required editing, but the editing time was much less than that needed for manual delineation.

DISCUSSION

The present study reported on the development, validation, and use of the ABAS tool. As shown in Fig. 4, the comparison with the reference delineation clearly shows the advantage of using a multiple-subject atlas for segmentation. The multiple-subject atlas Dice coefficients and mean distances were more satisfactory than those with the single-subject atlas. As demonstrated by figures 3-6, the OARs (parotid glands and mastication muscles) were accurately segmented. From Fig. 6, the resemblance is apparent, but the autocontours still required editing to be used in the treatment planning process. The Dice coefficients for the different structures are listed in Table 3. From these results, about 80–90% agreement between the autocontours and the

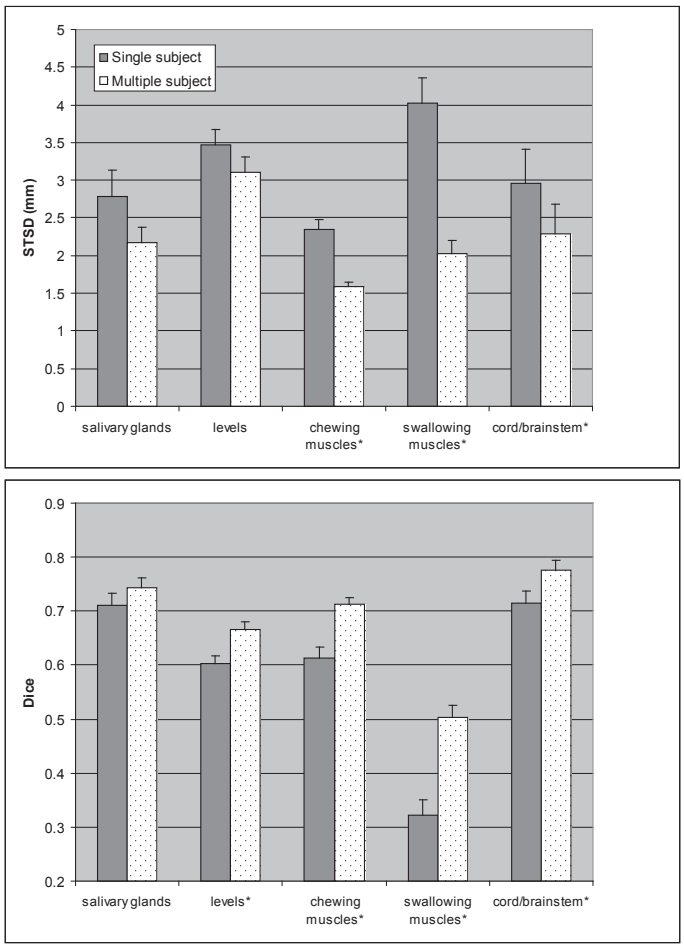

Figure 4: Comparison of mean distance and Dice coefficient for single-subject and multiple-subject approaches. Both metrics quantified agreement between autocontours and reference standard. Error bar indicates standard error; asterisk denotes significant difference for subgroup of structures at p = 0.01 (paired t test). Overall, multiple-subject method performed better (p < 0.001, paired t test).

edited autocontours was found, similar or slightly better than that of other published data [14-16]. Although our data showed considerable interpatient variability in intravenous contrast uptake, head pose, dental artifacts, and the use of a tongue depressor, all the autocontours were scored as “minor deviations, editable” or better by the expert panel, a promising result. The expert panel scored 88% of the edited contours as good and 83% of the clinically used contours as good. From these data, we can state that the edited contours (88% good) were closer to the published atlas than the ones used in clinic (83% good); the former might make the delineations for radiotherapy plans for cancer patients more accurate.

Chao et al. (15) used a computer-assisted target volume delineation system and reference templates. They found that the variation was significantly reduced, but not

	Neck Levels	Parotid glands	Subman-dibular glands	Chewing muscles	Swal-lowing muscles	Cord-brain-stem
Dice	0.67	0.79	0.70	0.71	0.50	0.78
Mean distance* (mm)	3.4 ± 3.1	2.5 ± 2.8	1.9 ± 1.4	1.6 ± 1.4	2.0 ± 1.9	2.3 ± 1.4

* Mean ± standard deviation

Table 2: Dice coefficient and mean distance for multiple-subject autocontours vs. reference standard contours.

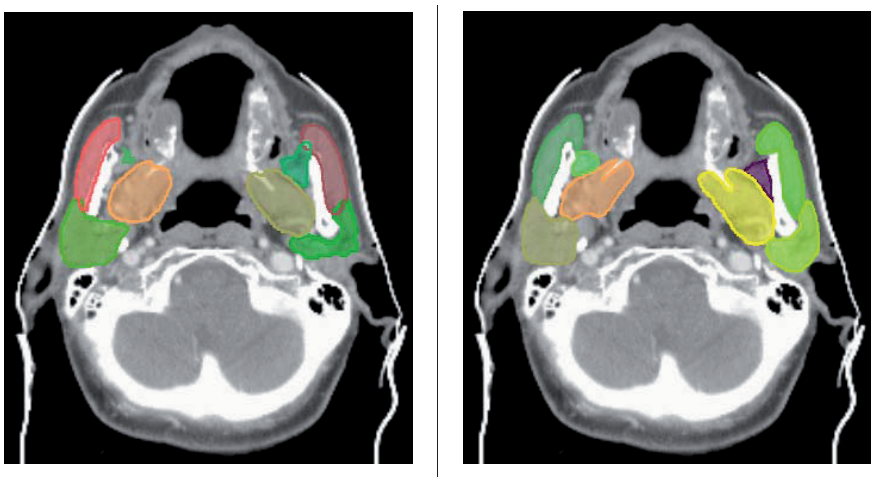

Figure 5: (Left) Autocontouring of organs at risk (mastication muscles and parotid glands) vs. (Right) reference contours (reference standard).

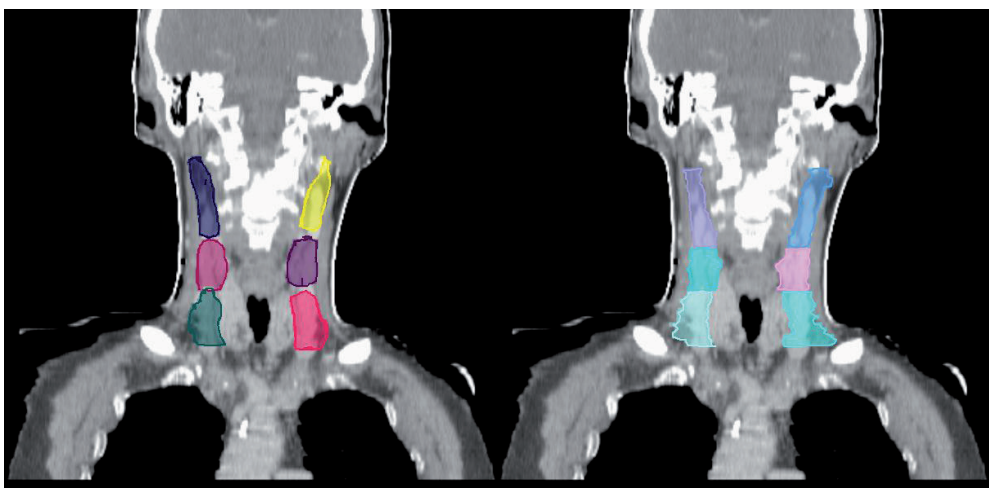

Figure 6: Coronal view of (Left) autocontours of neck levels vs. (Right) reference contours (reference standard).

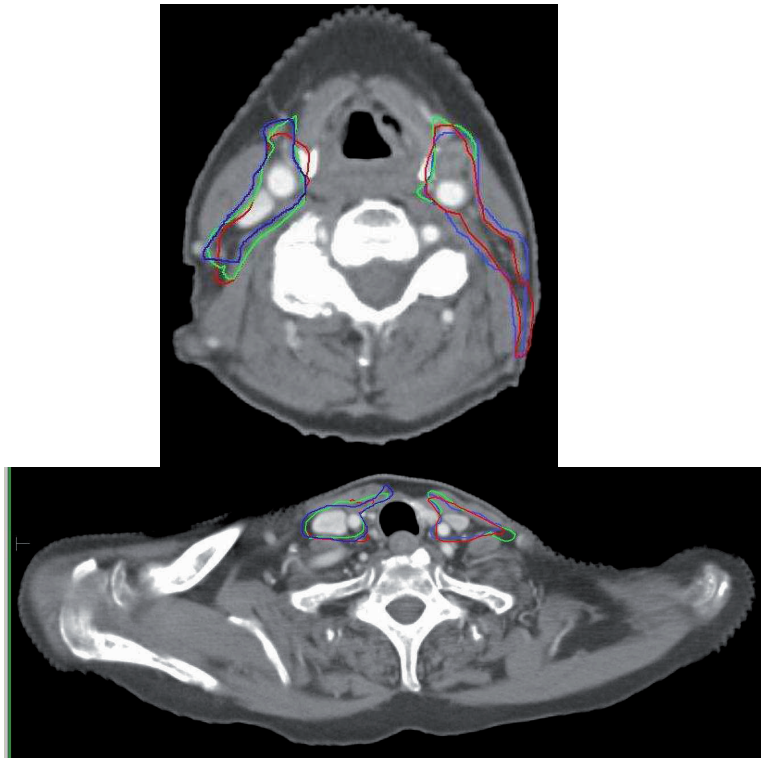

Figure 7: Autocontouring of levels (red) vs. observer contouring (blue and green).

necessarily the accuracy, which was beyond the scope of their study. It should be remembered that the border in N+ patients with invaded muscle in the present group was defined differently than those without invaded muscle. Therefore, the invaded muscle must be manually added to the autocontour of the level [12]. Castadot et al. [14] compared 12 voxel-based deformable registration strategies for adaptive radiotherapy for head-and-neck tumors. Their data set contained 5 patients. They concluded that the level-set Demon's algorithm (voxel-intensity-based registration) implemented in multiresolution is a good strategy for head-and-neck adaptive radiotherapy, because it was the best compromise in terms of the median and interquartile range for the Dice similarity index and correlation coefficient [14].

Sims et al. [17] sought to establish the accuracy of ABAS, such that a priori information was used to delineate a limited set of organs of interest (e.g., brainstem, parotid glands, and mandible). The Dice coefficient for all OARs was 0.68 ± 0.25 for a first center and 0.82 ± 0.13 for a second center. Systematic oversegmentation of the parotids and undersegmentation of the brainstem occurred that required careful review and editing in most cases [17]. They concluded that the autocontours and substantial time reduction in contouring proved that the ABAS would be a useful novel tool in the rapid delineation of neck levels and the limited number of OARs evaluated. Wang et al. [18] mapped contours from the planning CT scan onto daily CT or four-dimensional CT images using an image intensity-based deformable registration algorithm. They also only evaluated a limited set of contours (i.e., clinical target volume, parotid

glands, and brain stem). The volume overlap index ($A \cap B / (A+B) / 2$)) and the mean absolute surface-to-surface distance was 83% and 1.3 mm, respectively. They concluded that a final review by physicians is highly recommended [18]. Commowick et al. [8] presented a method for creating an anatomic atlas of the head-and-neck region from a database of 45 manually delineated CT images. They constructed a mean CT image set with atlas contours from a database of patients. The constructed mean atlas was then applied to a new patient. The evaluation of the built atlas showed good results both qualitatively and quantitatively, although some important structures were not included in their database. Our report described an autosegmentation system with all possibly important (normal tissue) structures needed for treating head-and-neck cancer included. Zhang et al. [16] showed for 7 patients that atlas-based image segmentation can automatically delineate the OARs (i.e., mandible, brainstem, and parotid glands only) on daily CT images. Quantitative validations demonstrated that the method was robust. Their Dice coefficients were slightly lower than ours.
Other studies [19] and [20] have shown anatomic changes in the parotid and submandibular glands during radiotherapy, as assessed using nonrigid registration. The nonrigid registration framework of Vásquez Osorio et al. [20] is an effective method to simultaneously register the anatomic changes of multiple organs with very different magnitudes and complexity. General shrinkage and deformation of the irradiated

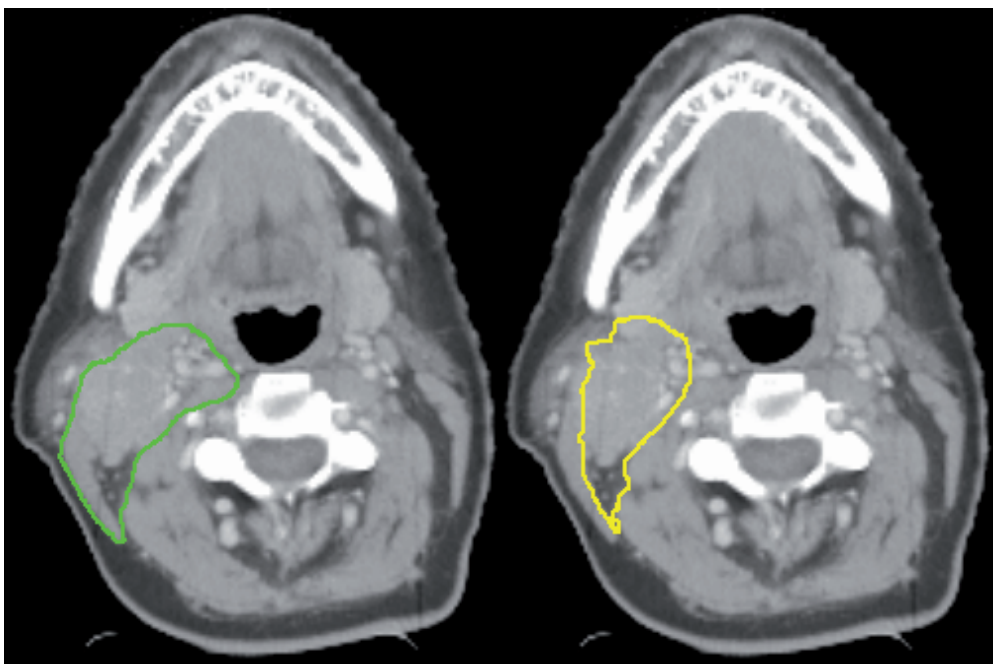

Figure 8: Autosegmentation example for neck level with invaded muscle (reference contour in green and multiple-subject autocontour in yellow). Invaded muscle not included in autocontour because algorithm used level of N0 atlas patients to autosegment involved level of N+ patient. At medial site, some vessels were not encompassed. Both issues were quickly fixed by editing the autocontour.

Variable	Clinical contour vs. AC	Clinical vs. e-AC	AC vs. e-AC	$e\text{-}AC_1$ vs. $e\text{-}AC_2$
Dice coefficient				
Neck Levels	0.73	0.79	0.83	0.81
Parotid glands	0.80	0.81	0.91	0.89
Submandibular glands	0.72	0.77	0.83	0.86
Mean distance ± SD (mm)				
Neck Levels	3.2 ±3.6	2.2 ± 2.8	1.5± 2.8	1.8 ± 2.5
Parotid glands	2.3 ± 3.8	2.1 ± 3.0	0.8 ± 1.2	1.1 ± 1.3
Submandibular glands	1.6 ± 1.4	1.2 ± 1.2	1.4 ± 1.8	1.0 ± 1.1

Table 3: Dice coefficient and mean distance around mean distance of different structures. e-AC= edited auto-contours, $e\text{-}AC_1$ = edited auto-contour of observer 1 and $e\text{-}AC_2$ = edited auto-contour of observer 2.

glands were observed. The spared glands showed few changes.Anatomic changes can be accommodated by repeat planning (adaptive radiotherapy); however, repeat planning requires recontouring of the new CT image or cone beam CT data set, which is tedious and time consuming. In the future, the ABAS tool might be used to ease adaptive radiotherapy.

CONCLUSIONS

Despite the large interpatient variability in the study population, the neck levels and OARs could be accurately contoured using the ABAS tool. The multisubject atlas performed better than the best single-subject atlas. Although the requirement for editing the autocontours was inevitable (66 min for 30 structures), a substantial time reduction was achieved by editing instead of manually contouring. Therefore, the new algorithm for autosegmentation could substantially reduce the clinical workload spent on organ delineation. This is even more relevant, because the edited contours were scored as having similar or better quality than the clinically used contours.

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Discussion

INTRODUCTION

A brief summary of the treatment of head and neck cancer is given in the introduction section of this thesis. More detailed information about oropharyngeal cancer is described in chapter 2. In recent years intensification of therapy for head and neck cancers in general, either by altered fractionation radiotherapy (RT) schemes and/or by the addition of concomitant chemotherapy (CHT), results in improved local–regional tumor control [1,2]. The 5-year survival rate (on the basis of SEER data) for all stages of head and neck cancer is about 60%, but for locally advanced disease still below 40%, despite the multi-modality treatment approaches [3]. Data (actuarial local control (LC), disease free survival (DFS), and overall survival (OS)) at 5 years for cancer of the oropharynx and nasopharynx) from our institute showed a trend for a better outcome for the more recent time periods 2001–2007 as opposed to the time period 1991–1995. Most likely cause is that the treatment regimes used have been modified as per protocol and have become indeed more effective. As from 2000 onwards, all head and neck cancer (HNC) patients were treated by 6 fractions / week (accelerated); as from 1996, concurrent CHT for advanced cancers was introduced. The results obtained by more effective and aggressive treament modalities do not only impact tumor control outcome; for the patients being at least 1 year without evidence of disease, quality of life was investigated for the items dysphagia, sticky saliva, xerostomia, and pain. In short, best quality of life was observed for patients treated curatively and with maximal conformality that is in sequential treatments using boost techniques such as brachytherapy (BT) or stereotactic radiation (Cyberknife) (Chapters 8-10).

Quality of Life: Dysphagia

Intensification of therapy for head and neck cancer in general, results in improved localregional tumor control, although unfortunately, late sequelae do increase as well. For example, the prevalence of dysphagia in organ preservation therapy is reported to be as high as 50% according to some papers on head and neck cancers [4-7], and an aspiration rate of 21–81% with chemoradiation [4,8-14] has been observed. Elevation of the larynx and pharynx during swallowing is essential for protection of the airway and propulsion of the bolus. Eisbruch et al.[15] reported on the toxic effects of concomitant chemotherapy and RT: several months after treatment, aspiration was experienced by 62% of patients [4]. The types of impairments of the swallowing function after radiotherapy are described in the literature as follows: poor pharyngeal motility, with subsequent pharyngeal residue, epiglottic immobility, reduced laryngeal excursion, poor closure of the laryngeal vestibule and aspiration [4,16-20]. Chapter 3 analyzes the dose–volume effect relationships for dysphagia of patients with oropharyngeal cancer treated by 3DCRT and IMRT. The prevalence of grade 3 and 4 dysphagia for the items of the H&N35 ranged from 7% to 18%; the dysphagia RTOG grade 3 and 4 equivalent scores for the M.D. Anderson dysphagia inventory (MDADI) ranged from 21% to 32%. Patients were additionally seen in last follow-up at the outpatient clinic: severe xerostomia (VAS) and grade 3 and 4 dysphagia in long-term follow-up were present at the time of the last follow-up visit in 59% (30/51) and 12% (6/51), respectively. For the late dysphagia grade 3 and 4 (data taken from chart review) significant relationships were found for the superior constrictor muscle (scm)($p = 0.002$), middle

constrictor muscle (mcm)(p = 0.003) and inferior constrictor muscle (icm)(0.006). In the multivariate analysis, if dose (received by the swallowing musculature) and BT are entered simultaneously in the logistic regression analysis for H&N35 (swallowing items), general MDADI, and late dysphagia taken from chart review, only BT remains a significant factor (p = 0.05). The responses obtained by the QoL questionnaires demonstrate that the probability of swallowing disorders increased significantly with dose (±19% per 10 Gy after 55 Gy) in paraticular with regard to the scm and mcm. Chapter 4 analyzes the dose–volume relationships for dysphagia. It relates the late side-effects to the different treatment techniques for widely separated anatomic locations. That is, the primary sites studied were base of tongue (BOT), tonsillar fossa (TF) and/or soft palate (SP), and the nasopharynx. From the series of 132 patients, chart review showed that 24 (18%) patients experienced moderate to severe dysphagia with more problems in patients with BOT (32%) cancer as opposed to patients with cancer of the TF/SP (22%) and NP (6%). Also according to the responses to the QoL questionnaires, swallowing problems are most frequently encountered in patients with tumors of the BOT. Moreover, patients seem to experience more complaints of dysphagia with longer follow-up. If grouped by treatment technique, most severe dysphagia was found in IMRT/3D-CRT compared with BT group and SRT/CBK group. Most significant were the relationships between EORTC H&N35 'Swallowing' complaints and the dose in the superior constrictor muscles / middle constrictor muscles and the association of the PSS (normalcy of diet) and the dose in the scm (p values < 0.01). Xerostomia and dysphagia are strongly associated. Previous findings suggest that BT dose distributions are more sparing to the swallowing musculature as opposed to the CBK/SRT and IMRT techniques.

To differentiate between the intrinsic values of the irradiation techniques used, and whether it is simply because of margins, we computed for the six gross tumor volumes of patients irradiated by CBK, the dose in the scm, mcm, left and right parotid glands, cord, and delineated the PTV with margins of 0, 2 and 5 mm, respectively. In a clinical situation, by comparing a PTV margin of 0 mm in case of BT vs. CBK with 2-mm margin and a 5-mm margin for IMRT, an advantage can be observed for the BT and CBK with respect to the dose contributed to the normal tissues. Margins do seem to have a substantial effect on the dose received by the swallowing muscles. When comparing IMRT, frameless stereotactic robotic radiosurgery and brachytherapy, these modalities can be considered as highly accurate techniques to boost a primary tumor (Chapter 9). Due to the smaller margins, one could arrive at smaller irradiated tumor volumes for BT and CBK, BT and CBK being somewhat more conformal as opposed to IMRT (Chapter 4). Because of the differences in treated volumes, smaller risks for overdosing critical normal tissues and potentially a lower risk for RT induced second malignancies for CBK as opposed to IMRT can be expected. Patients treated with a variety of disease sites (TF/BOT/NPC) and treated by various RT techniques (IMRT/3D-CRT/BT/SRT/CBK) vary in their prevalence of severe dysphagia. Although NPC patients receive the highest dose because of the treatment boost techniques used, sequentially, dysphagia is still less as opposed to patients with cancer of the BOT. The explanation of this phenomenon remains somewhat obscure; it is speculated that this might have to do with the infiltrative (muscles) nature of the BOT cancers.

Chapter 5 compared the Michigan, USA and Rotterdam, NL dysphagia studies. Both

studies found statistically significant correlations between the dysphagia endpoints, including aspiration, and the dose–volume parameters for the scm and mcm. The mechanisms of swallowing and protection from aspiration, as well as our results, suggest that the benefits from efforts to spare the swallowing structures are likely to be maximized if they include the superior constrictor muscles. They motivate efforts to reduce these doses as much as possible using either IMRT or BT, or both.
In chapter 6, the severity of dysphagia was measured by the FEES (Fiberoptic Endoscopic Evaluation of Swallowing) procedure in tumors originating from the tonsillar fossa (TF) and/or SP or BOT. FEES for examining swallowing have some subjective nature. Kelly et al. investigated whether FEES and videofluoroscopy examinations influence the scoring of penetration and aspiration, penetration aspiration is perceived to be greater (more severe) from FEES than for the videofluoroscopy recordings [21]. This has to be taken into account when looking at our data. A total of 24 patients agreed to the FEES procedure. When calculating the total doses received, BT doses were added to EBRT by physical summation. The BT dose contributing to the target is only maximally one-third of the total dose, so the contribution of the BT is even less. Recently Vasquez-Osorio et al. did calculate the 3D summation of BT- and EBRT dose, and concluded that our 'physical dose' summation is a good estimation of the real 3D summation (Chapter 13). For the scm a dose–effect relationship for the total FEES score was found. Also, the total FEES score is correlated well with the capability of swallowing of pureed and solid foods (H&N35), and with the normalcy of diet item from the PSS and total mean score of the MDADI.
Several dysphagia dose-effect relationships findings were reported in chapters 3-6. Because of the limited availability, its clinically silent nature and lack of awareness of objective measures to assess swallowing disorders, the incidence of this dysfunction was up to 2005 underreported [22], although recently there is increased focus on dysphagia as the last few years, more and more data regarding swallowing problems after radiotherapy are published in reputable journals. E.g. Feng et al. demonstrated significant relationships between dose–volume parameters of structures and objective and subjective measurements of swallowing dysfunction [23]. Other groups also showed significant correlations of various dysphagia endpoints with dose: the supraglottic lesions 24 and glottic cancers [24,25]. Other institutions at the same time or later had similar results although sometimes it is difficult to compare as we do not always have exactly the same definitions of the contoured organs at risks [24,26-34].

Quality of Life: Trismus

Xerostomia and dysphagia has been well documented in recent years in patients treated with CHT and/or RT. However few studies examined trismus as was the purpose of the analysis presented in chapter 7. Trismus has a significant impact on the QOL of head and neck cancer patients [35]. Dijkstra et al reported that a reduced opening mouth of 18% (SD, 17%) was found in patients treated by RT involving the structures of the temporomandibular joint and/or pterygoid muscles [36]. The authors found a cut-off point of 35 mm for the inter-incisal distance [37]. Kent et al showed a high prevalence of trismus (47%) in cancer patients following >55 Gy to the masseter and/or pterygoid muscles [38]. Our population studied is based on 81 patients diagnosed with cancer of the oropharynx and treated curatively between 1999 and 2005 by highly conformal radiation therapy techniques. According to the charts no-

tes, 3 (4%) patients experienced trismus. Anatomical structures involved in mastication were defined (masseter, temporalis, pterygoid muscle, condyl, and coronoid process), and the mean dose in each individual structure were computed. Less favorable parameters for trismus complaints were tumors located in the BOT, and treatment by 3DCRT, cCHT, non-BT, and high-dose radiation. None of these factors, however, were found to be significant. The mean measured inter-incisal distance was 39 mm (range, 10-65 mm). In the group of patients with a poor trismus-related QOL (H&N35), being defined as having a score of less or equal than 50%, the mean inter-incisal distances were less (33 mm) as opposed to those patients with a good QOL score (40 mm). Similar conclusions about the inter-incisal distance can be drawn from the chart review (and last follow-up clinic), with chart review showing a significant difference in inter-incisal distance (28 vs. 40 mm) between patients having trismus or no trismus ($p = .0001$). By univariate analysis, a significant relationship was found between dose in the masseter muscles as well as the pterygoid muscles and coronoid bone, and trismus complaints. In the multivariate analysis BT was the only remaining significant factor. For those patients whose trismus-related muscles were irradiated bilaterally, a significant increase of the probability of trismus was observed, but only with regard to the item opening mouth (H&N35, $p = 0.02$). For every additional 10 Gy in the pterygoid muscle, after a dose of 40 Gy, an increase of probability of trismus of 24% was observed. Currently having the availability of IMRT techniques, one may decrease the dose received by putting constraints on masseter and pterygoid muscles. Because of the several reported dose-effect relationships in HNC (chapters 3-7), specific attention deserves the balance between local control and late side-effects.

Brachytherapy

Chapters 8-10 describe BT techniques used in Erasmus MC. BT is an extremely conformal RT technique. Manual afterloading of the sources into applicators or afterloading tubes replaced direct loading of sources into the patient. In skillful, well-trained hands, BT remains an extremely gratifying technique for applying high doses of radiation for small volume disease with highly conformal and accelerated properties. Results for local control of patients treated at the Erasmus MC between 1991 and 2007 were at 5 years 88% for BT and 68% for non BT. Details are described in chapter 9. Selecting the right patients for BT, however, remains important. BT patients were found to have fewer swallowing problems compared with the non-BT group (chapters 9 and 10). Univariate analysis also demonstrated an advantage (ie, less dysphagia) related to T stage, boost treatment, neck surgery, and neck irradiation. The multivariate analysis showed a significant effect for BT (implicating fewer swallowing complaints because of the lower doses of radiation received by the superior swallowing constrictor muscles). The tolerance of the swallowing muscles depends to some extent on the treatment modality used. In patients who receive BT as boost therapy, dysphagia is seen in 14% treated with an average dose of 53 Gy in the swallowing muscle. In contrast, dysphagia was seen in 40% of patients treated with EBRT to a mean dose of 68 Gy in the swallowing muscle. So far, no significant relationship has been seen between quality indices of BT implants and local control, overall survival and/or quality of life.

Hyperbaric Oxygen

When radiation is used to treat cancer, it also (partly) affects a variety of critical surrounding normal tissues, as seen in previously, which can become hypocellular, hypovascular, and hypoxic, frequently eluded to as “3 H tissue.” The hypoxic status of tissues can be counteracted to some extent by oxygenation of normal cells with hyperbaric oxygen treatment (HBOT). The effects of hyperbaric oxygen can be briefly summarized as follows: short-term effects are enhanced by oxygen delivery, reduction of edema, and phagocytosis activation, as well as anti-inflammatory effects. Long-term effects are neovascularization, osteoneogenesis, and stimulation of collagen formation by fibroblasts 39. So a lot of morbidity still exists after radiation therapy in HNC patients especially xerostomia and dysphagia although good results are reported when treating with brachytherapy (Chapters 8-10). It was recently found that a significant increase in mobilization of stem cells from the bone marrow occurs in the course of HBOT [40,41]. Wound healing and recovery of normal-tissue radiation injury are the end result [42-44]. In a review by Bennett et al. 40, the authors concluded that there is some evidence that hyperbaric oxygen improves outcomes in late radiation tissue injury affecting bone and soft tissues of the head and neck, for proctitis, and to prevent the development of osteoradionecrosis following tooth extraction in an irradiated field. Although there are some conflicting experimental results [45], it is now believed that HBOT does not promote cancer growth (primary or metastasis). In the hyperbaric oxygen pilot trial described in chapter 11, we applied 30 sessions of hyperbaric oxygen after the series of radiotherapy. A great benefit for the quality of life of patients was seen in patients who were randomized for hyperbaric oxygen after radiotherapy. A significant difference of different aspects of quality of life was seen for H&N35 ‘swallowing problems’, H&N35 ‘sticky saliva’, H&N35 ‘dry mouth’, visual analogue scale (VAS) ‘Dry mouth’, PSS ‘eating in public’ and VAS ‘pain in mouth’ in favor of the hyperbaric oxygen group. No significant effect of hyperbaric oxygen was shown for early side effects (≤ 13 weeks post-treatment) as opposed to the late side effects (≥ 13 weeks post-treatment). The beneficial effects of how HBOT given shortly after radiotherapy is believed to work, is associated with a number of unknowns. It clearly demonstrates the need for a more detailed exploration of fundamental pathways [46]. Because questions remain regarding HBOT after radiotherapy, currently, a larger randomized HBOT trial is running in a multi-institutional study for more sites in the head and neck, that is besides the oropharynx and nasopharynx also for the oral cavity, hypopharynx and larynx the roleof HBOT is investigated. This trial should confirm our promising results of the pilot randomized study.

Non-Rigid Registration / Atlas-Based Auto-Segmentation

To delineate all the described structures on CT in a busy clinic in this thesis on a daily basis, is extremely time-consuming. To solve this problem, we developed an auto-contouring program in cooperation with an industrial partner (Elekta – CMS Software). The basis of atlas-based auto segmentation (ABAS) is non-rigid registration which is presented in chapter 12. This non-rigid registration method is a powerful tool to accurately assess local shape and position changes in HNC patients. To keep the systematic component of the delineation error small, in this study, the same person delineated both CT scans. When the found transformation was applied to CT scans, a good alignment between the transformed structures and original

contours was found. The local anatomic changes observed in this study were consistent with the global measurements reported in published papers [47-50]. When using the volume decrease rate found by Barker et al. [47] for 23 treatment days, a volume decrease of 13.8% is obtained. The average volume reduction for both parotids in our study was 14%. We observed asymmetric shifts in parotid gland surfaces, with average displacements of 1 ± 3 mm and 3 ± 3 mm for the medial and lateral regions of the irradiated glands, respectively. Our data showed that the planned mean dose is significantly related to the observed parotid gland volume reduction ($p < 0.001$, $r = 0.68$). We have demonstrated that for irradiated parotid glands, the lateral regions (with the lower planning doses) displace inward (i.e., toward the higher doses, with the spared parotid glands presenting little and near homogeneous deformation). Volume reduction and shape and position changes in glands belonging to non-treated necks showed few changes. Glands belonging to treated necks showed a general shrinkage and deformation. Non-rigid registration is an ideal tool with which to perform additional studies in larger patient series to investigate the relationship between the local dose and local shape and position changes in more detail.
With ABAS, the clinician now only has to edit the auto-contour from any given structure: This has proven to be much faster, contouring time is down from 3 hours to 55 minutes (chapter 14). Moreover, in retrospect, the edited auto-contours were somewhat more in concordance with the corresponding levels of this atlas as opposed to the originally contoured levels. Auto-contouring thus seems to be an adquate way to go in daily radiotherapy practice.

CONCLUSION

Oropharyngeal Cancer (Chapter 2)

Good tumor control but late-side effects occur e.g. dysphagia.

Quality of Life: Dysphagia (Chapters 3-6)

Dose-effects relationships in base of tongue, tonsillar fossa and nasopharyngeal cancer are found for swallowing problems.

Quality of Lfe: Trismus (Chapter 7)

Dose-effects relationships in base of tongue and tonsillar fossa are found for trismus problems.

Brachytherapy (Chapters 8-10)

Patient treated by brachyhterapy have better local control, disease-free survival and overal survival than those treated with EBRT. Also BT patients were found to have fewer swallowing problems compared with the non-BT group of patients.

Hyperbaric Oxygen (Chapter 11)

A great benefit for the quality of life of patients was seen in patients who were randomized for hyperbaric oxygen after radiotherapy. A significant difference of different aspects of quality of life was seen for H&N35 ‘swallowing problems’, H&N35 ‘sticky saliva’, H&N35 ‘dry mouth’, visual analogue scale (VAS) ‘Dry mouth’, PSS ‘eating in public’ and VAS ‘pain in mouth’ in favor of the hyperbaric oxygen group.

Non-Rigid Registration / Atlas-Based Auto-Segmentation (Chapters 12-14)

Non-rigid registration method is a powerful tool to accurately assess local shape and position changes in HNC patients. When using ABAS, edited auto-contours were somewhat more in concordance with the corresponding levels of this atlas as opposed to the originally contoured levels.

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16

Nederlandse Samenvatting

Afgelopen jaren is de behandeling van hoofd hals kanker intensiever geworden door andere fractionerings-schema's te gebruiken in de radiotherapie en / of door toevoeging van chemotherapie. Sinds 2000 krijgen alle patiënten met een hoofd hals kanker de bestraling in het Erasmus MC-Daniel den Hoed Kliniek, 6 fracties per weeek. Door middel van een licht geaccelereerd schema is er een verbetering in de locale controle van de tumor nagestreefd. Bijwerkingen na de radiotherapie blijven nog een punt van onderzoek. In hoofdstuk 1 is een samenvatting gegeven van de behandeling van hoofd hals kanker (HHK). Een meer gedetailleerde beschrijving van oropharynx kanker behandeling is in hooofdstuk 2 te lezen.

Kwaliteit van leven en bijwerkingen (slikklachten, droge mond en pijn) na bestraling zijn in de verdere hoofdstukken geanalyseerd in dit proefschrift. Slikproblemen zijn naast de droge mond een veel voorkomende bijwerking na bestraling van HHK die echter tot een paar jaar geleden vaak onderbelicht bleef. In hoofdstuk 3 iwordt een dosis-effect relatie voor dysfagie beschreven: een signifacte relatie tussen de dosis die de musculus constrictor superior ontvangt bij de bestraling en de slikklachten van de patient. De kans op slikklachten stijgt met 19% per 10 Gy toename in de slikspier na 55 Gy. In hoofdstuk 4 is de dosis-effect relatie gerelateerd aan de verschillende radiotherapie technieken en primaire hoofd hals tumor sites. 18% van de 132 patienten die geanalyseerd zijn hadden slikproblemen. Patienten met een tongbasis tumor hadden de meeste problemen (32%) gevolgd door patiënten met tonsiltumoren (22%) en nasopharynx tumoren (6%). Meer slikklachten komen voor bij patiënten die bestraald zijn met IMRT/3DCRT technieken in vergelijking tot brachytherapie en stereotactie / Cybernknife technieken. Xerostomie en dysphagie zijn sterk gecorrelleerd aan elkaar. In hoofdstuk 5 zijn de bevindingen uit Michigan, USA en Roterdam beschreven. Beide instituten hebben min of meer gelijktijdig dezelfde dosis-effect relaties gerapporteerd.

Hoofdstuk 6 presenteert data van de FEES (Fiberoptic Endoscopic Evaluation of Swallowing) in relatie tot de slikklachten ondervonden door de patiënten en de stralingsdosis in de slikspieren. Hierbij werden significante relaties gevonden. In de hoofdstukken 3 tot en met 6 zijn verschillende dysfagie dosis-effect relaties beschreven die tot 2005 ondergerapporteerd zijn gebleven. Nadien zijn er verschillende publicaties verschenen in tijdschriften over slikklachten na de radiotherapie. Hoofdstuk 7 beschrijft het trismus probleem na bestraling van hoofd en hals kanker patiënten. Uit status onderzoek blijkt dat 4% van de patiënten een beperkte mondopening hebben gehad. Anatomische structuren die de beperkte mondopening kunnen veroorzaken zijn gedefinieerd en ingetekend op CT. De gemiddelde stralingsdosis die deze structuren hebben ontvangen zijn berekend en gecorreleerd aan de klacht beperkte mondopening. De gemiddelde mondopening gemeten is 39 mm. Een significante relatie is gevonden tussen de musculus masseter, musculus pterygoid en trismus. Ook een significant verschil is beschreven tussen de patiënten die bilateraal bestraald zijn in vergelijking tot unilaterale bestraling. Voor elke 10 Gy die in de musculus pterygoideus terechtkomt is een toename in kans op trismus van 24% na 40 Gy.

De hoofdstukken 8 tot en met 10 beschrijven de brachytherapie. Een zeer conformele radiotherapie techniek. Goede lokale controle van de tumor is gerapporteerd met brachyhterapie. Minder bijwerkingen zijn gezien wanneer patiënten met een brachytherapie boost (14%) zijn behandeld. Een behandeling met brachytherapie boost geeft gemiddeld een stralings dosis van 53 Gy op de slikspier, in tegenstelling tot een gemiddelde dosis van 68 Gy op de slikspier wanneer patiënten alleen uitwendig bestraald worden.

De hyperbare zuurstof therapie trial om de bijwerkingen van bestraling in het hoofd hals gebied te reduceren is gepresenteerd in hoofdstuk 11. Wanneer normaal weefsel bestraald wordt dan kan deze “3 H weefsel” worden: hypocellular, hypovascular, and hypoxic. De hypoxische status van weefsels kan min of meer bestreden worden door hyperbare zuurstof therapie. In het kort samengevat zijn de korte termijn effecten: reductie van oedeem, fagocytose activatie en anti-inflammatoire effecten. Lange termijn effecten zijn neovascularisate, osteoneogenesis en stimulatie van collageen formatie door fibroblasten. Hoewel er tegenstrijdige experimentele resultaten zijn, is nu min of meer consensus bereikt dat hyperbare zurstof niet tot vermenigvuldiging van kankercellen zal leiden. In de beschreven trial kregen de patiënten met oropharynx of nasopharynx kanker wel of niet een extra behandeling met hyperbare zuurstof na de complete radiotherapie behandeling. De hyperbare zuurstof behandeling bestaat uit 30 sessies van ongeveer 2 uur. Een postief resultaat werd gezien in verschillende aspecten van kwaliteit van leven tussen de patient groepen die wel of niet de behandeling kregen. Vooral de late effecten (13 weken na behandeling) van bestraling zoals slikklachten, droge mond en pijn in de mond zijn duidelijk verminderd in de groep patiënten die de hyperbare zuurstof behandeling hebben gehad. De exacte werking van hyperbare zuurstof in deze groep patiënten is nog in mist verhuld en er is daarom meer fundamenteel onderzoek nodig.

De verschillende normale weefsels die ingetekend moeten worden om het eventueel te sparen bij de bestraling is arbeids intensief. Daarom is een auto-contouring programma een perfect hulpmiddel voor de arts. De basis van atlas-based auto segmentation (ABAS) is non rigide registratie, welke gepresenteerd wordt in hoofdstuk 12. De non-rigid registratie methode ontwikkeld door Vásquez-Osorio is een krachtig instrument om accuraat lokale vorm en positie veranderingen te presenteren in patiënten met hoofd hals kanker. Met ABAS worden de contouren van te voren beschikbaar gesteld aan de arts. Deze hoeft dan de auto-contour alleen nog te wijzigen indien nodig. Dit blijkt inderdaad veel sneller te gaan qua tijd die gespendeerd wordt met intekenen op CT in vergelijking tot het intekenen vanuit een nieuwe CT. De tijd die gereduceerd wordt is van 3 uur tot 55 minuten. De gewijzigde auto-contouren bleken ook nog dichter te staan bij de richtlijn voor hals level intekening.

Conclusies

Oropharyngeal Cancer (Hoofdstuk 2)

Goede tumor controle bij keelkanker bestraling maar late bijwerkingen zoals dysfagie ontstaan na radiotherapie.

Quality of Life: Dysphagia (Hoofdstukken 3-6)

Doisis-effect relaties in patiënten met tongbasis, tonsil en nasopharynx kanker zijn beschreven voor slikproblemen.

Quality of Lfe: Trismus (Hoofdstuk 7)

Doisis-effect relaties in patiënten met tongbasis, tonsil en nasopharynx kanker zijn beschreven voor beperkte mondopening (trismus).

Brachytherapy (Hoofdstukken 8-10)

Patiënten die zijn bestraald met brachytherapie (inwendige bestraling) hebben een betere lokale controle, ziektevrije overleving en totale overleving in vergelijking tot de patiënten die uitwendig bestraald zijn. Ook hebben patiënten behandeld met brachytherapie minder slikklachten.

Hyperbaric Oxygen (Hoofdstuk 11)

Patienten die gerandomiseerd waren voor hyperbare zuurstof behandeling na radiotherapie hebben in verschillende kwaliteit van leven items (oa. sliklkachten, droge mond) een betere score dan degenen die geen hyperbare zuurstof behandeling hebben gehad.

Non-Rigid Registration / Atlas-Based Auto Segmentation (Hoofdstukken 12-14)

Non-rigide registratie methode is een krachtig instrument om accuraat lokale vorm en positie veranderingen te presenteren in hoofd hals kanker patiënten. Met ABAS wordt tijd die gespendeerd wordt met intekenen van CT gereduceerd en zijn de uiteindelijke gewijzigde ingetekende structuren meer in overeenkomst met de atlas richtlijn dan de oorspronkelijke intekeningen.

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Acknowledgements
Curriculum Vitae
List of Publications

Curriculum Vitae

David Teguh studied medical information science for three years at the University of Amsterdam / Academic Medical Centre. Afterwards he studied medicine at the VU University Medical Centre, also in Amsterdam. During his medical school he did clerkships / internships at the Nihon University in Tokyo, at the UKI hospital in Jakarta and at the UGM /Sardjito Hospital in Yogyakarta and attended a 2 days Formula 1 Medical Seminar in Kuala Lumpur. After obtaining his medical degree he is employed at the department of radiation oncology at the Erasmus MC University Medical Center / Daniel den Hoed Cancer Center. During this period he attended the following courses: Evidence-based radiation oncology, a clinical refresher course with a methodological basis from ESTRO (self-sponsored), the workshop animal imaging by AMIE (Applied Molecular Imaging Erasmus MC), from mouse to man, and a workshop on Photoshop and Illustrator CS4. In weekends he is sometimes part of the medical team at motor, autosport and rally events.

Presentations (outside Erasmus MC)

- Comprehensive Cancer Centre West, Leiden 2005
- World Congress on Oncology of the International Academy of Oral Cancer, Amsterdam, 2007
- Paramedical Working Group Head and Neck Cancer, The Hague, 2010
- Dr. Cipto Mangunkusumo Hospital, Jakarta, 2010
- Dr. Sardjito Hospital, Yogyakarta, 2010
- 19th Annual Radiation Oncology Elekta Users Meeting, San Diego, 2010

BOOKS (CHAPTERS):

- Perez and Brady's Principles and Practice of Radiation Oncology; 5th edition, Edward C. Halperin, Carlos A. Perez, Luther W. Brady; Lippincott Williams and Wilkins; December 2007. Chapter 42: Oropharynx; Peter C. Levendag, David N. Teguh, Ben J. Heijmen. ISBN: 978-0-7817-6369-1.
- Contouring in Head & Neck Cancer. Peter C. Levendag, Abrahim Al-Mamgani, David N. Teguh. 2009. Elsevier Professional Education. ISBN 978-3-437-59904-0.
- Robotic Radiosurgery, Vol. 1 by Richard F. Mould (Editor), Raymond A. Schulz (Editor), R. D. Bucholz (Editor), G. J. Gagnon (Author), P. C. Gerszten (Author), J. J. Kresl (Author), P. C. Levendag (Author), R. A. Schulz (Author). Chapter 21: Future Role for Cyberknife in organ preservation of Tonsillar Fossa & Palate Tumors, Peter C. Levendag, Peter Voet, David Teguh, Henrie van der Est, Erik de Klerck, Willy de Kruijf, Cees Meeuwis, Mischa Hoogeman, Ben J.M. Heijmen. 2005. ISBN: 978-0-975312414.
- Function Preservation and Quality of Life in Head and Neck Radiotherapy. Section Treatment Techniques with Potential Impact on Quality of Life. Edited by P.M. Harari, N.P. Connor, and C. Grau. Chapter XI: Dysphagia Related Quality of Life of Patients with Cancer in the Oropharynx: An Advantage for Brachytherapy? Peter C. Levendag, M.D., Ph.D., Peter van Rooij, M.Sc., David N. Teguh, M.D., Inge Noever, R.T.T., Peter Voet, R.T.T., Henrie van der Est, R.T.T., and Paul I. M. Schmitz, Ph.D. Springer, 2009. ISBN : 978-3-540-73231-0.
- Head and Neck Cancer: Multimodality Management. Edited by Jacques Bernier. Chapter 11: Interstitial Radiation Therapy in Cancer of the Orophayrnx and Oral Cavity. Peter C. Levendag, M.D., Ph.D., David N. Teguh, M.D. and Paul I.M. Schmitz. Springer, 2011. ISBN: 978-1-60327-934-5.

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3. Levendag PC, Teguh DN, Voet P, van der Est H, Noever I, Sewnaik A, van Rooij P, de Kruijf W, Schmitz PIM and Heijmen BJ. Dysphagia related quality of life of patients with cancer in the oropharynx is significantly affected by the radiation therapy dose received by the superior- and middle constrictor muscle: A dose-effect relationship. International Journal of Radiation Oncology Biology Physics 2006;66:S132-S133. Abstract Oral Presentation ASTRO, Philadelphia 2006.

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