Prevention of normal tissue complications in radiation therapy of head and neck cancer

The role of 3D conformal radiation therapy (3DCRT)

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The role of 3D conformal radiation therapy (3DCRT)

Preventie van schade aan de gezonde weefsels bij radiotherapie van hoofd-hals carcinomen

De rol van 3D conformatie radiotherapie (3DCRT)

PROEFSCHRIFT

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Wees niet bevreesd langzaam vooruit te komen maar wel stil te blijven staan.

Chinees spreekwoord.

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CHAPTER 1

Introduction

1.1 RADIATION THERAPY FOR HEAD AND NECK CANCER PATIENTS

Head and neck cancers are an important group of tumors with respect to morbidity and mortality (1-4). In 1997 the number of new cancer patients in the Netherlands was approximately 58,500. Head and neck malignancies were diagnosed in 2300 patients and constituted thereby the sixth most frequent invasive tumor in males (4.9%) and the eighth most frequent invasive tumor for the entire population (3.9%). The male/female ratio for head and neck tumors is approximately six. The most frequently encountered head and neck tumor site is the larynx with a total of 712 cases (604 males and 108 females) in 1997 (5). Of all cancers in the head and neck, approximately 48 % are treated by radiation therapy only, 23% by surgery only, and 19 % by combined modality (surgery and radiation therapy) (6-8). Both radiation therapy as a single modality and chemoradiation therapy play an important role in organ preservation protocols (9-11).

Radiation therapy (RT) is the clinical application of ionizing radiation to eradicate malignant tumor cells. By direct or indirect interaction, radiation can induce (ir)reparable DNA damage in the cells resulting in direct cell kill or apoptosis (12,13). Unfortunately the radiation effect is not limited to tumor cells but affects normal tissue cells as well. The normal tissue tolerance for radiation is in fact the most important limiting factor in the application of radiation therapy; optimal radiation therapy implies delivering a maximum dose of radiation to the tumor while keeping the dose to the surrounding normal structures below tolerance (14-17). Most frequently radiation is delivered by external beam radiation therapy (ERT) using a linear accelerator (18). Brachytherapy is another mode of delivering radiation therapy; usually brachytherapy is delivered as booster after ERT. High-dose-rate (HDR) or low-dose-rate (LDR) brachytherapy using radioactive sources either interstitially, endocavitary or by using a mould technique, is characterized by a rapid dose fall-off.

To reduce the risk of late normal tissue complications, hyperfractionation (HF) has been advocated. Hyperfractionation schedules deliver the prescribed tumor dose in multiple (small) fractions per day. In HF the difference in the fractionation sensitivity between rapidly (tumor) and slowly renewing, late reacting normal tissues, is exploited (19,20). Another important phenomenon predicted by radiobiological models is the effect of shortening the overall treatment time (OTT). This reduction in OTT can improve tumor control by minimizing accelerated repopulation of tumor cells which often starts 2 to 3 weeks after treatment. This accelerated repopulation accounts for approximately 0.5 to 1 Gy loss of

tumor dose effect per day of treatment extension (21-23). Accelerated fractionation (AF) schedules deliver the prescribed tumor dose in a shorter OTT by giving more fractions per week or per day either during the whole series or for only a part of the treatment (concomitant boost therapy) (24). AF schedules are almost invariably accompanied by an increase of early normal tissue reactions in particular mucosal reactions (25-27).

ERT has developed from conventional techniques using standard beam portals based upon the bony anatomy to CT-based 3D conformal radiation therapy (3DCRT). Recent developments in ERT delivery and treatment planning are stereotactic radiation therapy (SRT) and intensity modulated radiation therapy (IMRT). In conformal radiation therapy the goal is to conform the dose distribution to the target volume and to minimize the dose delivered to the surrounding normal structures (28). In 3DCRT the target volume is defined in three dimensions on a planning CT-scan. The so called beam's eye view (BEV) option of the treatment planning system is used to shape the individual x-ray beams to the two-dimensional projection of the target. This process of beam shaping eventually results in a three dimensional dose-distribution around the target. Classically plan optimization is realized by iteratively changing of e.g. weights, wedges, number and direction of beams (29,30).

The next technological step to increase conformality and thereby the therapeutic ratio is the application of intensity modulated radiation therapy (IMRT). IMRT techniques use modifications in the intensity of the beams across the beam portals as an additional degree of freedom to enhance the capability of conforming dose distributions in three dimensions. IMRT can yield dose distributions that conform closely to the three dimensional shape of the target volume while still avoiding high doses to the critical normal structures. By limiting the dose received by the normal tissues one can either dose-escalate with the potential of increased tumor control and/or decrease the incidence of (late) normal tissue complications and thus increase the chance of a complication-free tumor control (31-34).

Increasing the effectiveness of RT can also be achieved by the combination with concurrent chemotherapy (i.e. chemoradiation) (35-37). Meta-analyses of the role of chemotherapy in advanced head and neck cancer suggest an absolute survival benefit of 8% for the combination radiation therapy with concurrent chemotherapy (38). This is in the same order of magnitude as the gain achieved with AF schedules. Toxicity, especially acute toxicity, of altered fractionation schedules and chemoradiation in head and neck cancer patients, however, is of major concern (25,26,39,40). The radiation-induced toxicity can be minimized by excluding (parts of) the organs at risk out of the irradiated volume and/or reducing the radiation dose received by the normal tissues (e.g. conformal RT) (41). Radiation-induced

toxicity can also be minimized by enhancing the tolerance to radiation of the organs / structures at risk. The tolerance dose can be increased by using radioprotectors (e.g. amifostine) (42-44) and in the future by modifying the effects of radiation-induced inflammatory cytokines or by the application of other biologic modifiers of early reactions, such as growth factors (15,45-51).

Finally, the use of more conformal dose distributions has put great emphasis on the accuracy of target definition (52-57). In radiation therapy of head and neck tumors one of the important target volumes for which CT-based delineation definitions are mandatory is the clinical target volume (CTV) of the (un)involved cervical lymph nodes. How to decide which lymph node regions have to be included in the target volumes and how to delineate these lymph node regions on CT-scans is crucial in developing highly conformal treatment plans for head and neck cancer patients (58,59). Even more difficult and in need of standardization is the contouring of the various primary tumor sites.

1.2 OUTLINE OF THE THESIS

The potential of causing severe late normal tissues complications is a limitation of radiation therapy, in particular for the application of dose-escalation protocols (17,60,61). A significant late and not infrequently a permanent complication of radiation therapy for head and neck cancers is xerostomia or the so-called dry mouth syndrome (62-65). Xerostomia has a negative impact on basic functions in life such as eating, speech and sleep and can contribute to severe dental decay with an increased risk of osteoradionecrosis. Xerostomia and all of its interrelated problems is a major determinant in diminished quality of life (QOL) of head and neck cancer patients (66-75). In Chapter 2 the extent of the xerostomia problem in a population of long-term survivors is addressed. In addition to this inventory a simplified scoring instrument for evaluating the subjective impact of xerostomia was developed. The severity of the xerostomia problem and the virtually total lack of adequate therapeutic options was one of the reasons to explore the possibilities of 3DCRT for treating head and neck cancer patients. For the parotid gland a threshold mean dose of 26 Gy is reported; doses lower than this threshold resulted in a time-related recovery of the stimulated parotid gland salivary flow rates (76,77). It was argued that 3DCRT techniques might be a way to overcome the problem of xerostomia, that is a method to spare the major salivary glands from radiation.

The execution of conformal radiation therapy requires delineation of both target volumes

and critical normal structures (53,54). In treating head and neck cancer patients delineation protocols for the cervical lymph node target volumes, both the clinical target volume (CTV) and the planning target volume (PTV) are an absolute prerequisite. The first step towards conformal radiation therapy therefore was the development of a CT-based delineation protocol for the lymph node levels in the node negative neck. In the surgical literature Robbins *et al.* developed, on behalf of the American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS), a standardized system of terminology for neck dissections (78-80). This classification was based upon the lymph node level system as originally proposed by the Memorial Sloan-Kettering Cancer group (81). In the Robbins classification the neck is divided into six levels, including eight nodal groups. These surgical lymph node levels I to VI were translated into CT-based lymph node region definitions 1-6 (Chapter 3). Although this delineation protocol meets the requirements of standardization of the CTV, an important drawback of the implementation is the labor-intensive nature of the protocol. In order to facilitate a more general acceptance and introduction of conformal radiation therapy techniques, also in a busy radiotherapy department, a simplified version of the neck nodal delineation protocol was constructed. The simplified CT-based definitions for delineation of the cervical lymph node levels I to V are described in Chapter 4.

Another important dose-limiting side-effect is radiation-induced mucositis (82-84). The control of acute mucositis would enable intensification of (combined modality) radiation therapy (25,26). Many attempts to treat and/or prevent radiation-induced mucositis have been reported, none of which proved to be effective when tested in randomized controlled trials (85-87). Encouraging results were reported from selective elimination of the pathogen oral flora by using a combination of antibiotics (88-90). In Chapter 5 a randomized study on prevention of radiation-induced mucositis by using a combination of the antibiotics polymyxin E, tobramycin and amphotericin B (PTA) for selective elimination of oral flora pathogens is presented.

Modern 3D treatment planning systems (TPS) have tools to objectivate dose distributions and tools to localize the anatomical position of critical structures in relation to beam portals (i.e. the BEV-option). The importance of these tools in predicting radiation-induced (late) toxicity and thereby also the possibility to prevent these complications by conformal techniques is illustrated in the next chapter (91,92). In Chapter 6 a case of bilateral radiation-induced optic neuropathy is described after combined modality treatment (chemotherapy, ERT and brachytherapy) for a T4N2c nasopharyngeal cancer (93-95). The unexpected high dose in both optic nerves was due to inadequate shielding of the optic nerves. The shield-

ing (customized blocks) was based upon bony structures as seen on simulation films of conventional lateral radiation therapy portals. Exact positioning of the shielding using the BEV-option and dose-volume histogram (DVH) calculations of the optic nerves and chiasm could have prevented this complication (96-98).

Chapter 7 illustrates the potential of an increased tumor control probability (TCP) by dose escalation and treatment-intensification for high risk nasopharyngeal cancers. The combination of ERT with fractionated high-dose-rate endocavitary brachytherapy (BT) results in a cumulative dose of over 80 Gy to the nasopharynx proper. This high dose has been proven to be very effective, especially in early stage (T1,T2a) nasopharyngeal cancers (99,100). In advanced nasopharyngeal cancers, treatment intensification by adding chemotherapy (CHT) to the high-doses of radiation is now becoming standard therapy (101-104). In Chapter 7 the value and limitations of a boost dose of radiation by means of BT and the role of CHT in treating stage III-IVB nasopharyngeal cancers are discussed. For advanced tumors, apparently BT inadequately covers the primary target volume; stereotactic radiation therapy (SRT) and IMRT can probably overcome this problem (Chapter 8) (105-110).

In the evolution towards 3DCRT and IMRT the next step was the implementation of treatment planning tools for target dose optimization (30,33,111-113). In Chapter 9 a simple and fast algorithm for calculation of beam profiles and physical target dose optimization is described. A simplified IMRT technique for radiating cancers of the larynx and oropharynx, with dose- and volume sparing of the major salivary glands, was compared to a conventional treatment plan and is discussed in this chapter (planning study).

The feasibility of this approach and the initial promising results of the planning study in terms of major salivary gland sparing resulted in the clinical implementation of this IMRT technique for patients with a T1-4N0 supraglottic laryngeal cancer (Chapter 10). The developmental steps as mentioned in the previous chapters, that is from conventional radiation therapy towards IMRT, converge in this study. The preliminary results of this study in terms of salivary gland sparing and xerostomia are presented in chapter 10. Moreover, a comparative planning study is presented, comparing the simplified IMRT technique with more advanced IMRT techniques (76,77,114-121).

Finally, in Chapter 11 the future prospects of improving complication-free locoregional control and survival in head and neck cancer patients using conformal radiation therapy techniques, are discussed (122-126). With regard to diminishing the side-effects, priority is given to the elimination of the 'dry mouth syndrome' (63-65,127,128) as well as reduction of the degree of mucositis.

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CHAPTER 1

CHAPTER 2

Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors

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ABSTRACT

Background: *Xerostomia can have a significant impact on quality of life of patients treated by radiation therapy (RT) for cancer in the head and neck. The first aim of the study was to evaluate the degree of xerostomia in 39 long-term survivors, treated between 1965 and 1995 by conventional 2D- radiation therapy and currently without evidence of disease. The second aim was to develop a concise instrument to evaluate the subjective aspects of xerostomia.*

Methods: *A newly developed questionnaire and a visual analog scale (VAS) were used in analyzing the degree of a dry mouth and xerostomia-related problems. The radiation dose received by the major salivary glands was estimated by analyzing 2D simulation films.*

Results: *Sixty-four percent of the patients experienced a moderate to severe degree of xerostomia. In the multivariate analysis 3 questions, regarding dry mouth, eating and speech, were particularly discriminatory for establishing the degree of xerostomia as expressed by the VAS-score.*

Conclusions: *In the current survey, 64% of long-term survivors, after treatment by conventional 2D radiation therapy for a malignancy in the head and neck region, still experienced a moderate to severe degree of permanent xerostomia. A simplified instrument to evaluate xerostomia subjectively can consist of the VAS-score and three graded questions.*

CHAPTER 2

2.1 INTRODUCTION

The dry mouth syndrome is one of the most frequently encountered late side effects and usually a combination of interrelated side effects after conventional radiation therapy of tumors in the head and neck(1-5). Xerostomia has implications for important basic functions such as speech, chewing and swallowing and can have major consequences for dentition (6-13). Quality of life in patients treated for head and neck tumors is strongly influenced by xerostomia and all its ramifications (14-20). An effective therapy to treat salivary gland dysfunction and xerostomia does not exist as yet; prevention is mandatory (21-35). Currently implemented advanced radiation techniques, such as 3D conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT) focus on sparing (part of) the major salivary glands from radiation and thus reducing xerostomia (36-43). Altered fractionation schemes, such as accelerated fractionation and hyperfractionation, as well as combined modality treatment (chemoradiation) are currently implemented in multi-modality treatment of cancer of the head and neck. These newer strategies have the potential of improving tumor control and survival with preservation of organ function. However, in particular regarding accelerated fractionation schedules and/or concomitant chemotherapy (chemoradiation), there is an associated risk of increasing the acute and late morbidity as well (44-46). Introduction of any new treatment requires evaluation of the effectiveness of the treatment in terms of tumor control, functional status and overall well-being of the patients. In order to determine the most effective treatment with the least amount of side effects, it is of utmost importance to have a disease-specific, health related quality of life instrument and a reliable system for grading and registration of acute and late treatment related side effects. However, not only an objective evaluation of side effects is important but also the subjective impact of the somatic problems must be evaluated (47,48). With respect to grading and registration of late radiation sequelae major efforts are put into development of comprehensive system(s) (48-50). The SOMA-LENT system addresses late effects per organ system and / or structure (49). The subjective and objective aspects of xerostomia are scored in the salivary gland section. This scoring system still needs further validation. Also, knowledge concerning the tolerance dose and volume of the parotid gland is increasing; for instance Eisbruch calculated that to maintain a stimulated salivary parotid flow the mean dose of the parotid gland must be kept below 26 Gy and for the unstimulated flow the mean dose may not exceed 24 Gy (41,43,51). However, the correlation between objective measured parotid salivary flow rate, the dose distributions (DVH) of the

major salivary glands and the severity of subjective complaints of a dry mouth appears not to be unequivocal (9,27,52-56). Apparently, with regard to xerostomia the subjective appreciation is what matters most to a patient. The current paper is mainly focused on subjective parameters regarding chronic xerostomia.

2.2 MATERIALS AND METHODS

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

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

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

2.2.2 Patient selection: The patients were selected from three different, partially overlapping databases taken from the main database of the department of Medical Statistics of the Erasmus Medical Center-Daniel, spanning a time period of 30 years (1965-1995). Each of the three databases had been used previously for the purpose of evaluating particular clinical issues in different tumor sites treated by radiation therapy. The first database consisted of 151 patients treated for nasopharyngeal carcinoma between 1965 and 1995 (57). The patients of the second database (n = 110) were treated for an oropharyngeal carcinoma by

external radiation therapy (ERT) between 1975 and 1985 or by the combination of ERT and interstitial radiation therapy (IRT) between 1990-1994 (58). The third data base contained all patients (n =1493) treated in our institution between 1965 and 1985 for a head and neck malignancy by radiation therapy with curative intent (59). The data set of the third database was partly corrected because of overlapping the other two databases. Patients selected from these three data bases had to meet the following criteria: primary radiation therapy to the primary tumor with at least one side of the neck receiving a dose of 40 Gy or more; follow-up time since end of radiation therapy of at least two years; no signs or history of recurrence or second primary in the head and neck region. Due to the long time span of 30 years the majority of the patients had already died at time of this inquiry, resulting in a list of only 87 patients after the first selection from the three databases. Of these 87 patients 47 could be reached by phone and 41 consented in participation with the inquiry. After oral consent the questionnaire was send out; a return envelope was included for return of the VAS-form and an appointment was made for evaluation of the questionnaire by telephone, one week later. Thirty-nine patients responded to the telephone appointment and 36 returned their VAS-form. Table 1 summarizes the patient and treatment characteristics.

2.2.3 Radiation therapy technique: All patients were treated by conventional 2 dimensional (2D) radiation therapy techniques and conventional fractionation schedules. Patients were treated in supine position using an immobilizing head cast. The primary and the upper and middle cervical node levels were generally treated with two lateral parallel-opposed photon beams (4 or 6 MV), when necessary an abutting anterior photon beam was added to cover the lower cervical node levels. The posterior neck was taken off cord after 40 or 46 Gy and was supplemented with 10 MeV electrons if appropriate. In four patients with a nasopharyngeal tumor, the nasopharynx was boosted after a dose of 70 Gy ERT with intracavitary brachytherapy. Of further relevance is that 29 patients were irradiated to the primary and (bilateral) upper neck by external beam radiation therapy (ERT) to a cumulative tumor dose of 60 to 70 Gy. In 10 patients with an oropharyngeal tumor, the primary and the neck were irradiated to a dose of 46 Gy using ERT; subsequently, the booster dose to the primary was given by interstitial radiation therapy (IRT, 24-26 Gy). Five of these 10 patients underwent a neck dissection at time of the implantation for IRT.

2.2.4 Estimation of irradiated salivary gland volume: The irradiated volume of the major

Table 1. Patient Characteristics

PARAMETER	STUDY GROUP n = 39
AGE	31-85 years mean 64.7 years
SEX: male / female	27 / 12
FOLLOW-UP at time of evaluation since end of radiotherapy	3 – 22 years mean 9.6 years
TUMOR SITE /STAGE (TNM 1997)	
Nasopharynx:	14
T1	-
T2	9
T3	4
T4	1
Oropharynx:	15
T1	4
T2	7
T3	4
T4	-
Larynx:	9
T1	4
T2	3
T3	1
T4	1
Hypopharynx	1
T4	1
NODE STAGE	
N0	20
N1	6
N2	13*
RADIATION DOSE	
definitive ERT	
60 – 69 Gy	8
70 Gy	18
>70 Gy	3
ERT (46 Gy) + IRT	10†
SURGERY	
Neck dissection	
none	32
unilateral	4
bilateral	3

* N2 stage, not further specified

† Exclusively patients with an oropharyngeal carcinoma of the tonsillar fossa or soft palate.

salivary glands (i.e. both parotid and submandibular glands) was estimated for each radiation portal on simulation films using a 2D template. The template was composed of 10 randomly chosen lateral beams-eye-view (BEV) projections of the parotid and submandibular glands. From these 2D projections an average standard salivary gland 'volume' was chosen. A super-imposable template with grids of one by one cm was used to estimate the irradiated gland 'volume' (surface) and was expressed as a percentage of the total salivary gland standard 'volume'. The salivary gland 'volume' receiving a dose of 40 Gy or more was recorded. As all patients were treated by conventional 2D radiation therapy techniques, no information from CT scans was available. Due to this lack of CT-information, precise CT based dose and volume calculations, that is a dose volume histogram (DVH) analysis of the salivary glands could not be performed. Instead of DVH calculations we used, as a crude substitute, a 2D estimation for the 'radiation burden' of each salivary gland. The 'radiation burden' is the product of the 2D estimated irradiated gland volume (Vi) as a percentage of the total volume and the external radiation dose (Di) for that specific radiation field. The total radiation burden (B) is the sum of all partial radiation burdens:

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

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

2.3 RESULTS

2.3.1 Questionnaire and VAS-score: Table 2 summarizes the results of a selection of the most important questions of the questionnaire and the results of the VAS-score. All 39 patients complained of a dry mouth; 28% (11 patients) had considerable more complaints than before radiation therapy (G3) and 36% (14 patients) had permanent complaints of a very dry mouth (G4). The overall severity of xerostomia as expressed by the visual analog scale

Table 2 Results of a selection of the questionnaire and the VAS-score

QUESTION*	NASOPHARYNX number of ptn	OROPHARYNX number of ptn	LARYNX number of ptn
Dry mouth			
G1G2	3	6	5
G3G4	11	9	5
Night rest			
0	3	6	3
1-2	5	5	5
>3	6	2	2
unknown	-	2	-
Drink to Speech			
G1G2	3	8	7
G3G4G5	11	6	3
unknown	-	1	-
Drink to Eat			
G1G2	4	6	5
G3G4	10	9	5
Feeding pattern			
G1G2	13	10	9
G3G4	1	4	1
unknown	-	1	-
Bottle of fluid			
G1G2	5	10	8
G3G4G5	9	5	2
Tooth decay n / n	9 / 9	4 / 6	2 / 2
VAS-score			
G1 = VAS ≤ 2.4	0	4	4
G2 = VAS 2.5–4.9	3	3	2
G3 = VAS 5 – 7.4	4	5	1
G4 = VAS ≥ 7.5	5	3	2
unknown	2	-	1
mean VAS	6.7	5.3	4.1
range	3.6 - 9.8	0.5 - 9.7	0.4 - 9.4

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

varied from 0.4 to 9.8 with a mean of 5.4. Distribution by tumorsite: The mean VAS-score increased with localization of the tumor: 4.1 for the larynx, 5.3 for the oropharynx and the highest score of 6.7 for the nasopharynx subgroup. A statistical significant difference between the subgroups, however, was not found (*Figure 1*). In the univariate analysis most graded questions of the third section showed a significant correlation with the VAS-score. The strongest correlation was found between the VAS score and the question addressing xerostomia in general ($p = 0.0001$). In the multivariate regression analysis three questions contributed significantly to the severity of xerostomia as expressed by the VAS-score:

1. "How severe is your dry mouth problem" (G1 = normal; G2 = more xerostomia than before radiation; G3 = considerable worse than before radiation; G4 = permanent complaints of an extreme dry mouth);
2. " Do you need to sip water to facilitate eating" (G1 = no; G2 = sometimes, depending on the quality of food; G3 = more than previously; G4 = a sip of water with every bite of food);
3. "Do you need to drink to facilitate speech" (G1 = never; G2 = occasionally; G3 = regularly; G4 = always; G5 = even have to interrupt speaking to take a sip of water).

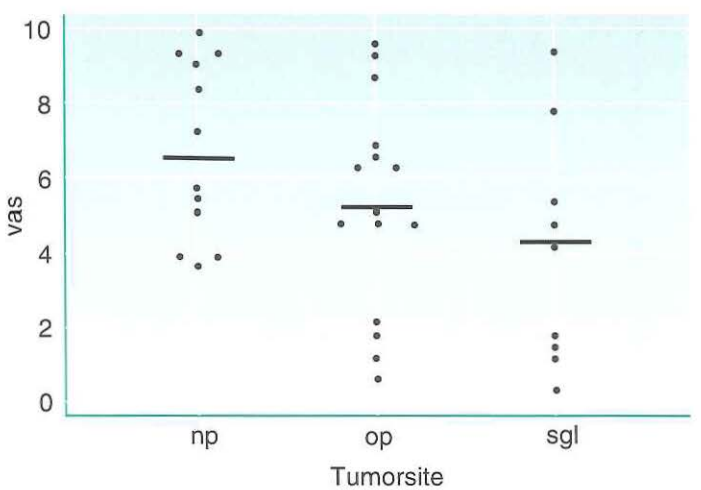

Figure 1. The correlation between VAS-score and tumor site shows a trend without reaching statistical significance. The horizontal bars indicate the mean values. Each dot represents one patient. np = nasopharynx; op = oropharynx; sgl = supraglottic larynx.

An overall xerostomia index (I) was calculated based upon these 3 questions:

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

Q1 = grade of question 1

Q2 = grade of question 2

Q3 = grade of question 3

g1, g2 and g3 are weighing factors of respectively 15.8, 8.5 and 5.9

K = a constant factor of – 33.2.

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

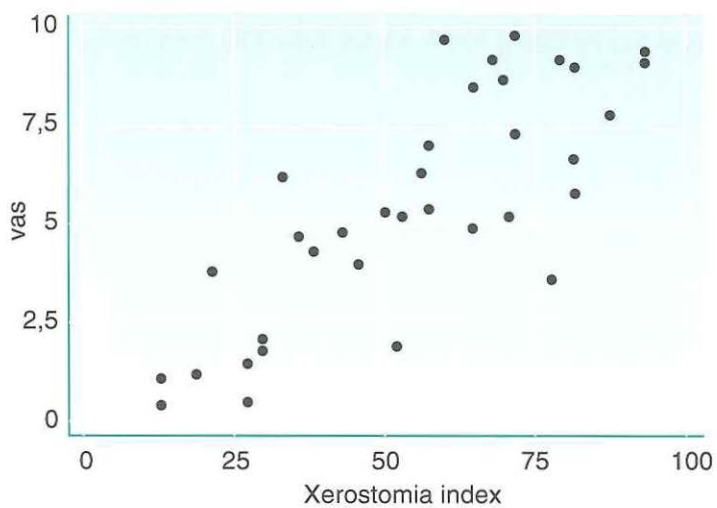

Figure 2. This graph shows the linear correlation between the VAS-score and the overall xerostomia index (I).
$I = Q1 \times g1 + Q2 \times g2 + Q3 \times g3 + K$.
Q1, Q2 and Q3 are the severity grades of three questions; g1, g2 and g3 are weighing factors, of respectively 15.8, 8.5 and 5.9; K is a constant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

2.3.2 Radiation therapy parameters (Table 3): The initial radiation portals were irradiated to a cumulative dose of 40 to 50 Gy and encompassed at least 65% of the left parotid gland volume, at least 45% of the right parotid gland volume and more than 95% of the submandibular gland volumes. After the field reduction still a considerable part of the salivary glands were within the treatment portals, with exception of the 10 oropharyngeal patients

Table 3. Radiation Parameters of the Major Salivary Glands

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

* 1 patient received radiation therapy to the right side only
† 10 patients were boosted by IRT and 5 patients received an ERT booster dose; 2 of these 5 were irradiated to one side of the neck (one left and one right).

who received IRT. The parotid glands were not encompassed by the reduced booster fields of the laryngeal cancer patients, however the submandibular glands could not be spared. Moreover, five oropharyngeal patients underwent a neck dissection with removal of the submandibular gland(s). The 'radiation burden' of the parotid glands shows the same trend as the VAS-score; the lowest values in the laryngeal group and the highest values in the nasopharyngeal group. Statistical significance between the tumor site subgroups and the radiation burden was not found, neither was a significant correlation detected between 'radiation burden' and VAS-score *(Figure 3)*.

2.4 DISCUSSION

Xerostomia is a serious, permanent and almost ubiquitous problem in patients treated by full course radiation therapy for a head and neck malignancy, especially when using con

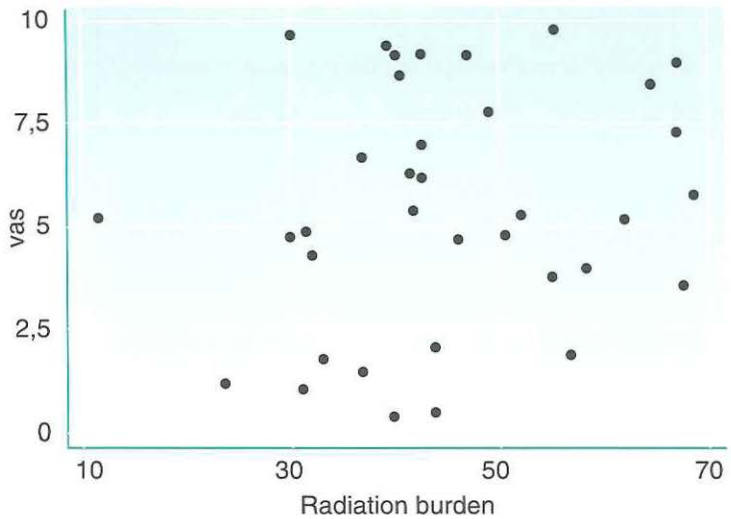

Figure 3. The lack of correlation (r = 0.16; *p = 0.35*) between the VAS-score and the mean radiation burden of the parotid glands is shown in this graph. Each dot represents one patient.

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

appeared to have a significant correlation with most questions in the univariate analysis. In the multivariate regression analysis three questions correlated significantly to the VAS score. It was therefore felt that the VAS-score reflects adequately the subjective aspects of the xerostomia problem. The relevance of the VAS-score is also demonstrated by the linear correlation with an overall xerostomia index based upon these three questions. However, as a general rule we feel it is not to be advocated to use only this particular 'severity index' to grade the problem of xerostomia. It carries the risk of losing essential information of individual parameters as is the case with all composite scores (19,47,50). The SOMA-LENT scoring system for similar reasons also advises against the use of the total composite score which was included in the original version.

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

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

Precise 3D CT-based DVH analysis and larger numbers of patients are needed to establish correlations between dose and volume parameters of the parotids (and other salivary glands), salivary flow rates and xerostomia complaints (51). In our study, based on crude 2D estimations, the majority of the patients received a dose of at least 40 Gy to more than 50% of the bilateral parotid glands. The tolerance dose of the parotid glands (i.e. according to Eisbruch *et al.*, at least 55 % of the parotid gland volume must receive a dose less than 30 Gy) (41) was thus surpassed in the majority of the patients. Recently, the importance of the submandibular, sublingual and especially minor salivary glands, for maintaining oral comfort, was re-emphasized by Eisbruch *et al* (52,64-66). According to their findings the mean radiation dose received by the oral cavity, as a substitute for the minor salivary glands, cor-

related significantly with the subjective xerostomia score ($p = 0.002$). The same holds for the submandibular gland ($p = 0.009$), whereas the mean parotid gland dose was only marginally significant ($p = 0.05$).

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

2.5 CONCLUSIONS

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

The most important questions destillated from our questionnaire were the questions addressing dry mouth in general and the questions regarding the necessity to drink water to facilitate eating and speech. These three questions together with the VAS-score constitute a simplified instrument for subjectively scoring xerostomia. In fact, the impact of the appreciation of the complaints by our patiens is in agreement with the philosophy of Bjordal (15,16) which was nicely summarized as follows: "In every QOL assessment the patients should be the primary source of data collection."

There is an increased awareness of the importance of scoring treatment-related morbidity at the present time and age. Also given e.g. the use of higher doses of radiation and chemoradiation for better tumor control and organ preservation, QOL analysis will be of increasing importance (19, 20, 61, 67-70). Finally, in any study on oral function and xerostomia the contribution of all salivary glands must be analyzed and especially the role of the minor salivary glands should be taken into account.

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2.7. APPENDIX; QUESTIONNAIRE

Part I

Administrative data

Part II

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

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

Part III. Xerostomia

1. **How severe is your dry mouth problem?**
   G1 = normal, as before radiation therapy (RT)
   G2 = somewhat more complaints than before RT
   G3 = considerable more complaints than before RT
   G4 = permanent complaints of a very dry mouth

2. **Under which circumstances does the dry mouth problem occur? Answer each question with yes / no / or not applicable.**
   a. in the open air
   b. in the open air in case of wind and cold
   c. in air-conditioned spaces
   d. especially dry mouth during daytime
   e. especially dry mouth at nighttime
   f. always dry mouth night and day
   g. especially bother of the dry mouth during meals

3. **How often do you wake up at night due to a dry mouth?**

4. **How would you describe the quality of your saliva?**
   G1 = normal, watery fluid
   G2 = normal watery but too little volume
   G3 = sticky saliva
   G4 = no saliva at all

5. **Do you have difficulties with speech due to the dry mouth?**
   G1 = no problems; unchanged with respect to situation before radiation therapy (RT)
   G2 = occasionally some difficulty with speech
   G3 = frequently speech problems
   G4 = always difficulties with speech
   G5 = always major speech problems

6. **Do you need to sip water to facilitate speech?**
   G1 = never
   G2 = occasionally
   G3 = frequently
   G4 = always
   G5 = even have to interrupt speaking to take a sip of water

7. **Is swallowing changed due to the dry mouth problem?**
   G1 = no problems; unchanged with respect to situation before radiation therapy (RT)
   G2 = occasionally some difficulty with swallowing
   G3 = frequently problems with swallowing
   G4 = always swallowing difficulties
   G5 = swallowing is seriously impaired due to the dry mouth problem

8. **Has the dry mouth a negative influence on chewing?**
   G1 = no change in chewing capability
   G2 = some difficulty with chewing
   G3 = frequently difficulties with chewing
   G4 = always difficulties with chewing
   G5 = chewing is seriously hampered due to the dry mouth problem

9. **Do you need to sip water to facilitate eating?**
   G1 = no never
   G2 = sometimes, depending on the quality of the food
   G3 = frequently; more often than before radiation therapy
   G4 = always need to take a sip of water/ fluid with every bite of food.

10. **Did you change your feeding-habits?**
    G1 = no change
    G2 = minor changes, such as avoiding some products
    G3 = can eat only mashed food
    G4 = can eat only liquid food
    G5 = tube-feeding

11. **Do you have painful, dry or crusted lips?**
    G1 = never
    G2 = sometimes, depending on the weather and environmental circumstances
    G3 = frequently
    G4 = always, day and night

12. **Do you need to carry a bottle of fluid with you when leaving home?**
    G1 = never
    G2 = occasionally
    G3 = frequently
    G4 = very often
    G5 = always

13. **What do you use to alleviate the complaints of a dry mouth? Please specify.**

14. **Do you have a sore or painful mouth?**
    G1 = never
    G2 = occasionally
    G3 = frequently
    G4 = very often
    G5 = always

15. **Did your taste change?**
    G1 = no change; normal taste sensation
    G2 = some reduction in taste discrimination and sensation
    G3 = considerable change in taste
    G4 = no taste sensation at all
    G5 = always a bad taste in the mouth

17. Do you often suffer from an infected oral mucosa or irritated gums?

G1 = never
G2 = occasionally
G3 = frequently
G4 = very often

18. Did your teeth deteriorate after radiation therapy ?

yes / no / not applicable.

CHAPTER 3

A three dimensional CT based target definition for elective irradiation of the neck

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ABSTRACT

Introduction: *Elective treatment of the clinically node-negative neck by radiation results in excellent control rates. However, radiation therapy with its organ-preserving properties is not without morbidity. Side effects of elective neck irradiation are mainly due to damage of the major and minor salivary glands, resulting in the dry mouth syndrome. Given that radiation therapy (RT) is the preferred treatment modality in case of elective treatment of the neck in many institutions, it is of utmost importance to try and reduce the associated sequelae of RT.*

Materials and methods: *With the introduction of CT-planning systems and the development of 3D conformal radiation therapy (3D-CRT) techniques, it has become feasible to deliver adequate doses of radiation to the target (neck) and at the same time saving (parts of) the salivary glands from doses beyond tolerance. A prerequisite for these techniques is that they require a precise knowledge of the target (i.e. of the elective neck) on CT. To be able to correlate borders of the surgical levels in the neck (I-VI) with structures seen on CT, an anatomical study, using two fixed (phenol, formaldehyde) human cadavers, was performed. Subsequently, the six potential lymph node regions in the neck on CT were defined.*

Results and Discussion: *The reference for the current 3D CT-based definition of the lymph node regions in the neck, is the official report of the American Academy of Otolaryngology, describing, based on surgical anatomy, the lymph node groups in the neck by levels I-VI. The present investigation depicts reproducible landmarks on transversal CT images, corresponding to anatomical reference structures known from surgical levels (I-VI) and, this way, CT-based lymph node regions (1-6) were constructed.*

CHAPTER 3

3.1 INTRODUCTION

Curability of patients with tumors in the head and neck is, among other factors, dependent on the presence of lymph node metastases in the neck. If lymph nodes are not clinically palpable or detectable by diagnostic means such as CT, MRI scans, or ultrasound, the potential for development of lymph node metastasis (i.e. the presence of subclinical disease in the clinically N0 neck) dictates whether (part of) the neck should be treated electively (1-4). Elective treatment of the clinically N0 neck by either surgery or radiation therapy (RT), results in excellent regional control rates (5-8). Obviously, elective neck dissection has its surgery-related morbidity. However, RT with its organ-preserving properties, is not without morbidity, as well. Side effects of elective neck irradiation (ENI) are due to damage of the major and minor salivary glands, resulting, for example in dental caries, swallowing disorders, speech disturbances and, most frequently in xerostomia. It is beyond the scope of the present paper to discuss the indications for either elective neck dissection or ENI. Suffice to say that it remains a fact that ENI is the preferred treatment in many institutions for a great number of patients with tumors in the head and neck, if the probability of subclinical disease is considered to be more than 10-20% (9). Therefore, it is of utmost importance to try and reduce the associated side-effects of RT.

It is generally felt that RT with doses of ≥ 40 Gy surpasses the tolerance limit of the (major) salivary glands (i.e. induces the dry mouth syndrome). Doses greater than 30 Gy will eliminate measurable salivary flow from half of all parotid glands (10-13). With the introduction of CT planning systems and the development of 3D conformal radiation therapy (3D-CRT) techniques, it has become feasible to deliver adequate doses of radiation to the target (neck) and at the same time sparing (parts of) the salivary glands from doses beyond tolerance and, therewith, treating the neck electively without undue sequelae. A prerequisite for these techniques is that they require a precise knowledge of the target (i.e. of the so-called elective neck) on CT. This target then has to be depicted on every planning CT slice.

Although a target (i.e. level) definition has been proposed for and is commonly used in surgery of the neck, no such 'anatomic' definition presently exists for CT. In fact, to our knowledge, this is the first detailed report to describe such a 3D definition of the target of the elective neck on CT for all Levels I-VI. The backbone for the current 3D CT-based definition was an official report of the American Academy of Otolaryngology-Head and Neck Surgery, issued in 1991 (14). With regard to the level definition, the most important objectives of the Subcommittee for Neck Dissection Nomenclature were to define the clinical and surgi-

cal borders of each of the lymph node groups to be removed with the neck dissection specimen, and to develop a classification system that correlates with current oncological principles for the head and neck. The lymph node groups were classified according to the level system as was originally proposed by the Memorial Sloan-Kettering Cancer Group (15). The level definition, however, was designed for surgical procedures and is defined by using soft tissue landmarks (e.g. muscles, carotid bifurcation etc.). Unfortunately, many of these anatomical structures are not easily distinguishable on CT and, therefore, are not particularly suitable for translation onto a CT-based target. Moreover, the definition of the target should be given in treatment position of the neck. For neck irradiation, this refers to a supine position without rotation of the head, therewith being somewhat distinct from the clinical position at the time of surgery (i.e. rotated and/or tilted head position).

3.2 MATERIALS AND METHODS

To be able to correlate the surgical borders of the Levels (I-VI) with structures seen on CT, an anatomical study using two fixed (phenol, formaldehyde) human cadavers, was performed.

First, a formal modified radical neck dissection was performed on one specimen. The sternocleidomastoid muscle and the spinal accessory nerve were spared. Borders of Levels I-VI were demarcated.

The second human cadaver was fixed in supine treatment position for radiotherapy on a wooden support using polyurethane construction foam; after adding lines with a marker pen for spatial orientation, CT slices were obtained every 3 mm with a Siemens Somaton Plus CT Scanner (Forchheim, Germany). This cadaver was then frozen to minus 80° Celsius and sectioned into 5 mm thick slices with an immobile bandsaw. The cryosectioning procedure has been described by Entius *et al.* in detail (16). Directly following the cryosectioning, the slices were rinsed with cold water. After alignment of the anatomical slices to the previously described orientation lines, photographs were taken (35-mm color film). The photographs were digitized and stored on photo-CD. The transversal CT and anatomic slices (photographs) were matched using a visualization system (AVS, version 5.02, Advanced Visual Systems Inc.,Waltham, MA). The cranial, caudal, ventral, dorsal, medial and lateral borders of the levels, as defined by the Memorial Sloan-Kettering group, of the first

specimen were translated onto every transversal anatomical slice of the second specimen. The delineated tissue borders then correspond precisely to the surgical target as given by the original level definitions, but now for transversal anatomical slices without the rotated position of the head commonly used in surgical procedures.

The level borders constructed on these transversal anatomic slices were electronically copied onto matched CT slices. The lymph node Levels I-VI on CT are denoted as lymph node Regions 1-6. Easy identifiable structures on CT were related to the borders of the regions and subsequently defined to be used as references to depict the borders (see also Table 1).

3.3 RESULTS

The aim of the present investigation was to depict reproducible landmarks on transversal CT images, corresponding to anatomic reference structures known from surgical Levels (I-VI), and this way construct the CT-based lymph node Regions 1-6. In case such structures could not be clearly identified, distances (in cm) are given in reference to well defined and easily recognizable structures on CT. On every CT slice the lateral, medial, ventral, and dorsal borders of the CT regions are defined. A particular border can be found by approaching it from the ipsilateral side, in search for the first structure listed in Table 1 for that specific border. Table 1 summarizes the CT-based target volumes for the elective neck with respect to all six CT-based lymph node regions. Because the flow of the major lymph node chain (i.e. jugular chain) is almost perpendicular to the transversal CT scan slices, the caudal and cranial border of Region 2 (Level II) and Region 3 (Level III), respectively, and of Region 3 (Level III) and Region 4 (Level IV), respectively, are depicted on the same CT slice. Or, the caudal border of Region 2 is the cranial border of Region 3, and the caudal border of Region 3 is too the cranial border of Region 4. Furthermore, the hyoid body is taken as the border between Region 1 (Level I) and Region 6 (Level VI). The outlines of the regions are represented by Figs. 1 through 5. Regions 1-5 are shown on the anatomic images (left panel of *Figures 1-5*), as well as on the CT slices (right panel of *Figures 1-5*). For clarity reasons, Region 6 is not depicted. In practice, to outline the CT-based regions, starting with the cranial CT slices will facilitate the delineation of the borders.

Region 1 is always treated as a single entity. On the other hand, it is easier to describe this

Table 1. Definition of lymph node regions for elective neck irradiation on transversal CT-slices

Target	Region 1 : submental (1A) and submandibular (1B)	Region 2: high-jugular	Region 3: mid-jugular	Region 4: low-jugular	Region 5: posterior triangle	Region 6: anterior
Cranial	1A Caudal CT slice mandible 1B CT slice middle part of ramus mandible / floor of mouth muscles	Cranial CT slice C-I	Caudal CT slice hyoid body	CT slice caudal to thyroid cartilage	Cranial border region 2	CT slice hyoid body
Caudal	1A CT slice hyoid body 1B CT slice hyoid body	CT slice hyoid body	CT slice caudal to thyroid cartilage	Cranial CT slice with origin sternocleido-mastoid muscle (approximately 2 cm cranial to sternoclavicular joint)	Caudal border region 4	Caudal border region 4
Ventral	1A Innerside mandible / platysma / skin 1B Innerside mandible / / platysma / skin	1/3 of ramus mandible / 2 cm ventral to vertebra / hyoid body	hyoid body / platysma / skin	platysma / skin./ sternocleidomastoid muscle / clavicle	Dorsal border regions 2, 3 and 4	Skin
Dorsal	1A Floor of mouth muscles / hyoid body 1B Digastric muscle / medial pterygoid muscle / 1 cm ventral to vertebra	2 cm dorsal to ventral border of vertebra.	Dorsal border vertebral body	Dorsal border vertebral body / transverse process / rib	1 cm ventral to spinous process vertebra / most ventral part trapezius / muscle / lung / ventral border rib	Vertebra
Lateral	1A Line depicted by symphysis mandible and medial border parotid gland / digastric muscle 1B Innerside mandible / platysma / skin	Medial border pterygoid muscle / parotid gland / sternocleidomastoid muscle / platysma / skin	Sternocleidomastoid muscle / platysma / skin	Most lateral part sternocleidomastoid muscle / platysma / skin	Most ventral part trapezius muscle / most medial part clavicle / platysma / skin	Carotid sheet / thyroid gland
Medial	1A *Not present* 1B Lateral border 1A	pharyngeal wall / medial border carotid artery / deep cervical muscles	Larynx / pharyngeal wall / medial border carotid artery / deep cervical muscles	Thyroid gland / medial border carotid artery / esophagus	Vertebra / deep cervical muscles	*Not present*

The upper parts of Regions 2 and 5 coincide: the junctional nodes. The caudal parts of Region 4 and 5 also coincide. The borders are defined delineating the target on the CT slices in a cranio-caudal direction. The / indicates that the border is either one of the structures mentioned; the first structure found on the CT slice is the border.

region by splitting it into the two Subregions 1A and 1B, like the surgical definition of Level I. Moreover, both subregions correspond to different anatomic sites; Region 1A encloses the submental lymph nodes, and Region 1B the submandibular lymph nodes. For these reasons Region 1 is represented in Table 1 by the two Subregions 1A and 1B. Due to the fixed position of the head of the human specimen, only two consecutive slices represent Region 1A. The cranial CT slice is presented (*Figure 1*). The borders of Region 1A are the mandible, the hyoid bone, the skin (platysma), the floor of mouth muscles (the mylohyoid and the hyoglossus muscle), and the digastric muscle. If the digastric muscle can not be identified clearly, the line connecting the symphysis mandible and the medial border of the parotid gland is used. The borders of Region 1B are the mandible, the hyoid bone, the skin (platysma), the floor of mouth muscles, the medial pterygoid muscle, and the digastric muscle (or the line running from the symphysis mandible to the medial border of the parotid gland). If the dorsal border cannot clearly be identified, it will be placed 1 cm ventral to the vertebral body. Region 1 corresponds to both the Levels IA and IB, without any further adjustments being necessary.

The borders of Region 2 in *Figure 2* are delineated by distances from the ventral border of the vertebral bodies (2 cm ventrally and dorsally), the medial borders of the medial pterygoid muscle and the parotid gland, the skin (platysma), the sternocleidomastoid muscle, the hyoid body, and the pharyngeal wall, medial border of the carotid artery and deep cervical muscles. The distance between the ventral border of the vertebra and one third of the ramus mandible is also roughly 2 cm. Given the different treatment position during RT as opposed to surgery (tilted rotation of the head), the dorsal border was slightly adjusted (wider). In view of the close relationship of the lymphatics with the carotid artery and the jugular vein, these blood vessels were included in the target volume. The cranial border is defined by the most cranial CT slice showing the top of vertebral body C-I, with the dens just visible. The caudal border is the CT slice showing a major part of the hyoid body. *Figure 3* summarizes the definition of Region 3. Some parts of the borders of this region correspond to segments of the borders of Region 2. The larynx will represent the medial border. The dorsal border corresponds with the width of the vertebral body (about 2 cm), situated dorsally from the ventral border of the vertebra. The cranial border of Region 3 is the caudal border of Region 2. The caudal border is represented by the CT slice caudal to the thyroid cartilage. *Figure 4* depicts Region 4. The borders are the skin (platysma), the sternocleidomastoid muscle, the clavicle, the transverse process of the vertebra, the rib, the thyroid gland, and the esophagus. The cranial border is the caudal border of Region 3. The caudal border ends at the inser-

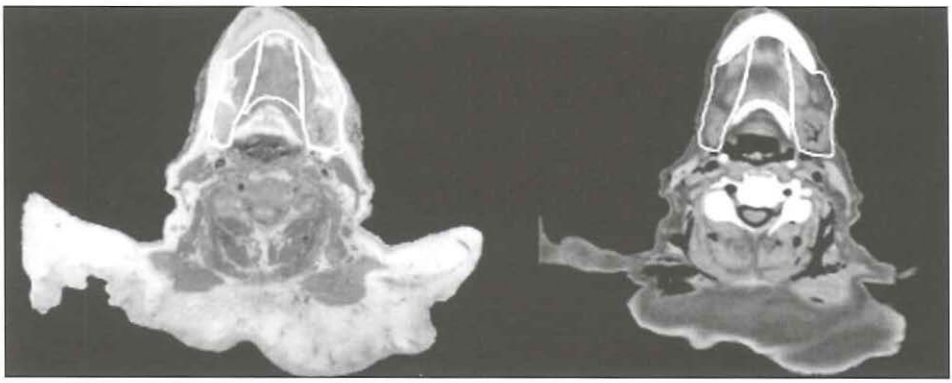

Figure 1. Region 1: this region is divided into Subregions 1A (submental lymph nodes) and 1B (submandibular lymph nodes). The borders are outlined on a transversal anatomy slice (left panel, see text) and the matched CT slice (right panel). The slices are at the upper border of Region 1A (see text). The borders are discussed in the text and in Table 1.

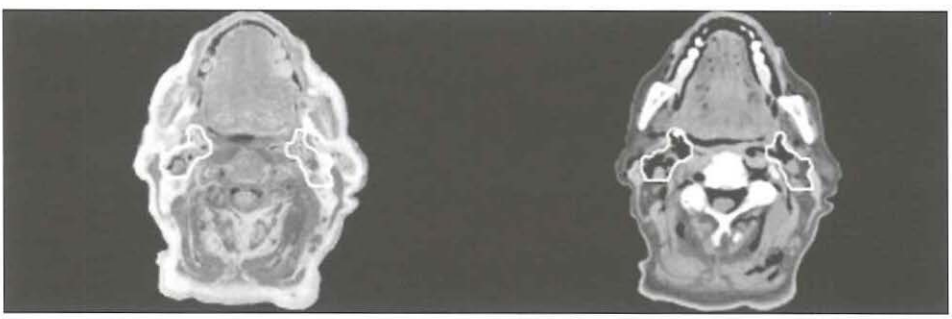

Figure 2. Region 2 (high-jugular lymph nodes): The borders of this region are outlined on a transversal anatomy slice (left panel) and the matched CT slice (right panel), in between the cranial (cranial CT slice through vertebra C-1) and caudal (hyoid bone) borders. The borders are discussed in the text and in Table 1.

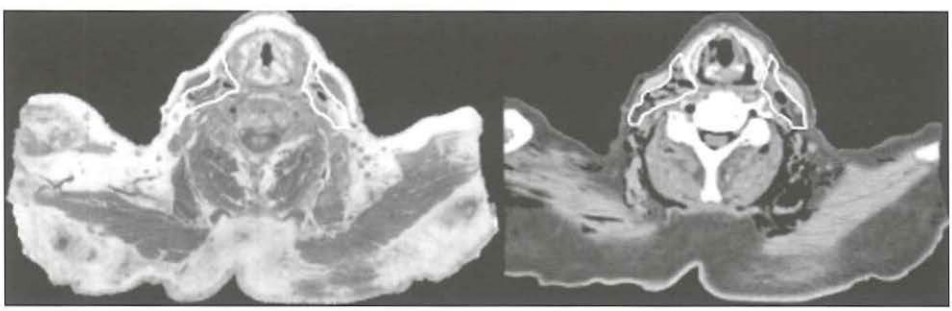

Figure 3. Region 3 (mid-jugular lymph nodes): The borders of this region are outlined on a transversal anatomy slice (left panel) and the matched CT slice (right panel), in between the cranial (hyoid bone) and caudal (one slice below the thyroid cartilage) borders. The borders are discussed in the text and in Table 1.

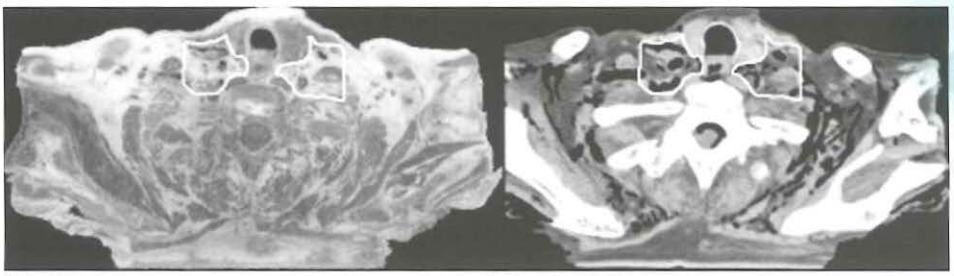

Figure 4. Region 4 (low-jugular lymph nodes): The borders of this region are outlined on a transversal anatomy slice (left panel) and the matched CT slice (right panel), in between the cranial (one slice below the thyroid cartilage) and caudal (2 cm cranial to sternoclavicular joint) borders. The borders are discussed in the text and in Table 1.

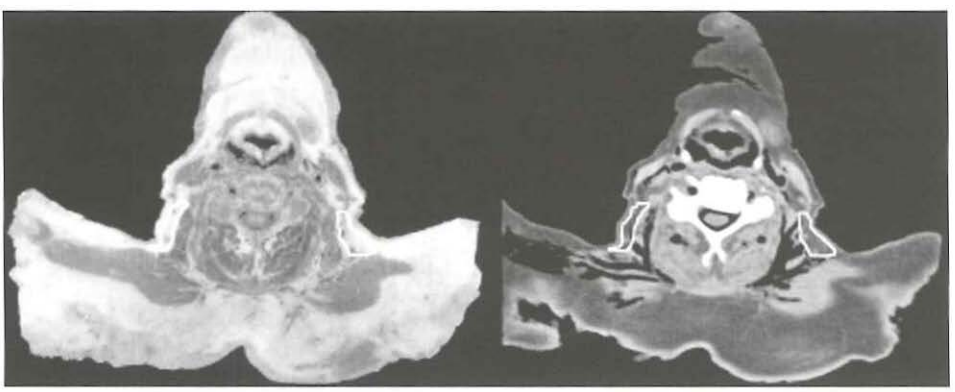

Figure 5. Region 5 (posterior triangle lymph nodes): The borders of this region are outlined on a transversal anatomy slice (left panel) and the matched CT slice (right panel), in between the cranial (cranial CT slice through vertebra C-I) and caudal (2 cm cranial to sternoclavicular joint) borders. The borders are discussed in the text and in Table 1.

tion of the sternocleidomastoid muscle onto the clavicle, which is approximately 2 cm cranial to sternoclavicular joint.

The ventral border of Region 5 in *Figure 5* is the dorsal border of Regions 2, 3, and 4. The cranial and caudal borders are the cranial border of Region 2 and the caudal border of Region 4, respectively. A cranial adjustment of the dorsal border was made, being now 1 cm ventrally to the spinous process of the vertebra. The most cranial part of Region 5 coincides more or less with Region 2. The common area of Regions 2 and 5 encompasses the junctional lymph nodes. The caudal part of this region coincides more or less with Region 4. The most complicated parts to delineate (and difficult parts to describe) are the lateral and dorsal borders, because the lymphatics of the posterior neck triangle move from cranially to

caudally, from the lateral and dorsal part of the neck to the medial and ventral part of the neck. The dorsal border is always ventral to the most ventral part of the trapezius muscle, the lung and the ribs. The lateral border is always medial to the most medial part of the clavicle and the most ventral part of the trapezius muscle. For the boundaries of Region 6, a region very seldomly included in the target in case of RT of the N0 neck, the reader is referred to the outlines given in Table 1.

3.4 DISCUSSION

ENI is the preferred treatment modality in many institutions for patients with tumors in the head and neck without clinically detectable lymph nodes (N0) in the neck. Many patients, however, suffer from a dry mouth syndrome due to the inclusion of (a major part) of the salivary glands in the radiation portals. Because RT is extremely effective for controlling microscopic disease (i.e. 90% control rate), it seems of utmost importance to try and reduce the associated side effects. With the introduction of CT planning systems and the development of 3D-CRT, it has become feasible to deliver adequate doses of radiation to the target (neck) and at the same time sparing (parts of) the salivary glands from doses beyond tolerance and, therewith treating the neck electively without undue sequelae.

Moreover, it has been shown for many primary cancers in the head and neck that the control rate increases substantially with higher doses of RT (17). To take advantage of this so-called dose response relationship, it has been proposed to treat the primary tumor and (part of) the neck by 3D-CRT; this way, the dose can be substantially raised without a consequential rise in side effects. Again, for this dose-escalation aspect of 3D-CRT, an adequate target definition for the primary cancer as well as for the (elective) neck and healthy surrounding tissues on CT is essential.

With regard to the elective neck target, because elective neck dissection and ENI result in similar regional control rates, the clinical target volume in RT should, in principle, be comparable to the target volume in surgery. The definition of the surgical levels, presented by the Memorial Sloan-Kettering Group was chosen as the reference for the definition of the target of the neck in case of ENI because this definition has proven to be consistent and valuable in clinical practice. By means of anatomic studies on human cadavers taken to CT, images were obtained with the critical (in reference to the surgical level definitions) structures depicted. We were able to delineate the lymph node Regions 1-6 in the neck, corre-

sponding to the originally described surgical Levels I-VI. However, because of a different position of the head for the two treatment modalities, some, albeit minor, adjustments had to be made. Also, the carotid arteries and internal jugular veins were included in the RT target definition. Finally, to distinguish the two definitions, in contrast to the surgical levels, the RT and the elective lymph node targets in the neck on CT were denoted as regions.

The region definitions in this paper are summarized in Table 1 and depicted in Figs. 1-5. The delineation of the regions has proven to be accurate but at some expense of the time needed to outline these regions (i.e. 1-3 hours). To verify reproducibility and to compare these borders with common clinical practice, three physicians independently outlined the target on CT of a single patient, using our CT-based region definitions (Table 1). Beams-eye-view images of these targets were created and superimposed on a digital reconstructed radiograph (*Figure 6*). A good agreement was observed between clinicians. Having these formal definitions of lymph node regions agreed upon, we will now embark on clinical studies to 1. validate the geometric reproducibility of these structures on a larger scale, and then 2. to start a multi-institutional study on 3D-CRT in cancer of the head and neck with special emphasis on preservation on saliva production.

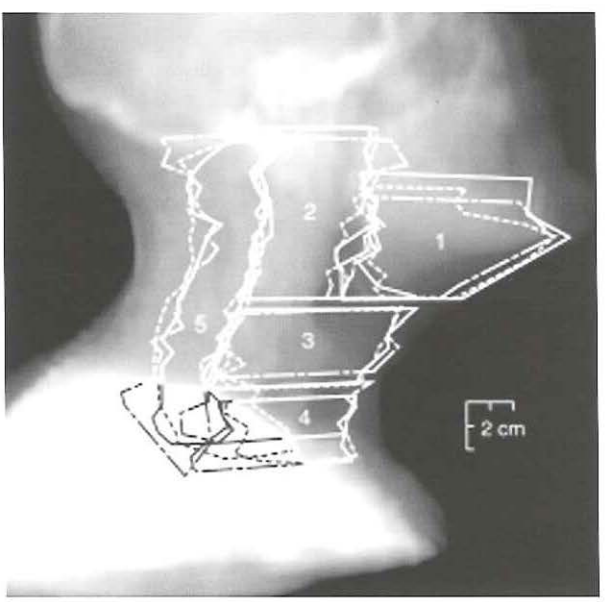

Figure 6. Delineation of the elective target in the neck by three radiation oncologists. Regions 1 through 5 were delineated on CT scans. A beams-eye-view reconstruction of these regions was superimposed on a digital reconstructed radiograph. Only minor deviations are seen in the beams-eye-view images. The targets are in good agreement with clinical practice.

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CHAPTER 4

A simplified CT-based definition of the lymph node levels in the node negative neck

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ABSTRACT

Introduction and purpose: *Using three dimensional (3D) conformal radiotherapy (CRT) techniques for elective neck irradiation (ENI) may allow for local disease control to be maintained while diminishing xerostomia by eliminating major salivary glands (or parts thereof) from the treatment portals. The standardization of CT based target volumes for the clinically negative (elective) neck is a prerequisite for 3DCRT. The aim of the present study was to substantially modify an existing ('original') CT-based protocol for the delineation of the neck target volume, into a more practical ('simplified') protocol. This will allow for rapid contouring and the implementation of conformal ENI in routine clinical procedures.*

Materials and Methods: *An earlier ('original') version of the CT-based definition for elective neck node regions 2-5 was re-evaluated, using CT-scans of previously treated patients. The contouring guidelines were simplified by (1) using a smaller number of easily identifiable soft tissue and bony anatomical landmarks, which in turn had to be identified in only a limited number of CT slices and (2) by subsequently interpolating the contoured lymph node regions. The adequacy of target coverage and the sparing using both 'original' and 'simplified' delineation protocols was evaluated by DVH analysis after contouring the primary tumor, the neck and the major salivary glands in a patient with supraglottic laryngeal (SGL) carcinoma who was treated using a 3DCRT technique.*

Results: *The BEV projections of the 'original' and the 'simplified' versions of the 3D elective neck target showed good agreement and were found to be reproducible. The DVH's of the target and parotid glands were not significantly different using both contouring protocols.*

Conclusions: *The 'simplified' protocol for delineation of the 3D elective neck target produced both comparable target coverage and sparing of the major salivary glands. When used together with an interpolation program, this 'simplified' protocol substantial reduced the contouring time and makes ENI with sparing of the major salivary glands a practical and achievable goal.*

CHAPTER 4

4.1 INTRODUCTION

Radiotherapy for cancers of the head and neck frequently results in xerostomia, the so-called dry mouth syndrome (18,19). Xerostomia has a major impact on social functioning as it may hamper swallowing, chewing, adequate food intake and speech. Moreover, the reduction in quantity and quality of saliva can contribute to dental decay, and may enhance the risk of osteoradionecrosis. The avoidance of xerostomia should be an important goal, particularly for patients who have a high probablity of cure. An important subset of such patients are those with a node negative (N0) neck, as elective neck irradiation (ENI) produces regional control rates which exceed 90% (12,13,20).

Both the elimination of the major salivary glands (or a major part thereof) from the treated volume and/or reducing the dose to salivary glands to below the tolerance level of 30-40 Gy are to reduce the incidence of xerostomia (6-9,18,19). The use of 3D conformal radiotherapy (CRT) can limit the volume of irradiated major salivary glands (4,5,10,11). An absolute prerequisite for CRT is the standardization of CT-based delineation of the clinical target volume (CTV) and planning target volume (PTV) of the primary tumor and the lymph node regions of the neck.

In a previous study, we translated the surgical lymph nodal levels I to V in the neck into CT-based regions 1-5 (14,15). However, this required the meticulous delineation of these CT-based regions on each slice of the planning CT making this protocol (referred to hereafter as the 'original' protocol) extremely laborious and this impeding its routine implementation in patients. The aim of the current study was to modify and simplify the 'original' definitions of lymph node regions in order to achieve a reproducible and fast contouring protocol for only a limited number of CT-slices of the neck.

4.2 MATERIALS AND METHODS

The surgical lymph nodal levels I-V of the neck, as defined by the Memorial Sloan Kettering Cancer Center group (16,17), have been recently translated into CT-based lymph node region definitions 1-5, in a study carried out on two human cadavers (14,15). In short the previous study can be summarized as follows: A formal modified radical neck dissection was carried out in one cadaver, and a planning CT-scan was obtained in the treatment posi-

Table 1. Simplified definitions of the lymph node regions for elective neck irradiation on transversal CT-slices.

Boundary of region	REGION 2 'upper neck volume'	REGION 3 'middle neck volume'	REGION 4 'lower neck volume'	REGION 5 posterior triangle
CRANIAL	Top of corpus C-1	Caudal border region 2 Caudal of hyoid body	Caudal border of region 3 Top of C-7 or bottom of thyroid cartilage	Cranial border region 2
CAUDAL	Hyoid body	Bottom of corpus C-6 or Bottom of thyroid cartilage	2 cm cranial to sternoclavicular joint	Caudal border region 4
VENTRAL	Ventral boundary of pharyngeal lumen	Ventral boundary of laryngeal lumen	Skin, excluding sternocleidomastoid muscle	Posterior borders of region 2 and 3 and lateral border of region 4
POSTERIOR	Center of spinal cord or Center of vertebral canal	Center of spinal cord or Center of vertebral canal	Transverse process or rib	At the level of regions 2 and 3: 1 cm in front of the tip of the spinous process At the level of region 4: in continuity with the posterior border of region 4, parallel to the skin
LATERAL	Skin, excluding pterygoid muscles, sternocleidomastoid muscle, parotid and submandibular glands	Skin, excluding sternocleidomastoid muscle	Lateral edge of sternocleidomastoid muscle or medial 2/3 of the volume between the vertebral body and the clavicle or trapezius muscle	At the level of regions 2 and 3: skin At the level of region 4: medial edge of the trapezius muscle or the clavicle
MEDIAL[a]	Pharyngeal wall and vertebral body	Laryngeal lumen wall and vertebral body	Trachea, thyroid gland, esophagus, vertebral body	At the level of regions 2 and 3: in continuity with the medial borders of these region and parallel to the skin or sternocleidomastoid muscle

a. The actual lymph nodes are located in the fat planes surrounding the large vessels, within the defined volumes. A more accurate target definition can be obtained by following the fat planes and excluding the deep cervical muscles.

tion of the other cadaver. The second cadaver was then frozen and sectioned into 5 mm thick anatomical slices. The level borders were constructed on images of transversal anatomical slices and electronically copied on the matching planning CT-slices. From the above study, CT-based definition of the elective lymph node regions in the neck (referred to in the following sections of this manuscript as the 'original' lymph node region delineation protocol) was derived: the definitions of the regions are detailed in Refs. (14,15).

The planning CT-scans of 15 patients who were previously treated patients for a head and neck tumor were used in designing the 'simplified' delineation protocol; the contours of the 'original' elective CTV of the neck regions 2-5 were delineated on these CT scans. Firstly, the 'original' definitions of the borders of nodal regions on each slice were amended, i.e. some structures used as anatomical landmarks for the 'original' protocol were eliminated and were replaced with more uniform and easily recognizable boundaries such as the corpus of the vertebra, the contours of the pharyngeal and laryngeal lumen, the salivary glands, and the skin. For a summary of the boundaries of the 'simplified' protocol, see Table 1.

Next, the CT slices were grouped into volumes and for each volume a single representative CT slice was selected. In this manner, the elective neck target could be subdivided into three volumes, i.e. the upper neck (suprahyoid), encompassing region 2 and the upper part of region 5; the middle third of the neck, consisting of region 3 and the corresponding part of region 5; and the lower third of the neck, covering region 4 and the lowest parts of region 5. Finally, the minimum number of CT slices for each of the neck volumes which needed to be contoured using the 'simplified' delineation protocol guidelines, were determined in order to allow for a computer programme to reconstruct the entire elective neck target by interpolating the intervening contours. In order to study the applicability and reproducibility of the 'simplified' protocol, lymph node regions 2-5 were then delineated on planning CT-scan (slices) of three separate patients by 2 physicians using the 'simplified' protocol. The beams-eye-view (BEV) projections of the elective neck target of the 'simplified' version could thus be compared to the BEV projection constructed with the 'original' protocol. To compare the amount of sparing in ENI using 3DCRT techniques, the primary tumor, the neck node regions 2-4 (using the 'original' and 'simplified' protocol), as well as the parotid and submandibular glands were contoured in a patient with a T3N0 supraglottic laryngeal (SGL) tumor. This patient was treated by a 3DCRT technique routinely used in our institution, with the goal of applying a total dose of 70 Gy to the primary and 46 Gy to the bilateral elective neck, the DVH's for both the primary tumor and major salivary glands were computed.

4.3 RESULTS

The simplified definitions for delineation of lymph nodal regions 2-5 are schematically depicted in *Figures1a, 2a* and *3a*. The corresponding representative CT-slices for the upper, middle- and lower part of the neck are shown on *Figures 1b, 2b* and *3b*. The entire elective neck volume (CTV) can be constructed by contouring only 10 CT-slices and interpolating the intervening slices by an interpolation program.

4.3.1 Boundaries lymph node regions 2-5 (Table 1, Figures1a,2a and 3a): The boundaries for regions 2 and 3 are very similar: the ventral border is defined by the ventral edge of the pharyngeal/laryngeal lumen; the medial border is composed of the pharyngeal/laryngeal lumen walls and the vertebral body; the posterior border corresponds to the center of the spinal cord; the lateral border is defined by the skin. In addition, the parotid glands, the submandibular glands, the pterygoid muscles, the sternocleidomastoid muscle and the mandible are excluded from the CTV, i.e. kept outside from the delineated lymph nodal regions, when outlining the regions.

Region 4 represents the lower part of the neck and encompasses the low jugular nodes. This region, which is more horizontally and ventrally orientated than regions 2 and 3, is more difficult to define unequivocally. The ventral extent of region 4 is defined by the skin; as for regions 2 and 3, the medial border is defined by the wall of the trachea or oesophagus, and the corpus of the vertebra; the posterior border follows the transverse process of the vertebra or the ventral border of the rib. The lateral boundary is demarcated by the lateral edge of the sternocleidomastoid muscle or, alternatively, by a line which divides the volume between the tracheal/oesophageal lumen and the clavicle into a medial two-thirds and a lateral one-third part. The volume medial to this demarcation line belongs to region 4 and the volume lateral to this line belongs to region 5. Excluded from region 4 are the sternocleidomastoid muscle and the thyroid gland.

Region 5, which is the posterior triangle of the neck, runs posteriorly to regions 2 and 3 and somewhat laterally to region 4. At the site of the junctional nodes cranially, part of region 5 coincides with the posterior part of region 2 and is very narrow at that site. The caudal part of region 5 is also very narrow at the site where it coincides with region 4. Region 5 is located posteriorly to regions 2 and 3; so the ventral border of region 5 corresponds to the posterior border of regions 2 and 3. The posterior border of region 5 corresponds to a level 1

cm ventrally to the tip of the spinous process. The lateral border of region 5 at this level is defined by the skin; the medial boundary runs parallel to the lateral boundary (i.e. skin) and is a continuation/extension of the medial border of region 2 and 3. At the level of the lower neck, region 5 becomes progressively smaller and narrower, and partly merges with the lowest part of region 4. Consequently, the CT-scan slices become more difficult to standardize in terms of delineation of borders. In the lower neck, region 5 is located laterally to region 4, with the medial border corresponding to the lateral border of region 4 and the posterior borders of both regions in continuity. Region 5 occupies the lateral one third of the volume between the trachea/esophageal lumen and the medial border of the clavicle/trapezius muscle.

4.3.2 Representative CT-slices upper, middle and lower neck volume (Figures 1b, 2b and 3b): *Figures 1b, 2b* and *3b* depict representative CT-slices of the upper, middle and lower neck volume, with the contoured regions 2 to 5.

For the upper neck, 4 slices are delineated, with the delineated lymph node regions corresponding to the schematic diagram of *Figure 1a* (diagram of representative CT slice upper neck). The 4 slices to be contoured are taken at the level of the top of the vertebral bodies C1, C2 and C3 and at the bottom level of the corpus of C3 (see also *Figure 1b*).

With regards to the middle neck volume: region 3 and the corresponding central part of region 5 can be constructed by contouring the slices at the cranial and caudal level of the body of C5 (*Figure 2b*). Delineation of these regions should be done corresponding to the contours depicted on the schematic diagram of the reference slice, schematically shown in *Figure 2a.*

The lower neck volume is delineated on three slices (*Figure 3b*) as well as on the most inferior slice of the neck; all 4 slices are contoured corresponding to the diagram of the reference slice shown in *Figure 3a.*

Finally, the BEVs of the elective neck CTV which were constructed according to the 'simplified' and 'original' protocol guidelines, were compared and showed good agreement (*Figure 4*). Interpolation of the intervening contours of the delineated 10 CT-slices (i.e. 4 CT-slices for the upper neck, 2 for the middle neck and 3 for the lower neck volume and 1 CT-slice at the caudal end of the lower neck) resulted in similar BEV projections as the BEV obtained using the 'original' protocol guidelines, and, moreover, diminished the contouring time by at least 1 hour. Also, preliminary testing of this interpolating program, indicates good agreement between the fully contoured – slice by slice – elective neck volume and

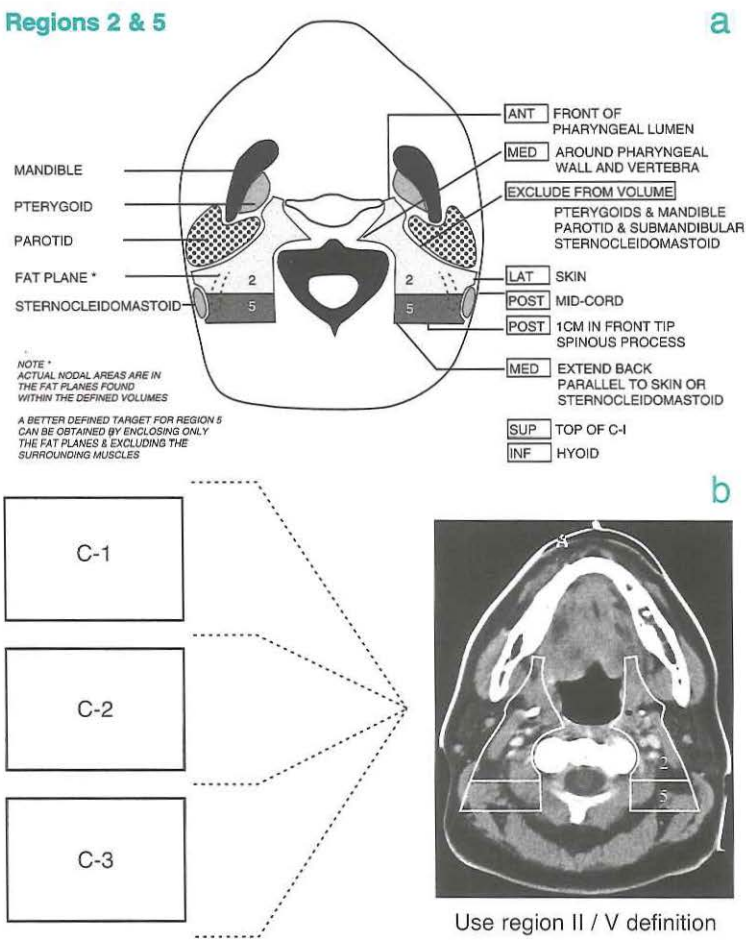

Figure 1 (a) The upper neck, consisting of region 2 and the corresponding cranial part of region 5. **(b)** For the upper neck 4 slices are contoured: i.e. at the level of the top of the vertebral bodies C1, C2 and C3 and the bottom of C3.

the achieved CTV by contouring 10 CT-slices only.

Importantly, no differences in the dose volume histograms (DVH) for the primary tumor and the major salivary glands were observed for the 'simplified' as opposed to 'original' protocol (*Figure 5*), i.e. similar sparing of the major salivary glands was achieved when treating the primary (70 Gy) and the bilateral elective neck (46 Gy) of a patient with supraglottic laryngeal carcinoma using a 3DCRT technique (10).

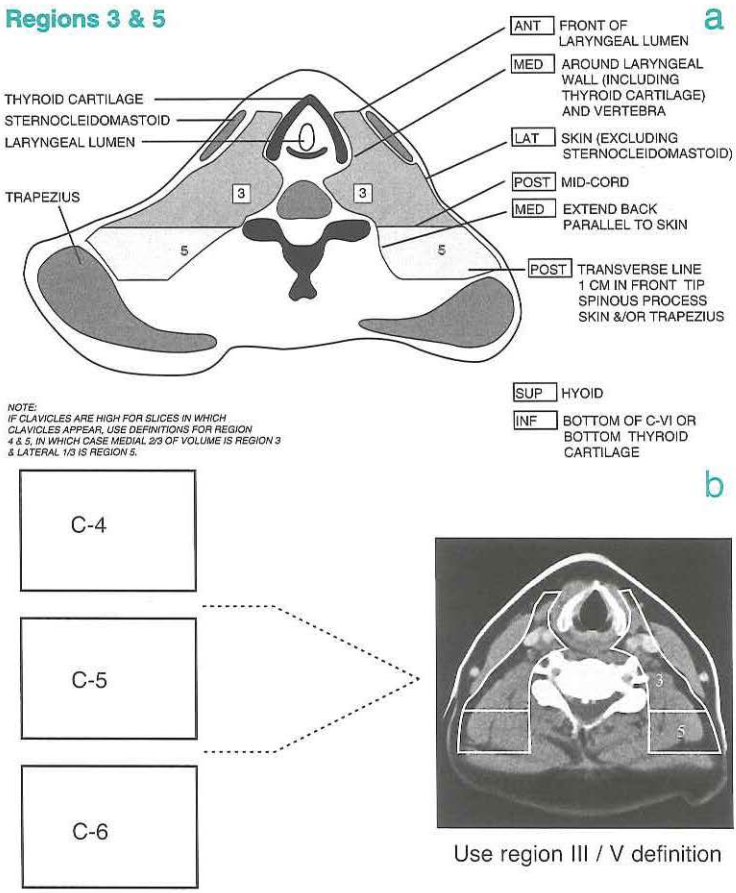

Figure 2 (a) The middle part of the neck (region 3) and the central part of the posterior neck triangle (i.e. region 5). **(b)** Region 3 and the corresponding central part of region 5 can be constructed by contouring the slices at the cranial and caudal level of the corpus of C5.

4.4 DISCUSSION

Both ENI and elective neck surgery give comparable regional control rates which exceed 90% (12,13,20). Radiotherapy, however, frequently results in xerostomia and this has a major impact on social functioning. Elimination of the major salivary glands (or parts thereof) from the treated volume using 3DCRT techniques may reduce the incidence or severity of this side effect. The application of 3DCRT for ENI requires standardization of the CT-based CTV of the elective neck and this should reflect the anatomical (surgical) defined lymph node levels (1-3,16,17). In a previous study, we demonstrated the feasibility of trans-

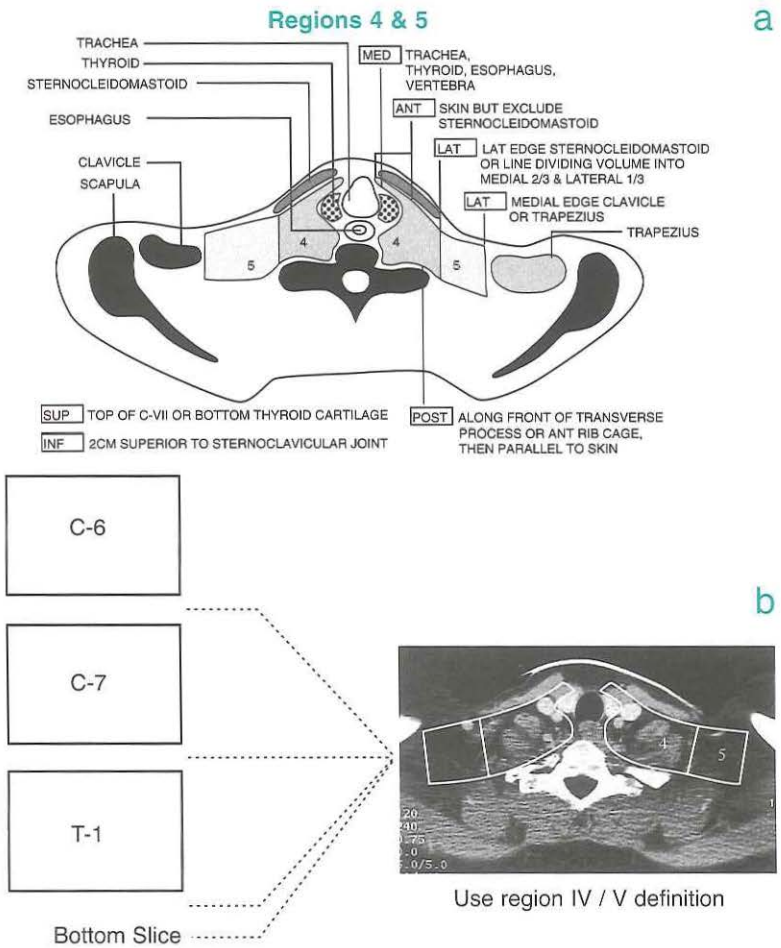

Figure 3 (a) Region 4 and the caudal part of region 5 on a representative slice of the lower neck. **(b)**The lower neck volume is delineated on three slices and, finally, the bottom slice of the entire elective neck volume should be contoured.

lating the surgical lymph node levels I-V into CT-based neck node regions 1-5, finally resulting in a reproducible, so-called 'original' lymph node delineation protocol (14,15).

However, the implementation of our 'original' protocol was found to be very time-consuming, and too cumbersome for routine use in a busy radiotherapy department. Therefore a 'simplified' version of the lymph nodal region delineation protocol was developed. This was done, firstly, by redefining the borders of the regions, by limiting the amount of anatomical landmarks. In this paper, we report the guidelines for using the 'simplified' CT-

tocol was developed. This was done, firstly, by redefining the borders of the regions, by limiting the amount of anatomical landmarks. In this paper, we report the guidelines for using the 'simplified' CT-based contouring protocol; for details regarding boundaries and landmarks of the specific regions 2-5, see Table 1 and results section of this paper. Secondly, a further substantial reduction in contouring time was found by limiting the number of the CT slices (i.e. 10 slices) to be delineated. The CTV of the elective neck was finally obtained by interpolating the intervening contours of the 10 CT slices.

In order to confirm the applicability of this 'simplified' protocol in the clinic, 2 clinicians contoured the lymph node regions on CT slices of 3 patients. The same contouring process was repeated using the 'original' protocol guidelines. The BEV projections for the elective neck volumes, using either the 'simplified' or the 'original' definitions, show good agreement. At the site of the medial borders of the lymph node regions, where with the 'simplified' version of the protocol the deep cervical muscles are partly included in the elective neck target volume, a small difference in coverage can arise between the protocols. However, in cases where the 'simplified' definitions result in too little sparing of the critical structures, one can still elect to exclude these muscles from the target volume by following the fat spaces surrounding the carotid artery and jugular vein. The last step will result in a more tighter delineation of the lymph node regions than would be the case with the 'simplified' protocol.

In a patient with a T3N0 supraglottic laryngeal carcinoma who was treated using 3DCRT, a comparable amount of sparing was achieved, with a similar coverage of the primary tumor

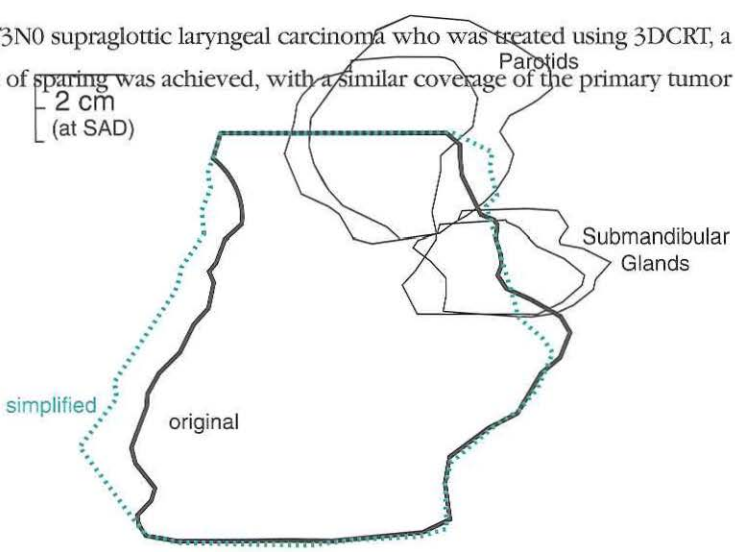

Figure 4. Lateral BEV (beams-eye-view) projections of the CTV of the elective neck (regions 2-4) shows good agreement between the 'original' (Refs.[14,15]) CT-based region definitions and the 'simplified' protocol (present paper).

and neck regions. We are currently using the 'simplified' neck delineation protocol routinely in patients with laryngeal carcinoma who are to be treated with ENI. Preliminary results in 20 such patients show an adequate coverage of the primary tumor and considerable sparing of the irradiated major salivary gland volume; i.e. 40 - 68 % of the parotid glands receive a dose of less than 40 Gy, with a mean dose to the parotid glands of 22 – 38 Gy (unpublished data).

In summary, the standardization of the delineation of lymph node regions in the neck and more specifically, the simplification of this procedure, has facilitated the introduction of 3DCRT of the neck in patients with a head and neck cancer. However, longer follow up is necessary to substantiate whether the sparing achieved in radiotherapy planning studies does in fact translate to subjective and objective improvement in the so called 'dry mouth syndrome'.

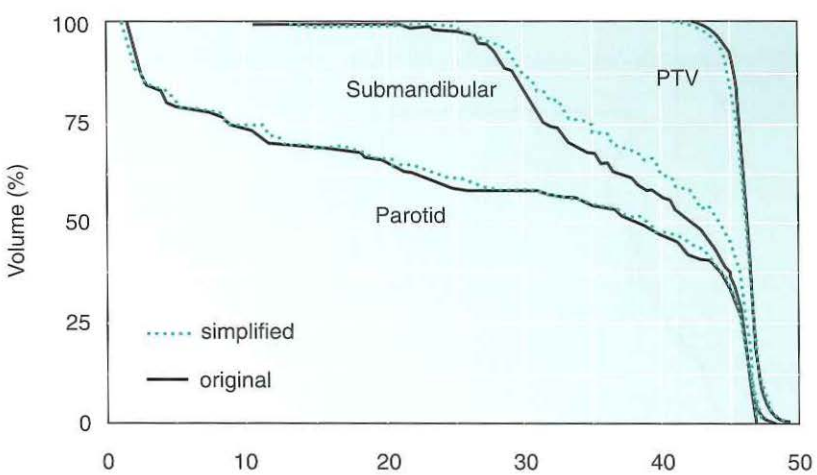

Figure 5. Dose volume histograms (DVH) of the major salivary glands and the primary tumor. The 'simplified' delineation protocol (present paper) was used for 3DCRT of a T3N0 supraglottic laryngeal carcinoma. ENI to a dose of 46 Gy was followed by a booster dose of 24 Gy to the larynx. This resulted in a similar sparing of the major salivary glands to that achieved using the 'original' (Refs.(14,15)) definitions to delineate the elective neck.

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CHAPTER 5

Mucositis reduction by selective elimination of oral flora in irradiated cancers of the head and neck: a placebo-controlled double blind randomized study

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ABSTRACT

Purpose: *The aim of the study was to test the hypothesis that aerobic Gram-negative bacteria (AGNB) play a crucial role in the pathogenesis of radiation-induced mucositis; consequently, selective elimination of these bacteria from the oral flora should result in reduction of the mucositis.*

Materials and Methods: *Head-and-neck cancer patients, when scheduled for treatment by external beam radiation therapy (EBRT), were randomized for prophylactic treatment with an oral paste containing either a placebo or a combination of the antibiotics polymyxin E, tobramycin and amphotericin B (PTA group). Weekly, the objective and subjective mucositis scores and microbiological counts of the oral flora were noted. The primary study end point was the mucositis grade after 3 weeks of EBRT.*

Results: *Seventy-seven patients were evaluable. No statistically significant difference for the objective and subjective mucositis scores was observed between the two study arms ($p = 0.33$). The percentage of patients with positive cultures of AGNB was significantly reduced in the PTA group ($p = 0.01$). However, complete eradication of AGNB was not achieved.*

Conclusions: *Selective elimination of AGNB of the oral flora did not result in a reduction of radiation-induced mucositis and therefore does not support the hypothesis that these bacteria play a crucial role in the pathogenesis of mucositis.*

CHAPTER 5

5.1 INTRODUCTION

Mucositis of the oral mucosa is a cumbersome acute side effect in the case of radiation and/or chemotherapy of tumors in the head and neck (1-4). Mucositis has a major impact on patients' well-being and can lead to treatment interruptions, with ultimately potentially detrimental effects on tumor control (and survival) (5-14). So far, there is no generally accepted and effective means to prevent or reduce treatment-induced mucositis. The most commonly suggested measures to alleviate part of the consequences of the treatment-induced mucositis are frequent oral rinsing with for example saline and maintaining good dental hygiene (3, 15-21). Unfortunately, none of the frequently used oral rinses such as chlorhexidine, benzydamine, and sucralfate seem to be effective when tested in a randomized setting (15,22-34). With regard to the pathogenesis of mucositis, it is felt that apart from loss of the cellularity in the mucous membranes as a direct consequence of the toxic agent, micro-organisms, especially the aerobic Gram-negative bacteria (AGNB), can come into play and have an important impact on the progression of mucositis beyond the phase of erythema (35-45). Sonis describes the evolution of mucositis biologically as a complex of 4 consecutive interacting phases (44). In one of the latter phases, i.e. during the bacterial or ulcerative phase with pseudomembrane formation (phase 3), the damaged mucosa starts to be colonized with aerobic Gram-negative bacteria; the subsequent release of endotoxins and the stimulation thereby of (more) cytokine release leads to further amplification of the mucositis. Several studies were therefore conducted aimed at reducing the amount of the potential pathogenic aerobic Gram-negative bacteria (and yeast) from the oral flora. However, none of the preliminary studies proved to be efficacious, either in reducing the total bacterial count or in preventing (the lattter phases of) mucositis (22-26). Foote (26) even demonstrated a detrimental effect of chlorhexidine on the oral mucosa. Spijkervet *et al.* (35,36), on the other hand were the first to recognize the potential benefit of preventing radiation-induced mucositis by selective elimination of the aerobic Gram-negative bacteria from the oral flora using lozenges containing a combination of 3 nonabsorbable antibiotics: polymyxin E, tobramycin and amphotericin B (PTA). Based on the encouraging results of the pilot study with the PTA lozenges, we initiated in 1993 a single institution, randomized double-blinded placebo controlled trial using the same 3 antibiotics (PTA) in an oral paste to test the hypothesis that selective elimination of potential pathogenic micro-organisms from the oral flora (aerobic Gram-negative strains and yeasts) leads to reduction of the severity of radiation-induced mucositis.

5.2 MATERIALS AND METHODS

All patients with a biopsy-proven malignant tumor of the head and neck, to be treated by either primary or postoperative external beam radiation therapy (EBRT) according to the treatment guidelines of the Rotterdam Head and Neck Cooperative Group, were eligible for this randomized trial. Excluded were those patients with a WHO performance score of 3 or 4 and those treated previously by EBRT of the head and neck or with adjuvant chemotherapy or systemic antbiotics less than 2 weeks before the planned EBRT. Between July 1993 and December 1997, 114 patients were randomized. After randomization, 37 patients refused further participation in the trial, either after the first (test) application of the paste (n = 26) or within four weeks after start of EBRT (n = 11). In total, 77 patients (38 placebo and 39 PTA) fulfilled the inclusion criterion of a minimum of 4 weeks of paste application and at least 3 weeks of EBRT and were therefore evaluable.

Patients who stopped after 4 study weeks (n = 59) were found to be equally distributed between the two study groups, i.e. 30 (PTA) vs 29 (non-PTA). The main reasons for stopping were bad taste of the oral paste and/or the unpleasant sensation of the paste texture in the mouth. These late 'dropouts' did not differ significantly from the patients who completed the study with respect to tumor characteristics, radiation therapy parameters, mucositis grade, and intensity and duration of pain and were therefore included as protocol compliant patients.

Table 1 summarizes the pretreatment characteristics of the study patients. The largest subsets of patients (62%) were treated for tumors in the oral cavity and oropharynx. In 67% of the cases, the histology was squamous cell carcinoma. Forty-eight patients (62%) underwent surgery of the primary tumor and were irradiated postoperatively. All patients were simulated in supine position. In the majority of cases conventional EBRT treatment techniques were used, consisting of two lateral opposed photon beams (4 or 6 MV) for the primary and the upper neck, and, if appropriate, an abutting low anterior field with or without midline shielding. The posterior neck region was taken off-cord after 40-46 Gy and supplemented with 10 MeV electrons if appropriate. Conventional fractionation schedules of 1 fraction per day and 5 fractions of 2 Gy per week were used. After an EBRT dose of 46 Gy, in 9 patients interstitial radiotherapy was implemented in the treatment as a booster dose to the primary. In the case of interstitial radiotherapy, the start of the brachytherapy marked the end of the evaluation period with regard to the (mucositis) study parameters. Before randomization, informed consent had to be obtained.

Table1. Patient characteristics

	Placebo-group	PTA –group
Age range; median	32 – 79 ; 57.4 years	20 – 78 ; 55.7 years
Gender: male / female	20 / 18	25 / 14
Tumorsite:		
Oral cavity	12	11
Oropharynx	12	14
Nasopharynx	2	1
Hypopharynx	2	2
Larynx	2	2
Maxillary sinus	2	0
Salivary glands	5	6
Miscellaneous	1	3
T-stage (TNM '97)		
T1	4	6
T2	15	12
T3	9	8
T4	6	9
Tx	4	4
N-stage (TNM '97)		
N0	17	19
N1	3	3
N2a	4	4
N2b	8	8
N2c	3	3
N3	1	2
Nx	2	0
Histology		
Squamous cell carcinoma	27	27
Adenocystic carcinoma	3	2
Miscellaneous / unknown	8	10
Surgery primary		
None	16	13
Local excision	8	6
Commando	8	11
Laryngectomy	1	2
Parotidectomy	4	6
Other	1	1
Neckdissection		
None	18	13
Unilateral	18	22
Bilateral	2	4
EBRT		
46 – 50 Gy	6	8
60 Gy	11	11
70 Gy	21	20
OTT: range; mean	31 - 66; 48 days	25 - 64; 46 days
Bilateral	28	28
Unilateral	11	11
IRT		
Number of patients	4	5
Dose in Gy	24 or 26 Gy	21, 24 or 26 Gy

Abbreviations: EBRT = external beam radiation therapy; IRT = interstitial radiotherapy.

In both groups an adhesive mouth paste containing hypromellose (16%) in a mixture of white paraffine (57%) and paraffine (24%) was used as a vehiculum. Taste was improved with saccharin sodium (0.67%) and peppermint oil (0.33%). The active PTA paste contained 0.2% Polymyxin E sulfate (Colistin sulfate), 0.18% Tobramycin and 1% Amphotericin B. The placebo paste was made identical in appearance to the PTA paste by adding cellulose (1.4%), amaranth (E123) and tartrazine (E102) to the vehiculum. One gram of PTA paste contained 2 mg Polymyxin E sulfate, 1.8 mg Tobramycin and 10 mg Amphotericin B. Labeling of the paste was blinded.

Patients were randomized to PTA or placebo paste. Both groups were instructed to apply 1 gram of paste 4 times a day starting 3 days before EBRT and the application was continued until the end of EBRT. All patients were seen weekly by the same, trained oral hygienist (A.M.G.T) for routine oral care and assessment of the mucosa score. Mucositis-related study parameters were assessed starting 1 week prior to radiation until 2 weeks after completion of EBRT. The primary study endpoint was the mucositis grade after 3 weeks of EBRT. Mucositis grade was expressed on a 5-point scale using the van der Schueren scoring system, as follows: Grade 0, no effects on mucosa; Grade 1, slight erythema; Grade 2, pronounced erythema; Grade 3, patchy mucositis; and Grade 4, confluent mucositis. As subjective study parameters, the intensity of pain due to the mucositis was scored on a 5-point scale, in which Grade 1 corresponded to no pain and Grade 5 to the most severe pain level. The duration of pain was expressed on a 3-point scale (no pain, occasionally painful, or continously painful mucosa) .

Bacterial cultures were taken weekly from 1 week before the start of EBRT until 2 weeks after completion of the treatment. For this purpose the mouth was rinsed with 5 cc of isotonic saline solution during 30 s; the mouthwash was collected in a special sterile container. The sample was inoculated on two bloodagar plates, on a similar bloodagar plate with 5% heated sheep erythrocytes (chocolate plate), and on a Sabouraudagar plate. One bloodagar plate was incubated anaerobically; the chocolate plate was incubated at 5% CO_2, and the two other plates were incubated aerobically. After overnight incubation, the broth was subinoculated on a bloodagar plate and a chromagar plate. Colonies with the appearance of 'normal respiratory pathogens' such as *H.influenzae*, pneumococci, hemolytic streptococci, and *S.aureus*, coliforms, *Pseudomonas* and other non-fermentative Gram-negative rods, as well as yeasts, were identified and quantified (colony-forming units per ml saliva: cfu/ml). Colonies belonging to the normal indigenous apathogenic oral flora, such as the viridans streptococci and the anaerobic microorganisms, were not further specified. However, for

each oral specimen the total amount of microorganisms was assessed and expressed in cfu per ml saliva.

A number of radiotherapy-related parameters was analyzed: i.e. cumulative EBRT dose given in a particular overall treatment time, fraction size, estimated percentage of oral mucosa surface irradiated, and estimated percentage of major salivary gland volume irradiated. The estimated total amount of oral mucosa (100%) was defined as the area depicted on lateral simulation films bounded by the hard and soft palate (upper and posterior boundary) and the inferior border of the mandible and the teeth (lower and anterior boundaries) (*Figure 1*). For each individual treatment field of every patient, the part of the oral mucosa within the treatment portals was delineated on the lateral simulation films and expressed as a percentage of the total oral mucosal area. Additionally, we constructed, as a rough guide to estimate the total irradiated major salivary gland volume, a CT-based template by using the lateral beams'-eye-view projections of 10 CT-delineated (of randomly chosen patients) parotid glands and submandibular glands. We estimated the percentage of the total irradiat

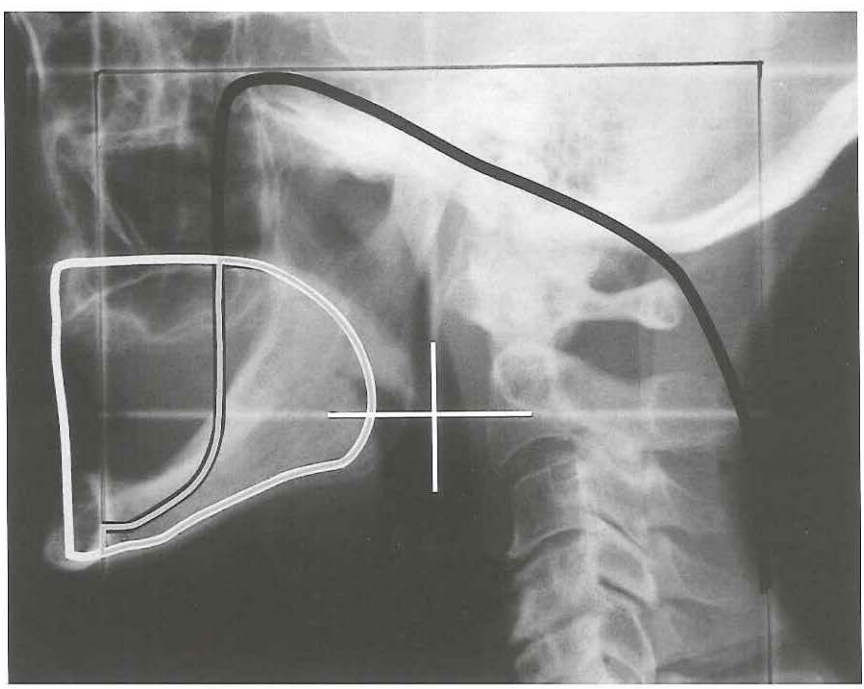

Figure 1. Lateral simulation film with the total oral mucosal surface outlined with a white line and the irradiated mucosal surface indicated by the grey line. The black line indicates the boundaries of the lateral portal.

ed surface ('volume') of the delineated major salivary glands within the treatment portals for each treatment field of each patient, relative to the template contour (*Figure 2*).

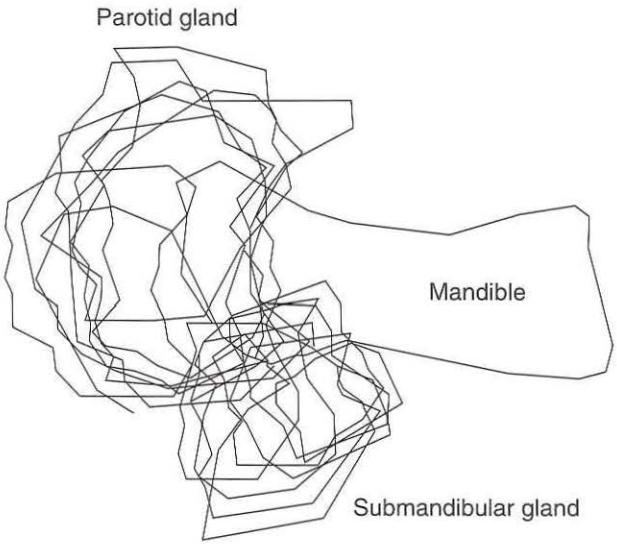

Figure 2. Template to estimate the irradiated parotid and submandibular gland 'volumes'. The template is composed of 10 beams'-eye-vieuw projections of the major salivary glands. The part of the salivary glands within the treatment portals is expressed as a percentage of the standardized surface of the template.

5.2.1 Statistical considerations: The sample size of the study was based on the data of the pilot study of Spijkervet et al. (36). Using a two-sided alpha of 5% and a power of 90% (beta = 0.10), 48 patients in both groups are necessary to detect a difference of one grade in mucositis score between the PTA and placebo group. Only 77 patients fulfilled the study criteria and were evaluable. With this number of patients, the power of the study is 83%, which is considered to be sufficient to draw conclusions. Mucositis scores and pain scores were compared with the Mann-Whitney test. The microbiological data were compared with the chi-squared test.

5.3 RESULTS

5.3.1 Mucositis grade and pain scores: Table 2 summarizes the mucositis grades and the pain scores. No significant differences were found between the two study groups for these study parameters with p values (Mann-Whitney test) of 0.75, 0.11 and 0.72 for the maximum mucositis grade, the maximum pain duration, and maximum pain intensity, respectively. Also, weekly evaluation of these parameters showed no significant differences between the PTA and placebo groups. Overall a Grade 3 or 4 mucositis occurred in 43% of the patients and was accompanied with moderate or severe pain, i.e. pain intensity of Grade 3 or higher by 31% of the patients. No difference was found regarding the time frame at which the maximum mucositis occurred; there was no difference in the duration of the mucositis, either. In both groups the most severe objective and subjective symptoms occurred from the fifth study week (corresponding to the fourth radiation week with a cumulative EBRT dose of 30-40 Gy) and remained at a plateau until the eighth study week.

5.3.2 Microbiology: The microbiology content of the oral specimens was divided into 6 groups: the normal indigenous flora, two groups of anaerobic Gram-negative strains (i.e. a group of coliforms and a group of *Pseudomonas* species), *Staphylococcus Aureus, Candida* species, and a miscellaneous group. Table 3 summarizes the weekly microbiologic results for both treatment groups. Microbiologic analysis before start of treatment revealed an AGNB carriage rate of 33.3% for the PTA group and 24% for the placebo group. A statistically significant reduction of the carriage rate of the coliforms was found in the PTA group from study Week 1 to 6 (*Figure 3*); on average, in 13 % of the patients of the PTA-group coliforms were isolated, in contrast to 34% in the placebo-group. *Pseudomonas* species were initially isolated by only 3 patients of the PTA-group and persisted in 1 patient.

5.3.3 Mucosa and major salivary glands: From 74 patients the treatment portals were analyzed for the total area of irradiated oral mucosa and irradiated salivary gland 'volume'. The estimated total irradiated oral mucosal surface ranged from 0-100%, with a mean of 65%. In the great majority of the patients (90%) at least 30% of the oral mucosa was within the radiation portals. For both treatment groups, a significant correlation was found between the irradiated oral mucosal surface (< 25%, 25 – 75%, > 75%) and the maximum grade of mucositis ($p = 0.0001$, Kruskall Wallis test), the maximum duration of pain ($p = 0.004$) an maximum pain intensity ($p = 0.006$).

Table 2. Mucositis study parameters

Study Parameter	PTA-group	Placebo-group	*p* value
Mucositis grade week 4			
G0	13	8	
G1	11	8	0.33
G2	7	10	
G3	3	8	
G4	5	4	
Max. mucositis grade			
G0	7	4	
G1	6	6	
G2	11	10	0.75
G3	4	12	
G4	11	6	
Moment of max.mucositis			
Week 0	7	6	
Week 1	9	9	
Week 2	12	9	0.92
Week 3	2	10	
Week 4	9	4	
Pain intensity at week 4			
1	12	8	
2	20	18	
3	3	8	0.37
4	3	4	
5	1	0	
Max.pain intenstiy			
1	6	5	
2	17	16	
3	7	5	0.72
4	5	11	
5	4	1	
Moment of max.intensity			
Week 1	10	9	
Week 2	17	15	
Week 3	3	4	0.71
Week 4	7	9	
Week 5	2	1	
Pain duration at week 4			
No pain	12	7	
Sometimes pain	18	18	0.36
Continuous pain	9	13	
Maximum pain duration			
No pain	6	6	
Sometimes pain	18	9	0.11
Continous pain	15	23	
Moment of max.duration			
Week 0	8	9	
Week 1	20	13	0.44
Week 2	11	15	
Week 3	0	1	

Table 3. Oral Flora content of potential pathogens per week

Species	Week 0 38 / 39*	Week 1 38 / 39	Week 2 38 / 39	Week 3 37 / 39	Week 4 37 / 39	Week 5 36 / 35	Week 6 31 / 27	Week 7 22 / 23	Week 8 11 / 14
Coliforms									
Placebo	8†	12	12	13	13	14	11	6	3
PTA	10	4	4	4	6	5	2	3	5
p value	0.65	0.03	0.02	0.01	0.06	0.01	0.005	0.27	0.31
Pseudomonas									
Placebo	0	1	2	3	2	1	0	0	0
PTA	3	1	0	2	1	0	1	1	1
p value	0.34	0.99	0.15	0.62	0.57	0.31	0.32	0.32	0.32
S.Aureus									
Placebo	0	2	3	3	3	4	3	3	1
PTA	3	2	1	0	1	1	1	0	0
p value	0.08	0.94	0.29	0.04	0.31	0.16	0.08	0.20	0.31
Miscellaneous									
Placebo	5	5	2	2	6	3	4	0	4
PTA	5	3	3	1	1	1	1	2	0
p value	0.94	0.38	0.67	0.55	0.04	0.31	0.16	0.16	0.04

* 38/39 = total number of patients in placebo/PTA group
† Absolute number of patients in whom the specified microorganism was isolated

A variable part (9% - 100%; mean 77%) of the parotid glands was encompassed by the treatment portals; the submandibular glands were almost entirely (mean 93%) included within the treatment portals. Neither in the placebo nor in the PTA group could a correlation be found between the irradiated parotid gland surface ('volume') and the mucositis-related study parameters with p values of 0.55 for the maximum mucositis grade, 0.80 for the pain duration and 0.88 for the pain intensity (Spearman test).

The EBRT dose groups 50 Gy, 60 Gy and 70 Gy did not correlate with the maximum mucositis grade, either in the placebo or in the PTA group ($p = 0.87$). Also the pain intensity ($p = 0.89$) and pain duration ($p = 0.48$) failed to show any correlation with the cumulative EBRT dose.

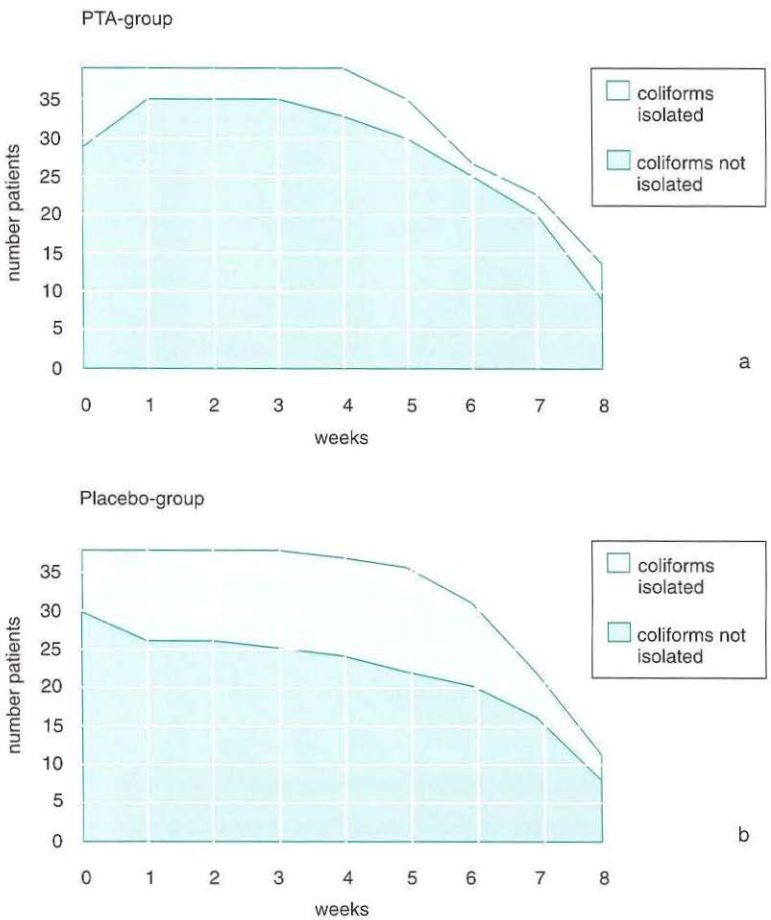

Figure 3. (a.) Coliforms isolated from the oral flora during the study weeks for the PTA-group and **(b.)** placebo group. In the PTA group a significant reduction of the percentage of patients in whom Coliforms were isolated was seen for study Week 1 through 6.

DISCUSSION

Mucositis is a common (acute) side effect of radiation therapy for head-and-neck tumors, because the oral mucosa is frequently incorporated in the beam portals. The most severe grades of mucositis are seen with intense schedules: well over 70% of patients treated with accelerated fractionation schedules have been reported to experience confluent mucositis (9,11,46-57). In conventional fractionated radiotherapy, the first signs of mucositis (erythema) appear after a latent period of approximately 1 week, with Grade 3 to 4 usually at the

end of the third week; the most severe amount of mucositis is scored usually around the fourth or fifth week, frequently associated with symptoms such as dysphagia, pain, and weight loss (20,37,57-59). When the (accelerated) regenerative response of the basal stem cells is large enough, healing can occur during the last weeks of treatment, resulting in the subsiding of signs and symptoms before the end of the radiation therapy (5,6,10,13,47,60--62).

Micro-organisms, especially the AGNB, are thought to play an aggravating role in the development of mucositis after the initial erythematous phase (20,35,38-40,44,63,64). In a pilot study, albeit in only 15 patients, Spijkervet *et al.* (36,37), using PTA lozenges, demonstrated a significant reduction in radiation-induced mucositis, paralleled by complete eradication of the AGNB and a significant reduction of *Candida* species from the oral flora. In the study by Spijkervet *et al.* (36) the maximum grade of mucositis was limited to erythema, and none of his patients developed pseudomembranes. In contrast, 33 of our patients (43%) experienced patchy or confluent mucositis (G3, G4) during their radiation treatments and no significant difference was observed between the two treatment groups ($p = 0.75$, Mann-Whitney). In fact, mucositis scores in patients participating in both arms of our study are not different from what is usually seen in conventional fractionated radiotherapy, even though the oral flora of the PTA-group showed a marked and statistically significant reduction of the aerobic Gram-negative strains (Coliforms) during the first six treatment weeks, i.e. 11% (PTA group) vs. 34% (placebo group). Since the initial report by Spijkervet *et al.* one pilot study with matched historical controls (41) and two placebo-controlled randomized studies (42,43) have been reported in the literature, showing a reduction in radiation-induced mucositis using PTA. However, in the randomized study of Okuna *et al.* (43), the significant difference was only true for the patient-reported subjective complaints. More importantly, no microbiological data are available. The findings by Kaanders *et al.* (41) were based on a nonrandomized trial, and positive results were true only for the 16 oral cavity tumors that underwent postoperative EBRT; that is, the 20 patients primarily irradiated for oropharyngeal tumors failed to show any benefit of the PTA-lozenges. Moreover, complete eradication of the AGNB was not achieved, and the low initial carriage rate (only 3 patients) does not allow further conclusions. In the carefully analyzed randomized study of Symonds *et al.* (42), with 224 evaluable patients, formation of intermediate and thick pseudomembranes as the primary study endpoint was not prevented, and the difference between the treatment groups for this endpoint was not statistically significant ($p = 0.12$). Statistical significant differences in favor of the PTA group were found for the maximum observed mucositis grade

($p = 0.009$) and associated subjective parameters. These results were, unfortunately, not paralleled by a complete eradication of the AGNB; i.e., no statistical significant difference was found between the two treatment groups in the overall percentage of patients with positive cultures ($p = 0.26$). However, as in our study, weekly evaluation data showed a significant reduction of the percentage of patients with positive cultures in the PTA group from Week 3 through Week 7 ($p = 0.01$). According to Symonds *et al.* the insufficient drug delivery of PTA by using lozenges is to be incriminated for the failing of total eradication of the AGNB and, in fact, the use of more efficient vehicles, such as an oral paste, to deliver the antimicrobials was advocated. In our study we used PTA in an oral paste that resulted in an efficient, selective elimination of the AGNB, especially the Coliforms, from the oral flora, although complete eradication was still not achieved and *Candida* species were not affected. The lack of any effect of selective elimination of AGNB on mucositis grade or related subjective symptoms in our study, therefore, does not support the hypothesis by Symonds *et al.* (42). Further support for rejecting the hypothesis is found in the study of Rahn *et al.* (65) and Adamietz *et al.* (66,67) with povidon-iodine as antimicrobial agent. Although a statistically significant reduction of the grade and severity of mucositis was found in the povidon group; this was again not paralleled by a significant reduction of the bacterial content of the oral flora. Whether micro-organisms other than the AGNB play a role remains to be tested. In this respect the persistence of the *Candida* species in 30% of our patients might be an explanation of the discrepancy between our results and the results of the studies of Spijkervet *et al.* (35-37), Kaanders *et al.* (41), and Symonds *et al.* (42). Kaanders *et al* (41) suggest that the importance of AGNB in the pathogenesis of radiation mucositis might be tumor site dependend (different colonization patterns); moreover, in the case of postoperative EBRT the oral defense mechanisms could be altered, and AGNB might play an even greater role in aggravating radiation mucositis. However, in our study the majority of patients were treated postoperatively, and no relation could be found between oral flora and mucositis grade, neither was there any tumor site dependence.

Analyzing simulation films of our patients, a significant correlation was found between the estimated irradiated oral mucosal area and all study parameters, suggesting that in order to reduce radiation-induced mucositis, obviously, as much mucosa from the treatment portals as possible should be eliminated (68). Other treatment-related parameters that might influence the severity and duration of mucositis, such as overall treatment time, cumulative EBRT dose, and the amount of salivary glands within the treatment portals were evenly distributed between the study arms. None of these parameters showed a significant correlation

with the mucosal study parameters in the present study.

From the present randomized study in head-and-neck cancer, analyzing the use of PTA oral paste for reducing radiation-induced mucositis, the hypothesis that aerobic Gram-negative bacteria play a crucial role in the evolution of radiation-induced mucositis, could not be corroborated by our data. It remains without dispute, however, that further efforts must be undertaken to find remedies to control or reduce this important clinical problem of radiation- and/or chemotherapy-induced mucositis (17,19-21,64,69-76). This is particularly relevant since (severe) mucositis can be of significant importance for quality of life endpoints such as eating, swallowing, chewing, pain and/or the use of tube feeding. As radiation-induced mucositis is, in essence, a (radio) biologically based phenomenon, where regeneration response of the basal stem cells and cytokines play a crucial role, finding new strategies is focussed on these fundamental mechanisms (6,60,77-81). Interesting developments in this respect are the use of growth factors, such as GM-CSF and G-CSF (82-87). An entirely different approach is the use of radioprotectors, such as amifostine (88-91).

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CHAPTER 6

Radiation-induced bilateral optic neuropathy in cancer of the nasopharynx

Case Failure Analysis and Review of the Literature

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ABSTRACT

Case Report: *A case history of unanticipated radiation-induced bilateral optic neuropathy, 18 months after induction chemotherapy and radiation therapy for a locally advanced nasopharyngeal carcinoma, is presented. Retrospective re-analysis of the radiation therapy technique, with emphasis on the doses received by the optic pathway structures, was performed. These recalculations revealed unexpectedly high doses in the range of 79 to 82 Gy (cumulative external and brachytherapy dose) at the level of the optic nerves, which explained the observed radiation injury.*

Conclusion: *Routine implementation of computed tomography for 3D dose planning purposes is therefore advocated. Review of the current literature confirms the importance of 3D dose planning in avoiding this complication and highlights the role of MRI in establishing the diagnosis of radiation-induced optic neuropathy.*

CHAPTER 6

6.1 INTRODUCTION

Radiation-induced optic neuropathy is an infrequent disorder of ischaemia affecting the optic nerve and/or optic chiasm. It is a dramatic late complication of radiation therapy for tumors involving structures in the vicinity of the visual pathway, such as those originating from the paranasal sinuses, nasopharynx and pituitary fossa, and meningioma (2,7,9,10,12,14,17,19, 20, 22, 31). This case report presents the medical history of a 42-year-old Caucasian male, developing bilateral optic neuropathy and unilateral retinopathy 18 months after combined treatment by induction chemotherapy, external beam radiation therapy (ERT) and intracavitary brachytherapy for a nasopharyngeal carcinoma. For failure analysis purposes, the conventional radiotherapy treatment technique used in our institute for nasopharyngeal carcinoma was re-analyzed retrospectively in detail, with special emphasis on the 3D dose distributions in the target volume and in the surrounding normal critical structures. The CT-based dose distribution data (ERT) revealed the presence of small circumscript high dose regions ('hot spots') at the level of both optic nerves (76 and 79 Gy) and also the right retina was located in a high-dose zone of 70 Gy. The findings pertinent to the danger of surpassing the tolerance levels of critical structures using this conventional radiotherapy technique, and the merits of CT-planning (15, 24) in this respect, are discussed in detail, and correlate with the existing data in the current literature on radiation-induced optic neuropathy.

6.2 CASE REPORT

6.2.1 Medical history: A 42-year-old patient was referred to our hospital because of nasal obstruction, hearing loss and diplopia. Clinical, radiological and pathological examination revealed a moderately differentiated squamous cell carcinoma originating from the nasopharynx, with partial destruction of the base of the skull and bilaterally enlarged cervical lymph nodes. Both on MRI and on CT scans there was no radiological evidence for tumor involvement of the pituitary gland, optic chiasm or optic nerves. Except for the left N.VI palsy, all other investigations did not reveal any additional abnormalities, that is, including a bilateral full visual acuity at the time of the start of treatment. According to the

UICC/AJCC recommendations (26), the patient was classified as having a T4N2cM0, stage IV cancer of the nasopharynx. Treatment was instituted according to the guidelines of the regional Head and Neck Cooperative Group for locoregional advanced tumor stages; that is, induction chemotherapy followed by radiotherapy to the primary tumor and the regional cervical lymph nodes. After completion of radiotherapy, except for a persisting left VIth nerve palsy, clinical examination and MRI follow-up investigations have to date not revealed evidence for tumor recurrence. However, 18 months after completion of the treatment the patient complained of rapidly progressive bilateral visual loss, with total loss of sight 2.5 months later.

6.2.2 Treatment: With induction chemotherapy (6 weekly cycles of Cisplatin (CDDP) [80mg/m^2]), a partial remission of the primary tumor mass and lymph nodes was obtained. For ERT the patient was placed in a supine position on the treatment couch of a linear accelerator, using an immobilizing head cast. The dose was prescribed according to the ICRU-50 recommendations (12). The target volume was irradiated by 4 MV photons with a daily fraction size of 2 Gy, 5 days per week. Two lateral parallel opposed fields for the primary and upper cervical lymph nodes (dose prescribed to the midline), and an anterior abutted supraclavicular field for the lower cervical lymph nodes (dose prescribed at a depth of 3 cm) were used. The dose calculations for the lateral parallel opposed photon fields were computed for an outline of the neck at the level of the isocenter using the CADPLAN planning system (Varian-Dosetek, Finland). Correction for dose inhomogeneities caused by bony structures and air spaces is, however, not possible without CT information. Based on the bony structures of the lateral simulation films customized blocks were implemented for shielding the eyes and parts of the oral cavity.

Because of tumor extension into the nasal cavity and ethmoid sinus complex, an anterior high-energy electron field (18 MeV) was added to boost the shielded part of the ethmoid sinuses to a cumulative dose of 60 Gy. In order to prevent overlap, the anterior nasal field and the parallel opposed photon fields were abutted by introducing a difference of 1 cm between the ventral borders of the parallel opposed lateral photon fields. By virtue of this difference the dose fall-off at the ventral edges of the photon fields becomes less acute, allowing a more smooth alignment of the photon and electron fields. The necessary electron energy was calculated by CADPLAN on a transverse outer contour at the level of the mid-orbits in such a way that at the junction of the electron and photon fields, a dose of at least 80% of the prescribed tumor dose was achieved, without exceeding a dose level of

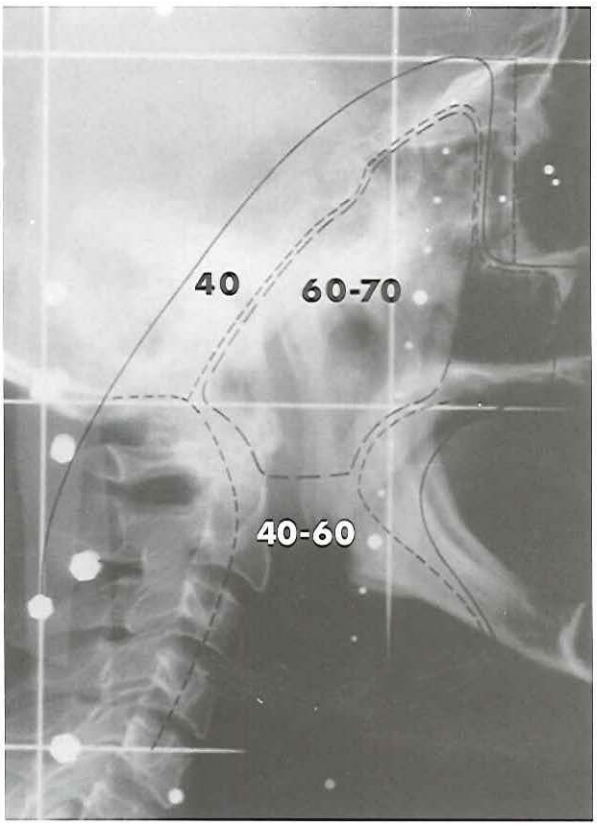

Figure 1. Lateral simulation X-ray film, showing the borders of field size reductions at 40 Gy, 60 Gy and 70 Gy, suggested total exclusion of the optic chiasm from radiotherapy after 60 Gy.

more than 120% of the prescribed tumor dose. The major reason to use such a high electron energy beam was to avoide underdosage at the tumor site. All dose calculations of the original radiation plan were carried out without CT information and thus without the opportunity to correct for dose inhomogeneities caused by bony structures and air spaces. The parallel opposed fields were coned down after 40 Gy to spare the cord and the sella; the reduced lateral opposed photon fields and the posterior strip of the neck (supplemented by 10 MeV electrons), were subsequently taken to 60 Gy. A second field reduction was instituted after 60 Gy. From 60 to 70 Gy, only the parapharyngeal space and nasopharynx proper were included in the lateral opposed photon fields and irradiated to a cumulative dose of 70 Gy (*Figure 1*); the neck nodes were boosted by 10 MeV electrons to 70 Gy, too. Two weeks after ERT, the primary site was boosted by means of high-dose-rate (HDR) intracavitary brachytherapy. Brachytherapy was given using the Rotterdam Nasopharynx Applicator (mould), connected to a remote controlled HDR afterloading machine; the tech-

nique of boosting by intracavitary brachytherapy has been eluded to in detail (16). The brachytherapy dose was prescribed to the nasopharynx at the level of the base of the skull; a fraction size of 3 Gy was given twice daily (interval 6 hours) with a total of 4 fractions. Therefore, the cumulative dose to the nasopharynx proper was 82 Gy (70 Gy ERT and 12 Gy brachytherapy). Due to the relatively small attribution of the brachytherapy dose to the total dose no correction for the different biological effect was made.

6.2.3 Ophthalmic examination: Eighteen months after completion of radiotherapy the visual acuity of the right eye was 1/60 and of the left eye 0.15. At fundoscopy a swollen optic disc, massive peripapillary exsudates and flame-shaped haemorrhages were seen, compatible with ischaemic optic neuropathy (*Figure 2*). Fluorescein angiography of the right eye revealed areas of capillary non-perfusion, indicating the first signs of retinopathy. Two and a half months after the first visual symptoms, that is, 21 months after completion of therapy, the patient had total loss of sight. Control fluorescein angiography of the right retina at 24 months after therapy showed extensive ischaemic areas with capillary non-perfusion and signs of neovascularization (*Figure 3*). Furthermore, there was rubeosis iridis with an

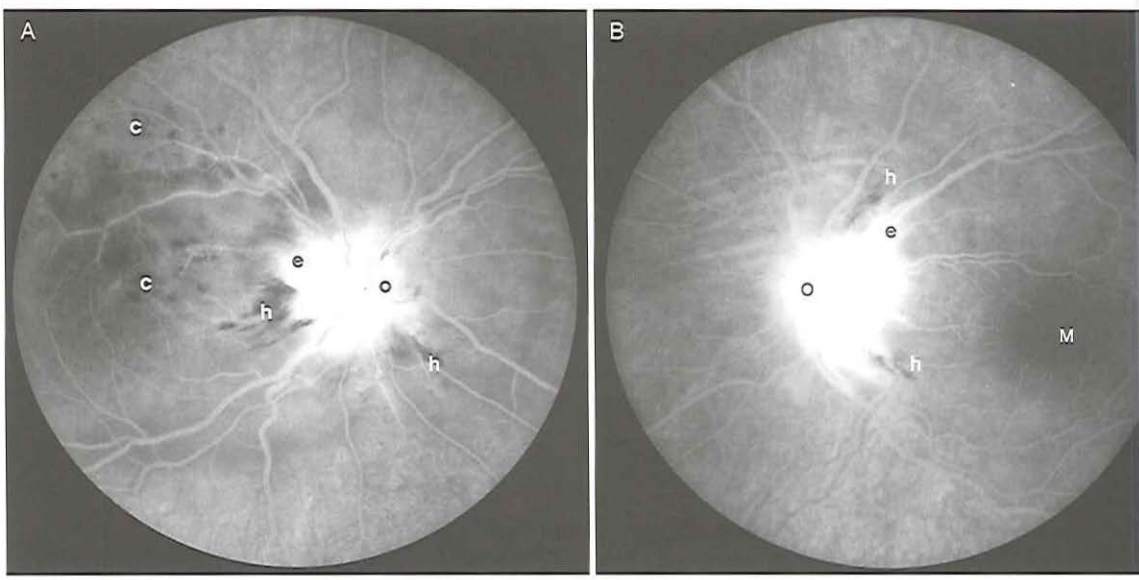

Figure 2a and 2b. Active stage of ischaemic optic neuropathy of the right (a) and left (b) eye. The edges of the optic disc (o) are blurred by flame-shaped haemorrhages (h) and exsudates (e). Note the marked signs of retinopathy with areas of capillary non-perfusion (c) of the right eye. (M = macula).

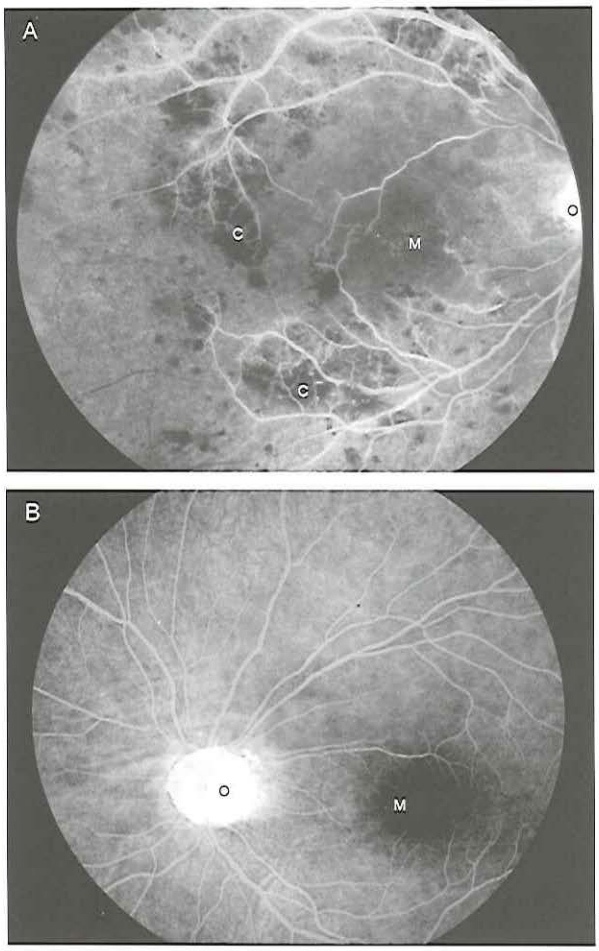

Figure 3a and 3b. Fluorescein angiography of the right eye (a) shows extensive areas of capillary non-perfusion (c). The atrophic optic disc (o) is seen at the edge of the picture. The left eye (b) also shows the marked atrophic optic disc, but no signs of retinopathy. (M = macula).

elevated ocular pressure of the right eye of 31 mm Hg. The ocular pressure in the left eye was found to be within normal limits. Consequently, the neovascular glaucoma of the right eye was succesfully treated with panretinal laser photocoagulation. The overall ophthalmic findings seemed fully compatible with bilateral radiation-induced optic neuropathy and unilateral rightsided retinopathy.

6.2.4 Follow-up MRI: Follow-up MRI-scans were made at regular 3- to 6-month intervals.

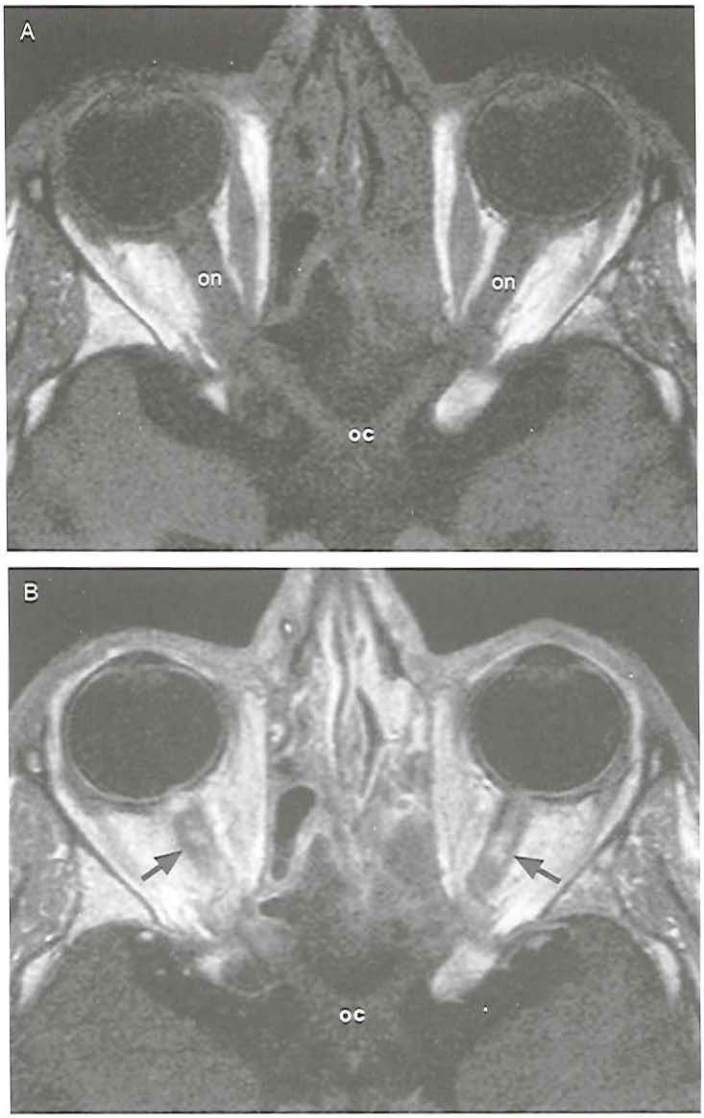

Figure 4a and 4b. T1-weighted transversal MR-images at the level of the optic nerves (on) and optic chiasm (oc) prior to (a) and after intravenous gadolinium-DTPA (b). The patchy enhancing lesions (arrow) within the optic nerves are typical for radiation-induced optic neuropathy.

Three months after the first symptoms of visual loss, T1-weighted MR-images showed only small contrast-enhanced deposits at the left side of the nasopharyngeal roof, the infratemporal fossa, both temporal lobes and the left cavernous sinus, but no signs of tumor recurrence. On pre-contrast detailed sections through the optic nerves, optic chiasm and pituitary gland, no evidence for a recurrent tumor in the vicinity of the structures of the optic pathways was found. However, after intravenous administration of gadolinium-DTPA, areas of

patchy enhancement typical for radiation-induced optic neuropathy were seen in both optic nerves (*Figure 4*).

6.2.5 Dose distributions: In retrospect, the dose distributions were re-calculated, with special emphasis to the optic nerves, optic chiasm and retina. The original treatment plan was developed without a planning CT. For the reconstruction, we therefore used the original pre-therapeutic CT scan, which was digitized and the data imported into the 3-D computer planning system CADPLAN (Varian-Dosetek, Finland). The optic nerves and optic chiasm were outlined and using the beam data of the original lateral opposed 4 MV photon fields and the anterior electron field, a dose distribution was reproduced and displayed on the CT-images (*Figure 5*). A part of the outer contour of the nose was unfortunately missing on the diagnostic CT scan. The reconstructed outer contour of the nose (on CT) was less protuberant than the original nose, as could be deduced from the original transverse outline. This difference in size was compensated for by reducing the electron beam energy for the reconstruction (16 MeV) as opposed to the original 18 MeV beam. The maximum, mean and min

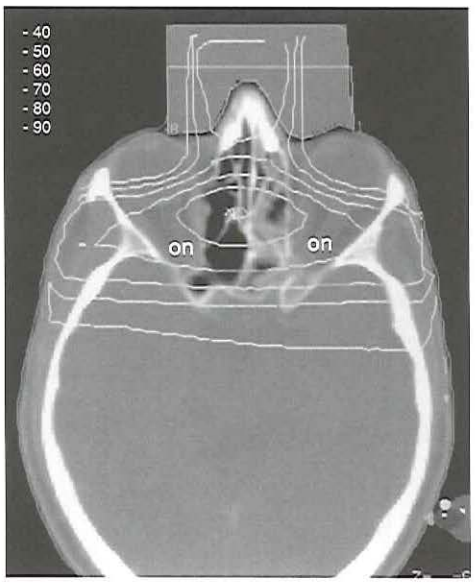

Figure 5. Isodose distribution in Gy on a transversal CT plot at the level of the optic nerves (on) with the summed 3D dose data of the lateral opposed 4 MV photon fields (70 Gy) and an anterior 16 MeV electron field (60 Gy). The asterisk indicates a maximum dose of 91.4 Gy.

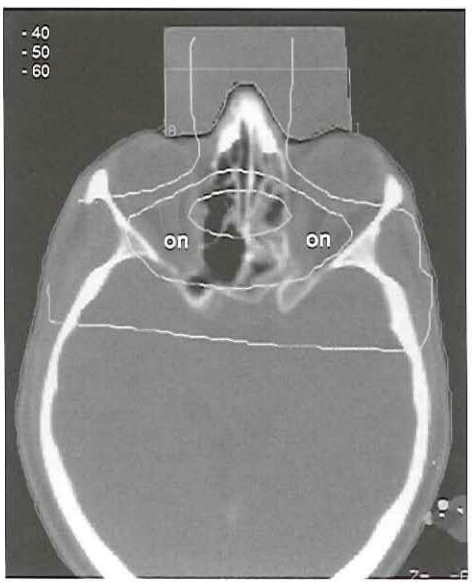

Figure 6. Isodose distribution in Gy for a hypothetical radiation plan of 2 lateral opposed photon fields (70 Gy) and an anterior 16 MeV electron field (46 Gy). The optic nerves (on) are laterally shielded off after a dose of 40 Gy.

imum doses delivered to the optic nerves, optic chiasm and retina were obtained from volumetric calculations; also, point doses were assessed. Using CT-information, CADPLAN 3D dose calculations corrects for tissue inhomogeneities, such as bony structures and air spaces. The brachytherapy doses given to the retina, optic nerves and chiasm were derived from the original dose distribution curves, which were calculated by the PLATO planningsystem (Nucletron, Veenendaal, The Netherlands).

Table 1 summarizes the doses received by the structures of the visual pathway. From these calculations (cumulative ERT and brachytherapy dose) it becomes clear that the tolerance dose of the optic nerves (79 and 82 Gy) and of the retina (74 Gy) were largely exceeded. The exceeding of the tolerance dose was mainly due to the unanticipated dose contributions of the photon beams after 60 Gy added to the large contribution of the anterior electron beam (9 and 18 Gy to the optic nerves), which created a circumscript hot spot at the site of the optic nerves.

Table 1. Dose contributions (maximum point dose) in Gy to the structures of the visual pathway

Radiation field	onl	onr	ch	rl	rr[1]
0 - 40 Gy photons; lateral opposed large fields	42	41.5	40.2	33.8	32.8
40 - 60 Gy photons; first field reduction	21.6	21.3	10.6	17.7	17.6
60 - 70 Gy photons; boost to nasopharynx proper	4.7	4.9	5.2	4.2	2.9
0 - 60 Gy 16 MeV electrons; an anterior field	9.1	18.4	5.1	20.3	30.6
Maximum cumulative dose of ERT[2]	76.1	79.0	60.6	71.7	70.0
Cumulative brachytherapy (BT) dose	3.2	3.1	2.9	2.3	2.1
Cumulative ERT and BT dose	79.3	82.1	63.5	74	72.1

[1] onl = left optic nerve; onr = right optic nerve; ch = optic chiasm; rl = left retina; rr = right retina.
[2] volumetrically calculated maximum total dose for external radiotherapy.

6.3 RESULTS AND DISCUSSION

This paper reports a case history of bilateral blindness due to radiation-induced optic neuropathy. The patient presented with a locoregionally advanced (T4N2c) cancer of the nasopharynx with partial destruction of the base of the skull. Local tumor control was, how-

ever, achieved after a combination of 6 courses of CDDP chemotherapy and 70 Gy ERT, followed by a 12 Gy brachytherapy boost.

The established treatment modality for nasopharyngeal carcinoma is radiotherapy (1, 18, 28). Some literature data corroborated the benefit of adding chemotherapy, particularly in case of advanced tumour stages (5). In cancer of the nasopharynx dose-effect relationships have been established for ERT (3, 4, 23, 30), as well as for combinations of ERT and brachytherapy (6, 29). The maximum doses which can be given by ERT alone are, however, severely limited because of the tolerance of the adjacent critical structures, such as the retinae, optic nerves, optic chiasm, and pituitary gland. Endocavitary brachytherapy allows to partly circumvent this problem, and thus cumulative doses in the range of 80 to 90 Gy can, in fact, be delivered safely. For example, Wang *et al.* (29) reported an uncomplicated local control rate of 91% for T1-T3 tumors treated with ERT plus a brachytherapy boost. Due to the rapid dose fall-off away from the radioactive sources, the treatment volume can be a major limitation when using brachytherapy. For dose escalation purposes, brachytherapy can therefore only be considered an effective means when given as a boost after ERT.

This patient presented with a huge tumor mass (T4) extending into the base of the skull at the level of the carotid syphon. Given the tumor extension, the up-front trade off was that, for a reasonable chance of local tumor control by virtue of high-dose radiotherapy, a slight risk for a serious late complication such as blindness to occur, should be anticipated. This was, in fact, discussed with the patient before the initiation of radiotherapy. Obviously, care was taken to limit the dose to the critical normal structures as much as possible.

According to the literature, the assumed tolerance dose for neural structures is, in general, about 50 to 60 Gy, also depending somewhat on the fraction size used (2,7,8,11,12,14, 19,20,22,25,27, 31). For example, Parsons *et al.* (20) describe 17 optic nerve injuries (14 patients) out of 215 irradiated optic nerves (131 patients). No radiation damage to the optic nerves was observed below 59 Gy. A 15-year probability of radiation-induced optic neuropathy of 11% was found for doses between 60 and 83 Gy with a fraction size of 1.9 Gy, as opposed to a probability of 33% to 50% for doses in the range of 60 to 70 Gy and 70 to 83 Gy, respectively, given in fractions of more than 1.9 Gy. Jiang *et al.* (14) reviewed a cohort of 219 patients radiated for cancers of the nasal cavity and paranasal sinuses and found that the total radiation dose was the most important determinant in predicting radiation-induced optic neuropathy and chiasm injury. Nerve and/or chiasm injury were rarely observed below a dose of 60 Gy (10-year incidence of less than 5%) and did not occur below a dose of 50 Gy. Due to the end-arterial system, the retina appears to be more sensi-

tive for radiation damage, but radiation-induced retinopathy can be asymptomatic if it predominantly involves small peripheral regions of the retina (14,19). Radiation-induced changes of the retina are observed at a dose of 45 Gy (19,21,22). The susceptibility of the retina for radiation damage is increased in case of chemotherapy and diabetes mellitus; both conditions increase the risk of vascular injury.

As can be seen from the radiation portals depicted in *Figure 1*, the optic pathways were considered at the time to have been adequately shielded from the primary beams at a dose level well below the generally accepted tolerance levels (40 to 60 Gy). The blocks, however, were drawn on conventional (2D) simulation films and no 3D calculation based on CT information was performed. Retrospectively, the CT information showed that the optic nerves were not completely shielded by the blocks and therefore received considerably more dose than the anticipated maximum dose of 60 Gy. Unfortunately, bilateral blindness occurred at 18 months after completion of therapy. Given that 4 years after the completion of radiotherapy the patient is still without evidence of tumor, radiation-induced optic neuropathy was obviously the suspected cause for the loss of vision.

The first signs of optic neuropathy are fundoscopically characterized by swelling of the optic disc, flame-shaped peripapillary haemorrhages, hard exsudates and subretinal fluid. Ultimately, optic neuropathy is characterized by an atrophic pale optic disc. The right eye of our patient additionally showed signs of retinopathy, commonly seen in half of the patients with optic neuropathy.

The pathogenesis of radiation-induced optic neuropathy and also of retinopathy is believed to be of ischaemic origin (8,11,14,19,22) due to vascular injury. Others feel that a direct injury to the optic nerve by ionizing radiation might play an important role as well, and still others conjecture an auto-immune mechanism as the aetiologic factor. Radiation-induced optic neuropathy usually occurs within 5 years (mean 27 months) after the initiation of radiotherapy; it can be quite sudden in onset and is found, in general, to be rapidly progressive.

The loss of vision of the patient presented in this case report was also rapidly progressive and resulted in bilateral blindness within 2.5 months after the onset of clinical symptoms. Diagnosis of radiation-induced optic neuropathy can be difficult in case of visual loss without marked signs at fundoscopy; in fact, the presence of tumor recurrence per se after radiotherapy for an extensive T4 nasopharyngeal carcinoma is probably more likely than radiation-induced optic neuropathy. For example, Perez *et al.* (23) calculated a 10-year local failure rate of 60% for T4 nasopharyngeal carcinomas, with the majority of the local failures

occurring within the first 3 years after treatment. The patient of this case report is an exception in surviving already more than 4 years without signs of tumor recurrence. That is, CT and MRI both had excluded tumor recurrence; in particular, no mass lesions were found at the level of the optic pathways. However, the T1-weighted MRI-scan after intravenous gadolinium-DTPA did show patchy contrast-enhanced lesions in the optic nerves (*Figure 4*). A particularly distinctive feature in many of the radiation-induced lesions of the optic nerves is that they frequently go undiagnosed on T2-weighted scans. As Guy *et al.* and others (10,11,31) have pointed out, this is probably due to a lesser signal-to-noise ratio; i.e. the cerebral spinal fluid surrounding the optic nerves has a high signal intensity on T2-weighted images, which may render high signal areas within the adjacent optic nerve difficult to detect. Optic nerve enhancement is believed to represent radiation-induced disruption of the blood-brain barrier and accumulation of gadolinium-DTPA within the optic nerve. Gadolinium-DTPA enhancement of (parts of) the optic nerve may indicate the persistence of endothelial cell proliferation, hyalinization and thrombosis of blood vessels, finally resulting in ischaemia of the optic nerve. Although the enhancement of the optic nerve and optic chiasm is a non-specific sign of disruption of the blood-brain barrier and might also be related to inflammatory and non-infectious disease (such as multiple sclerosis), in view of the medical history the diagnosis of bilateral radiation-induced optic neuropathy seems indeed the most likely explanation of the MRI findings. Moreover, the fundoscopic appearance in this case was quite characteristic for optic neuropathy and the association with retinopathy of the right eye is a very unlikely combination for any other cause of disease.

Since the reasons for this were not apparent at first sight, a retrospective analysis was performed, the outcome of which was in fact the basis for this report. In order to see whether the radiation-induced optic neuropathy and retinopathy could be explained due to unexpectedly high doses of radiotherapy received by the critical structures, e.g. because of some unforeseen technical error that might have occurred, a re-analysis of the applied techniques and the dose distributions was performed in retrospect, using a 3D computer planning system. The conventional radiotherapy technique in our cancer centre for patients with a nasopharyngeal carcinoma extending into the nasal cavity included a small anterior portal, using high-energy electrons, given to a total dose of 60 Gy and focused at the ethmoid sinus complex located between the eyes, a region that in essence receives no radiation otherwise because of the shielded orbits in the lateral portals. Wax on the bridge of the nose is customarily used to ensure that the lateral (photon) portals and the anterior (electron beam) field abut approximately at the 50% isodose lines. However, as shown in Table 1, 3D point

dose calculations, taking also into account the multiple surrounding air cavities, can give rise, at the level of the (fuzzy) junction zone, to a 'hot spot'. In defining the necessary electron beam energy for the anterior field, so as to obtain a dose range between 80% and 120% of the precribed tumor dose, we were in fact aware of potentially having such a 'hot spot'. However, its position in relation to the critical surrounding structures was not known, due to lack of CT information. Moreover, it appeared that this hot spot (*Figure 5*) was, unfortunately, positioned precisely at the level of the optic nerves. In general, one should be extremely careful in using anterior beam portals for intranasal tumor extension; we therefore now limit the use of high-energy electron fields to a dose of approximately 46 Gy (*Figure 6*). Another reason for the doses at the level of the optic pathways to be substantially beyond the expected levels, is the fact that one should keep in mind that 50% of the dose is still present at the block edges. A small contribution can also be accounted for by the transmission through blocks. Moreover, based on bony structures alone it is difficult to precisely locate the optic nerves and shield them by customized blocks without jeopardizing tumor dose. Since 1990 we have adopted the policy of combining ERT with a brachytherapy boost on a routine basis. Although small, this is another radiotherapy source that raises the dose in the optic pathway structures. Finally, our patient was treated by 6 cycles of CDDP prior to 70 Gy ERT, which might have generally enhanced the susceptibility to normal tissue injury. (8,12,14,22).

In conclusion: we feel that the patient presented in this case report was fortunate to some extent, because the applied protocol rendered him tumor-free. However, bilateral blindness is a severe and in principle unacceptable side effect of treatment. Moreover, in this case, the radiation optic neuropathy and retinopathy might have been avoided if a careful 3D CT planning procedure had been performed before the initiation of treatment. Three-dimensional treatment planning (15,24) provides comprehensive visualization of the tumor region and surrounding critical structures with the doses calculated for the target volume and the critical structures and also corrects for dose-inhomogeneities caused by bones and air spaces. In fact, nowadays, 3D CT (pre)-planning is mandatory for all nasopharynx cancer patients treated in our institute. In the near future it will be possible in our institution to depict the brachytherapy dose distribution on planning-CT-slices and to calculate dose contribution in the critical structures prior to radiation. In conjunction with the possibility to sum the external radiation contribution to the brachytherapy dose contribution, we feel confident that radiation optic neuropathy will be at large an avoidable complication of radiotherapy for nasopharyngeal tumors.

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CHAPTER 7

Role of endocavitary brachytherapy with or without chemotherapy in cancer of the nasopharynx

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ABSTRACT

Purpose: *We previously reported our preliminary experience with nasopharyngeal cancer boosted after 60-70 Gy external beam radiotherapy (ERBT) by fractionated endocavitary brachytherapy (ECBT) to cumulative doses of 78-82 Gy. As for Stage III-IVB disease, cisplatin (CDDP)-based neoadjuvant chemotherapy (CHT) was given. Aim of the present study was to define the role of ECBT more accurately.*

Methods and Materials: *Ninety-one patients with primary nasopharyngeal cancer, staged according to the 1997 UICC/AJCC classification system, were treated between 1991 and 2000 with 60-70 Gy external beam radiotherapy and 11-18 Gy ECBT. Of the 91 patients, 21 were treated in conjunction with CHT and 70 without CHT. Tumors were subdivided into undifferentiated (UD) and well, moderately, and poorly differentiated (WMP-D) subtypes. Treatment results were analyzed for local control (LC), disease free survival (DFS), freedom from distant metastasis, and overall survival (OS).*

Results: *A univariate and multivariate Cox regression analysis found stage, treatment period, age and grade significant for LC, DFS and OS. At 2 years, for Stage I-IIB (1st period, 1991-1996), the LC, DFS and OS were 96%, 88%, and 80% respectively, vs. 65%, 46% and 52% for Stage III-IVB. For the 2nd treatment period (1996-2000; CHT for Stage III-IVB), the LC, DFS and OS at 2-years were 100%, 90% and 61% (Stage I-IIB), respectively, vs. 86%, 74%, and 66% (Stage III-IVB). Three prognostic groups (PGs) were constructed. For the 1991-1996 period, at 2 years, patients in the good PG (UD Stage I-IIB disease) had 100% LC and 92% OS; those in the intermediate PG (UD Stage III-IVB or WMP-D Stage I-IIB) had 94% LC and 71% OS; and those in the poor PG (WMP-D Stage III-IVB) had 47% LC and 40% OS. For the 1996-2000 period, at 2 years, the good PG had 100% LC and 88% OS; the intermediate PG had 100% LC and 64% OS; and the poor PG 71% LC and 60% OS.*

Conclusions: *For Stage I-IIB disease treated between 1991 and 2000, at 3 years LC and OS was 97% and 67%, respectively. The results with 77-81 Gy without CHT warrant EBRT combined with ECBT to remain our standard of care in Stage I-IIB disease. For N2-3 and/or T3-4 tumors, in addition to high doses of RT, neoadjuvant CHT was administered as of 1996. For the 1991-2000 period, at 3-years, the LC 86% and the OS 72% with CHT, with little extra morbidity; they were 68% and 35% without CHT. Because of better target coverage and sparing, T3-4 tumors are currently boosted by stereotactic RT to 81.2 Gy.*

CHAPTER 7

7.1 INTRODUCTION

For nasopharyngeal cancer (NPC), a variety of treatment techniques are used to apply highly conformal, high doses of radiation to the primary tumor and neck (nodal) areas (1-14). The rationale for the application of these sophisticated and labor-intensive treatment techniques is underscored by dose-tumor effect relationships (4,9-12). Moreover, local control (LC), one of the most important prognostic factors in NPC, has been shown to be an independent prognostic indicator of distant metastasis (13). It seems obvious that with the application of external beam three-dimensional conformal radiotherapy (3D-CRT) techniques to the primary tumor and neck, sparing of the surrounding critical normal tissues, such as the optic apparatus, pituitary gland, brainstem, inner ear, temporal lobes, and salivary glands, comes within reach (1,15-21) With its steep dose falloff and dose optimization potential when implementing stepping source technology (with in the foreseeable future even the realization of inverse planning), fractionated high-dose-rate endocavitary brachytherapy (ECBT) typically has the prerequisites of becoming a fully 3D-CRT (IMRT) treatment modality (1,7,8). ECBT, a relatively straightforward technique for supplementing the dose of external beam radiotherapy (EBRT) to high cumulative doses and, moreover, a patient-friendly procedure that can easily be applied on an outpatient basis, has been routinely implemented in our institution to treat primary and recurrent NPC. We reported a local relapse-free survival of 95% at 5 years for early- stage primary tumors, with cumulative doses of ≥ 78 Gy (14,22).

Until recently, ECBT has been the preferred modality for boosting NPC in patients treated between 1991 and 2000. It could be argued, however, that fractionated ECBT dosimetrically is a less adequate boost technique in case of more advanced T stages (i.e., advanced lesions with significant extension of disease into the parapharyngeal space [T2b] or bone/paranasal sinus [T3] or in / beyond the base of the skull / cranial nerves / infratemporal fossa / hypopharynx [T4], according to the revised UICC/AJCC TNM classification of malignant tumors, 1997 edition [23,24]). The primary focus of the present study was to define, on the base of this recently introduced 1997 classification system, the role of ECBT more accurately.

In Stage III-IVB disease, the use of chemotherapy (CHT) in NPC has now become standard for improving LC, disease-free survival (DFS), freedom from distant metastasis, and overall survival (OS), although the debate on concomitant vs. neoadjuvant CHT is not as yet entirely settled according to the data derived from the literature (25-30). The second aim of this

study was to evaluate the outcome for LC, DFS, distant metastases (M+), and OS in Stage III-IVB patients treated before or after the per protocol implementation of neoadjuvant CHT. This is particularly relevant, because neoadjuvant CHT according to the University Hospital Rotterdam-Daniel NPC protocol is to be followed routinely by high-dose, high-precision RT to cumulative doses of 78-81 Gy, either by BT or sophisticated 3D conformal EBRT techniques. It is interesting to note that that little if any additional toxicity has been experienced to date in the current protocol by neoadjuvant CHT combined with high cumulative doses of radiation; this is in contrast to some of the toxicity reports of conventional dose levels of EBRT in combination with concomitant CHT (25-32).

7.2 METHODS AND MATERIALS

7.2.1 Evolution Rotterdam NPC protocol: All primary NPC patients are seen in joint consultation by the radiation-oncologist and ear, nose, and throat surgeon. The diagnosis was established by clinical examination, endoscopy, CT or (at a later date during the study period) preferably by MRI of the head and neck, local biopsy, and ultrasound-guided fine needle aspiration biopsy of the regional lymph nodes. As of 1991, patients with undifferentiated (UD; World Health Organization [WHO] Type 3), well/moderately differentiated (WM-D; WHO Type 1) and poorly differentiated (PD; WHO Type 2) carcinoma are treated by a combination of EBRT and ECBT (3, 14). In the case of cancer confined to the nasopharynx proper, 60 Gy EBRT was applied to the primary, with 2 Gy daily, 5 fractions per week. For the more advanced tumors (e.g. parapharyngeal extension and the T3-4 category), a total dose of 70 Gy was given by EBRT. The neck was radiated electively to a dose of 46 Gy; metastatic neck nodes were boosted to 70 Gy. The EBRT was delivered by a linear accelerator with a 4 to 8-MV photon beam using a conventional three (shrinking)-field technique; two parallel-opposed lateral fields and an abutted low-anterior field with shielding of the larynx. The eye was blocked in the lateral portals; in the case of tumor extension into the nasal cavity or ethmoids, a high anterior, high-energy electron field was added. After 46 Gy, the portal was taken off cord; the posterior neck was supplemented by high-energy electrons. The second, and usually third field size reduction was implemented to finally reach the prescribed total dose by EBRT in the clinically positive neck nodes and the nasopharynx. The EBRT was prescribed according to International Commission on Radiation Units and Measurement (ICRU)-50 recommendations. These conventional treatment techniques

for delivering EBRT have remained the same during the study 1991-2000 period. Currently, we are working on a class solution for radiating the nasopharynx and both sides of the neck by intensity-modulated radiotherapy.

After a rest period of 1-2 weeks, EBRT was supplemented by fractionated ECBT. The ECBT was applied by means of the silicone Rotterdam Nasopharynx Applicator, connected to a computerized afterloading machine (microSelectron HDR; stepping ^{192}Ir point source, activity ± 370 GBq). The design of the Rotterdam Nasopharynx Applicator has proved to be extremely user friendly. In short, it can be easily introduced, after topical anaesthesia has been applied to the nasal mucosal linings, on an outpatient basis. Moreover, the flexible silicone afterloading applicator can remain in situ for the duration of the treatment without causing severe discomfort to the patient (22).

A boost dose of 6 fractions of 3 Gy each (≥ 6 hour interval between fractions) for early T-stages (cumulative dose to nasopharynx of 78 Gy) and 4 fractions of 3 Gy each for advanced T2b-4 stages (cumulative dose to nasopharynx of 82 Gy) was chosen at the time. For dose prescription and dose reporting, tumor tissue and normal tissue dose points, based on easy-to-identify anatomic landmarks depicted on lateral and AP X-ray films, were used. Details on these so-called patient points and this easy-to-comply dose prescription and dose reporting system have been previously published (22).

Also analyzed were the dose distributions with tumor tissue points positioned on the CT-based contoured target; the mean dose was calculated in the contoured volumes of the critical surrounding normal tissues, such as the retina, optic nerve, optic chiasm, brainstem, pituitary gland, soft palate, spinal cord, temporal lobe, submandibular gland and parotid gland. For that purpose, dose-volume histograms of the target and critical normal tissue structures were generated. These data have been recently been submitted (33,34). In short, it was found that ECBT and the dose prescription to patient points would mean significant underdosage in case of more advanced T3-4 tumors. In contrast, with doses prescribed to CT-based contours with the more extensive targets, the critical normal tissues are at a higher risk for overdosage. Finally, dose prescription to CT-based contours is also more labor intensive.

In 1997, the UICC/AJCC TNM classification system for malignant tumors introduced significant changes with respect to the T and N categories and stage groupings (23,24). To analyze the results of NPC treated between 1991 and 2000 (current study), all primary NPC tumors treated by fractionated ECBT in our institution were restaged according to the revised 1997 edition (Table 1).

Table 1. T and N categories for 91 patients treated in 1991-2000 classified according to UICC/AJCC classification system, 1997 edition.

	N-stage				
T-group	N0	N1	N2	N3	Total
T1	1	5	1	3	10
T2a	9	9	1	5	24
T2b	4	8	9	3	24
T3	1	3	2	0	6
T4	8	4	14	1	27
Total	23	29	27	12	91

On the basis of a previously published detailed analysis on NPC treatment results at our institute (14) and because of radiobiological considerations (35,36), the University Hospital Rotterdam protocol was adjusted in October 1996. Thus, for the advanced tumor stages (T3-4 and/or N2-3), per protocol, neoadjuvant CHT (3 monthly courses of cisplatin 100 mg/m^2 combined with 5-fluorourcil (5-FU) 1000 mg/m^2 for UD tumors or 6 weekly courses of cisplatin 70 mg/m^2 for WMP-D tumors) was given. Radiobiology and clinical research dictate that the overall treatment time (OTT) should be kept to a minimum; this principle is now frequently pursued in cancers of the head-and-neck by instituting multiple fractions per day (37,38). As of 1999, for NPC, as for all head-and-neck cancers treated in our institute, the routine EBRT fractionation schedule consists of 6 fractions of 2 Gy weekly, given during 5 working days. Moreover, the clinician should make an effort to adhere to a split of ≤1 week between the EBRT and ECBT. Although scarce, data on maximizing the therapeutic difference between tumor control and the normal tissue complication probability, by individually adjusting doses in different parts (e.g., at the start and at end) of the treatment schedule (39), are available.

Given the biologic optimization, and also to accelerate the ECBT schedule, for tumors confined to the nasopharync proper (Stages ≤ T2a), after 60 Gy EBRT, the primary is boosted with a fractionation high-dose-rate schedule. Thus, 4 Gy is followed by 3 x 3 Gy (2 fractions daily, ≥ 6 hour intervals) and 4 Gy, with thus a cumulative dose to the primary tumor of 77 Gy. For the more advanced primary tumors (T2b-4), after 70 Gy EBRT, the primary is boosted with 4 Gy, 3 Gy and 4 Gy (2 fractions daily; cumulative dose to the primary of 81 Gy). Therefore, the ECBT boost was mostly completed within 2-3 days.

7.2.2 Characteristics of patients treated according to Rotterdam NPC protocol: 1991-2000

All primary NPC patients treated between 1991 and 2000 with EBRT and ECBT were in principle, after restaging, eligible for the study. The censor date for patient entry was January 1, 2000; all patients had a minimum of 1 year of follow-up. Excluded from the present analysis were patients with morphology other than UD or WMP-D carcinomas ($n = 3$), those with M+ at presentation ($n = 1$), those with recurrent tumors ($n = 9$) and those treated with purely palliative intent, (e.g. using fractionation schedules totally defiant from the Rotterdam protocol guidelines [EBRT ≤ 60 Gy and/or those not treated by ECBT; $n = 2$]). Five patients were excluded because of synchronous second primaries ($n = 3$), or because they were lost to follow-up (i.e. no additional information was available or patients had left the country immediately after reaching complete clearance of disease at treatment end [$n = 2$]). From the 91 remaining eligible patients, 63 were men (69%), 28 were women (31%). Because of the small number of patients per differentiation subgroup, consistent with our previous analysis (14), and because the differences in LC and OS at 3 years were not significantly different ($p = 0.28$ and 0.3, respectively), the WM-D and P-D tumors were combined into one subgroup (WMP-D; WHO Types 1 and 2). In total, 50 UD tumors (55%), 35 WMP-D tumors (38%), and 6 carcinomas of unknown differentiation (7%) were analyzed. As the OTTs during the 1991-2000 study period were still slightly variable, biologic effective dose for tumor effects with of 10 (BED_{10}) and the BED_{10} corrected for the OTT ($BEDcor_{10}$) were calculated in addition to the physical dose.

The BED_{10} was defined as the summation of the total EBRT dose (by applying the LQ-model as suggested by Fowler [40]) and the total fractionated ECBT-dose (computed by means of the model proposed by Brenner and Hall [35]). Subsequently, the $BEDcor_{10}$ was computed from the corresponding BED values by subtracting a repopulation correction term, with Tpot = 5 days, $\alpha = 0.28$ Gy^{-1}. This repopulation correction term resulted in a calculated loss of 0.5 Gy daily.

The details for calculations can be found in Levendag *et al.* (41). The dose-tumor effect relationships were studied for the physical dose, BED_{10} and $BEDcor_{10}$.

The Kaplan-Meier method and log-rank tests were used to perform a crude analysis for the independent factor stage in the 1st period (before October 1996; no CHT used) and 2nd period (1996-2000, with neoadjuvant CHT per protocol for advanced III-IVB stages). The same tests were used for the factors $BEDcor_{10}$, age, and differentiation grade during the 1991-2000 period. The influence of all four factors was studied for the endpoints LC and OS at 2 years in the univariate and multivariate Cox proportional hazard model. Finally, the chemoradiation toxicity in the neoadjuvant setting, was investigated.

Table 2. Grade and treatment of 19 Stage III-IVB patients treated with neoadjuvant chemotherapy according to protocol (1996-2000).

Grade	Cisplatin + 5-FU	Cisplatin	Cisplatin + Taxol	All Regimes
UD	7	4	1	12
WMP-D	1	4	1	6
Unknown-D		1		1
All Grades	8	9	2	19

Abbreviations: 5-FU = 5-fluorouracil; UD =undifferentiated; WMP-D = well, moderately, and poorly differentiated; Unknown-D = unknown differentiated; CHT = chemotherapy. One patient, with unknown differentiation grade, received cisplatin weekly, 6 courses total, for T4 tumor. Two patients with Stage III-IVB disease were treated with 6 weekly courses of cisplatin (70 mg/m^2) and Taxol (90 mg/m^2). Two patients were treated with neoadjuvant CHTT outside protocol during 1st treatment period (not shown)

7.3 RESULTS

The LC at 5 years for P-D (WHO Type 2; $n = 19$) and WM-D (WHO Type 1; $n = 16$) NPC was 74% and 46% ($p = 0.28$), respectively; the OS was 38% for P-D and 28% for WM-D tumors ($p = 0.31$). To compare with previous findings (see Levendag *et al.* [22]), and because the LC and OS at 5 years were not statistically significantly different ($p = 0.31$), the WM-D and P-D tumors were analyzed as one subgroup (WMP-D; WHO Types 1 and 2). For all stages combined, at 5 years, a LC rate of 92% for UD (WHO Type 3; $n = 50$) vs. 59% for WMP-D tumors (WHO Type 1-2; $n = 35$) ($p = 0.0002$) was found (*Figure 1*). For the same subgroups an OS of 61% (UD) and 34% (WMP-D) ($p = 0.01$) was observed.

During the treatment period (1996-2000), 19 (73%) of the 26 Stage III-IVB patients received CHT. The grade of NPC and type of chemotherapeutic agents / regimens used for the patients treated with neoadjuvant CHT as of October 1996 are tabulated in Table 2. Two patients were treated with 6 weekly courses of a combination of cisplatin (70 mg/m^2) and Taxol (90 mg/m^2); one patient received 6 courses of weekly cisplatin for a T4 tumor with unknown differentiation grade. Two patients were treated during the 1st treatment period outside the protocol (data not shown in Table 2). With respect to the compliance to the protocol, of the 17 patients with UD Stage III-IVB tumors, 7 (41%) were given 3 weekly courses of cisplatin/ 5-FU according to protocol (cisplatin 100mg/m^2 in combination with 5-FU, 1000 mg/m^2), and of the 8 patients with WMP-D Stage III-IVB tumors, 4 (50%) received weekly courses of cisplatin (70 mg/m^2) single- agent therapy. For patients treated with cisplatin plus 5-FU, 8 (100%) received at least 2 courses. In the case of single-agent cis

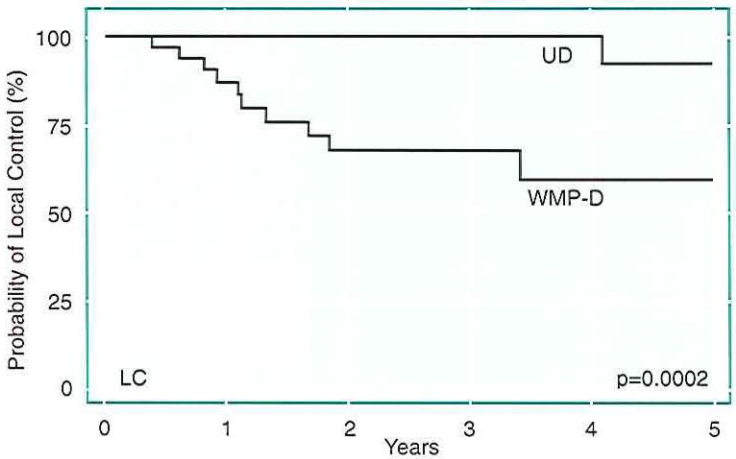


Figure 1. LC for 85 patients treated between 1991 and 2000. Tumors with unknown differentiation grade ($n = 6$) were not included. UD, WHO Type 3, $n = 50$. WMP-D, WHO Type 1 and 2; $n = 35$. $p = 0.0002$, log-rank test.

platin, 9 (100%) patients received a minimum of 4 courses.

Four factors were studied univariately with the Kaplan-Meier method and log-rank test: stage and period (i.e. Stage I-IIB vs. III-IVB and before or after October 1996), $BEDcor_{10}$, age and differentiation grade. The influence of these four factors for endpoints LC and OS was analyzed multivariately with Cox proportional hazards model. On the basis of the order of the prediction scores of the Cox model in the 1st period, three prognostic groups were constructed and evaluated with the data in the 2nd period, to adjust for too optimistic result (Table 3).

Dose (physical dose, BED, and $BEDcor_{10}$) appeared not to be a significant factor in univariate and multivariate analyses. In contrast, stage, treatment period, age, and differentiation grade were significant. Stages I-IIB and stages III-IVB were analyzed for LC and OS per treatment period (*Figures 2 and 3*). At 2 years (1991-1996), the LC and OS was 96% and 80% (Stage I-IIB) vs. 65% and 52% (Stage III-IVB), respectively. For the 2nd treatment period (1996-2000), the LC and OS at 2 years was 100% and 61% (Stage I-IIB) vs. 86% and 66% (Stage III-IVB), respectively. Analyzing combinations of stage and grade per treatment period, 3 prognostic groups (PG), that is, patients with a 'good', 'intermediate' and 'poor' prognosis, were constructed (*Figure 4*). In the 1st treatment period, the patients in the good PG (UD Stage I-IIB tumors), at 2 years, had a LC rate of 100% and an OS rate of 92%; those in the intermediate PG (WMP-D Stage I-IIB tumors and UD Stage III-IVB cancers) had a LC and

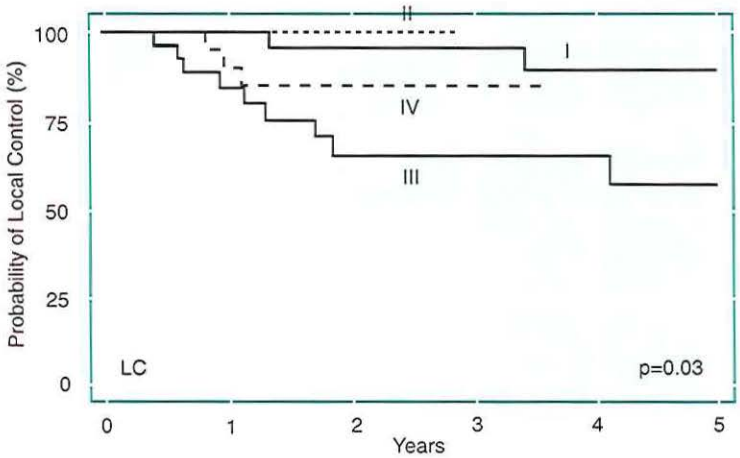


Figure 2. LC for 91 patients with Stage I-IIB (Group I) vs. III-IVB (Group III) in 1st treatment period (1991-1996) and Stage I-IIB (Group II) and Stage III-IVB (Group IV) in 2nd treatment period (1996-2000) (p = 0.03, log-rank test).

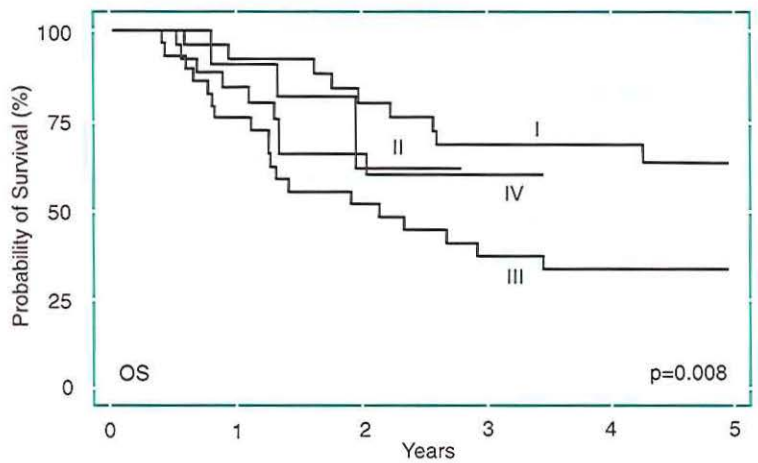


Figure 3. OS for 91 patients with Stage I-IIB (Group I) vs. Stage III-IVB (Group III) in 1st treatment period (1991-1996) and Stage I-IIB (Group II) and Stage III-IVB (Group IV) in 2nd treatment period (1996-2000) (p = 0.008, log-rank test).

OS rate at 2 years of 94% and 71%, respectively; and those in the poor PG (WMP-D Stage III-IVB tumors), at 2 years, had a LC rate of 47% and an OS rate of 40% (*Figure 4* solid lines). For the 2nd treatment period, at 2 years, the LC and OS rate was 100% and 88% for the good PG, 100% and 64% for the intermediate PG and 71% and 60% for the poor PG. *Figure 4*; dotted lines.

A decrease of the OTT during the 1991-2000 period for patients treated by EBRT (60 or 70 Gy) and ECBT, is depicted in *Figure 5*. *Figure 5A* shows all tumor stages of the 91 patients

for both treatment periods; patients were labeled as having local relapse (LR), M+ or as no evidence of disease. As is evident from *Figure 5A*, the outcome parameters LR and M+ seem more frequent in the pre-CHT era (1991-1996) than in the 1996-2000 period: 1st period, 54 patients, crude number of LR, 12 (22%) of 54 (i.e. including 1 patient with LR and M+), and M+, 8 (15%) of 54; 2nd period, 37 patients, crude number LR 3 (8%) of 37 and M+ 3 (8%) of 37. The actuarial computations of LR and M+ in 1st treatment period as opposed to 2nd treatment period were as follows: LR 32% vs. LR 18% ($p = 0.37$), M+ 33% vs. M+ 8% ($p = 0.60$; log-rank test).

Denoted in *Figure 5B* are the 55 Stage III-IVB individuals, treated with CHT (2 outside pro

Table 3. Kaplan-Meier 2-year log-rank tests results and multivariate estimates for LC and OS for Stages I-IIB vs. III-IVB during the 1st (1991-1996) and 2nd (1996-2000) treatment period, respectively.

	Patients*	LC*(%)	*p* (log-rank)	*p* (Cox model)	OS (%)	*p* (log-rank)	*p* (Cox model)
Stage							
Treatment period 1991-1996							
I-IIB	25	96	0.02	0.46	80	0.08	0.05
III-IVB	29	65			52		
Treatment period 1996-2000							
I-IIB	11	100			61		
III-IVB	26	86			66		
Dose ($BEDcor_{10}$)							
<63 Gy	25	80	0.64	0.80	68	0.93	0.66
63-<66 Gy	26	87			69		
66-<68 Gy	19	73			58		
≥68 Gy	21	95			58		
Age (y)							
<40	19	82	0.39	0.97	84	<0.0001	<0.001
40-<55	27	92			80		
55-<65	25	84			62		
≥65	20	75			30		
Grade							
Undifferentiated	50	100	0.0002	0.009	81	0.01	0.09
Well/moderately/ poorly differentiated	35	68			50		

Abbreviations: LC = local control; OS = overall survival; $BEDcor_{10}$ = biologic effective dose for tumor effects with α/β of 10 corrected for the overall treatment time.
Same analysis shown for the parameter subsets dose ($BEDcor_{10}$), age and grade.
* Number of patients analyzed in treatment period 1991-2000.

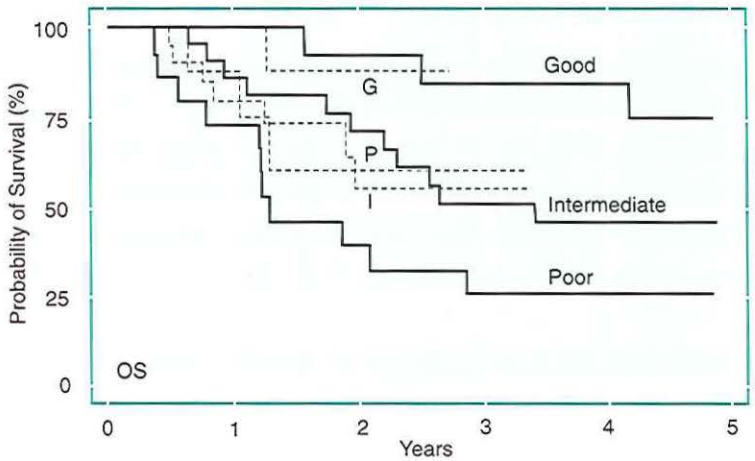


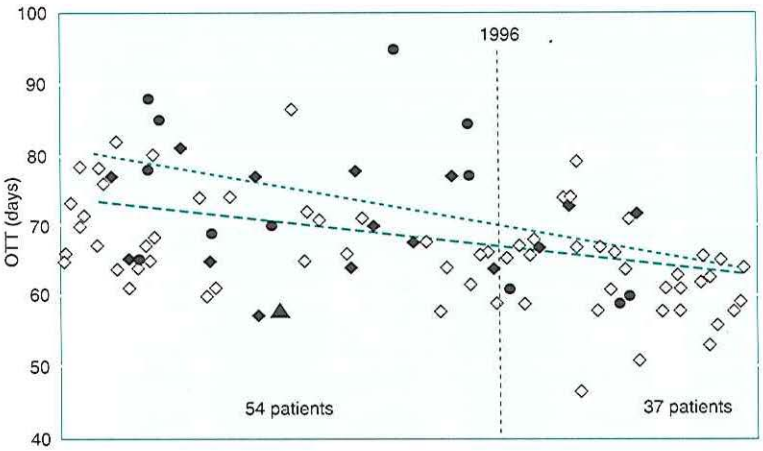
Figure 4. OS of patients with good prognosis (G; UD Stage I-IIB [13 vs. 8 patients]), intermediate (I; WMP-D Stage I-IIB [21 vs. 20 patients]), and poor (P; WMP-D Stage III-IVB [15 vs. 8 patients]) prognoses (combinations of stage and grade) for treatment periods 1991-1996 (no CHT) and 1996-2000 (plus neoadjuvant CHT). Eight poor PG patients were treated between 1991 and 1996 compared with 15 poor PG patients treated between 1996 and 2001($p = 0.23$). Solid lines indicate treatment initiated between 1991 and 1996; dashed lines treatment initiated between 1996 and 2000.

tocol before 1996, 19 according to protocol after 1996) or without CHT (27 patients before 1996; 7 patients after 1996). Of the 34 Stage III-IVB patients treated between 1991and 2000 with RT only, 10 (30%) developed LR and 8 (24%) M+.

All 10 LRs and 6 of 8 M+, were observed during the 1st treatment period. Nine (27%) patients died intercurrently.

Of the 21 Stage III-IVB patients treated with neoadjuvant CHT between 1991 and 2000 (with 19 according to protocol during the 2nd treatment period), only 3 (14%) experienced LR and 1 (5%) M+ (*Figure 5B*). The actuarial computations of LR, M+, and OS of Stage III-IVB patients treated without CHT as compared with those treated with CHT were LR 30% vs.LR 14% ($p = 0.37$), M+ 22% vs.M+ 5% ($p = 0.13$) and OS 35% vs.72% ($p = 0.005$; log-rank test).

Only 1 patient experienced an isolated regional relapse (1st treatment period, with neck relapse salvaged). Two (10%) of 21 patients died of intercurrent causes. With the addition of neoadjuvant CHT for Stage III-IVB patients, the crude (and actuarial) percentages of LR and M+ decreased, which also translated into an improvement of the actuarial LC and survival (Tables 4 and 5). However, one must realize that in the present series, the follow-up of patients in the 1st treatment period (without CHT) was substantially longer than that of the patients of the 2nd treatment period (with CHT). The time to follow-up could obviously



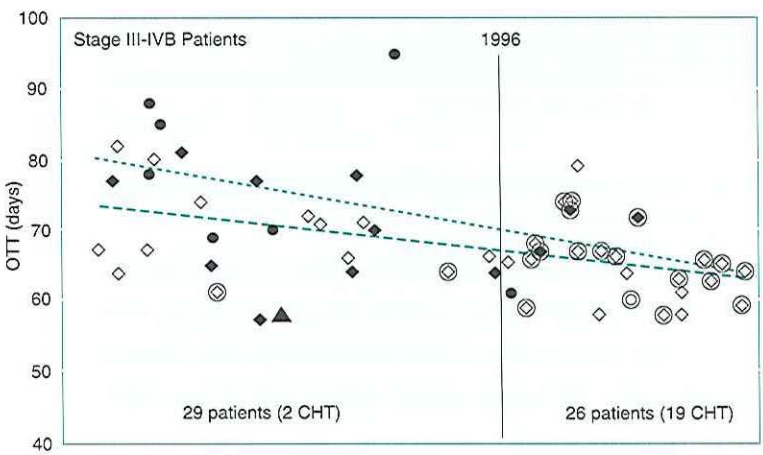


Figure 5 A. All 91 patients. Regression of OTT (days) during 1991-2000 for the duration of EBRT and ECBT combined indicated by stippled (...) lines for 60 Gy and dashed (---) lines for 70 Gy EBRT. Vertical line indicates change in protocol (as of October 1996 neoadjuvant CHT was administered per protocol to Stage III-IVB patients). Of 54 patients treated before October 1996, 12 (22%) LR (◆) and 8 M+ (15%) were observed. In the 2nd treatment period, 3 of 37 experienced a LR (8%) and 3 M+ (8%) were observed. Actuarial computations of LR and M+ in 1st treatment period vs 2nd treatment period: LR 32% vs. 18% (p = 0.37), M+ 33% vs. M+ 8% (p = 0.60; log-rank test). Also shown those with no evidence of disease, without LR or M+ (◇), and 1 patient with a LR as well as M+ (▲).

Figure 5B. All 55 Stage III-IVB patients treated with or without CHT. Regression of OTT (days) during 1991-2000 for duration of EBRT and ECBT combined indicated by stippled (...) lines for 60 Gy and dashed (---) lines for 70 Gy EBRT. Vertical line indicates change in protocol (as of October 1996 neoadjuvant CHT was administered per protocol to Stage III-IVB patients). First treatment period (1991-1996): 27 patients without CHT, 2 patients with CHT but outside protocol. Second treatment period (1996-2000): 18 patients with CHT, 8 patients without CHT. LR (◆) and distant metastasis (●) are denoted. Overall, of 34 patients treated between 1991 and 2000 with RT only, 10 (30%) LR and 8 (24%) M+ were seen. Of 21 patients treated between 1991 and 2000 with CHT, 3 (14%) LR and 1 (5%) M+ were observed. Actuarial computations of LR and M+ patients treated without CHT vs. those treated with CHT: LR 30% vs. 14% (p = 0.01), M+ 22% vs. 5% (p = 0.12, log-rank test). Also shown are those with no evidence of disease (◇) patients. Circled symbols denote patients treated with CHT.

Table 4. Kaplan-Meier estimates of LC, M+, DFS, freedom from distant metastasis, and OS for Stage III-IVB and T3-4 NPC patients at 2 years.

	Stage III-IVB 1991-2000			T3,4 1991-2000		
	No CHT* (%)	CHT # (%)	*p*	No CHT* (%)	CHT # (%)	*p*
LC	68 (12)	86 (11)	0.01	42 (5)	76 (8)	0.15
DFS	48 (11)	74 (10)	0.004	38 (5)	77 (8)	0.12
Freedom from distant metastasis	78 (12)	95 (10)	0.12	83 (6)	100 (8)	0.56
OS	43 (13)	78 (11)	0.005	38 (6)	70 (8)	0.02

Abbreviations: CHT = chemotherapy; LC = local control; DFS = disease-free survival; OS = overall survival; RT = radiotherapy. Number in parentheses are number of patients at risk.
* Patients at risk treated with RT only (cumulative dose 77-82 Gy) between 1991-2000.
# Stage III-IVB patients at risk treated with neoadjuvant CHT (2 patients were treated before 1996, 19 patients between 1996-2000) followed by RT to a cumulative dose of 77-82 Gy.

influence the incidence of LR, M+ and/or intercurrent disease. Because of these differences in follow-up time, the results have to be interpreted with caution.

Considering the entire study period 1991-2000, for Stage III-IVB disease at 3-years, the LC, M+, DFS, and OS rate was 95%, 5%, 74%, and 72%, respectively, for patients treated with CHT compared with the LC, M+, DFS, and OS rate of 68%,22%,48% and 35% without CHT. For comparison, patients with Stage I-IIB disease treated without CHT during 1991-2000 had a LC rate of 97% and an OS rate of 67% at 3 years.

The toxicity of the treatment has been in general within normal limits; this contrasts with some of the toxicity reports on conventional dose levels of EBRT in combination with concomitant CHT (25-32). Only a very few patients experienced some synechiae of the nasal mucosal linings. This was mainly the case in the beginning of the 1st treatment period and has been reported previously (22). Except for the usual reduction in blood counts due to the CHT, a persisting nadir prevented only a very few patients from receiving their subsequent planned courses of CHT. In fact, no specific CHT-related toxicity was otherwise observed, and most patients received their prescribed number of courses. Of those treated with CDDP + 5-FU, 8 (100%) received at least 2 of 3 courses. In case of single-agent CDDP, 9 (100%) patients received a minimum of 4 of 6 courses. The great majority of patients, complained of the well known (and mostly permanent) dry-mouth syndrome due to amount of radiation received by the salivary glands.

Table 5. PFS, DFS, and OS at 3 years for Stage III-IVB patients according to Kaplan-Meier analysis.

Patients (*n*)		LR%	M+%	PFS%	OS%
Intergroup study 0.099* (Al-Sarraf *et al.* [22]; 147 Stage III-IVB patients)					
Conventional EBRT 70 Gy	69	33	35	24	47
Conventional EBRT 70 Gy	78	10	13	69	78
Concomitant CHT and adjuvant CHT				$p = 0.001$	$p = 0.005$
Rotterdam* (current series; 55 Stage III-IVB patients)				DFS	
EBRT + ECBT 78-81 Gy	34	30 [32]	24 [22]	48	35
Neoadjuvant CHT	21	14 [14]	5 [5]	74	72
EBRT + ECBT 78-81 Gy		$p = 0.01$	$p = 0.12$	$p = 0.002$	$p = 0.005$
MSKCC* (Wolden *et al.* [96]; 81 stage II-IV patients)				PFS	
Conventional EBRT 70-75.6 Gy/8wk	51	[26]	[32]	54	71
Accelerated RT 70 Gy/6 wk	50	[11]	[21]	66	84
Concomitant CHT		$p = <0.01$	$p = 0.10$	$p = 0.01$	$p = 0.04$

Abbreviations: LR%: crude local relapse percentage for Stage III-IVB; M+ = distant metastasis; PFS = progressive-free survival; DFS = disease-free survival; OS = overall survival; EBRT = external beam radiotherapy; CHT = chemotherapy; ECBT = endocavitary brachytherapy; MSKCC = Memorial Sloan-Kettering Cancer Center. Numbers in brackets are actual percentage LR and M+ at 3 years for Stage III-IVB disease.
* Experimental arms in 3 studies: Intergroup Study - Stage III-IV, 70 Gy EBRT plus concomitant CHT ; Rotterdam - Stage III-IVB, neoadjuvant CHT plus EBRT in combination with EBCT (77-82 Gy); MSKCC - Stage II-IV, accelerated EBRT (70-75.6 Gy / 6 weeks) plus concomitant CHT.

Two patients, with Stage T4N2 and T4N0, respectively, were treated with EBRT and ECBT to a cumulative dose of 82 Gy. According to the charts, deep biopsies were repeatedly taken from the heavily pretreated nasopharyngeal mucosa at 4 months and at 2 years follow-up. No histologic proof of recurrence was obtained, but, because of these procedures, a fatal hemorrhage occured in both.

7.4 DISCUSSION

In brief, our findings can be summarized as follows. Acceptable conformal dose distributions can be achieved with fractionated ECBT when boosting the nasopharynx after 60-70 Gy EBRT to high cumulative doses of 78-81 Gy. Fractionated ECBT has an excellent clinical track record for early-stage disease. In Stage I, only 1 patient was available for analysis. The LC and DFS rate for Stage IIA disease at 2 years was 100% for patients treated with high doses of RT only. The LC and DFS rate for Stage IIB disease was 95% and 86%, respective-

ly, for patients treated without CHT. In our view, given these results and the potential for extra morbidity, as well as the considerable cost factor of CHT, we believe that CHT is not warranted for Stage I and II disease. Therefore, EBRT combined with ECBT remains our standard of care for Stage I-IIB. Neoadjuvant CDDP-based CHT has been implemented per protocol in Stage III-IVB disease as of October 1996 and has been shown to be of significant benefit in combination with the high cumulative doses of RT. This has been achieved with hardly any change in the toxicity profile in these patients. The next paragraphs put these observations into perspective.

To date, RT remains the mainstay of treatment for NPC (3-6). A study by Lee *et al.* (5) reported for 5037 patients treated by RT alone, a cumulative incidence of 13% persistent local disease; of the remaining 4399 complete local responders, 20% developed a local recurrence at a mean interval of 1.7 years. M+ were found in 6% at presentation, another 29% developed M+ after a median interval of 0.9 years. At 10-years, the actuarial local failure-free survival rate was 61%, the OS rate 42%. As is apparent from this landmark study, local recurrences represent a significant proportion of radiation failure. The same was observed in a more recent overview on NPC by Sanguinetti and Corvo (6). They reported LC rates with RT alone for T1-T4 tumors ranging from 95% to 40%. LC has also been shown to be an independent prognostic indicator of M+ (13). Moreover, although based almost exclusively on historical data, there is now a reasonable body of evidence that LC is related to the total dose of radiation administered (1-14).

However, given this apparent dose-tumor effect relationship, the nasopharynx being a cuboid midline structure in direct continuity with surrounding critical tissues, poses however a significant dose-tolerance problem (15-18,21).

One route we have exploited since 1991 in an attempt to maximize the LC rate and limit toxicity is to dose escalate by fractionated ECBT, making use of an accelerated treatment schedule (short OTTs, increased effectiveness) and rapid dose falloff (maximum sparing of neighbouring adjacent structures), both basic components of brachytherapy. To study the effectiveness of RT, we analyzed a series of 151 primary NPC patients treated between 1965 and 1995. All patients were treated by EBRT to total doses of 60-70 Gy; as of 1991, the nasopharynx was routinely boosted by means of high-dose-rate ECBT to cumulative doses well over 80 Gy. A dose-effect relationship was established, with a gain in local control of approximately 15% for every additional 10 Gy (14). The improvement in LC had an impact on survival as well. Thus, for the DFS and cause-specific survival, a hazard ratio of 0.28 ($p < 0.001$) and 0.43 ($p = 0.009$), respectively, was found in favor of patients boosted by

means of ECBT.

The beneficial effect of ECBT was also corroborated by the data reported by Teo *et al.* (1) for a large Hong Kong patient population. Comparing 163 T1-2 cases (N2-3: 28%) treated by EBRT followed by high-dose- rate ECBT (18-24 Gy, 3 fractions), with 346 T1-2 patients (N2-3: 35%) treated by EBRT-alone, the LR rate at 5 years was 5% vs.11% (T1), and 8% vs.16% (T2). This demonstrates a doubling in the LC rates for both T categories in favor of EBRT supplemented by ECBT. Multivariate analysis showed ECBT to be the only significant prognostic factor predictive of fewer local failures (risk ratio 0.49). Syed *et al.* (2) reported on 15 primary NPC patients treated by 50-60 Gy EBRT, followed after 2-3 weeks by an ^{192}Ir interstitial implant of the nasopharynx combined with ECBT (total boost dose of 33-37 Gy). Although their ECBT procedure might seem technically somewhat more difficult to execute, at 5 years high LC rates (93%) were claimed, with an OS rate of 61%. In summary, excellent clinical control rates were reported by Teo *et al.* (1) and Syed *et al.* (2) using high cumulative doses of RT for early T stage disease.

Given these and other established dose-effect relationships and that LC is a prognosticator for M+, at the time, the use of fractionated ECBT as a high-dose, high-precision boost technique after 60-70 Gy EBRT for all T stages was suggested at our institute (14,22). The purpose of the present paper was to establish the role of fractionated ECBT more accurately per stage groupings, with or without neoadjuvant CHT, in particular given the alternative treatment techniques currently available for more advanced lesions (20,34,42-51).

Between 1991 and 2000, 91 patients were treated in the University Hospital Rotterdam with EBRT combined with fractionated high-dose-rate ECBT and boosted to high doses of radiation. The high cumulative doses of radiation were systematically applied to all T stages. In contrast to the NPC patients treated between 1965 and 1995, no dose-effect relationship was found. However, in the previous paper by Levendag *et al.* (14), a more mixed patient population who were treated with EBRT only or EBRT combined with ECBT with substantial variations and longer OTTs was analyzed. It is therefore conceivable that in the current study on ECBT patients with shorter OTTs (*Figure 5*), we were already 'high-up' or perhaps even 'plateau-ing' on the dose-effect curve, and thus, no further dose-effect relationship could to be detected with regard to the physical dose, BED_{10}, or $BEDcor_{10}$.

7.4.1 Stage I-IIB disease: At 2 years the LC and OS rate for Stage I-IIB in the 1st treatment period was 96% and 80%, respectively, and in the 2nd treatment period, 100% and 61%. Moreover, when analyzing combinations of stage and grade (the most important prognos-

tic factors), at 2 years, for UD Stage I-IIB tumors (good PG), the LC rate was 100% (1st and 2nd period) and the OS rate was 92% (1st period) and 88% (2nd period).

As is the case in most patients with cancers in the head and neck treated by EBRT to the primary and (part of) the neck, with total doses of 60-70 Gy, optimal sparing of the major salivary glands poses a significant treatment planning problem. Most of these patients experience xerostomia as a long term side-effect. Only minor side effects related to fractionated ECBT per se were seen in long-term follow-up. As previously reported, some of the patients experienced synechiae of the nasal mucosal linings (14,22). This, however, was mainly seen in the 1st series of patients treated according to the Rotterdam NPC protocol. Moreover, the synechiae can be surgically corrected and even prevented by adjusting the loading pattern at the site of the nasal mucosal linings ('optimization'; see also Levendag *et al.* [14,22]). These results allow us to conclude that from a clinical perspective, there is essentially no role for CHT for Stage I-IIB disease. With the nasopharynx proper defined as the space within the nasopharynx between the lines that can be drawn on CT/MRI slices (52) to connect the medial pterygoid plate and styloid process, dosimetrically adequate target coverage without overdosing the normal tissue can be realized for early T1-2a tumors using ECBT. For T2b tumors, however, this is only the case for those cancers that have regressed to a clinical target volume confined to the nasopharynx proper after having been pretreated by neoadjuvant CHT and/or EBRT (37,42,53-55).

Finally, the Rotterdam Nasopharynx Applicator for fractionated ECBT is easy to introduce on an outpatient basis. The dose prescription and dose-reporting method with patient points denoted on AP and lateral X-ray films is straightforward to execute and reproducible (14,22). EBRT combined with EBCT remains our high-dose, high-precision treatment option of choice for NPC in patients with early- stage disease.

7.4.2 Stage III-IVB disease: From *Figures 5* one can appreciate that neoadjuvant CDDP-based CHT has routinely been implemented at our institute to treat Stage III-IVB disease as of October 1996 and has been shown to be of significant benefit for advanced-stage disease (Table 5 and *Figure 5*). For Stage III-IVB, all grades combined, during the entire study period from 1991 to 2000, after the implementation of CHT, the LC rate at 3 years improved from 68% to 86% ($p = 0.01$), DFS from 48% to 74% ($p = 0.002$), and OS from 35% to 72% ($p = 0.005$) (Table 5). Neoadjuvant CHT for advanced cases is in our current institutional protocol by treatment regimen to be followed by high doses of radiation (77-81 Gy). The limited toxicity experienced so far with the combination of neoadjuvant CHT and these

high cumulative doses of radiation is in contrast to some of the reports on conventional dose levels of EBRT (70 Gy) with concomitant CHT (25-32). In 1996, we decided on the routine application of neoadjuvant CHT in NPC for stage III-IVB disease. The design of the Rotterdam protocol has significant shortcomings. First, it is a non-randomized study testing the added value of CHT compared to high-dose, high-precision RT alone to treat Stage III-IVB disease. The impact of neoadjuvant CHT is at best difficult to separate from the attribution of high doses of radiation (77-81Gy), as was demonstrated by the improvement in LC, as well as the decrease in M+ (Table 5). At the time, a significant body of evidence was available in favor of the standard implementation of CHT in Stage III-IVB NPC, whether neoadjuvant or concomitant. This was to some extent corroborated by the findings of the present report. As shown by the a number of randomized phase II/III trials on the role of CHT in NPC, the choice of neoadjuvant - as opposed to concomitant- CHT remains a subject of debate. With respect to the data on neoadjuvant CHT in combination with conventional doses of radiation, Chua *et al.* (56) reported in their efficacy analysis a trend for improved relapse-free survival favoring the CHT arm. At 3 years, a relapse-free survival rate of 58% vs. 46% ($p = 0.053$), and an OS rate of 80% vs. 72% ($p = 0.21$) were found.

In their subgroup analysis of patients with bulky neck nodes (> 6cm), the relapse-free survival rate at 3 years was 63% vs. 28% ($p = 0.026$); the OS rate was 73% vs. 37% ($p = 0.057$). Rossi *et al.* (57) randomized NPC patients for adjuvant CHT and reported a DFS of 58% vs. 56% (not significant) and an OS rate of 59% vs. 67% (not significant). Chan *et al.* (58), with a neoadjuvant / adjuvant CHT combined treatment modality, observed nonsignificant differences at 2 years in DFS (68% vs. 72%) and OS (80% vs. 81%). In the VUMCA I trial (55), with a median follow-up of 49 months, a significant difference in DFS favoring neoadjuvant CHT of 67% vs. 45% ($p < 0.01$), but a nonsignificant difference in OS of 40 vs. 46%, was observed. From recent data in the literature, however, one could argue that most studies tend to favor concomitant CHT as a more effective way to decrease the number of local relapses (25-30,32,55,59). Indeed, excellent results for concurrent CHT in NPC have been reported by the Intergroup Study 0099 (26) with an improvement at 3 years in LC of 23% and in OS of 37% for the concomitant CHT arm as opposed to their control patients. Basically, this is in agreement with the findings of the meta-analyses for concomitant CHT in head-and-neck cancer in general. Pignon and Bourhis (31) analyzed 63 randomized trials and reported an improvement in OS of 8% in favor of concomitant CHT. However, El-Sayed and Nelson (32) in their meta-analysis of 42 randomized trials found an increased risk of severe toxicity (even toxic deaths), with a hazard ratio of 2.17 for concomitant CHT. At the

time our group believed strongly that CHT, applied in a concomitant fashion in combination with high cumulative doses of radiation (81Gy), could stand the risk of severely compromising the critical sensitive structures located around the base of skull. This has become even more of an issue at present, because with the current high-dose, high-precision protocol one experiences similar DFS and OS rates with relatively few side effects related to the neoadjuvant chemoradiation per se. Finally, the basic concept of the protocol was to increase LC by high cumulative doses of RT and to use neoadjuvant CHT to decrease the number of M+. In fact, the actuarial LR rate in the non-CHT treated patients as opposed to the combined modality group, decreased from 32% to 14% ($p = 0.37$), the M+ decreased from 24% to 5% ($p = 0.13$) and the OS increased from 35% vs. 72% ($p = 0.005$).

Except for the synechiae of the nasal mucosa linings and the side-effects related to the dry-mouth syndrome (frequent and often irreversible xerostomia and dental decay, mainly due to EBRT), only rarely were any other specific CHT-related severe side effects seen. Furthermore, as in all areas heavily pretreated by radiation and/or CHT, one should be extremely cautious and preferably refrain from taking deep biopsies from the nasopharynx or base of the skull, because severe complications such as nonhealing osteoradionecrosis and fatal hemorrhaging could occur.

In Table 5, recent data on the role of CHT in NPC obtained from the frequently cited paper by Al-Sarraf *et al.* for Stage III-IV NPC disease (26), findings from our own series Stage III-IVB patients (current study), and observations reported by Wolden *et al.* (59) on Stage II-IVB NPC are summarized. The Intergroup Study 0099 population consisted of 41% UD, WHO Type 3, tumors. In our study, 55% were the UD tumor type. In the Intergroup Study 0099, patients were randomized for a cumulative dose of 70 Gy EBRT conventional fractionation (control arm) vs. the same EBRT dose schedule in combination with concomitant and adjuvant CHT (experimental arm). The results observed at 3 years in Intergroup Study 0099 with respect to LC (90%), progression-free survival (69%), and OS (78%) are in reasonable agreement with the findings in our Stage III-IVB patients: 86% LC, 74% DFS, and 72% OS (Table 5). Some have criticized the Intergroup 0099 data because of the unusual low progression-free survival of 24% in the control arm of patients treated by RT only. In our series, the DFS rate was 48%, and the progression-free survival rate from Wolden *et al.* (59) was 54%. An interesting report for comparison purposes is the Memorial-Sloan-Kettering Cancer Center study, in which concomitant CHT was given in combination with a more effective (accelerated) RT regimen, delivering 70 Gy in 6 weeks. The results of the experimental arm were compared to the control arm, in which conventional fractionated

EBRT was used without CHT (70-75.6 Gy in 8 weeks) (59). Again, these results seem to be not very dissimilar to our data: LC 89%, progression-free survival 66%, and OS 84%. However, when trying to compare the results as presented by Wolden *et al.*, the study generates some interpretation difficulties. First, like the present series, it was also a nonrandomized study. Moreover, the results were generated in a somewhat more favorable patient subset (i.e., Stage II-IV disease compared with Stage III-IVB disease of the Intergroup Study 0099 and the present series). Finally, in the study by Wolden *et al.* (59), the RT schedule in the control arm and experimental arm were dissimilar (Table 5).

7.5 CONCLUSION

Fractionated ECBT has shown to be a reproducible, nonlaborious, fast (accelerated) and patient-friendly 3D conformal technique, with an excellent clinical track record for early-stage disease. For patients with Stage I-IIB disease, treated according to the Rotterdam NPC protocol without CHT during the observation period 1991-2000, a LC rate of 97% and an OS rate of 67% was found at 3 years. Our results demonstrate that for Stage I-IIB NPC patients CHT has no specific role for and that EBRT in combination with ECBT remains the standard of care.

For Stage III-IVB disease, it is evident from the literature, as well as from our own data that RT should be combined with CHT. At the time of designing the Rotterdam protocol, the combination of high cumulative doses of radiation (77-81 Gy minimal dose being the mainstay of our treatment protocol) and concomitant CHT was considered to be potentially hazardous for the many surrounding critical normal tissues. To reduce LF and M+ in Stage III-IVB disease, we therefore decided to apply the CHT per protocol in a neoadjuvant fashion. For Stage III-IVB disease with CHT in combination with high cumulative doses of radiation, we observed a LC rate of 86%, freedom from distant metastasis rate of 5%, DFS rate of 74%, and an OS rate of 72% at 3 years. One of the prerequisites of our treatment protocol for locally advanced disease is that EBRT (70 Gy) is followed by a booster dose of 11 Gy. In case of T1, T2a and T2b tumors that respond well to a first series of radiation (46 Gy), the boost dose should be applied by ECBT. As of 2001, the boost dose for poorly responding T2b and T3-4 tumors is delivered by stereotactic RT (4 fractions of 2.8 Gy). Because of better target coverage, an additional improvement in LC (and survival) is anticipated with stereotactic RT. For the poorest subset of patients (WMP-D Stage III-IVB), the use of other potent agents,

such as paclitaxel, is being investigated (60). A future challenge remains the optimal sparing technique for the major salivary glands (parotid and submandibular glands), to eliminate the dry-mouth syndrome. Recently, we completed a CT-based standardization of the elective neck nodal regions (19,20). At present, we are trying to arrive at class solutions for 3D conformal RT /intensity-modulated RT treatment planning of the primary and bilateral neck. To achieve this goal, the development of contouring guidelines for the clinical target volume of the primary site on CT / (matched) MRI scans is mandatory.

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CHAPTER 8

High-dose, high-precision treatment options for boosting cancer of the nasopharynx

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ABSTRACT

Purpose: *The aim of the study is to define the role and type of high-dose, high-precision radiation therapy for boosting early staged T1,2a, but in particular locally advanced, T2b-4, nasopharyngeal cancer (NPC).*

Materials and methods: *Ninety-one patients with primary stage I-IVB NPC, were treated between 1991 and 2000 with 60-70 Gy external beam radiation therapy (ERT) followed by 11-18 Gy endocavitary brachytherapy (ECBT) boost. In 1996, for stage III-IVB disease, CDDP-based neoadjuvant chemotherapy (CHT) was introduced per protocol. Patients were analyzed for local control and overall survival. For a subset of 18 patients, a magnetic resonance imaging (MRI) scan at 46 Gy was obtained. After matching with pre-treatment computed tomogram, patients (response) were graded into four categories; i.e. LD (T1,2a with limited disease, i.e. disease confined to nasopharynx), LRD (T2b, with limited residual disease), ERD (T2b, with extensive residual disease), or patients initially diagnosed with T3,4 tumors. Dose distributions for ECBT (Plato-BPS v. 13.3, Nucletron) were compared to parallel-opposed, three-dimensional conformal radiation therapy (Cadplan, Varian Dosetek v. 3.1), intensity modulated radiation therapy (IMRT) (Helios, Varian) and stereotactic radiotherapy (SRT) (X-plan, Radionics v. 2.02).*

Results: *For stage T1,2N0,1 tumors, at 2 years local control of 96% and overall survival of 80% were observed. For the poorest subset of patients, well/moderate/poorly differentiated T3,4 tumors, local control and overall survival at 2 years with CHT were 67% and 67%, respectively, vs local control of 20% and overall survival of 12% without CHT. For LD and LRD, conformal target coverage and optimal sparing can be obtained with brachytherapy. For T2b-ERD and T3,4 tumors, these planning goals are better achieved with SRT and/or IMRT.*

Conclusions: *The dosimetric findings, ease of application of the brachytherapy procedure, and the clinical results in early staged NPC, necessitates ERT combined with brachytherapy boost to be the therapy of preference for LD and LRD. For locally advanced T3,4 tumors, our current protocol indicates neoadjuvant chemotherapy in conjunction with high cumulative doses of radiotherapy (81 Gy); IMRT and/or SRT to be the preferred technique for boosting the primary tumor.*

CHAPTER 8

8.1 INTRODUCTION

Currently a variety of treatment techniques are being used in the treatment of nasopharyngeal cancer (NPC) in order to apply highly conformal, high doses of radiation to the primary tumor and neck (nodes). The rationale for the application of (some of) these sophisticated and labor-intensive treatment techniques is based on established dose-tumor effect relationships in NPC (13,15). Local control has also been shown to be an independent prognostic indicator of distant metastasis (M+) (9). With the application of external beam three-dimensional conformal radiation therapy (3D-CRT) techniques to the primary tumor and neck, sparing of the surrounding critical normal tissues can be achieved. This is of particular relevance, since our current protocol implies the routine administration of neoadjuvant CHT and high cumulative doses of radiation (77-81 Gy) in stage III-IVB disease (13,14). This paper first briefly summarizes our experience with 10 years of endocavitary brachytherapy (ECBT) for all stages (I-IVB) of NPC. From this analysis, it is argued that in T3,4 tumors, there is a need for a better treatment technique (target coverage and sparing) for boosting the NPC. The focus of the present paper is therefore to define the role of some of the currently available treatment options for high-dose, high-precision boosting locally advanced NPC. For this purpose, ECBT, conventional parallel-opposed fields, 3D-CRT, intensity modulated radiation therapy (IMRT), and/or stereotactic radiation therapy (SRT), were explored and compared in a planning study (8,20,23). Target coverage as well as dose distributions in the surrounding critical normal structures at significant risk, such as e.g. the parotid glands, cord, optic chiasm and brainstem, are compared for the different treatment options.

8.2 MATERIALS AND METHODS

8.2.1 Rotterdam NPC Protocol 1991-2000: Since 1991, patients with undifferentiated (UD) tumors and well/moderate/poorly differentiated (WMP-D) carcinoma of the nasopharynx (NP) are treated by a combination of external beam radiotherapy (ERT) and ECBT. For analyzing the results of NPC between 1991 and 2000, all primary tumors treated by fractionated ECBT, were (re)staged according to the AJCC/UICC classification system (1997 edition) (2). ERT was given with 2 Gy per fraction to a total dose of 60 Gy (T1,2a) or 70 Gy (T2b-4). ECBT was applied by means of the silicone Rotterdam Nasopharynx Applicator, con-

nected to a computerized afterloading machine (microSelectron HDR; stepping ^{192}Ir point source, activity ± 370 GBq). The booster dose was applied by fractionated HDR; with a boost dose of 11 Gy (three fractions) or 17 Gy (five fractions), the cumulative dose in the NP reached 77 Gy or 81 Gy. Details of dose prescription and dose reporting with regard to the tumor tissue and normal tissue dose points have been published elsewhere (12,13). The neck was radiated electively to a dose of 46 Gy; metastatic neck nodes were boosted to 70 Gy. For the advanced tumor stages (T3,4 and/or N2,3), according to our 1996 guidelines, CDDP-based neoadjuvant chemotherapy was to be given according to protocol. Kaplan-Meier method and log-rank tests were used to obtain crude estimates for local control and overall survival. The clinical results are briefly summarized in Section 8.3.1; for a detailed account, the reader is referred to the analysis recently presented by Levendag *et al.* (14).

8.2.2 Treatment planning studies

8.2.2.1 High-dose-rate ECBT: From 1998 through 1999, for a subset of 18 patients, a magnetic resonance imaging (MRI) scan at 46 Gy was obtained and matched with a pre-treatment computed tomography (CT) scan (16). The response to 46 Gy external radiotherapy (RT) was graded and the tumor subdivided into one of four categories i.e. LD category (limited disease; NPC originally staged as T1-2a; six patients), LRD category (limited residual disease; initially T2b tumor, regressed to within confines NP proper; six patients), ERD category (extensive residual disease; initially T2b tumor, still extending beyond NP proper; four patients) or patient initially diagnosed with T3,4 tumor (T3,4 category, irrespective of response; two patients). For the clinical target volume of LD and LRD, the NP proper is taken, being defined as the nasopharyngeal space laterally encompassed by the two lines that can be drawn on CT/MRI from the medial pterygoid plate to the styloid process. For the clinical target volume of ERD, a 5 mm margin is added to the ERD gross target volume. In case of a brachytherapy boost, the planning target volume equals the clinical target volume.

After 60-70 Gy ERT, a pre-brachytherapy CT scan (Siemens Somatom AR, slice thickness 5mm, table movement 5 mm) with the head of the patient, with the NP applicator in situ, in a custom-made fixation shell was obtained. A CT-assisted 3D brachytherapy computer planning computation (Plato-BPS v. 13.3, Nucletron) with geometrical optimization of dose distributions in target and critical tissues, was performed (Table 1). Dose distributions were analyzed with patient points (PP) positioned on the CT-based contoured target, and mean dose was calculated in the contoured volumes of critical surrounding structures, such as

Table 1. Mean dose (%) in critical normal tissue[a]

	PP LD + LRD (n=12)	CT LD + LRD (n=12)	LRD (n=4)	ERD (n=4)
Retina	9 ± 2	6 ± 3	6 ± 2	10 ± 4
Optic Nerve	14 ± 4	10 ± 6	10 ± 4	15 ± 6
Optic Chiasm	19 ± 5	15 ± 9	14 ± 6	21 ± 7
Pituitary Gland	25 ± 7	20 ± 11	20 ± 8	26 ± 10
Temporal Lobe	10 ± 2	9 ± 4	8 ± 3	15 ± 5
Soft Palate	71 ± 15	64 ± 34	55 ± 12	91 ± 39
Parotid Gland	10 ± 2	10 ± 4	8 ± 4	24 ± 14
Brain Stem	18 ± 2	18 ± 7	17 ± 5	26 ± 8
Submandibular Gland	10 ± 5	10 ± 6	7 ± 2	15 ± 8
Spinal Cord	10 ± 4	9 ± 4	8 ± 3	23 ± 17

[a] For explanation, see section 8.3.2.1. Mean dose (%) in critical structures for ECBT when dose is prescribed to 'patient points' for 12 patients with LD (six patients T1,2a) and LRD (six patients T2b)(first column). Second to fourth column: dose prescribed to dose points on CT-based contours of target volume with resulting doses in CT-contoured critical normal tissues (NT). Second column: mean dose (%) in six T1,2a (LD) and six T2b (LRD); third column: mean dose (%) in four T2b (LRD); fourth column: mean dose (%) in four T2b (ERD). For calculations of the more extensive T3,4 lesions, data would be extremely variable, depending on size (extension) of T3,4 tumors (data not shown in table).

retina, optic nerve, optic chiasm, brainstem, pituitary gland, soft palate, spinal cord, temporal lobe, submandibular gland and parotid gland. For this purpose, first dose-volume histograms of the target and critical normal tissue structures were generated. For routine clinical use, depending on stage, the prescribed boost dose was 11 Gy (three fractions) or 17 Gy (five fractions) (Table 1).

8.2.2.2 External beam treatment planning technique: For the same subset of 18 NPC patients, external beam 3D conformal treatment plans were generated (Tables 2 and 3). This ERT treatment planning part of the study compared parallel-opposed 3D-CRT, IMRT and stereotactic radiotherapy (SRT). An example of dose distributions obtained using ECBT, 3D-CRT, IMRT or SRT, for a patient with a poorly responding ERD-T2bN2 tumor to three courses of CDDP + 5-FU and a first series of 46 Gy ERT, is given by *Figure 1*.

Two groups were analyzed: six LD and six LRD (first group, early cancers, 12 patients), and four ERD / two T3,4 (second group, advanced cancers, six patients). For both groups a CT-scan scan was obtained at 60-70 Gy ERT. The 3D margin around the clinical target volume to arrive at the planning target volume was 5 mm, except for the SRT (2 mm), reflecting the

Table 2. Target coverage and normal tissue doses (% (SD)) boosting 12 patients with limited disease (LD) and limited residual disease (LRD) with external beam radiotherapy techniques (i.e.3D-CRT, IMRT and SRT)[a].

Mean Dose (% (SD))								
	PTV	RPG	LPG	BS	C	OC	LSG[b]	RSG[b]
Par Opp	99.1 (1.3)	79.6 (15.3)	81.3 (12.8)	10.1 (6.3)	3.4 (1.1)	5.4 (3.8)	1.6 (0.6)	1.5 (0.6)
3DCRT	100.1 (0.3)	14.7 (5.2)	16.1 (6.7)	20.9 (9.8)	14.3 (8.2)	8.1 (3.7)	8.3 (7.9)	9.7 (7.0)
IMRT	99.9 (0.4)	11.9 (3.4)	11.8 (3.8)	12.4 (3.4)	6.7 (1.6)	9.9 (7.4)	8.9 (8.5)	15.6 (12.9)
SRT	119.4 (1.8)	8.6 (3.2)	8.8 (3.1)	16.6 (3.6)	9.8 (2.6)	7.5 (3.2)	5.5 (5.7)	6.5 (5.5)

[a]For abbreviation and explanation LD and LRD, see text. Par-Opp, parallel-opposed fields; PTV, planning target volume; RPG, right parotid gland; LPG, left parotid gland; BS, brainstem; C, cord; OC, optic chiasm; LSG, left submandibular gland; RSG, right submandibular gland.
[b]CT Data on submandibular gland (L/R) were available in six patients.

rigidity in immobilization of the head with the Gill Thomas Cosman (GTC) frame. The 3D-CRT treatment plans were based on uniform flat beam profiles (Cadplan; Varian Dosetek v. 3.1, Finland), implementing five non-coplanar 6 MV photon beams (class solution). For IMRT, the Helios (Varian) inverse-planning module was used with the same beam arrangement. After determination of baseline constraints for planning target volume (PTV) and critical structures, intensity profiles were calculated and optimized for the sliding window technique. The final dose distributions were recalculated using Cadplan. The dose was prescribed according to the ICRU 50 guidelines in case of 3D-CRT (total boost dose 12 Gy, six fractions). For SRT (X-plan; Radionics v. 2.02, Burlington, USA), multiple static fields were applied with a miniMultileaf Collimator (mMLC). Dose was prescribed to the 80% isodose line (2.8 Gy per fraction, four fractions in total).

8.3 RESULTS

8.3.1 Clinical results: 1991-2000: The results of the multivariate analysis in 91 NPC stage I-IVB NPC patients treated between 1991 and 2000 in Rotterdam were, in brief, as follows

(14): for all stages combined, at 5 years a local control rate for UD vs. WMP-D tumors of 92 (UD) vs. 59% (WMP-D) ($p = 0.0002$) was found. For T1,2N0,1 staged tumors, local control and overall survival at 5 years were 92% and 62% (without the use of CHT), respectively. For T3,4 tumors, without chemotherapy, local control and overall survival at 5 years were 57 and 12%, respectively. With CDDP-based neoadjuvant CHT, a local control of 77% and overall survival of 70%, was observed. For the poorest subset of patients, WMP-D T3,4 tumors, local control and overall survival at 2 years with CHT were 67 and 67%, respectively, vs. local control of 20% and overall survival of 12% without CHT. *Figures 2* and *3* illustrate the impact of T-stage, differentiation grade and the role of CHT in locally advanced disease at 3 years.

8.3.2 Treatment planning studies

8.3.2.1 High-dose-rate ECBT: For a subset of 18 NPC patients, the anticipated doses were computed which would have been received by the listed critical normal tissues (Table 1). The doses were prescribed and reported to either 'patient points' (PP) (12,13) or to dose points on CT based contours. In Table 1, mean dose (%) in critical structures is presented

Table 3. Target coverage and normal tissue doses (% (SD)) boosting six patients with extensive residual disease (ERD; four tumors) and T3,4 disease (two tumors) with external radiotherapy techniques[a].

Mean Dose (% (SD))								
	PTV	IPG	CP	BS	C	OC	ISG[b]	CSG[b]
Par Opp	99.6 (0.3)	84.4 (20.4)	91.8 (12.7)	10.0 (5.1)	4.6 (3.2)	5.0 (0.6)	4.7 (4.9)	4.4 (4.5)
3DCRT	100 (0.3)	33.9 (11.7)	18.4 (3.0)	21.5 (5.0)	16.6 (15.1)	11.9 (4.9)	15.7 (9.7)	12.6 (9.6)
IMRT	99.9 (0.2)	37.6 (20.4)	13.7 (4.7)	14.8 (1.2)	7.0 (3.2)	15.9 (4.8)	22.3 (17.0)	16.3 (11.5)
SRT	118.3 (10.4)	22.5 (7.7)	13.7 (6.3)	16.7 (3.5)	12.9 (13.4)	10.1 (6.5)	15.1 (7.0)	11.7 (6.1)

[a]The 3D-CRT, IMRT and SRT techniques were aimed at sparing the contralateral parotid gland. For abbreviation and explanation of ERD, see text. Par-Opp, parallel opposed fields; PTV, planning target volume; IPG, ipsilateral parotid gland; CPG, contralateral parotid gland; BS, brainstem; C, cord; ISG, ipsilateral submandibular gland; CSG, contralateral submandibular gland; OC, optic chiasm.
[b]CT Data on the submandibular glands were available in five patients.

for fractionated brachytherapy when dose is prescribed to PP for 12 patients with LD and LRD (first column). In the second to fourth columns, dose prescribed to dose points on CT based contours of target volume with resulting doses in CT-contoured critical normal tissues (NT) is given. With more locally advanced lesions, ECBT and dose prescription to PP would mean significant underdosage in case of ERD, in particular, in case of more advanced T3,4 tumors. In contrast, with doses prescribed to CT-based contours, with the more extensive target the critical normal tissues are at higher risk for overdosage (see, for example, dose in brainstem and cord, Table 1).

8.3.2.2 External beam treatment planning techniques: For the same 18 patients used in the brachytherapy section, 3D conformal ERT techniques were compared; that is 3D-CRT, IMRT, or SRT.

Of prime concern to the clinician are the availability of adequate imaging techniques for delineating the primary lesion (gross tumor volume) and hence be able to contour the precise extent of the clinical target volume (CTV) and the PTV. It often proves complicated to contour these infiltrating tumors accurately, and because of the uncertainties, at times the contouring has to be individualized, i.e. slightly more liberal in the case of advanced lesions (ERD or T3,4). As a general departmental rule, according to the protocol guidelines, for the PTV, a 3D margin of 5 mm around the clinical target volume is taken, except in case of SRT (2 mm).

The computed dose distributions in target and critical surrounding tissues with the NP proper as clinical target volume (LD or LRD) are listed in Table 2; for the four ERD and two T3,4 tumors, dose distributions are presented in Table 3.

8.4 DISCUSSION

To date, radiation therapy remains the mainstay of the treatment for cancer in the NP(7). A study by Lee *et al.* (10) reported a cumulative incidence of 13% persistent local disease for 5037 patients treated by RT alone. At 10 years, the actuarial local failure-free survival was 61%, the overall survival was 42%. As is apparent, local recurrences represent a significant proportion of radiation failures. Also, local control in NPC is an independent prognostic indicator for development of M+ (9). Moreover, there is now a reasonable body of evidence that local control is related to the total dose of radiation administered, either by ERT alone

or combined with brachytherapy (11,13,18,21,22). For example, a recent update of a large experience on the effectiveness of ECBT when used as a boost for NPC was reported by Teo *et al.* (22). Out of a consecutive series of 504 early staged NPC from Hong Kong, 163 T1,2 cases were treated by ERT followed by a boost with high dose rate ECBT (18-24 Gy, three fractions), and 346 T1,2 patients treated by ERT-alone. Local failure (LF) rates at 5 years were 5 vs.11% (T1), and 8 vs.16% (T2), for ECBT and ERT only, respectively. In summary, considering the evidence for dose-response relationships in NPC (13), there is cumulative data emerging in the literature on excellent local control rates indeed to be obtained with brachytherapy in early staged NPC (21,22). Furthermore, the literature is suggestive of the 'translation' of an increase in local control into an improved overall survival (13).

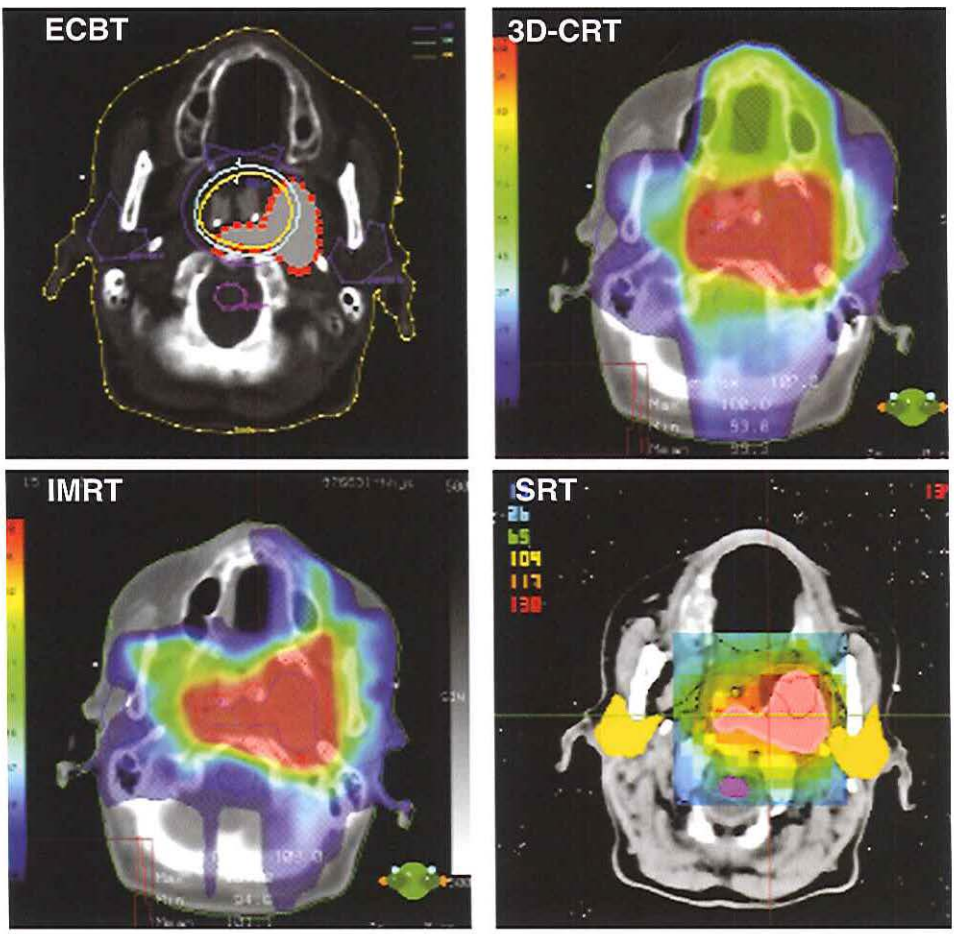

Fig. 1. Example of patient with a poorly responding T2b tumor (ERD), with dose distributions in target and normal tissues when using ECBT, 3D-CRT, IMRT and SRT (for details, see text).

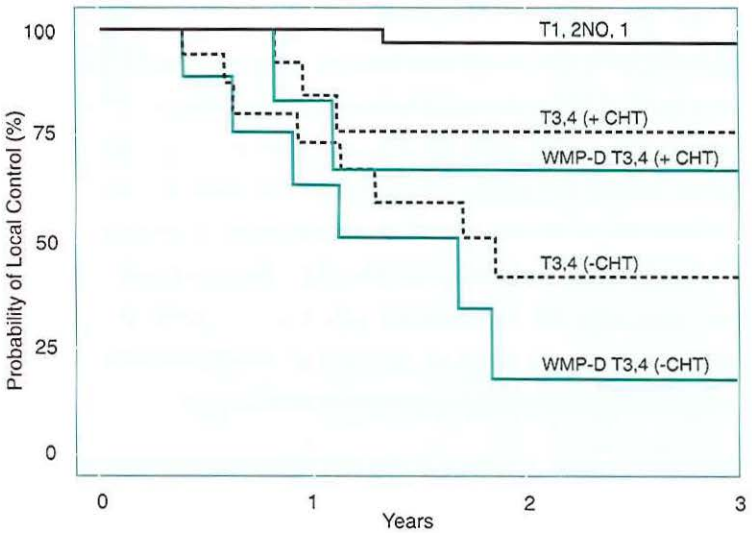

Fig. 2. Local control of patients with T3,4N± NPC treated with neoadjuvant chemotherapy (+ CHT) (15 patients; at 3 years five at risk) vs. T3,4N± tumors treated without chemotherapy (- CHT) (18 patients; at 3 years two at risk). Also depicted in the figure are WMP-D T3,4N± tumors with chemotherapy (+ CHT) (six patients; at 3 years four patients at risk) vs. WMP-D T3,4N± tumors treated without chemotherapy (- CHT) (10 patients; at 3 years no patient at risk). For comparison purposes, the local control of T1,2N0,1 tumors of 33 patients treated by Rotterdam protocol guidelines (high cumulative dose of radiation, no chemotherapy) is plotted.

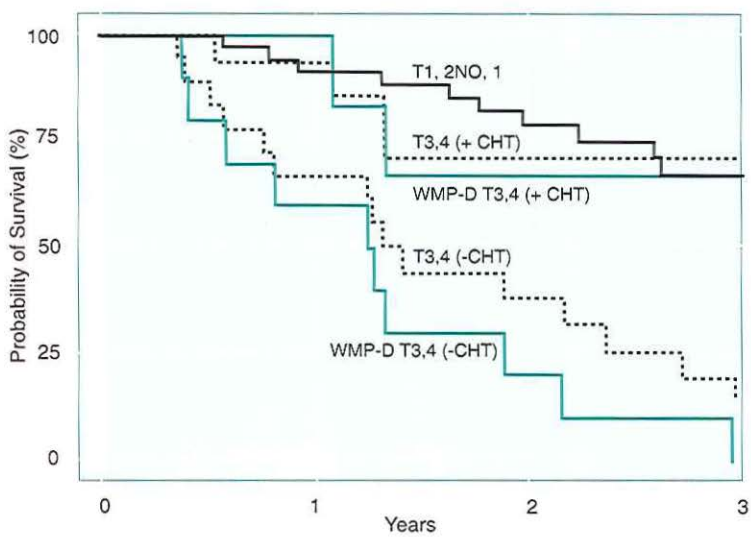

Fig. 3. Overall survival of patients with T3,4N± tumors treated with neoadjuvant chemotherapy (+ CHT) (15 patients; at 3 years five at risk) vs. T3,4N± tumors treated without chemotherapy (- CHT) (18 patients; at 3 years two at risk). Also depicted in the figure are WMP-D T3,4 tumors treated with chemotherapy (+ CHT) (six patients; at 3 years four at risk) vs. WMP-D T3,4 tumors treated without chemotherapy (- CHT) (10 patients; at 3 years none at risk). For comparison purposes, the overall survival of T1,2N0,1 tumors of 33 patients treated by Rotterdam protocol guidelines (high cumulative dose of radiation, no CHT) is plotted.

In an attempt to maximize local control (and survival) and limit toxicity at the same time, the method adopted by the University Hospital Rotterdam since 1991, is to routinely deliver high cumulative doses of RT to the NP; booster doses are to be applied per protocol by means of fractionated high-dose-rate brachytherapy, making use of the accelerated treatment schedule (increase in effectiveness) and rapid dose fall off (maximize sparing neighbouring adjacent structures). At the time it was suggested to use the fractionated high-dose-rate ECBT as a high-dose, high-precision boost technique for all tumor stages (12,13). In fact, this policy has been rewarding: ECBT as a boost has shown to be a simple, reproducible, and fast (accelerated) 3D conformal technique with excellent clinical control rates (stage I-IIB: 5 years local control 92%, overall survival 62%).

Some subsets of NPC patients are at high risk for local failure and distant metastasis, i.e. in particular those harboring T3,4 and/or N2,3 disease. Therefore, in addition to the high cumulative doses of radiation, in order to treat this patient category more aggressively, in 1996 the implementation per protocol of CDDP-based neoadjuvant CHT was introduced (13). Taking into account the literature on the subject, there is still some controversy on neoadjuvant vs. concomitant CHT (1,3,4,6,19,24). To date it is of interest to note that only limited toxicity (e.g. infrequently some synechiae of nasal mucosal linings and crustae in NP vault are seen) is experienced. This observation contrasts with some of the toxicity reports on conventional (lower) dose levels of ERT in combination with concomitant CHT in cancer of the head and neck (6,19). On the other hand, we strongly feel that if chemotherapy is not given in a concomitant fashion (as is presently done for most other cancers in the head and neck), this will enforce the need for adequate dose coverage by high doses of RT. Albeit as it may, the rationale for chemotherapy was corroborated by the data presented in our recent analysis (14): For T3,4 tumors, treated without chemotherapy, local control and overall survival at 5 years were 57 and 12%, respectively, as opposed to 77% (local control) and 70% (overall survival) when treated in conjunction with CDDP-based neoadjuvant CHT. However, with respect to the WMP-D T3,4 tumors, the poorest prognostic subgroup, local control and overall survival at 2 years were 20 and 12%, respectively, with RT only, and 67 and 67%, respectively, when treated in conjunction with chemotherapy (*Figures 2* and *3*). Obviously, there is a need for improvement in this last category.

In view of the supportive data from the literature as well as from our own findings on the existence of dose-tumor effect relationships, one argument for an increased failure rate in T3,4 NPC even if boosted by high doses of radiation, would be a geographical miss. In fact, it can be concluded from our planning studies (Tables 1-3), by comparing brachytherapy to

alternative 3D conformal ERT boost techniques, that from the dose distribution point of view, we did 'underdose' to some extent the 'periphery' of the clinical target volume in T2b-ERD and T3,4 tumors when treated by ECBT as a boost. The purpose of the present paper is to compare dose distributions (target coverage and sparing) obtained by ECBT to 3D-CRT, IMRT and SRT, and therefore to design the most optimal radiation therapy technique for early and advanced tumor stages. One can appreciate from Tables 1-3 that adequate target coverage, without overdosing the NT, can be realized with IMRT and SRT, but for early staged tumors this can be achieved just as well with fractionated ECBT. With these techniques, substantial sparing (approximately 10% of prescribed dose) of both parotid glands was achieved. For T2b tumors, however, this is only the case for those cancers that have regressed after chemotherapy and/or ERT to a clinical target volume confined to the NP (LRD). For poorly responding T2b cancers after a first series of 46 Gy (ERD), as well as for those tumors initially staged T3,4 disease, best dosimetric results with regard to target coverage and sparing are obtained when boosting the PTV with SRT or IMRT techniques. Also, as a result of the smaller margins that can be used with SRT and the rapid dose fall off around the target volume, hypofractionation (four fractions, 2.8 Gy per fraction) is feasible without compromising the normal surrounding critical tissues. It is anticipated that this could even further increase its effectiveness.

Finally, it remains a challenge to design the optimal treatment technique for sparing both the major (parotid and submandibular) and the majority of the minor salivary glands, when the target comprises the primary tumor and neck and is to be treated to high doses of radiation (5). Recently we completed a CT-based standardization of the neck nodal regions (17,25). What is still needed is standardization of the primary target and adequate delineation guidelines for contouring the primary tumor (work in progress).

8.5 CONCLUSIONS

Acceptable dose distributions in target and normal tissues can be achieved, with fractionated high-dose-rate brachytherapy boosting the NP after 60-70 Gy ERT to a cumulative dose of 77-81 Gy; that is, if the clinical target volume for the high-dose, high-precision boost after 46 Gy is confined to the NP. Fractionated brachytherapy has been shown to be a simple, reproducible and effective 3D conformal technique with excellent clinical control in early

cancers: at 5 years stage I-IIB local control of 92% and overall survival of 62%, without the addition of chemotherapy, is observed. With the addition of CHT to locally advanced WMP-D T3,4 tumors, local control and overall survival were only 67%. From the dosimetric analyses (target and normal tissues) in the present paper one can deduct that for T2b-ERD or T3,4 tumors, SRT and/or IMRT seem to be the more appropriate treatment techniques, and improvement in local control (and survival) is anticipated. Future work in our department is focused at present on implementing 3DCRT / IMRT techniques in large volume (neck nodal regions and primary) disease.

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CHAPTER 9

Beam intensity modulation using tissue compensators or dynamic multileaf collimation in three-dimensional conformal radiotherapy of primary cancers of the oropharynx and larynx, including the elective neck

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ABSTRACT

Introduction: *The treatment of midline tumors in the head and neck by conventional radiotherapy almost invariably results in xerostomia. This study analyzes whether a simple three-dimensional conformal radiotherapy (3D-CRT) technique with beam intensity modulation (BIM) (using a 10-MV beam of the MM50 Racetrack Microtron) can spare parotid and submandibular glands without compromising the dose distribution in the planning target volume (PTV).*

Materials and Methods: *For 15 T2 tumors of the tonsillar fossa with extension into the soft palate (To) and 15 T3 tumors of the supraglottic larynx (SgL), conventional treatment plans, consisting of lateral parallel opposed beams, were used for irradiation of both the primary tumor (70 Gy) and the elective neck regions (46 Gy). Separately, for each tumor a 3D conformal treatment plan was developed using the 3D computer planning system CadPlan (Varian-Dosetek) and Optimize, a noncommercial program to compute optimal beam profiles. Beam angles were selected with the intention of optimal sparing of the salivary glands. The intensity of the beams was then modulated to achieve a homogeneous dose distribution in the target for the given 3D-CRT techniques. The dose distributions, dose volume histograms (DVHs) of target and salivary glands, tumor control probabilities (TCPs), salivary gland volumes absorbing a biological equivalent dose of greater than 40 or 50 Gy, and normal tissue complication probabilities (NTCPs) of each treatment plan were computed. The parameters of the 3D-CRT plans were compared with those of the conventional plans.*

Results: *In comparison with the conventional technique, the dose homogeneity in the target volume was improved by the conformal technique for both tumor sites. In addition, for the SgL conformal technique, the average volumes of the parotid glands absorbing a BED of greater than 40 Gy (V40) decreased by 23%, and of the submandibular glands by 7% (V40) and 6% (V50). Consequently, the average NTCPs for the parotid and submandibular glands were reduced by 7% and 6%, respectively. For the To conformal techniques, the V40 of the parotid glands was decreased on average by 31%, resulting in an average reduction of the NTCP by 49%. Both the average V50 and the NTCP of the submandibular glands were decreased by 7%.*

Conclusion: *For primary tumors of the oropharynx, the parotid glands could be spared to a considerable degree with the 3D-CRT technique. However, particularly the ipsilateral submandibular gland could not be spared. For primary tumors of the larynx, the 3D-CRT technique allows sparing of all salivary glands to a considerable and probably clinically relevant degree. Moreover, the conformal techniques resulted in an increased dose homogeneity in the PTV of both tumor sites.*

9.1 INTRODUCTION

Elective neck irradiation (ENI) in primary cancers of the head and neck region is very effective in reducing the number of neck relapses. Studies have shown regional control rates of well over 90% with doses in the range of 40–50 Gy (1–5). However, treatment is not without significant morbidity, with the dry mouth syndrome being most prominent.

In our institution, we conducted a retrospective survey among long–term survivors after irradiation for primary cancers in the head and neck. Almost all patients experienced some degree of xerostomia; those patients treated for primary cancers of the larynx experienced this to a lesser degree as compared to those with tumors originating in the nasopharynx. This survey corroborates findings that have been published before in the literature: Including (part of) the parotid and submandibular glands in the RT portals and/or surpassing the tolerance levels of these major salivary glands, leads to a change in the quantity and quality of saliva (6–9). This, in turn, can lead to severe side effects such as xerostomia, dental caries, and osteoradionecrosis.

A simple reduction of portal sizes per se could reduce the extent of the dry mouth syndrome, but this might eventually interfere with tumor control rates. Hence, it seems interesting to investigate with three-dimensional conformal radiotherapy (3D-CRT) techniques whether control rates may be maintained while critical structures, such as the major salivary glands, can be spared.

In this respect, a CT-based protocol for 3D delineation of lymph node levels I–V in the neck has recently been designed (10, 11). This protocol allows contouring of the elective target volume of the neck on CT within 1/2 to 1 h, which is acceptable for 'routine' clinical practice.

Physical and biological optimization of beam angles and intensity profiles using these targets may be less practical, because current programs may require considerable computation times (12–17), or because the resulting technique is very complex (many fields, steep intensity gradients). Application of only a few well selected beams with standard beam angles, in combination with simple, speedy algorithms to calculate the beam profiles, such as target dose optimization (18, 19) may be more easily applied.

In this study, the feasibility of such an approach was studied for irradiation of the elective and booster volume of two midline tumors, the supraglottic larynx (T3N0) and the right tonsillar fossa with extension into the soft palate (T2N0).

9.2 MATERIALS AND METHODS

9.2.1 Patient data and planning technique: The planning CT data and original simulator films of 15 patients, previously irradiated for a variety of cancers of the head and neck were used. The planning CT scans were made in a supine treatment position using an immobilizing headcast, scanning from the level of the orbits to just below the sternoclavicular joints, using a slice distance of 5 mm. On these CT scans, two primary tumors, a T2 tumor of the right tonsillar fossa with extension into the soft palate (To) and a T3 tumor of the supraglottic larynx (SgL) were outlined. Furthermore, the CTV of the bilateral elective neck was outlined using the CT-based protocol for lymph node Regions 2–4 (10, 11). Finally, the parotid glands, the submandibular glands, the larynx (as a critical structure for the To treatment plans), and the spinal cord were outlined. In this way, a CT database of 30 'patients' (15 To and 15 SgL tumors) was created.

The CTV of each primary tumor (SgL or To) was combined with the CTVs of the lymph node Regions 2–4. An elective planning target volume (PTV1, 46 Gy) was created by adding a 3D margin of 5 mm to the CTV (20). The CTV of the primary tumor volume was expanded separately, again using a 3D margin of 5 mm, to generate PTV2 for the booster treatment (46–70 Gy).

Treatment plans were created using a 10-MV photon beam of the racetrack track microton (MM50, Scanditronix, Sweden). (Dose-profile measurements were performed especially in the build-up region and compared to a 6-MV photon beam. No clinically significant differences were found). The conventional lateral portals for both tumor sites, which would have been applied in our clinic, were drawn on the original simulation films, digitized, and imported into the planning system (CadPlan, Varian–Dosetek, Finland) to compute dose distributions for this technique.

Next, a CT based 3D-CRT plan was developed for PTV1 and PTV2, using beam intensity modulation (BIM) to irradiate the PTVs to a homogeneous dose of 46 and 70 Gy, respectively. The 3D-CRT technique for PTV1 of the SgL consisted of two tilted lateral fields with gantry angles of 70° and 290° (*Figure 1a*). A margin of 8 mm from PTV1 to the leaves of the multileaf collimator (MLC) was used, except on the ventral side at the level of the submandibular glands, where a margin of 4 mm was used (*Figure 1b*). For PTV2, a similar field setup was used (*Figure 1c*).

The 3D-CRT technique for PTV1 of the To consisted of a combination of two asymmetric techniques, with the isocenter positioned between the tonsil and the larynx. The cranial

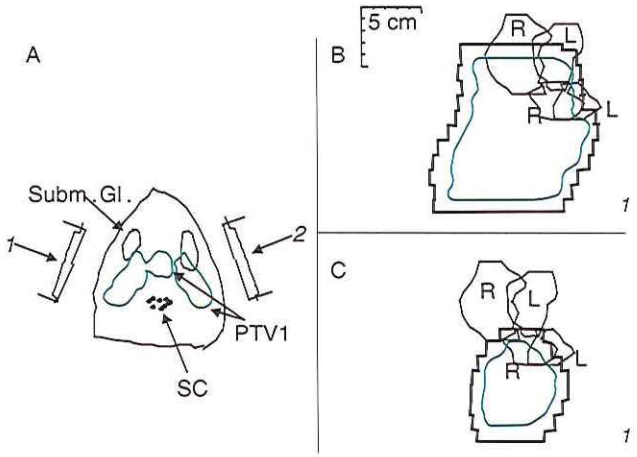

Figure 1. A schematic view of the three-dimensional conformal radiotherapy technique for a tumor of the supraglottic larynx, including the neck (PTV1) and booster to the primary tumor (PTV2). (a) Transversal view of the beam setup. Positions of submandibular glands and spinal cord (SC) are indicated. (b) Beams' eye view of field 1 (PTV1: green line, left (L) and right (R) salivary glands: thin lines). (c) Beams' eye view of field 1 (PTV2: green line, left (L) and right (R) salivary glands: thin lines).

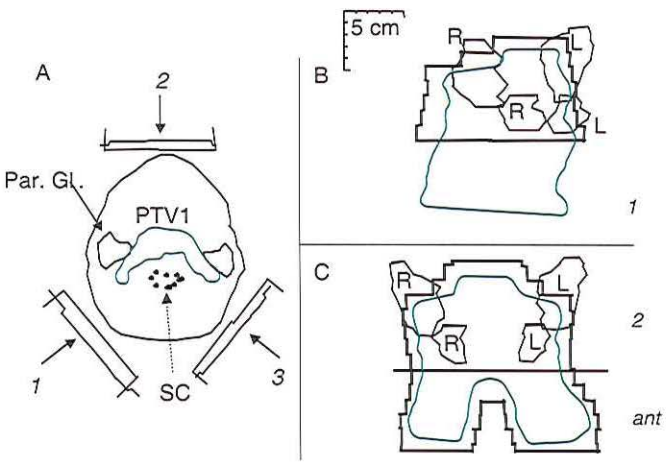

Figure 2. A schematic view of the three-dimensional conformal radiotherapy technique for a tumor of the tonsil/soft palate, including the neck (PTV1). (a) Transversal view of the beam setup in the cranial part of the target volume. Positions of parotid glands and spinal cord (SC) are indicated. (b) Beams' eye view of field 1 (PTV1: green line, left (L) and right (R) salivary glands: thin lines). (c) Beams' eye view of field 2 and the anterior field (PTV1: green line, left and right salivary glands: thin lines). The thick solid line indicates the position of the junction between field 2 and the anterior field. The larynx block is shown schematically in the anterior field.

part of the technique consisted of 3 fields (*Figure 2*), the caudal part of an anterior field with a central larynx/spinal cord block. To prevent dose errors near the field junction (21, 22), the junction was never positioned at or near the primary tumor volume. For PTV2 of the To, 3 asymmetric fields were used (*Figure 3*), using the same isocenter as for the first part

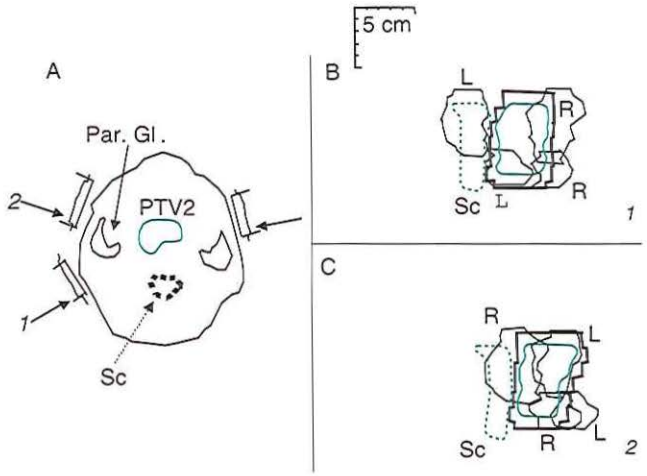

Figure 3. A schematic view of the three-dimensional conformal radiotherapy technique for the booster to the primary tumor of the tonsil/soft palate (PTV2). (a) Transversal view of the beam setup. Positions of parotid glands and spinal cord (SC) are indicated. (b) Beams' eye view of field 1 (PTV2: green line, salivary glands: thin lines, and spinal cord: dotted line). (c) Beams' eye view of field 2 (PTV2: green line, salivary glands: thin lines, and spinal cord: dotted line).

of the treatment (*Figures 3b, 3c*). Care was taken not to irradiate the spinal cord to a dose of more than 50 Gy.

To be able to minimize the margin between the PTVs and the MLC, and to correct for both the tilted gantry angles and the nonuniform body contour, BIM was used. Optimal profiles were calculated using 'Optimize', a program developed to achieve a homogeneous dose distribution in the target (19) (see Appendix 1). In short, the program iteratively modifies beam intensities to homogenize the average dose distribution in the PTV. Between iterations, CadPlan is used to recompute the dose, using a pencil beam algorithm (CadPlan, Varian–Dosetek, Finland).

For each patient, dose volume histograms (DVHs) were generated for both tumor sites for the conventional and conformal techniques. To facilitate comparison between conventional and 3D-CRT techniques for the PTVs, the (small) parts of the PTV outside the body contour (which are assumed not to absorb any dose in the CadPlan planning system) were ignored during computation of DVHs. For the salivary glands, where the inhomogeneity in dose is substantial, biological equivalent doses (BED) were calculated from physical doses (D), using an α/β of 3 Gy and a correction for fraction size (n) (23, 24):

$$BED = D * (\alpha/\beta + n) / (\alpha/\beta + 2) \qquad [1]$$

Salivary gland volumes absorbing a BED greater than 40 Gy (V40) were calculated. This

parameter may predict the amount of remaining functional volume (25–28). Because submandibular glands are probably more resistant to radiation than parotid glands, the submandibular gland volumes absorbing a BED greater than 50 Gy (V50) were also calculated (29, 30).

The normal tissue complication probabilities (NTCPs) of the salivary glands were calculated, using the dose–volume reduction technique (31), applied to the (biological) DVH. For the submandibular glands, the parameters for the parotid glands (26) were used.

Tumor control probabilities (TCPs) of the elective and primary PTVs were calculated assuming a TCP of 97% at 46 Gy (PTV1) and 90% at 70 Gy (PTV2). The steepness of the TCP dose curve at TCP = 50% (31) was chosen to be 2 Gy^{-1} for all PTVs.

All V40, V50, TCPs, and NTCPs of the 3D-CRT technique were compared to those of the conventional technique. In addition, the average, maximum, and minimum values of these parameters of the 15 'patients' were computed and compared. The left and right salivary glands were evaluated separately, and the results were averaged.

9.3 RESULTS

9.3.1 Conventional techniques: Figure 4 shows, for a typical patient of the database, the projection of the salivary glands on the conventional parallel opposed beams, for the SgL (left) and the To (right). As can be seen, the salivary glands are largely encompassed by the elective portals. Even for the SgL booster technique, the portals cover at least one-half of the sub-

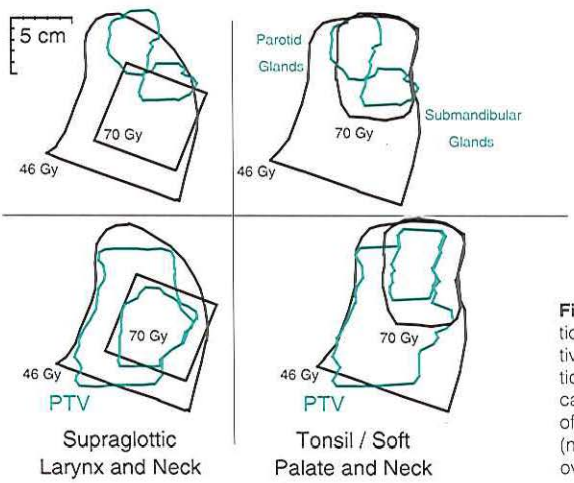

Figure 4. A Beams' eye view of the conventional lateral parallel opposed portals (elective: PTV1 and booster: PTV2) for a supraglottic larynx (left) and a tonsil/soft palate (right) carcinoma. The top row shows the projection of the parotid and submandibular glands (merged to one contour, since they nearly overlap), the bottom row PTV1 and PTV2.

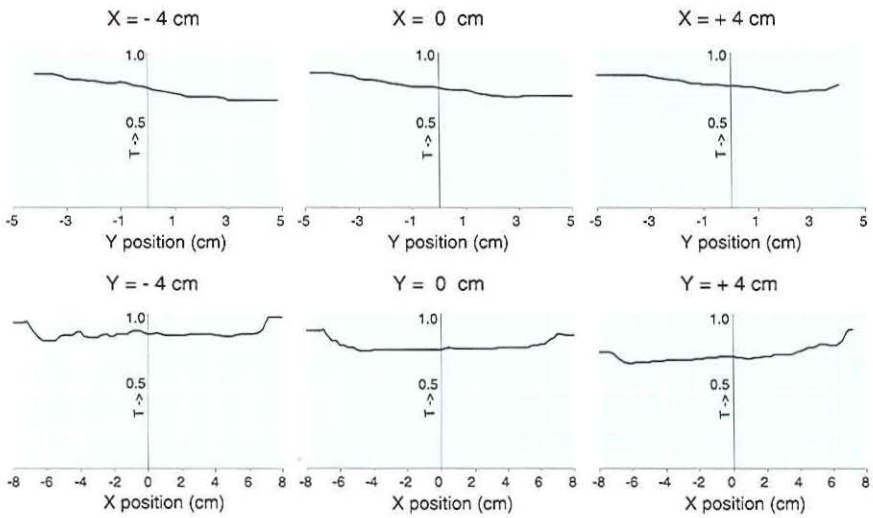

Figure 5. Typical intensity profiles computed for the planning target volume for a tumor of the supraglottic larynx, including the neck. Top row: dorsoventral direction (X). Bottom row: caudocranial direction (Y).

mandibular gland volumes. *Figure 4* also shows the projection of the conventional portals on the PTV, for the SgL (left) and the To (right). Obviously, the routine portals do not completely cover the entire CT based PTV.

9.3.2 Conformal 3D–RT techniques: Figure 5 shows a typical example of the intensity profiles, calculated for the conformal technique of PTV1 of the SgL. The variation in intensity in these profiles is about 30%. In the X–direction (IEC coordinate system), the profiles are wedge shaped. The 'wedge' angle and height of the profile is different for each position, correcting for the beam obliquity with respect to the body contour and the PTV. The cranial profile (Y = 4) deviates from the wedge shape ventrally, to enhance dose in the PTV near the blocked submandibular glands. In the caudocranial direction, the thinner neck in the central part of the field is corrected by reducing intensity. The cranial and caudal penumbras are counteracted by field edge enhancements of about 10%.

Figure 6 depicts the PTV, salivary glands, and the dose distribution of the 3D-CRT techniques on transversal CT slices (see also *Figure 2*). The 95% isodose surface of all 3D-CRT plans encompasses the PTV, except occasionally in the caudal part of the To elective technique (PTV1), where the larynx/spinal cord block in the anterior field may result in underdosage in small parts of the PTV. The major salivary glands are spared to some degree. The

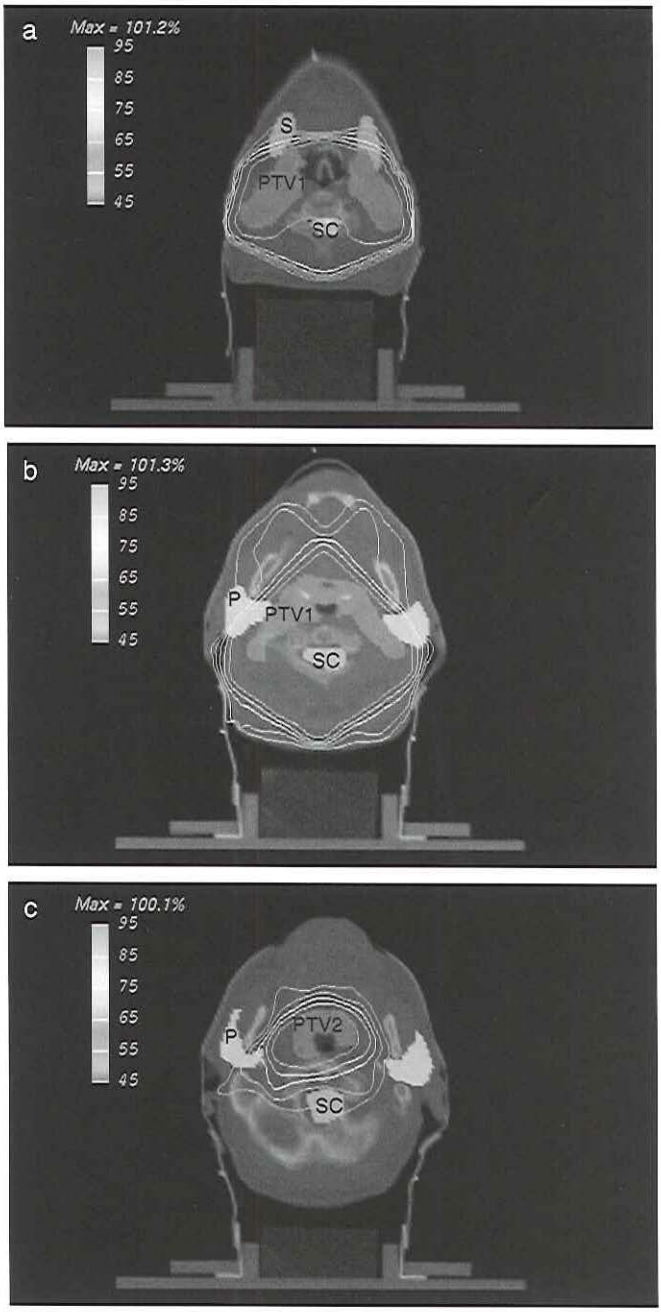

Figure 6. The transversal dose distributions for one of the 15 'patients' for the positions shown schematically in Figs. 1, 2, and 3. (a) Planning target volume of a T3 tumor of the supraglottic larynx, including the neck. (b) Planning target volume of a T2 tumor of the tonsil/soft palate, including the neck. (c) Planning target volume for the booster of a T2 tumor of the tonsil/soft palate.

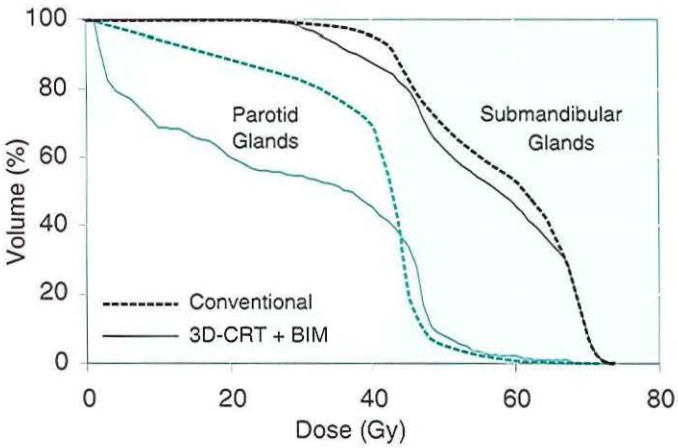

Figure 7. Mean dose-volume histograms of the salivary glands for the tumors of the supraglottic larynx, comparing conventional (dotted lines) and three-dimensional conformal radiation techniques with beam intensity modulation (3D-CRT + BIM, solid lines).

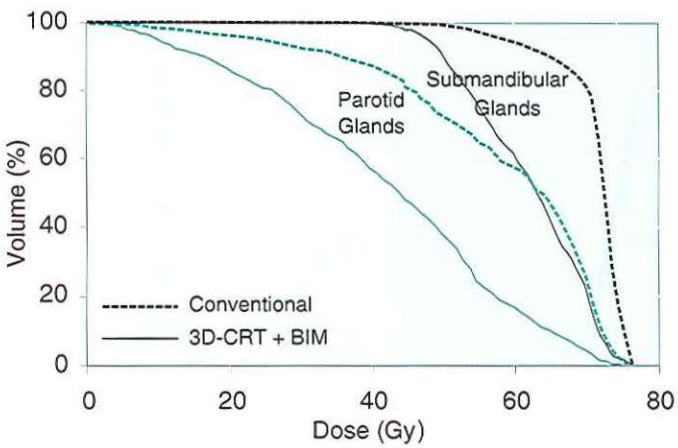

Figure 8. Mean dose-volume histograms for the salivary glands for the tumors of the tonsil/soft palate, comparing conventional (dotted lines) and conformal (solid lines) techniques.

3D-CRT techniques of PTV1 result, however, in quite large irradiated volumes, and the 95% isodose encompasses the spinal cord. The computed mean TCP for the conformal technique is 87% (SgL, PTV1) and 98% (SgL, PTV2), 73% (To, PTV1) and 97% (To, PTV2). For each 3D-CRT plan, the computed TCP was larger than that of the conventional technique. The mean DVHs for the salivary glands (left and right averaged) are shown in *Figures 7* and *8*. There is a considerable reduction of the dose absorbed in the parotid glands for the SgL conformal technique in comparison with the conventional portals. This is reflected in the average V40 (Table 1) and the average NTCP (Table 2), which are reduced by 23% and 7%,

Table 1. Volume (%) absorbing more than 40 or 50 Gy.

	Parotid glands 40 Gy		Submandibular glands 40 Gy		50 Gy	
	Conv.	3D-CRT	Conv.	3D-CRT	Conv.	3D-CRT
SgL						
minimum	43	16	86	62	31	16
mean	69	46	95	88	69	63
maximum	97	71	100	100	100	98
To						
minimum	63	28	100	100	89	69
mean	87	56	100	100	98	85
maximum	100	77	100	100	100	100

Mean, minimum, and maximum volumes in percentages, receiving more than 40 Gy (V40) and more than 50 Gy (V50) for the entire treatment (70 Gy) of a supraglottic larynx carcinoma (SgL) and a tonsil/soft palate carcinoma (To) by conventional (Conv.) and three-dimensional conformal radiotherapy (3D-CRT) techniques. Numbers are averages of the left and right salivary glands.

respectively. The mean dose to the parotid glands decreased from 38.7 Gy to 29.2 Gy. The sparing of the submandibular glands is much less pronounced; the average V40 and V50 are decreased by 5-10 %, and the average NTCP by 6%. The mean dose to the submandibular glands decreased from 58.0 Gy to 56.1 Gy.

Sparing of the parotid glands by the conformal To technique is considerable. The V40 is

Table 2. Normal Tissue Complication Probabilities (%).

	Parotid glands		Submandibular glands	
	Conv.	3D-CRT	Conv.	3D-CRT
SgL				
minimum	2	0	49	34
mean	10	3	88	82
maximum	26	15	100	100
To				
minimum	23	4	99	79
mean	79	30	100	93
maximum	100	59	100	100

Mean, minimum, and maximum normal tissue complication probabilities (NTCPs) for the entire treatment (70 Gy) of a supraglottic larynx carcinoma (SgL) and a tonsil/soft palate carcinoma (To) by conventional (Conv.) and three-dimensional conformal radiatiotherapy (3D-CRT) techniques. Numbers are averages of the left and right salivary glands (in percentages).

reduced by about 30% (Table 1). The reduction in average NTCP is from 79% to 30% (Table 2). The mean dose to the parotid glands was reduced by 15.9 Gy (from 57.4 to 41.5 Gy). Sparing of the submandibular glands in terms of dose is better than for the SgL techniques. However, the absolute doses are higher; the V40 (100%) is equal to that of the conventional technique. The average V50 and NTCP are somewhat better (a reduction of 13% and 7%, respectively). This is also reflected in the mean dose, which decreased from 70.8 Gy to 61.6 Gy.

A comparison between the 3D-CRT and the conventional techniques for each 'patient' shows that the NTCP of the parotid glands of all 15 'patients' is improved for both primary tumor sites. In addition, the 3D-CRT technique of the SgL results in a smaller NTCP of the submandibular glands in 9 'patients'. However, the 3D-CRT technique of the To reduces the NTCP only in 5 'patients' for the left submandibular gland and in 3 'patients' for the right (ipsilateral) submandibular gland.

9.4 DISCUSSION

In the present study, we tried to assess the merit of a simple 3D-CRT technique for treatment of primary tumors of the head and neck, including the elective neck, by comparison of the conformal technique with conventionally used portals in terms of anticipated tumor control and toxicity.

In the beams' eye view of the conventionally used portals it can be seen that these portals encompass a large part of all major salivary glands. This is consistent with the fact that the majority of the patients treated with conventional techniques develop xerostomia (25). Moreover, the conventional portals show an incomplete coverage of the CT based PTV. This is true for the primary as well as or the regional lymphatics. It can, at least partially, be explained by the fact that the lymph node Regions 2–4 include all possible anatomical positions of the lymph nodes (10). Being based on anatomical landmarks and clinical practice (32), conventional portals are actually not well defined.

Consequently, the portals for the 3D-CRT techniques were larger than the conventional portals. It is, therefore, unlikely that application of the CT-based delineation protocol and a 3D-CRT technique based thereupon would result in loss of local control with respect to the historical clinical data.

The present study also showed that sparing of the major salivary glands is possible. This is

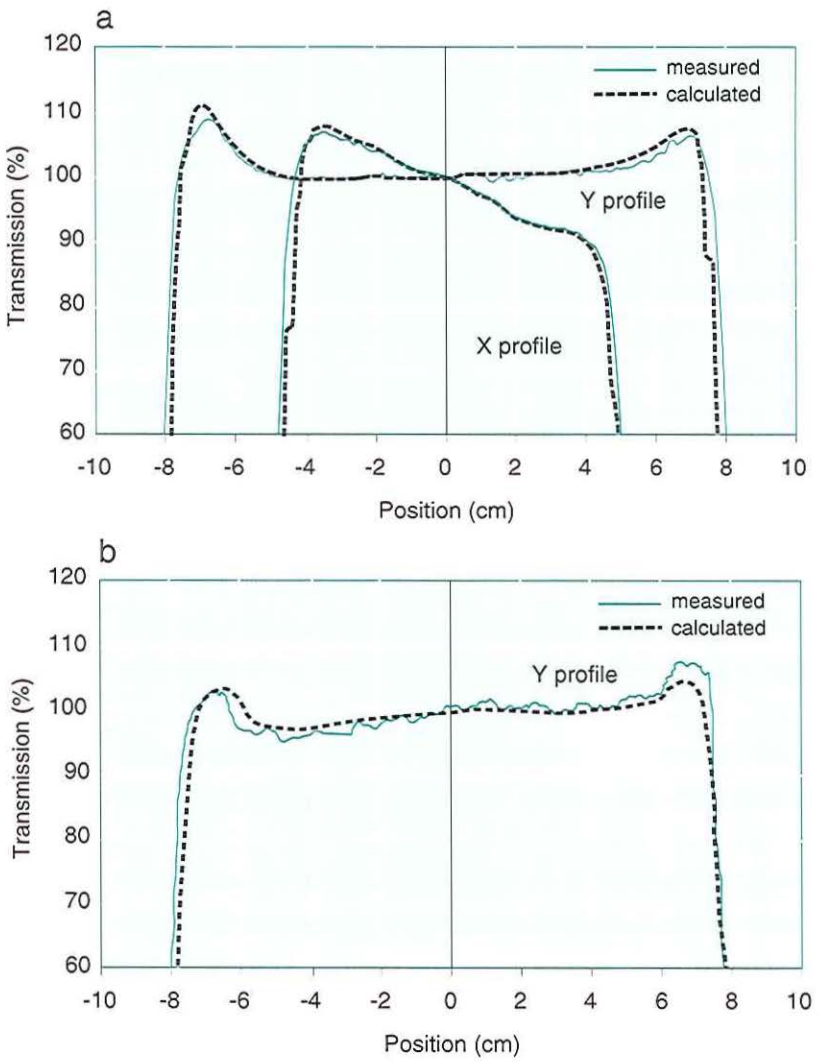

Figure 9. Comparison of measured (film dosimetry, solid lines) and calculated (dotted lines) intensity profiles for a 10-MV beam on the MM50. **a.** through the central axis, in the dorsoventral direction (X) and in the caudocranial direction for tissue compensators (Y). **b.** through the central axis, in the caudocranial direction (cross leaf) using dynamic multileaf collimation.

particularly due to the application of BIM, allowing less 'traditional' beam angles and, by counteracting the beam penumbras at the cranial and caudal field edges, smaller PTV to MLC margins than for open beams. Studies have shown that the latter is feasible (see Appendix II and *Figure 9*) and reduces the dose in surrounding critical structures (33).

The 3D-CRT technique of the tonsil/soft palate carcinoma results in a substantial sparing of the parotid glands. The selected beam angles for PTV1 (*Figure 2*) provide optimal sparing

of these glands in almost all patients. It is known that the submandibular glands contribute considerably to the salivary flow in resting conditions (34). Sparing of the submandibular glands is largely sacrificed in this technique, because the maximum tolerance of the spinal cord (50 Gy) prevents selection of more sparing beam angles.

If better sparing of the submandibular glands is needed, several options exist. First, reduction of the size of the CTV to PTV margin, e.g. by on-line patient setup verification and positioning or improved immobilization (35, 36). Second, the use of brachytherapy or non-coplanar external beams for PTV2. Third, a larger maximum dose to the spinal cord, e.g. to 52 Gy (37), would allow application of additional (salivary gland sparing) beams.

It is anticipated that the 3D-CRT technique of SgL carcinoma results in similar tumor control rates in combination with sparing of all major salivary glands. Particularly, sparing of the parotid glands, which are located at some distance from the primary tumor volume, is good. It remains difficult to spare the submandibular glands because of their partial overlap in the BEV with PTV1, and the proximity to PTV2. This is in agreement with another study (38). Still, with regard to the submandibular glands, 13 out of 15 patients benefit to some extent from the 3D-CRT technique, in terms of dose, DVH, and NTCP. In addition, this technique is simple (two fields), speedy (planning within 2 h, Appendix 1), and dosimetrically feasible; the agreement between computed and measured dose is 2–3% (see Appendix 2). Therefore, in our institution, patients with a larynx carcinoma including the lymph-node regions of the neck, have been treated since July 1998 using the described 3D-CRT technique. Before introduction into clinical practice, the conformal technique for tumors of the tonsil will be improved. Finally, efforts are being taken to develop conformal techniques for other tumor sites of the head and neck.

APPENDIX 1

The program Optimize is based on the algorithm proposed by Ulso (1988), to increase the dose homogeneity in the planning target volume. Iteratively, the program reads a stored (CadPlan) plan. Each ray–line i is traced from the focus through the PTV and the average dose $D_{avg,i}$ in the PTV is computed. After determination of the minimum average dose, $D_{avg,min}$, the fluence of each ray–line T_i is modified, according to:

$$T_{i,new} = T_{i,old} * D_{avg,min} / D_{avg,I} \quad [2]$$

For the first iteration $T_{i,old}$ is 1.

After each modification of the fluence matrices, CadPlan recomputes the dose, using a pencil beam algorithm, which has been shown to be suitable for both blocked and intensity-modulated fields (39, 40). This iterative process continues until improvement of the dose distribution in the PTV is negligible.

Usually, one iteration is sufficient for the techniques proposed in this study, which typically requires 10 minutes (50 CT slices, the PTV delineated on 25, and a 3-field technique). Three minutes are required for each additional iteration (HP 712/166 MHz with 32 MB memory). Computation by CadPlan demands 15 minutes during each iteration (target volumetric calculation) or 1/2 hour (final volumetric calculation). Hence, intensity modulated 3D-CRT requires only 1–2 hours of additional planning time in this study.

APPENDIX 2

Realization of intensity profiles by either tissue compensators or dynamic multileaf collimation: The program Optimize currently stores intensity profiles as tissue compensator files in the CadPlan plan. Profile points are spaced 2.5 mm in both the X- and Y-direction (IEC coordinate system). For dynamic multileaf collimation, the profiles are limited in the Y-direction because of the leaf width of the MLC (1.25 cm for the MM50).

To simulate this difference, tissue compensator plans were generated with Optimize. The tissue compensator profiles were replaced by dynamic MLC profiles, by attributing to each MLC profile the average of the four tissue compensator profiles encompassed by the same leaf. The profile between two adjacent leaves was attributed the minimum of the two overlapping tissue compensator profiles. The differences in the TCPs and NTCPs were computed for 5 randomly selected patients from the present study. The difference between the values of the tissue compensator plans and the dynamic MLC plans was never more than 0.1%. The dose distribution profiles were also measured. *Figure 9* compares computed and measured intensity profiles, using film, for tissue compensators (41) and for dynamic MLC (33). The measured profiles agree with the computed ones within 2–3%. It can be concluded that tissue compensators and dynamic MLC are equivalent, at least from a dosimetric point of view for the head and neck patients in this study.

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CHAPTER 10

Optimization of conformal radiation therapy by intensity modulation

Cancer of the Larynx and Salivary Gland Function

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ABSTRACT

Purpose: *Prevention of damage to critical normal tissues is of paramount importance for the quality of life of patients irradiated for cancers in the head and neck. The purpose of this paper is to evaluate the - parotid gland sparing - 3D conformal radiation therapy technique (3DCRT) in a prospective study in node negative cancer of the larynx.*

Materials and Methods: *Twenty-six patients with node negative squamous cell cancer of the larynx were irradiated by a 3DCRT technique (class solution) to both sides of the neck (elective dose 46 Gy to levels II, III and IV) and primary tumour (70 Gy). Dose distributions of the major salivary glands were correlated with objective (stimulated whole saliva flow, WS) and subjective (questionnaire; visual analogue scale, VAS) salivary gland function. Apart from the clinically used 3DCRT technique, in order to optimize 3DCRT dose distributions, intensity modulated (IMRT) treatment plans were generated for the same patient population. Dose volume histograms of 3DCRT and IMRT treatment plans were analysed and compared.*

Results: *For the 26 patients irradiated with the 3DCRT class solution technique: VAS-scores and questionnaires reached their nadir 3 months post-radiotherapy; WS reached its nadir 6 months post-radiotherapy. WS flow rates improved significantly, but never normalised; two years post-treatment WS measurements were 55% of the pre-treatment values. VAS-scores deteriorated during ERT from 0 pre-treatment to 5.6 immediately post-treatment. Compared to pre-treatment, questionnaires were answered affirmative by increasing numbers of patients. For all patients, IMRT treatment plans resulted in a significant reduction of the dose delivered to the parotid glands compared to the 3DCRT-treatment technique.*

Conclusions: *The class solution for the 3DCRT salivary gland sparing technique is inadequate for fully preserving salivary gland function, given the dose distributions (DVHs) as well as the subjective and objective salivary gland function assessments. The results can be optimized in the future, that is a further reduction of xerostomia can be achieved, by using IMRT techniques focused at sparing major and minor salivary glands.*

CHAPTER 10

10.1 INTRODUCTION

Organ preservation by radiation therapy (RT) in advanced laryngeal cancer has proven to be feasible and safe for selected patients (4,49,68,70). If in head and neck cancer patients radiation is used for organ preservation therapy, xerostomia is the most frequently occurring serious late side effect (18,31,34,53,63,64). This dry mouth syndrome is not to be underestimated; although quite variable in frequency and severity, for some patients it can be a very debilitating sequence of events and significantly reduce the quality of life (QOL) for the remainder of their lives (37). Even in the event of bilateral elective neck irradiation to a dose of 46-50 Gy, often substantial parts of the parotid and submandibular salivary glands are encompassed by the treated neck volume, in particular if a parallel opposed portal beam arrangement is used. Suggestions to overcome this significant clinical problem of xerostomia have been manifold, such as the use of radioprotectors (9,11,12,72), saliva production stimulatory agents (32,36,39,42,51,75,78), saliva substitutes (41,60) and even acupuncture has been tried (7,8,43). But ultimately, prevention remains of pivotal importance. In the design of optimal beam configurations, one should try to reduce the amount of salivary gland tissue, including the minor salivary glands, receiving a significant dose (25-27). Laryngeal cancer seems in this respect the most favourable site for sparing of the major salivary glands (73) since in case of elective irradiation of the neck the cranial edge of the radiation portals can be taken relatively low (45). It was therefore felt worthwhile to try and aim for eliminating the xerostomia problem in this favourable subset of patients. Besides limiting the field size (geometry), one other route to circumvent this problem is to implement 3D conformal radiation therapy (3DCRT) techniques. In fact, the main purpose of this paper is to report on the possible correlation between the dose distributions of the salivary glands and the objective or subjective findings on xerostomia in these laryngeal cancer patients. Finally, in optimizing the clinical treatment of patients with cancer in the head and neck in the future, the CT-contoured data sets of all patients of the prospective clinical study were re-planned using intensity modulated radiation therapy (IMRT) treatment techniques. To establish the value of these optimized conformal therapy techniques, the IMRT dose distributions (dose volume histogram analyses, DVHs) for the elective neck (46 Gy prescribed dose to levels II, III, and IV) and primary tumour (70 Gy prescribed dose to the larynx), were compared to the DVHs obtained with 3DCRT.

10.2 MATERIALS AND METHODS

In 1998 a prospective study was initiated by the department of Radiation Oncology of The Rotterdam Co-operative Head and Neck Cancer Group. All patients with node negative cancer of the larynx, and for whom elective nodal irradiation was indicated, were treated by a 3DCRT technique (class solution). Besides salivary gland function assessments, toxicity of the mucosa, skin and larynx were evaluated; that is, acute toxicity was scored according to RTOG criteria (20), late toxicity according to the SOMA-LENT scale (58). For clarity purposes, except for xerostomia, these data are not reported and discussed in the current paper. The first aim of the study was to objectively and subjectively assess salivary gland function before the initiation of the treatment, during radiation therapy and in follow-up, and correlate these observations to the dose distributions in the major salivary glands (I). The second aim of the paper was to analyse whether optimization of the conformal radiation therapy treatment techniques was feasible (II). For that purpose, first a treatment planning survey on the feasibility and potential benefit of IMRT was conducted among the departments of Radiation Oncology of 3 other major Head and Neck cancer centres (University of Michigan, Ann Arbor, Michigan, USA; University of Gent, Gent, Belgium; Netherlands Cancer Institute, Amsterdam, The Netherlands). Next, all patients of the prospective cancer of the larynx study were re-planned for IMRT, and subsequently, the IMRT results were compared with the 3DCRT treatment planning findings.

10.2.1 Prospective study of patients with node negative cancer of the larynx

10.2.1.2 Patient characteristics: From July 1998 to January 2000, twenty-six consecutive patients with node negative, histological proven squamous cell carcinoma of the larynx were entered in the protocol. All patients were treated with primary external beam radiation therapy (ERT), exclusively. Table 1 summarises patient and tumour characteristics. Patients were staged according to the UICC/AJCC classification, 1997 edition (47). The censor date was January 1, 2002, with a median follow-up of 18 months, from the start of radiation therapy. A detailed account of the clinical outcome, however, will be the issue of a separate report.

10.2.1.2 Pre-treatment planning procedure: ERT was applied in all 26 patients using a 3DCRT treatment technique (class solution). A CT scan was acquired for virtual simulation (ACQSim, Marconi PQ5000) and computer planning purposes (Cadplan versions 2.7.9 and

3.1.2, Varian-Dosetek, Finland). The CT scan was made with the patient in supine - treatment - position, using an immobilising PVC headcast. Primary tumour (larynx), elective neck nodal levels (levels II, III and IV), major salivary glands and the spinal cord were delineated on every 5 mm CT-slice according to the delineation protocol described in previous papers (57,74). The clinical target volume (CTV) was expanded with an additional 3D margin of 5 mm to arrive at the planning target volume (PTV).

10.2.1.3 3DCRT treatment planning larynx and bilateral neck: Per protocol, a total prescribed dose of 46 Gy was delivered to the primary tumour and lymph nodal levels of the neck (PTV1); after 46 Gy the radiation plan was adapted to the PTV of the primary tumour (PTV2) and boosted to a cumulative dose of 70 Gy. Dose prescription and dose reporting was according to ICRU 50 recommendations. A conventional fractionation scheme of 2 Gy per fraction, 5 fractions per week was used. Patients were irradiated with a 10 MV photon beam on the Scanditronix Racetrack Microtron linear accelerator (MM50). The quality index of this 10 MV photon beam equals 0.704 and its percentage depth dose curve is similar to a 7 MV photon beam (15). To allow both for sparing of the parotid glands as well as for adequate target coverage, a non-commercial inverse planning module 'Optimize', devel

Table 1. Patient Characteristics

		Number of Patients			
		All	(%)	Glottic Carcinoma	Supraglottic Carcinoma
Total		26	(100)	7	19
Age (years)	*Median*	62		57	62
	Range	42- 81		54-70	42-81
Male		20	(76.9)	7	13
Female		6	(23.1)	0	6
T-Stage	*T1*	6	(23.1)	0	6
	T2	10	(38.5)	3	7
	T3	9	(34.6)	4	5
	T4	1	(3.8)	0	1
Differentiation Grade	*Well*	3	(11.5)	1	2
	Moderate	15	(57.7)	5	10
	Poor	4	(15.4)	0	4
	Unknown	4	(15.4)	1	3

oped in our clinic, was implemented (21). 'Optimize' aims at target dose optimization and generates fluency profiles, yielding the 95% isodose closely tailored to the actual 3D shape of the PTV, irrespective of the geometrical beam set-up parameters used for treatment planning. To standardise the process of treatment planning and dose volume histogram (DVH) analyses, a 3DCRT class solution was developed. The initial treatment technique used was an isocentric two-field coplanar radiation technique, for which the incoming directions of the beams were tilted 20° ventrally (290°, 70°). The prescribed dose according to the calculated dose fluency profiles of the treatment plan can be delivered by so called 'missing tissue compensators' (TC), mounted on the MM50 multileaf collimator, or by dynamic multileaf collimation (dMLC). Initially, TC were used (six patients). In order to reduce the time consuming production of TC, it was replaced by dMLC (six patients), with a similar dose profile (21). To guarantee continuation of patient treatment in case of a prolonged breakdown period of the MM50, a standardised backup treatment plan was developed.
The backup technique was designed with use of the beam set-up parameters of the initial treatment plan. To allow for the use of the same tight margins around the PTV as with 'Optimize', and in order to reduce the dose delivered to the parotid glands, narrow surdose fields were added to enhance the delivered dose at the PTV1 borders (22,23). The sparing of the parotid glands and the coverage of PTV1 proved to be similar to the 'Optimize' treatment plan; this backup technique was finally implemented in the routine daily practice for the subsequent 14 patients. For PTV2, the 3DCRT booster dose for the primary target (46-70 Gy) was delivered with two coplanar isocentric parallel opposed radiation fields. The cumulative dose was derived from the summation of the two treatment plans and was analysed for the primary tumour, the elective neck nodal levels II, III and IV, the spinal cord and the major salivary glands.

10.2.1.4 Treatment verification: EPID images were produced according to our routine practice (protocol) once weekly to verify and, if necessary, to correct set-up errors. Details of the procedure have been reported before (6).

10.2.1.5 Objective and subjective salivary gland function assessments: Salivary gland function was objectively evaluated by stimulated whole saliva flow measurements (WS) (50,65) and subjectively by queries from a specifically designed simplified questionnaire as derived from previous investigations, as well as by means of a Visual Analogue Scale (VAS). Salivary gland function was evaluated prior to, weekly during, and at regular intervals (1-3-

6-12-24 months) after radiation therapy. Only those patients who gave oral informed consent participated in the salivary flow study. Whole saliva measurements were assessed by the department of Dentistry and Oral Hygiene. For that purpose, salivary glands were stimulated by application of 2% citric acid to the dorsal surface of the tongue and the patient was asked to expectorate during 1 minute in a pre-weighted cup. The saliva volume was gravimetrically determined assuming a specific gravity of 1.0. The total saliva production was expressed in ml/min and as a percentage of baseline flow before irradiation. The questionnaire consisted of three yes / no questions regarding xerostomia: 1) Do you have complaints of a dry mouth?; 2) Do you have a dry mouth when you are eating?; 3) Do you wake up at night due to a dry mouth?

With respect to the VAS scores: a ten-point scale reflects the severity of patient's complaints on the dry mouth syndrome (zero equals no complaints; 10 severe complaints, totally dry mouth). Before, during and after radiation therapy the same questionnaire was to be completed, and patients were asked to mark the Visual Analogue Scale. Factors influencing saliva production, such as smoking (73% more than 10 cigarettes per day) and medication were scored before the start of the treatment. Use of medication, which might influence saliva production, e.g. beta blocking agents and antidepressants, was relatively infrequent (15%). Finally, the objective and subjective findings on salivary gland function are related to the dose distributions (DVHs) obtained from the major salivary glands.

10.2.2 Optimization 3DCRT techniques by intensity modulation

10.2.2.1 Multi-institutional IMRT planning survey single patient: For this purpose we conducted a comparative survey between 4 major Head and Neck Cancer Centers (including Rotterdam), evaluating the potential benefit in terms of salivary gland sparing of intensity modulation when to treat node negative laryngeal cancer. Randomly assigned one patient out of the original 26 consecutively treated laryngeal cancer patients was selected, again with the pre-condition to treat both sides of the neck to 46 Gy and the primary tumour to 70 Gy by highly conformal radiotherapy techniques (IMRT). The planning CT scan of this particular patient with the contoured CTV of the primary tumour, the CTV of the elective neck nodal levels II - IV and the contoured critical structures, was mailed to the three participating Head and Neck Cancer Centers electronically as well as by surface mail (hard-copy). All participating institutions are well experienced with 3DCRT and IMRT in case of cancer of the head and neck. Each participant was asked to use their own 3D treatment planning system for developing an IMRT treatment plan for this pre-contoured laryngeal

cancer case, aiming at maximum sparing of at least one parotid gland. As an additional soft constraint, the generated IMRT plan had to be practical for the own institute, that is, it had to be feasible to execute the developed IMRT treatment plan as a daily routine. With regard to the treatment planning systems, the University of Gent, Gent (Belgium) used *Gratis - Extension Sherouse*, the Netherlands Cancer Institute, Amsterdam (the Netherlands) and the University of Michigan, Ann Arbor (USA) used *UM Plan - Extension Fraass* (33); both are forward treatment planning systems, using step-and-shoot technique. Erasmus Medical Center, Rotterdam (the Netherlands) used *the Helios Extension of Cadplan*, an inverse treatment planning system; dynamic MLC mode.

The findings regarding target coverage and sparing of critical structures, obtained with the 3DCRT class solution used in the Rotterdam prospective laryngeal cancer study, were compared with the IMRT treatment plans generated by the four institutions (including the IMRT Helios treatment plan from Rotterdam).

Each center was asked to provide DVHs of the CTV, of the primary tumour (treated to a cumulative dose 70 Gy), the CTV of the left and right neck nodal levels II, III, and IV (electively irradiated to 46 Gy), and the separately contoured normal tissues such as spinal cord, parotid and submandibular glands. Conform the parameters reported by Eisbruch *et al.* (25-27) the following sets of data were generated: mean dose (D_{mean}, in Gy) of parotid and submandibular glands, left and right separately; the percent volume of the parotid glands receiving more than 30 Gy (V_{30}) and more than 45 Gy (V_{45}); the maximum dose (D_{max}, in Gy) in the CTV of the primary tumour and the elective neck levels (left, right and sumvolume); the percent volume of the primary tumour and elective neck receiving at least 95% (V_{95}) or more than 107% (V_{107}) of the prescribed dose; the CTV-PTV margins in millimetres for both primary tumour and elective neck nodal levels.

10.2.2.2 IMRT planning study 26 patients: In order to confirm these findings (see previous paragraph), we have evaluated the consistency of the results obtained in 26 patients with IMRT over 3DCRT, in terms of target coverage as well as sparing of critical surrounding normal tissues. The built-in inverse planning module *'Helios'* was used to design the IMRT treatment plans. Inverse planning tools allow for homogeneous dose delivery to tumour targets (- 5%, +7 % of prescribed dose), with the 95% isodose sphere tightly encompassing the target. Sparing of normal tissue (e.g. parotid glands) by putting additional dose constraints has now come within reach. Initially, for the prescribed dose of 46 Gy, we implemented hard constraints; that is a maximum of 44 Gy, 40 Gy, and 10 Gy was allowed to be

received by 5%, 10% and 40% of the parotid gland volume, respectively. Somewhat lesser constraints were used in the other major salivary glands, that is a maximum dose of 44 Gy and 40 Gy, in 50% and 90% of the submandibular gland volumes, respectively. At a later stage, during treatment plan optimization, in a few cases some fine-tuning of these constraints was done interactively. Beyond 46 Gy, parallel-opposed fields were used; only 1.5% of the booster dose of 24 Gy was added to the dose already received by the parotid gland volumes.

For all patients, the same standard beam set-up arrangement was used for plan generation: A five-field coplanar isocentric radiation technique with pre-defined incoming beam directions, gantry angles being 232°, 290°, 0°, 70° and 142°, respectively, was used for delivering 46 Gy to neck and 70 Gy to primary tumour. In a few cases the two posterior incoming beams were slightly ventrally tilted to avoid spinal cord overdose (maximum cord tolerance: 50-52 Gy). All dose distribution calculations were performed using Cadplan (Dosetek-Varian v. 6.1.5), after the fluency profiles and beam weights were generated by the built-in inverse planning module *'Helios'*. For final dose distribution assessment, in particular regarding the major salivary glands, the same parameters were analysed as stated in the previous paragraph.

10.3 RESULTS

10.3.1 Prospective study of patients with node negative cancer of the larynx

10.3.1.1 Locoregional control: Censor date January 1, 2002. All patients completed radiation therapy without treatment interruptions. In brief, the early clinical results are as follows: Follow-up varied with a median of 18 months and ranged from 2.4 (early death) to 39.6 months. Eleven patients relapsed locally after a median of 6.3 months (range 3.2 - 23.4 months). All patients underwent salvage surgery for recurrent disease, which rendered them tumour free, except for two patients, who developed a regional recurrence at a later stage. One patient developed distant metastasis during follow-up. In summary: a one- and two-year actuarial disease-free survival of 69% and 57%, and an overall survival of 88% and 85%, respectively, calculated according to Kaplan-Meier, was found. Given the short follow-up, a more detailed analysis is at this time inappropriate and also beyond the scope of the present paper; in fact, it will be the subject of a future report.

10.3.1.2 Objective and subjective salivary gland function assessments: Eighteen patients (69%) consented in participation in the WS flow study (*Figure1*). Pre-treatment median whole saliva flow was 1.96 ml/min (range 0.06-6.25). Salivary flow decreased to 37% of basal flow at six and 12 months post-irradiation (nadir, 11 patients); thereafter partial recovery was observed with a median of 55% of pre-treatment flow at two years post-treatment (nine patients). Subjectively, complaints of the dry mouth syndrome, as reflected by both VAS score and questionnaire, increased during radiation therapy and remained elevated during follow-up (*Figures 2* and *3*). The median VAS increased gradually from zero pre-treatment (18 patients) to 6.1 at end of treatment (21 patients). The maximum VAS score was reached at three months post-irradiation, median 7.0, thereafter VAS scores decreased gradually to median 3.2 at one year post-treatment (17 patients) and 5.2 at two years post-treatment (15 patients). The questionnaire on the dry mouth syndrome reflects that over time an increasing number of patients complained of a dry mouth; highest numbers of affirmative answered questionnaires was reached at three months post-irradiation. A significant correlation was found between VAS and the questionnaire (p-value <0.001, GEE-regression Generalised Estimating Equations], i.e. an autoregressive correlation adjusting for the longitudinal character of the data), whereas no significant relationship was found between sali-

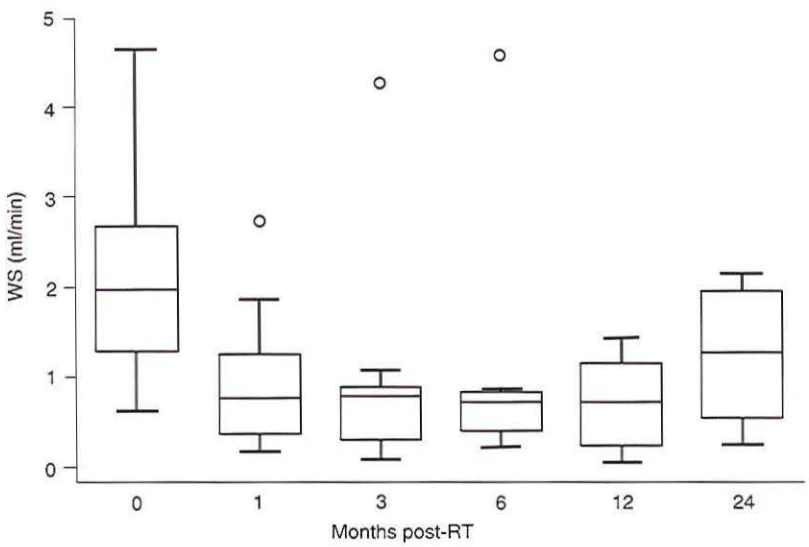

Figure 1. Whole Saliva Flow Measurements (WS) in ml/min. Boxplots graphically display median and interquartile range. Box = 25th to 75th percentiles. Line = median. Error bars = cases not more than 1.5 times the interquartile range beyond the quartiles. Circles = extreme examples. X-axis: 0 = baseline point in time before start of treatment.

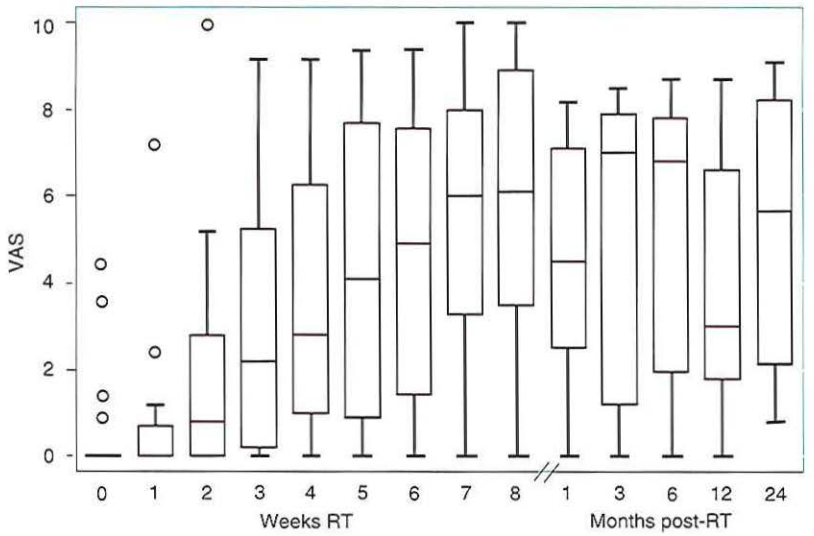

Figure 2. Visual Analogue Scale (VAS). Boxplots graphically display median and interquartile range. Box = 25th to 75th percentiles. Line = median. Error bars = cases not more than 1.5 times the interquartile range beyond the quartiles. Circles = extreme examples. X-axis: 0 = baseline point in time before start of treatment.

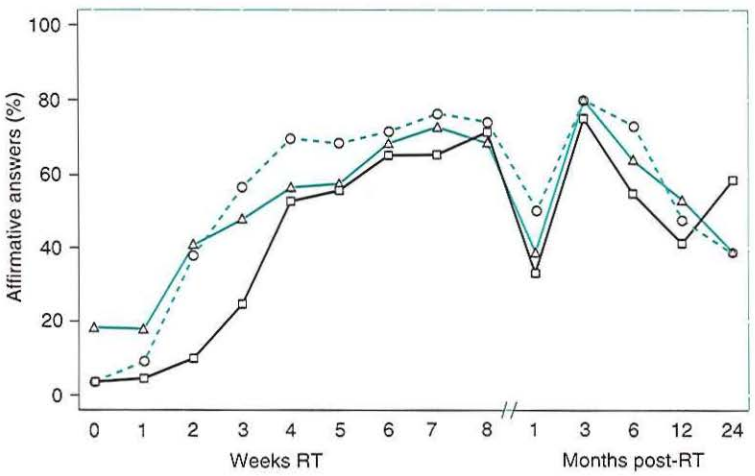

Figure 3. Three-Item Questionnaire. O = Do you have complaints of a dry mouth? ❑ = Do you have a dry mouth when you are eating? Δ = Do you wake up at night due to a dry mouth? X-axis 0 = baseline, before start of treatment. Y-axis = percentage of patients with affirmative answers to the posed questions.

vary flow rates and the questionnaire.

10.3.1.3 Dose volume histogram analyses parotid glands: A mean dose of 29.2 Gy and 28.7 Gy for the right and left parotid gland, respectively, was found. The mean percent vol-

ume of the parotid glands receiving more than 30 Gy (V_{30}) was 54% and 53%, for right and left parotid gland, respectively. The mean percent volume of the parotid glands receiving more than 45 Gy (V_{45}) was 39% and 37% (right and left parotid glands, respectively). For 13 patients at least one of the thresholds (D_{mean}, V_{30}, V_{45}) was not surpassed for one or both parotid glands. Only six patients fulfilled all three criteria for at least one of the parotid glands, of whom two patients fulfilled criteria for both parotid glands. Table 2 summarises these results in relation to the volume and dose thresholds as reported by Eisbruch *et al. Figure 4* illustrates the (lack of) correlation between the dose distribution parameters (D_{mean}, V_{30}, V_{45}) and the objective (WS flow) and subjective (VAS) salivary gland function parameters at one- and two years post-treatment.

10.3.2 Optimization 3DCRT Techniques by intensity modulation

10.3.2.1 Multi-institutional planning survey single patient: For a summary of the results with respect to the various IMRT treatment planning parameters, see Table 3. With regard to the CTV of the primary tumour: the V_{95} by IMRT ranged from 97-99%, with minimum doses in the CTV ranging from 60-64 Gy and maximum doses ranging from 73-77 Gy. The elective neck nodal levels were adequately covered by the 95% isodose (V_{95}) in all treat-

Table 2. Dose distribution of the parotid glands

	Thresholds	Right parotid gland	Left parotid gland	Right and Left parotid gland	Criteria conform Eisbruch&
A	D_{mean}	29.2 Gy	28.7 Gy	-	≤ 26 Gy
	patients ≤ 26 Gy#	8	11	6	
B	V_{30}	54 %	53 %	-	≤45 %
	patients ≤ 45 % *	8	9	5	
C	V_{45}	39 %	32 %	-	≤24 %
	patients ≤ 24 % *	6	2	2	
	patients ≤ A and ≤ B and ≤ C	6	2	2	
	patients ≤ A and/or ≤ B and/or ≤ C	8	11	6	

Number of patients not surpassing the threshold of 26 Gy mean dose for the parotid gland, according to Eisbruch (26). * Number of patients in which a maximum 45 % and 24 % of the parotid gland volume was treated to a dose of ≥ 30 Gy and ≥ 45 Gy, respectively (26). &Reference thresholds for stimulated parotid salivary flow.

ment plans (range 95-99%). Concerning the dose to the parotid glands, every one of the co-investigator institutions, including Rotterdam when using the *'Helios'* (inverse planning) module of Cadplan, reached a D_{mean} to the parotid glands of 26 Gy or less in at least one of the parotid glands. For all four investigator institutions, the partial volumes of the parotid glands receiving a dose of 30 Gy and 45 Gy remained below the thresholds in at least one

Table 3. Results of multi-institutional comparative treatment planning study

	Amsterdam *IMRT*	Ann Arbor *IMRT*	Gent *IMRT*	Rotterdam *IMRT*	Rotterdam *3DCRT*
CTV-Larynx					
D_{mean}	72 Gy	70 Gy	70 Gy	68 Gy	71 Gy
D_{max} *	77 Gy	76 Gy	73 Gy	74 Gy	73 Gy
D_{min} †	63 Gy	60 Gy	64 Gy	64 Gy	69 Gy
V_{107} (70 Gy) ‡	7%	0%	0%	0%	0%
V_{95} (70 Gy) *	97%	98%	98%	99%	100%
Neck Total					
V_{107} (46 Gy)	3%	0%	0%	1%	0%
V_{95} (46 Gy	97%	99%	95%	99%	99%
Parotid Left					
D_{mean}	21 Gy	29 Gy	22 Gy	22 Gy	24 Gy
D_{max}	56 Gy	54 Gy	53 Gy	64 Gy	63 Gy
D_{min}	1 Gy	0 Gy	0 Gy	2 Gy	1 Gy
V_{30} ¶	31%	51%	42%	34%	44%
V_{45} §	13%	21%	9%	15%	29%
Parotid Right					
D_{mean}	20 Gy	20 Gy	20 Gy	20 Gy	24 Gy
D_{max}	50 Gy	53 Gy	53 Gy	61 Gy	60 Gy
D_{min}	1 Gy	0 Gy	0 Gy	2 Gy	1 Gy
V_{30}	31%	39%	35%	29%	45%
V_{45}	9%	10%	5%	11%	25%
Submand Left					
D_{mean}	49 Gy	53 Gy	53 Gy	51 Gy	52 Gy
Submand Right					
D_{mean}	49 Gy	49 Gy	49 Gy	51 Gy	53 Gy
Spinal Cord					
D_{max}	45 Gy	37 Gy	38 Gy	45 Gy	48 Gy

*D_{max}: maximum dose received; † D_{min}: minimum dose received; ‡ V_{107}: percent volume receiving ≥ 107% of prescribed dose; *V_{95}: percent volume receiving ≥ 95% of prescribed dose; ¶ V_{30}: percent volume receiving ≥ 30 Gy; § V_{45}: percent volume receiving ≥ 45 Gy.

parotid gland, and were significantly lower than the 3DCRT dose distribution data generated by the Rotterdam group (this paper).

10.3.2.2 IMRT planning study 26 patients: With IMRT the mean parotid gland dose was 23.0 Gy, compared to 28.9 Gy with 3DCRT, an absolute mean dose reduction of 19.4 ± 7.5 % (1 S.D.). The mean parotid gland volume receiving 30 Gy was less with IMRT (38.1 and 53.7 %, for IMRT and 3DCRT, respectively), the same was seen for the volume receiving 45 Gy (22.5 vs. 38.0 %, for IMRT and 3DCRT, respectively).
Both parotid gland volumes were better spared with IMRT (on average a 15% volume reduction receiving 30 Gy) (*Figure 5*). In all patients a superior target conformity index (TCI) was achieved with IMRT planning, both for 46 Gy and for the additional 24 Gy boost treatment (*Figure 6*).

10.4 DISCUSSION

10.4.1 Radiation therapy treatment intensification: There are a number of ways to increase the effectiveness of radiation in cancer of the head and neck. One way is to increase the biologically effective dose to the clinical target volume by reducing the overall treatment time (5). Furthermore, during the past decade altered fractionation schemes per se (hyperfractionation and accelerated fractionation) and various combinations, have been clinically tested (4,9,10,30,48). For example, an 8% increase in locoregional tumour control has been found in favour of hyperfractionation and acceleration by concomitant boost technique (35). Finally, 3DCRT and IMRT are means, which allow for applying of high doses of radiation through minimising toxicity (14,33,77). One can then dose-escalate, taking advantage of existing dose-effect relationships in solid tumours. Obviously dose-escalation and reduction of overall treatment time (acceleration) have their limitations and in fact the various altered fractionation schemes are carefully designed not to surpass tolerance of normal structures (44,67). An interesting current approach to increase effectiveness in head and neck cancer treatment is radiating tumours with concomitantly applied chemotherapeutic agents (chemoradiation) (2,3). Pignon found in his meta-analysis an overall absolute 5 year survival benefit of 8% after concomitant chemoradiation for malignancies in the head and neck region (59). However, the acute complication rates are not negligible either; El-Sayed *et al.* report a significant increase in overall toxicity, in particular for mucositis, in the

chemoradiation group versus radiation therapy alone (relative risk of 2.17 and 2.97, respectively, after combined modality treatment, $p < 0.001$). This increased toxicity is also reflected in an increased number of days of treatment delay and even toxic deaths (relative risk 2.87 and 2.40, $p < 0.001$) (29). Thus, it seems fair to conclude that with the intensification of the treatment schedules, better control rates are to be expected but there is a definite need for exploring ways to overcome, or even better, to prevent the associated increase in acute (mucosal) toxicity.

10.4.2 Xerostomia - dose volume thresholds: With regard to the toxicity profile of radiation therapy for cancer in the head and neck, the most frequently occurring permanent late side effect, by far, is the dry mouth syndrome (71). It is essential to eliminate (reduce the degree of) xerostomia when trying to maintain or improve QOL. Currently there are a number of papers addressing this important issue of trying to preserve salivary gland function by sparing (parts of) the major salivary glands from receiving too high doses of radiation. Eisbruch *et al.* were able to reduce the mean dose to the contralateral parotid gland to 32% of the prescribed tumour dose by using static multisegmental intensity modulation, resulting in

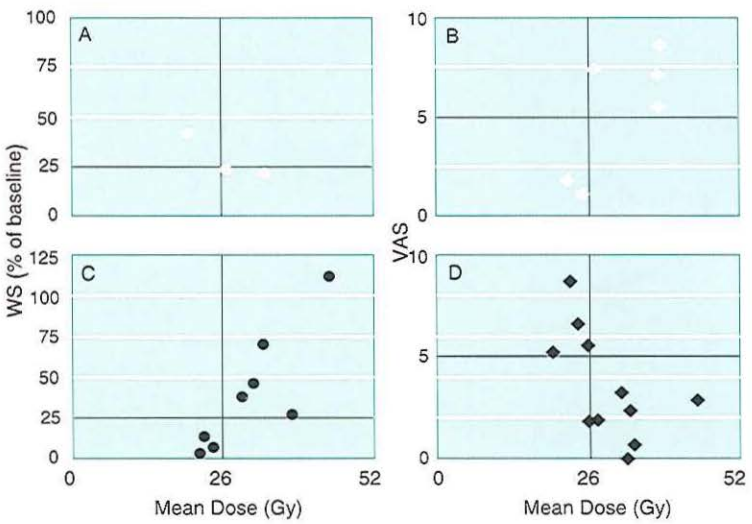

Figure 4. Salivary gland function analysis. The upper two panels (A, B) of the diagram show datasets in which a positive correlation between D_{mean} of the parotid glands and WS or VAS can be depicted (three and six patients, respectively). The lower two panels (C, D) of the diagram show datasets in the which dose distribution of the parotid gland do not correlate with outcome on xerostomia (objectively or subjectively) (8 and 11 datasets, respectively, 14 patients). Solid black horizontal and vertical lines represent thresholds for D_{mean} (26 Gy), VAS and WS (25% of baseline flow).

higher (un)stimulated salivary flow rates of the 'spared' parotid gland (25). In a later publication Eisbruch *et al.* established dose thresholds for the parotid gland: mean dose ≤ 24 Gy and ≤ 26 Gy for unstimulated and stimulated salivary flow, respectively. Also partial volume thresholds were established: 67%, 45%, 24% of the parotid gland volume receiving ≥15 Gy, ≥ 30 Gy, ≥ 45 Gy, respectively. They observed that if the dose to the parotid glands exceeds (one or more of) these thresholds, parotid salivary flow would significantly decrease (26). Chao *et al.* report excellent sparing of the parotid gland by IMRT, with only 27% (± 8%) of parotid gland volume receiving a dose ≥ 30 Gy, without compromising the dose delivered in the target volume (16). In a prospective study of the same authors a dose-response correlation between (un)stimulated WS flow and mean dose delivered to the parotid glands was found, as well as a significant correlation between WS flow rates and QOL. They predict a slightly higher threshold dose to the parotid gland than Eisbruch *et al.*: that is, 32 Gy for stimulated WS (17). Apparently IMRT is one suggested treatment approach to prevent xerostomia. Many other suggestions to manipulate the degree of xerostomia have been

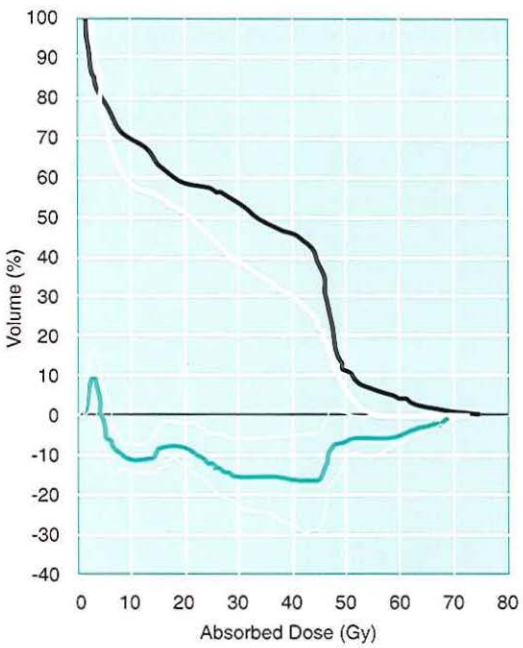

Figure 5. Mean DVHs of the parotid glands of 26 node negative laryngeal cancer patients, treated by 3DCRT to neck levels II, III, IV to a prescribed dose of 46 Gy, and primary tumour to a prescribed dose of 70 Gy (class solution), are depicted: 3DCRT = black upper line in graph; dMLC IMRT = white line. The grey bottom line depicts the improvement of IMRT over 3DCRT in terms of sparing of parotid glands (thin bottom white lines: ± 1 sd). As depicted in the figure, parotid gland volumes were better spared with IMRT (on average a 15% volume reduction).

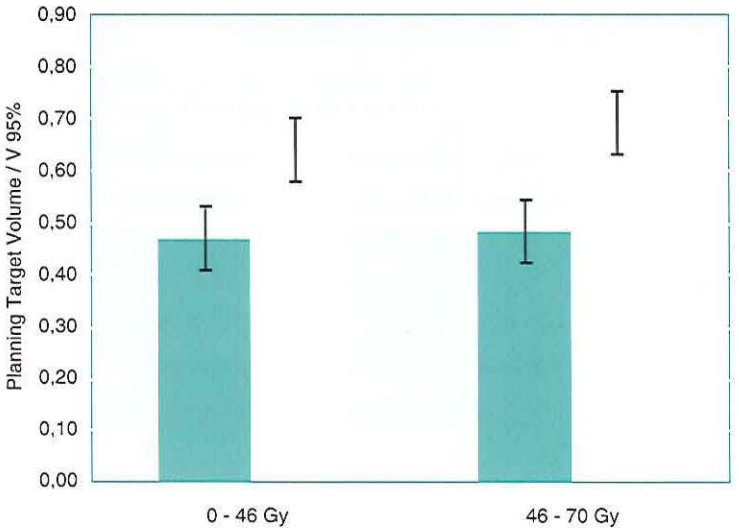

Figure 6. TCI = target conformity index = planning target volume /V95. Not only were the parotid glands spared to a greater extent with IMRT, also, in all 26 patients a superior TCI was obtained; with IMRT planning, both for 46 Gy (neck) and for the additional 24 Gy boost (primary tumour). V95 = volume treated to a dose of at least 95% of the prescribed dose. 3DCRT in grey; IMRT in white.

brought forward. For example, saliva substitutes may decrease symptoms of xerostomia (60). Pilocarpine given either concomitantly with radiation therapy or post-irradiation as a stimulant of remaining functioning salivary glands, may relieve symptoms of xerostomia as well as increase saliva production ($p < 0.05$) as compared to placebo or to a control group (42,78). The role of radioprotectors, such as Amifostine, still remains to be established in clinic. Amifostine is known for its ability to reduce acute xerostomia (xerostomia in RT versus RT + Amifostine; 78% versus 51%, respectively; $p < 0.0001$) as well as chronic xerostomia (57% versus 34%, $p = 0.002$) (11) and increases the QOL post-irradiation (± Amifostine, $p<0.05$) (72). However, the issue on tumour growth or tumour protection is still unclear and controversial (52).

The aim of the current investigation was to objectively and subjectively evaluate salivary gland function before the initiation of the treatment, during radiation therapy and in follow-up, and correlate these observations to the dose distributions of the major salivary glands. This was studied in a prospective fashion in 26 patients with node negative cancer of the larynx, using conformal radiation therapy as a means to reduce the dose to the major salivary glands. All patients entered in the study were treated by the same at the time in Rotterdam available 3DCRT technique (class solution). Preliminary results of the 26

patients depict a disease-free survival of 69% and 57%, and an overall survival of 88% and 85% at one and two years, respectively. Treatment planning was characterised by tightly shaped beam configurations around the PTV, with a margin of 4-8 mm from the PTV to the leave positions. In retrospect, we verified the accuracy of the beam configurations in all 26 patients. For that purpose primary tumour localisation and the precise localisation of recurrent disease, taking the surgical and histological data as well as the treatment planning data into account, have been retrieved and reconstructed relative to the boundaries of treatment portals used. A detailed failure analysis generated four 'marginal' local recurrences at the edge of the radiation portal, and one 'out-field' regional recurrence. The failure analysis illustrates once again the caveat of treating (extensive) tumours by 3DCRT techniques with very tight margins.

*10.4.3 Objective and subjective salivary gland function assessments:*With respect to salivary gland sparing, the findings of this prospective clinical study for the whole group are as follows: D_{mean} 29.2 Gy and 28.7 Gy, V_{30} (mean) 54% and 53%, with V_{45} (mean) 39% and 32%, for the right and left parotid gland, respectively. All values exceeded, albeit only slightly, the thresholds of Eisbruch *et al.* (see also previous paragraph) (26). Despite this, a measurable salivary flow rate of 55% of baseline (1.08 ml/min) remained, which implicates considerable preservation of salivary gland function. The time course of the whole saliva flow rate is quite similar to the data that can be retrieved from the literature (54); a minimum flow rate shortly after initiating the radiation, and increasing flow rates at one and 2 years post-irradiation (*Figure 1*).

However, the results of both the nadir (37% of basal flow) and the results at two years (55% of pre-treatment value), are far better than in the case of inadequate sparing, when salivary flow rates of less than 10% of the baseline values can be anticipated (13). According to the VAS-scores, the xerostomia related complaints were appreciated by the patients as being 'moderately severe' (median VAS value 5.2 at two year). Apparently, in summary, the WS flow rates do recover partially post-irradiation, but the increase is insufficient to result in considerable decrease of xerostomia (i.e. decrease in VAS scores).

We could not establish a significant correlation between dose-volume data of the parotid glands and salivary flow; this could be explained in several ways (*Figure 4*). First, the thresholds were only marginally surpassed. In 13 out of 26 patients, one up to three of the 'Eisbruch criteria' (V_{30}, V_{45}, D_{mean}) were met for at least one of the parotid glands.

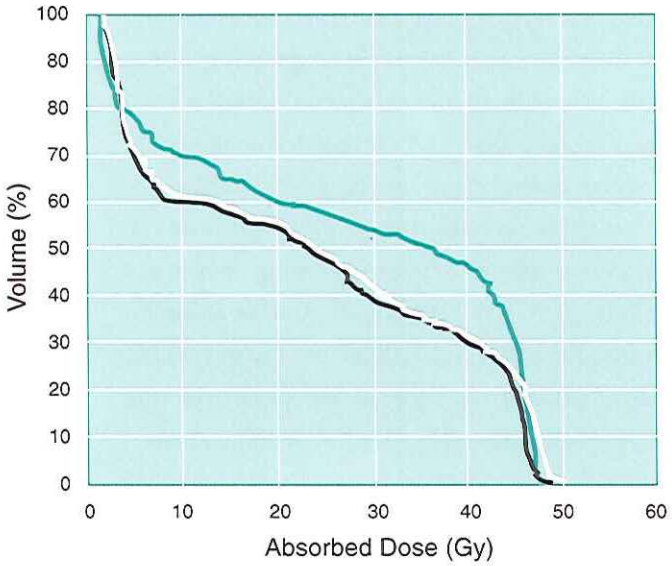

Figure 7. Mean DVH of parotid glands. IMRT by dynamic multileaf collimation (dMLC) was also compared to IMRT using a step-and-shoot technique in five patients. As shown by the graph, the curves of step-and-shoot for the parotid glands in case the neck was treated to a dose of 46 Gy, were super-imposable to the mean DVH obtained by dMLC IMRT (solid black line = dMLC IMRT; white line = step-and-shoot IMRT), and superior to 3DCRT (grey upper line).

Moreover, if the threshold value of Chao *et al.* had been taken as a reference (17), the D_{mean} of our patients would have even stayed below the threshold of 32 Gy. Next, salivary flow rates show a large inter- and intra-individual variation (36), whereas DVHs obviously vary little in our case, given the standardisation of the 3DCRT technique (class solution). Scintigraphic evaluation (SPECT) of salivary gland function, as reported by Van Acker *et al.* (1) also substantiate this inter-individual variation in function. Finally, the dose-volume values in this study were correlated with whole saliva measurements, reflecting the flow of all major and minor salivary glands. However, the various types of glands differ in their capacity of producing saliva and some believe they may even differ in their radiosensitivity. For example, it is well known that the submandibular / sublingual glands are the main source of saliva in resting (at night; no stimulation) conditions, and the dose to these glands might therefore have serious implications for the dry mouth syndrome (13). In summary, it can be argued that the borderline threshold values, the inter- and intra-variability of the salivary glands function, and whole saliva type of flow measurements are possible considerations for the lack of correlation in most patients between dose-volume and salivary flow (*Figure 4*).

The VAS-score and the three-item questionnaire seem to adequately reflect the xerostomia-related complaints. They are significantly related, as is shown by the identical shape of the curves depicted in *Figures 2* and *3*. An increasing mean VAS score correlates with an increasing number of patients answering the questionnaire on dry mouth complaints affirmative. VAS values reach maximum scores around three months post-irradiation and decrease gradually after three months, but never normalise (*Figure 2*). A significant relationship between VAS and WS flow rates was not found in our patient group, which is in concordance with observations from others (26,31,65). Finally, apart from the amount of saliva, its composition, is an important determinant of oral comfort and health (24). For instance, the mucins (glycoproteins) play an essential role as they are crucial for lubrication of mucosal membranes. These mucins are predominantly produced by the minor salivary glands and the sublingual salivary gland and to some extent by submandibular glands. The increasing body of evidence on the importance of the minor salivary glands for maintaining a sufficient basic salivary flow and the fact that one is currently able to measure the function of these glands separately (28,40,66,76), has important implications for the future. Dose and volume thresholds have to be established for all types of major as well as for the minor salivary glands; also, the relative importance of the various glands with respect to xerostomia has to be re-established (13,62).

10.4.4 Optimization treatment planning: The less than optimal dose distribution (DVH) results of the Rotterdam 3DCRT larynx study prompted our department to optimize the currently used techniques. One obvious way one can improve on the results is by implementing IMRT. To explore this potential benefit for future patients, first a comparative treatment planning survey between four major Head and Neck institutions was performed. A data set with the pre-contoured CT-slices of a randomly assigned patient treated previously by 3DCRT in the prospective larynx study, was used by all four participants of the planning survey. The dose distribution data of the IMRT treatment planning survey showed a significantly better sparing of the major salivary glands (unilaterally or bilaterally) for IMRT as opposed to 3DCRT, without compromising the dose to the target, for all 4 institutions (*figures 5* and *6*). To confirm the adequate target coverage and improved sparing by IMRT in this single case of the multi-institutional planning survey, DVHs obtained with IMRT treatment techniques for conformal radiation therapy of elective neck levels II, III, and IV on both sides of the neck (46 Gy) and the primary tumour (70 Gy, larynx) have been computed for all 26 patients. Compared to 3DCRT, a significantly improved sparing of the

parotid glands was found, without compromising the target coverage (*Figures 5 and 6*). Also, although we favour the dMLC technique in our institution, to be complete on the matter, IMRT by dynamic multileaf collimation (dMLC) was also compared to IMRT using a step-and-shoot technique in five patients. In brief, dose-volume findings with regard to IMRT step-and-shoot for the neck levels II, III and IV to a dose of 46 Gy were super-imposable to similarly the obtained dose distributions data obtained of by dMLC IMRT and superior to 3DCRT (*Figure 7*).

10.5 CONCLUSIONS

Xerostomia appeared not sufficiently prevented by 3DCRT techniques, even in the event of node negative laryngeal cancer. Taking the dose-distribution data, sparing of the parotid glands is improved when using IMRT based treatment techniques. Whether using IMRT techniques will lead to an increased therapeutic window remains to be established. We did not find a significant relationship between generated dose-volume data of the parotid glands and the degree of xerostomia. The various other subjective and objective methods to assess the grade of xerostomia did not correspond with dose-volume histograms of the parotid glands either. This raises the question how to evaluate xerostomia in future trials. To predict the outcome of salivary flow post-irradiation and the subjective assessment of a dry mouth, that is which objective parameter should be used best and thus, which constraint should be used for IMRT based treatment planning techniques, is still a matter of debate. It is argued that the role of the minor salivary glands for xerostomia should be taken into account.

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CHAPTER 11

Discussion and future prospects

11.1 INTRODUCTION

In the treatment of head and neck cancer by radiation therapy, xerostomia is the most frequent occurring late side effect with important implications for the quality of life (1-9). Radiation-induced mucositis is an important dose-limiting acute side effect, frequently hampering the introduction of intensified treatment modalities, such as chemoradiation and accelerated fractionation schedules (AF) (10-15). In this thesis examples of both acute (e.g. mucositis) and late (e.g. xerostomia and optic neuropathy) side effects of radiation therapy are addressed. Normal tissue complications such as these are the main reason for investigating new radiation therapy techniques aiming at prevention (16,17). In fact, prevention of especially late normal tissue complications can be achieved with the now rapidly developing new radiation therapy techniques, such as 3D conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT)(18-21). In the following sections, first the preconditions of having adequate target definitions, i.e. standardization, with special emphasis on the definitions for the cervical lymph node levels is reviewed. Next, the importance of recording and grading of normal tissue complications with respect to developing biological constraints for inverse planning modalities is discussed. Finally, the future concerning optimal ways of sparing, i.e. prevention of xerostomia, mucositis and other complications, as well as dose-escalation, is discussed.

11.2 TARGET VOLUMES

11.2.1 Target volumes – general: The ICRU-50 report describes in detail definitions regarding volumes of interest in radiation therapy planning: i.e. the gross tumor volume (GTV), the clinical target volume (CTV), the planning target volume (PTV), the treated volume, the irradiated volume and the organs at risk (OAR) (22,23). The delineation of the GTV and CTV are based on anatomical, topographical, and biological considerations. The PTV is a geometrical concept of which the delineation in principle can be automated. The fundamental principles of 3D conformal radiation therapy are to define the target volume(s) in three dimensions and subsequently to shape the treatment volume to the target(s) (24). Accurate targeting is becoming increasingly important as techniques move forward towards higher conformality (3DCRT / IMRT) (25). The anatomy of the head and neck, however, is

complex; sophisticated treatment planning approaches require a great deal of training and effort to finally arrive at the appropriate target volumes (20,26-28). Image registration of different modalities will hopefully enhance the accuracy of GTV delineation in head and neck tumors as already has been demonstrated for brain tumors and prostate cancer (29). Knowledge of tumor growth patterns and lymph node involvement is essential in deciding on the correct CTVs. Unfortunately, substantial differences (still) exist between CTVs when contoured by different physicians for a particular case (30-33). To improve on the accuracy of the delineation of the CTV, new technical developments in functional imaging (PET, SPECT, functional MRI) and image registration will in the future help to overcome part of this problem (34). Patient and organ movements are of concern when delivering conformal radiation therapy. Dose escalation requires that the geometric uncertainties in treatment and the associated margins used in treatment planning be reduced as much as possible. This underscores the importance of good immobilization techniques and the use of realistic planning margins (35-42). Finally, there is this associated risk of adverse late sequelae when too generous margins are used, which could impair to some extent the application of IMRT in dose-escalating clinical procedures (43).

11.2.2 Clinical target volume neck: Regardless of tumor site and size, the cervical lymph nodes are a pivotal prognostic factor in cancer of the head and neck. Relevant questions in the treatment of head and neck cancer are whether or not to treat the cervical nodes electively and by which modality; also, in case of metastatic nodes, which lymph node levels to treat, by which modality and, in case of irradiation, to what dose. There is still some controversy with regard to the proper treatment of the non-involved (N0) neck (44-47). In general, if the risk of occult cervical metastasis exceeds 15%, it is generally agreed upon that the neck should be treated, either surgically or by radiation therapy. The preferred modality generally depends on the elected treatment mode for the primary tumor. Both have their own specific modality related morbidity (48,49). For early staged tumors, elective neck irradiation and elective neck dissection are equivalent in the control of subclinical neck disease when the primary tumor is adequately controlled, with cervical failure rates reported in the order of 0-10% (46,50-52). In general for metastatic lymph nodes of a size of more than 3 cm, surgery and postoperative irradiation is the treatment of choice. The head and neck area has an abundance of lymph nodes. Of the approximately 800 lymph nodes in the body, about 300 are located in the neck. In patients with previously untreated squamous cell carcinoma, particularly in early staged disease, the topographic distribution of lymph node

metastases appears to occur in an orderly predictable sequence as demonstrated by the anatomic studies of Rouvière of 1938. The clinical study of Lindberg of 1972 (53), later on confirmed by studies of e.g. Skolnik *et al.* (55,56), described the pattern of the most frequently involved lymph node groups for various tumor sites. Further evidence for the patterns of lymph nodal metastases was provided by Shah in a retrospective study on radical neck dissection specimens. Rouvière was the first to develop a classification system for the cervical lymph nodes based on anatomical landmarks that had their origin in the superficial triangles of the neck, areas which were easily accessible to palpation (57). In 1981 head and neck surgeons at Memorial Sloan Kettering Cancer Center proposed that this anatomically based terminology should be replaced with a 'level' based system, in which each level contained several lymph node groups (55). This is now the most widely accepted nomenclature for categorizing the lymph node groups in the neck. However, not all clinically relevant lymph node groups are incorporated in this level system; for example, the retropharyngeal lymph nodes are not represented in levels I-VI.

The discussion on specificity and sensitivity of different diagnostic methods to detect neck nodal metastases is beyond the scope of this chapter; suffice it to say that the most commonly used methods such as palpation, ultrasound and CT/MRI are still largely based on size criteria (58-62). Many new methods currently available may further improve diagnostic accuracy in the near future, such as (combinations of) Positron Emission Tomography (PET) / new contrast agents / radiolabeled monoclonal antibodies for immuno imaging of cervical metastasis (SPECT), molecular genetics (e.g. search for molecular markers)etc (63-66).

If the final decision is made that the negatively staged (N0) neck is to be irradiated electively, standardization of the CTV on CT is of greatest importance. For surgery of the cervical lymph nodes, standardized definitions of neck dissections are available as developed by the task force of the American Academy of Otolaryngology-Head and Neck surgery (AAO-HNS). This so-called classification of Robbins is based on surgical (anatomical) boundaries of the levels I-VI as proposed by the Memorial Sloan Kettering Cancer Center group (67,68). A prerequisite for CT-based definitions of the (non-involved) neck, so that 3DCRT/IMRT can be implemented, is that the CTV for radiation therapy should include at least the same lymph node groups as those which would have been removed by a (selective) neck dissection (69-73). In chapters 3 and 4 the translation process of the surgical level definitions to CT-based definitions for radiation therapy planning is described. Differences between a CTV for neck dissections and a CTV for radiation therapy is that the latter always contains

non-lymphatic structures, such as the internal jugular vein, the carotid artery and the accessory nerve. In the further refinement of the Robbins classification cq level system, levels II, IV and V are divided into two sublevels (69). These subdivisions are based on the biological behavior of tumors and patterns of lymph node metastases spread; these are helpful in choosing the correct CTV for selective neck dissections. Despite the clinical importance of these subdivisions, radiologically it remains difficult to distinguish level IVA from IVB and level IVA from level VI. Finally, the distinction of level V in two or three subdivisions is also a point of discussion. In this thesis level V is divided in an upper, middle and lower subgroup corresponding with the cranial and caudal borders of level II, III and IV. This is in accordance with the AJCC staging system and is also used by Som *et al.*(72). The AAO-HNS chooses for a division of level V in an upper level VA and a lower level VB, which is probably more logical as the upper AJCC level contains few if any nodes and correlates better with the biologic behavior of tumors. Moreover, as stated by Rouvière: 'any distinction between the upper internal jugular nodes (IIB) and the upper spinal accessory nodes (V) may be impossible, as the group of nodes merges at this level'. In conclusion, standardization of the CTV of cervical lymph nodes in head and neck cancer patients is crucial for both surgeons and radiation oncologists. Radiological (CT-based) definitions of the lymph node levels are necessary for both staging and radiation therapy planning.
Nodal classifications are continuously evolving, with modifications being proposed to better allow physicians to plan the most appropriate therapy for neck nodal disease. Correlation between clinical, surgical and radiological findings must be accurate. Multidisciplinary input for further refinements of the classification system remains essential.

11.2.3 Imaging to improve delineation variation: At this time, 3D treatment planning is CT based. The treatment planning process will benefit from CT technologies which yield more specific information on the extent of the gross tumor volume (GTV). Imaging is currently incapable of directly detecting areas of subclinical tumor involvement (CTV).Therefore efforts should focus on the imaging of normal tissues that are at risk for microscopic tumor involvement, such as the precise location of the lymph nodes, the nerves (perineural extension) and vessels (perivascular involvement). Volume rendering is an alternative visualization technique, which can be very helpful in CTV delineation and in diagnostic procedures (26). Improvement of GTV detection comes from new functional imaging modalities, which are beginning to contribute to the detection of areas of macroscopic tumor spread (74). Positron emission tomography (PET) is a metabolic imaging

technique that reflects biochemical and physiological processes; this technique is sensitive to small physiological differences between normal and diseased tissues (75,76). A drawback of PET and other functional imaging modalities is that the physical image resolution is less than that of the 'anatomical' imaging modalities, such as CT and MRI. SPECT (single photon emission computed tomography), using for instance radiolabeled monoclonal antibodies is another type of metabolic imaging. To use the information from PET / SPECT in 3D treatment planning the functional imaging studies need to be registered with the anatomic imaging studies (planning CT-scan) used for treatment planning (29,74,77,78). In the future further refinements of the GTV will be possible and a new target volume definition can than be introduced: the biological target volume (BTV). Until now the entire GTV is considered to have an equal density of tumor cells with identical radiosensitivity. With molecular imaging, differentiation within the GTV will be possible. Future methods of imaging should address the issue of tumor cell burden and tumor cell radiosensitivity within the GTV e.g. tumor-specific cell surface markers, receptor ligands and genetic differences. This can result in several GTVs with different associated risks and different dose prescription levels or the combination of radiation therapy (IMRT) with molecular targeting: multidimensional conformal radiotherapy (MD-CRT) (66,80-87).

11.3 RADIATION THERAPY INDUCED NORMAL TISSUE COMPLICATIONS

Normal tissue irradiation is an unavoidable consequence of adequate dose delivery to the tumor site. The extent of normal tissue irradiation and the resulting normal tissue complication probability (NTCP) depend on several factors. Prevention of undue levels of normal tissue complications is a major goal in radiation therapy practice. Moreover, recording of toxicity should be an integral part of the radiation oncologist's daily routine and should be a critical endpoint in clinical trials (88-94). Cancer treatment research is no longer solely directed at prolonging life as illustrated by the fact that both the RTOG, the EORTC and also the NCI consider quality of life (QOL) outcomes in clinical trials as important as the traditional endpoints of tumor response and survival. In other words, complication free survival should be the main goal of cancer treatment.

Head and neck cancer is a locally aggressive disease; the disease itself as well as the current

treatment modalities have great impact on basic functions such as respiration, swallowing, chewing and speech (1,2). From the viewpoint of the patient the essential issue is not so much whether a complication occurs, but to what extent the QOL is diminished by the event. The task of improving QOL in patients treated for head and neck tumors should begin with analyzing the factors which dominate QOL. All studies conclude that xerostomia with all its ramifications is one of the most important determinants of QOL (7-9,95-97). Prevention of xerostomia, as a late and frequently permanent normal tissue complication, is one of the important goals of modern radiation therapy techniques, such as 3DCRT and IMRT (98-100). However, prevention of xerostomia and other normal tissue complications requires knowledge of the pathogenesis. Knowledge of pathogenesis, radiobiology and the molecular biology is necessary to develop clinically relevant constraints for radiation therapy planning purposes. For radiation therapy planning purposes both physical, such as dose and volume, and biological criteria (NTCP) are needed (101-108). The necessity to develop such criteria increases with the introduction of inverse planning, where these constraints are an essential part of the planning process. Clinically relevant radiobiological response models are needed. Biological models available nowadays are too simplistic and are based on predominantly empirically derived data for normal tissue tolerance limits. These models should therefore not be used as single criteria in radiation therapy optimization.

In IMRT optimization algorithms the physical constraints are predominantly based on dose and dose-volume constraints to the target volumes and critical structures. The relation between these volume-based constraints and normal tissue complication probabilities is not straightforward for all OAR. Volume as such is not a relevant criterion, since critical radiosensitive structures are not always homogeneously distributed within organs (109). Different structures and elements within the same organ may show large differences in radiation responsiveness (110); only where these were homogeneously distributed over an organ, volume, as such, would be a relevant criterion for the tolerance of the organ. Moreover, different structures within one organ may respond to irradiation in very different ways and lead to different pathological processes with identical or different clinical sequelae. These differences cannot be modeled by a volume-based algorithm. Little is known about those critical structures, their localization, their size, their dose-response and the potential for interaction between damage in one critical structure and radiation damage in another critical structure in the same organ. Identification of these critical structures has become the most important challenge in the further development of conformal radiation therapy. Dose inhomogeneity in organs at risk is difficult to model and this also hampers the

application of biological algorithms for optimization processes. It is even questionable whether the current knowledge of NTCP justifies algorithm driven treatment plan optimization. The main difficulty in validating models for NTCP is the absence of controlled human data for which physical details of the nonuniform exposures (e.g. DVH) are documented. What is required are prospective clinical trials specifically designed to identify the critical structures and elements for each dose limiting organ/tissue, their anatomical position and their radiation response. If models of the 'volume effect' in radiation therapy are to be clinically applicable in the optimization process for high precision conformal radiation therapy, they have to be based on clinical studies. This situation is changing with 3D-planning data. Development of solid TCP (tumor control probability) and NTCP models that accurately predict clinical outcome will emerge from ongoing 3D conformal therapy clinical trials as dose-volume outcome data are gathered and analyzed. The limitations of the various possible models must be well understood; the uncritical use of NTCP must be avoided (17,111-113).

The shortcoming of these models reflects the inadequate biological and radiobiological understanding of radiation injury and the scarcity of reliable experimental data. However, this situation is rapidly improving as a result of molecular biological research (114-118). Increasingly the role of cytokines and growth factors is becoming recognized in the pathogenesis of normal tissue reactions and complications. A variety of cytokines are upregulated following radiation therapy. Induction of cytokines may produce very early effects after irradiation as well as longer term effects. Radiation induced normal tissue injury involves complex interactions among parenchymal cells and endothelial cells. The inflammatory cytokines play an important role in the development of late damage. The 'target cell view' of parenchymal or vascular cells as passive bystanders dying when they attempt mitosis is too simple. These new insights in molecular biology have resulted in a newly proposed classification system of radiation effects in three categories instead of the classical dichotomy of acute and late effects (119). The three proposed categories are the cytocidal effects, indirect effects and functional effects. The cytocidal effects of radiation relate to the 'classic' target cell model. Indirect effects are reactions in other cells or tissues as response to radiation-induced injury, e.g. effects secondary to vascular damage or secondary to the release of cytokines and growth factors. The functional effects (non-lethal) are all other effects. In most tissues all three effects occur. A major challenge and area of research is to determine the relative contribution of the three effects in a given setting. This will facilitate development of new tools for predicting and monitoring normal tissue complications and provide

a foundation for biologically based intervention strategies in the future. This will also contribute to the development of more reliable NTCP models for optimization purposes. As many of the described basic molecular processes are dose-dependent, avoidance strategies (3DCRT and IMRT) will always have a major role in preventing radiation induced normal tissue complications.

The iterative process of data gathering, analysis of results, model development and refinement may eventually lead to a better understanding of radiation-induced tissue damage. And, thereby, to better prevention of radiation-induced injury by both improved radiation therapy techniques and biologically based interventions. The importance of recording and grading of normal tissue complications for all treatment modalities is beyond dispute. A better characterization of the nature, frequency and severity of the various complications will allow a rational development of preventive measures. The LENT SOMA scale is now the registration system for late toxicity which has received the widest recognition (90,91). However many of its recommendations remain untested and unapplied. A critical use of the LENT SOMA scale and emerging clinical data will lead to further adjustments, verification and refinements of the system. Apart from separate registration of the various normal tissue complications, the impact of these complications on QOL should also be assessed (7-9). QOL instruments assess the impact of treatment toxicities on normal living as rated by the patient. Finally, the increased use of combined modality treatment options, such as chemoradiation, raises new questions. Interactions of other modalities with radiation therapy require constant monitoring to recognize and mitigate sequelae.

An understanding of the cell compartments at risk from each modality (RT and chemotherapy) is essential to predict additive or complementary effects (14).

Published tolerance doses should not be viewed uncritically as safe doses until sufficient experience has been gained with these doses within each of the two major modes of cancer treatment. The addition of chemotherapy may also have different effects on acute and late reactions. Many chemotherapeutic agents are dose limited by their toxic effect on rapidly proliferating tissues, but others have specific toxicity to slow turnover tissues. The additive toxicities may therefore also differ for acute and late reactions of tissues included in the irradiated volume.

11.3.1 Xerostomia: Xerostomia or the dry-mouth-syndrome due to radiation therapy is a significant problem (Chapter 2). In this thesis the importance of preventing xerostomia by 3DCRT and IMRT is underlined (99-101). Radiation therapy planning efforts are focused on

sparing of the parotid glands (Chapter 9, 10). The exact pathogenesis of radiation-induced xerostomia, however, is not fully elucidated. The serous acinar cells appear to be the most radiosensitive cells and apoptosis plays a dominant role (110,117,118,120-123). Recently clinical 3DCRT and IMRT studies have established dose and volume constraints for the parotid glands. These constraints correlate very well with objectively measured salivary flow rates of the parotid glands. Constraints for the other salivary glands are still lacking. Moreover, the correlation between the parotid salivary flow rates and the subjective xerostomia related complaints is weak. An absolute threshold of saliva output which can characterize the xerostomia patient is lacking (124). Reliable and valid scoring systems to assess xerostomia and xerostomia related QOL are now rapidly emerging (96,97,125). The relative contribution of the different salivary glands to maintain oral hygiene and subjective oral well-being is unfortunately largely unknown. Increasing data on xerostomia research, including QOL surveys, indicate a pivotal role for the minor salivary glands in maintaining oral health. This is attributed to the significant mucin production of these glands. Mucins serve as an important mucosal lubricant. The minor salivary glands produce 70% of the mucin content of saliva. In contrast, parotid glands produce hardly any mucins (126-128). To establish clinically relevant dose, volume and biological constraints for xerostomia prevention by IMRT, several problems have to be solved. The relative contribution of the major and minor salivary glands to maintenance of oral health should be established. Therefore the objective functions (i.e. salivary flow rate) of all salivary glands should be assessed separately and correlated with both DVH analysis and validated subjective xerostomia and QOL scores (129). Salivary flow rates of the minor salivary glands are difficult to assess. Delineation of the minor salivary glands as 'organs at risk' (OAR) for DVH analysis is impossible; Eisbruch has proposed to use the non-involved oral cavity as substitute (130). Finally, increasing insight in the basic molecular processes (e.g.DNA repair mechanisms) might ultimately lead to other solutions to mitigate radiation injury of the salivary glands and can be complementary to improved dose distributions that can be obtained by IMRT (66,118,131).

11.3.2 Mucositis: For many aggressive treatment programs mucositis is the dose-limiting toxicity. This accounts for both radiation therapy and chemotherapy (2,10,12,132). Studies combining chemotherapy with radiation therapy all show an increased rate of acute side effects. In comparison to radiation therapy alone chemoradiation has a relative risk for mucositis of 2.97 and the relative risk of delay of radiation therapy is 2.87 (14,133). As the

mucosa is an intrinsic part of most target volumes, IMRT alone will not yield the solution for mucositis prevention. Moreover, the application of IMRT with an integrated boost (SMART = simultaneous modulated accelerated radiation therapy) is restricted by dose-limiting normal tissue (mucosa) within the high dose boost region (134). Further increase in treatment intensity will require a better understanding of the pathophysiology of mucositis and is dependent on the development of active pharmacological modifiers of this toxicity (95).

The biology of ulcerative mucositis involves the sequential interaction of cells, cytokines and the oral microflora (135). The initial response to radiation is the release of proinflammatory cytokines, such as IL-1, IL-6 and TNFα (136). Increasing levels of cytokine peak just before the development of ulcerative lesions. Research is now concentrating on inhibiting this cytokine response. Benzydamine for instance is an inhibitor of TNFα and can to some extent prevent radiation-induced mucositis (137). However, in case of a high rate of biological dose accumulation (high fraction dose) benzydamine is ineffective. Other approaches, such as antibiotics, growth factors (G-CSF) and radical scavengers (amifostine) are still under investigation (138-143). Unfortunately however, with regard to the implementation of antibiotics: the in Chapter 5 reported randomized study using placebo versus an oral paste consisting of the antibiotics polymyxin E, tobramycin and amphotericin B, failed to show any benefit. The potential of growth factors (G-CSF) and amifostine of having also a tumor protective effect is of concern (14,144).

11.3.3 Normal tissue toxicity: Optic nerve / retina / chiasm: The tolerance dose of the structures of the visual pathway are extremely important dose-limiting structures in radiation therapy for e.g. nasopharyngeal cancers and paranasal sinus tumors (145-147). Exceeding the tolerance dose of these structures can result in severe late normal tissue complications, such as blindness (Chapter 6). The need for prevention is obvious. This is even more obvious when one considers the in Chapter 7 reported data of dose-escalation in the treatment of nasopharyngeal cancer (NPC). These data suggest the existence of a steep dose-effect relationship for tumor control (148-150). Early stages of NPC can be treated by combined ERT and high dose rate (HDR) brachytherapy to high cumulative doses of radiation (77-81 Gy) resulting in a 5 years local control rate of over 90%. Also, for the more advanced lesions, the high cumulative doses of radiation seemed to be of benefit especially when combined with neoadjuvant chemotherapy. These high cumulative doses to the nasopharynx could be achieved without increased normal tissue complications of the visual pathway structures

thanks to the sparing properties of the highly conformal brachytherapy boost. The brachytherapy boost can now, in case of very advanced lesions, be replaced by another way of applying highly conformal types of radiotherapy, that is by stereotactic radiation in combination with IMRT (Chapter 8). From a dose distribution point of view, a further improvement in local control and survival is anticipated (151-155). These new techniques aiming at dose-escalation require careful consideration of the tolerance limits of the structures of the visual pathway (156,157).

Data on the tolerance dose of the visual pathway structures are fairly well established (145-147). However, a reliable NTCP model which can be used as constraint for inverse planning is lacking (158). NTCP's based upon the Lyman model seemed to overestimate the observed rates of optical nerve damage (107,108). Adjustment of the TD50 in the Lyman model still did not result in a reliable NTCP; i.e. mild complications occurring at doses below 60 Gy were not predicted accurately. Moreover, care must be taken when applying dosimetric analysis for structures with very small volumes. The effect of treatment set-up variations on the dose distribution to the visual pathway should be considered in the interpretation of the results. The recent ICRU recommendations include therefore a margin around the organs and structures at risk to account for set-up errors and organ movement (23). For small critical structures, errors of only 1-2 mm may have a dramatic effect on whether the tolerance dose related to the volume is exceeded. Finally, the critical volume of the visual pathway structures is unknown. Therefore, plan optimization, and dose-escalation based upon NTCP values should be interpreted with caution (105,106). It is important to combine NTCP's for all structures that are part of the visual pathway to assess the overall complication risk for each individual patient.

11.4 CONCLUSIONS

Three dimensional conformal radiation therapy and in particular IMRT is one of the exciting achievements in radiation-oncology of recent years (18,21). IMRT allows one to further push the dose conformality potential to the physical limits (102). IMRT is also the key to clinical implementation of newly biologically optimized treatment techniques (66,82,105). It offers the future avenue of combining dose-escalation with improved sparing of normal tissues and thus improved complication free survival. Examples of save dose-escalation pro-

tocols in the nasopharynx by conformal techniques are presented in this thesis. Although IMRT implementation in clinic is rapidly progressing, many issues still have to be resolved. This thesis addresses some of the clinical issues related to normal tissue toxicity and sparing capabilities of conformal radiation therapy and IMRT.

The issue of standardization of the neck target volume is addressed and CT-based definitions for the CTV of the node negative neck are presented (69,70,72). Further improvement of primary target volume definitions and delineation have to be investigated and will come from improved functional and anatomical imaging techniques The issue of recording and grading of acute and late normal tissue complications is stressed (2,59,90,91,95,159-161). Studying sequelae of radiation therapy in relation to dosimetric analysis of 3D treatment plans is essential for developing clinically relevant constraints for inverse planning algorithms. IMRT can not offer a total solution for all radiation therapy related complications, of which mucositis is one of the most important examples. The fundamental research in molecular radiobiology and genetics will have to further elucidate the processes of radiation injury of normal tissues and tumor cells and vice versa the repair mechanisms (162-164). Multidimensional conformal radiation therapy is a promising future route for a complication free survival and therewith better QOL for head and neck cancer patients (66,165-168).

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Summary

INTRODUCTION

In The Netherlands, head and neck cancer (3.9%) ranks the eighth most frequently diagnosed malignant tumor. Radiation therapy (RT) plays an important role in the treatment of patients with head and neck cancer, as they constitute approximately 6% of those treated in a routine radiation therapy department. Radiation therapy can be used as a single treatment modality, but is also often combined with surgery and/or chemotherapy (chemoradiation) in multimodality treatment protocols. Radiation therapy and (concurrent) chemotherapy play an important role in organ preservation protocols. The effect of ionizing radiation is unfortunately not limited to the malignant cells; it also affects normal surrounding tissues which can lead to acute and late normal tissue complications. The head and neck region harbors organs and structures essential for basic functions, such as swallowing, speech and respiration. Preservation of quality of life (QOL) in conjunction with cure, i.e. complication-free survival, has become a key-issue in cancer treatment. In radiation oncology the rapid technological development in linear accelerators and treatment planning systems (TPS) have significantly increased the accuracy and applicability of high doses of radiation. High-dose, high-precision RT has come within reach for many patients. This so called 3D conformal radiation therapy (3DCRT) enables one to conform the dose distribution to the target volume (tumor) and therewith a better sparing (avoidance) of the surrounding normal structures is achieved.

In this thesis the capabilities of 3DCRT for sparing normal tissue structures, such as the major salivary glands, are explored. Also examples of dose-escalation without increased toxicity are presented. Moreover, the merit of other preventative measures to limit acute normal tissue complications, such as the use of antibiotics to eliminate severe mucositis, is reported.

Chapter 2

Xerostomia is one of the most frequently occuring and usually permanent late side effect of radiation therapy for head and neck tumors. It is the most important determinant of reduced QOL in patients treated for head and neck tumors.

In this chapter the severity and frequency of xerostomia and the interrelated side effects (i.e. the dry mouth syndrome) are evaluated in a group of 39 long-term survivors, treated with primary radiation therapy. Sixty-four percent of the patients experienced moderate to severe degrees of xerostomia. A questionnaire and a visual analog scale (VAS) were used for

evaluation. In the multivariate analysis three questions regarding dry mouth, eating and speech were particularly discriminatory for the degree of xerostomia as expressed by the VAS-score. These three questions and the VAS-score constitute a simplified instrument for evaluation of the subjective aspects of xerostomia.

Chapter 3 and 4

A prerequisite for 3DCRT is standardization of (CT-based) definitions of the target volumes. The planning process of 3DCRT starts with meticulous delineation of the target volume(s) and organs at risk (OAR) on a planning CT-scan. Subsequently the 3D dose distribution is shaped around the delineated target(s) and the OAR are maximally spared from receiving a significant dose of radiation. The cervical lymph nodes are an important target when treating head and neck cancer patients. Therefore CT-based definitions for the clinical target volume (CTV) of the (non-)involved neck were developed as a first step towards 3DCRT.
The Memorial Sloan Kettering Cancer Center group divided the neck into six lymph node levels, each containing several lymph node groups. The American Academy of Otolaryngology-Head and Neck surgery (AAO-HNS) proposed a standardized nomenclature for neck dissections. The surgical landmarks of the neck levels I-VI were 'translated' and used for defining the CT-based definitions for the neck node regions 1-6. In Chapter 3 the CTV definitions for the node-negative neck are described. To improve the ease of the delineation process when implementing these neck CTV definitions in a routine radiation therapy department, a simplification of the CT-based delineation atlas is proposed in Chapter 4.

Chapter 5

Acute complications, occurring during radiation therapy, are usually temporary but can lead to unwanted treatment interruptions with a detrimental effect on tumor control and survival. Mucositis is an example of a significant acute complication. It hinders the introduction of treatment-intensification such as accelerated fractionation (AF), chemoradiation and dose-escalation. The pathogenesis of radiation-induced mucositis is complex; cytokines play an important role. Micro-organism, in particular the aerobic gram negative bacteria (AGNB) are ascribed a crucial role in the pathogenesis. In this chapter the hypothesis that AGNB play such a crucial role in the pathogenesis of radiation-induced mucositis is tested. In a placebo-controlled randomized double-blind study the effect of a combination of antibiotics (PTA = polymyxin, tobramycin, amphothericin B) on selective elimination of the AGNB from the oral flora is tested. The percentage of patients with a positive culture of AGNB was signifi-

cantly reduced ($p = 0.01$) in the PTA group. However, this was not reflected in a reduced rate of mucositis, neither objectively ($p = 0.33$), nor subjectively ($p = 0.37$). Finally, the severity of mucositis correlated significantly with the area of irradiated mucosa ($p = 0.0001$).

Chapter 6

Radiation-induced optic neuropathy leading to blindness is an infrequently occurring dramatic late complication that can occur in patients treated for tumors of the nasopharynx or paranasal sinus. With the advent of the tools of sophisticated treatment planning systems (TPS) it becomes a largely avoidable complication. The so-called beams-eye-view option (BEV) enables the visualization of the critical normal structures and the tumor volume related to the beam portals. This makes adequate shielding of critical structures feasible. Dose received by the critical structures can be calculated, displayed as iso-dose lines and/or expressed as a dose volume histogram (DVH). The importance of 3D dose calculations, BEV and DVH-analysis is illustrated by a case report presented in this chapter. A patient with bilateral radiation-induced optic neuropathy after conventional 2D radiation therapy for a T4N2c nasopharyngeal cancer is presented. Reanalysis (CT-based) elucidated that the complication was due to inadequate shielding of the optic nerves because of the lack of 3D CT-information.

Chapter 7 and 8

For nasopharyngeal cancers a steep dose-response curve with respect to primary tumor control has been established. This implies that nasopharyngeal cancers potentially benefit from (dose) treatment intensification. The case presented in the previous chapter was treated by combined modality treatment, consisting of neoadjuvant chemotherapy, external radiation therapy (ERT) and high dose rate (HDR) brachytherapy (BT). In Chapter 7 the role of endocavitary fractionated HDR brachytherapy (ECBT), as a method for escalating the dose and the role of chemotherapy is discussed. For early nasopharyngeal cancers ERT in combination with fractionated HDR brachytherapy is the therapy of choice, resulting in high cure rates. The addition of neoadjuvant chemotherapy is advocated for the more advanced tumors. Improved conformality of the dose distribution around the tumor volume for those tumors extending into the parapharyngeal space without jeopardizing the normal tissue tolerance can be achieved by stereotactic radiation therapy (SRT) and/or intensity modulated radiation therapy (IMRT). Improved target coverage is expected to result in better tumor-

control rates and survival. The rationale to choose for either ECBT or SRT and/or IMRT as conformal techniques to deliver the booster dose of radiation to the nasopharynx, is addressed in Chapter 8.

Chapter 9

IMRT adds an extra dimension to 3DCRT by varying the intensity of the radiation beam across the field. IMRT results in an improved target dose homogeneity and better sparing of the normal tissues. The intensity profiles can be calculated by either forward or inverse treatment planning systems. In this chapter a noncommercial algorithm, 'Optimize', to compute optimal beam intensity profiles for better target dose homogeneity is described. The sparing potential of a simplified IMRT technique using 'Optimize' for treating laryngeal and oropharyngeal tumors is evaluated in a treatment planning study. The addition of beam intensity modulation (BIM) to 3DCRT allowed the use of smaller margins around the target volumes and resulted in conjunction with a steeper dose fall-off in better sparing of both parotid glands.

Chapter 10

This chapter addresses the clinical implementation of the in chapter 9 described simplified IMRT technique for T1-4N0 laryngeal cancers. The salivary gland function was analyzed objectively by measurement of the stimulated whole saliva flow and subjectively by a short questionnaire and a visual analog scale (VAS). The results of the salivary gland function analyses were compared with dose volume analysis of the parotid glands. The extent of parotid gland sparing in terms of volume and dose reduction, was less than expected from the planning study described in chapter 9. According to recently published threshold values, the sparing was for at least half of the patients insufficient to guarantee full restoration of parotid gland salivary flow rates. Despite insufficient or marginal sparing, the results of the salivary gland function analysis showed residual salivary flows in most patients.

The salivary flow results, however, did not correlate with subjective complaints and DVH analysis of the parotid glands. This has also been reported by others. Moreover, recent literature indicates a pivotal role for the minor salivary glands in preserving oral hygiene and preventing xerostomia.

To improve salivary gland sparing by 3DCRT, the Rotterdam technique was compared with IMRT plans of 3 other institutes in a multi-institutional treatment planning study (one patient). Finally, for all 26 patients of the clinical study IMRT plans were designed using the

recently commercially available planning module (HELIOS). Both the multi-institutional planning study and the 26 'HELIOS' IMRT plans showed significant better sparing of the parotid glands compared to the clinically used 3DCRT Rotterdam technique. However, whether this optimal (better) sparing of the parotid glands results in less xerostomia complaints, remains a subject of debate.

Chapter 11

One of the problems to be solved when routinely implementing IMRT is standardization of treatment protocols and in particular standardization of definitions for the different primary tumor target volumes. Standardization of target volumes remains of paramount importance for the future of Radiation-Oncology. Target delineation will benefit from new functional imaging techniques and other diagnostic modalities. Registration and grading of treatment related toxicity's in conjunction with DVH analyses is essential for defining thresholds and constraints which can be used in algorithm driven inverse TPS. Molecular biological research is necessary to further elucidate the pathogenesis of radiation-induced injury. Moreover, knowledge of DNA repair mechanisms will also help to develop clinical relevant biological models and new treatment strategies. The prevention of radiation-induced toxicity depends on both optimal sparing radiation therapy techniques (IMRT, SRT and brachytherapy) and (pharmacological) agents which can selectively interfere with the radiation-induced effects. The future will be one of multidimensional conformal radiation therapy and this will in the end result in complication free survival for head and neck cancer patients and therewith a better quality of life.

Samenvatting

INLEIDING

In Nederland komen 3.9% van de gediagnosticeerde maligniteiten voor in het hoofd-hals gebied. De hoofd-hals tumoren staan hiermee op de achtste plaats van meest frequent voorkomende maligniteiten. Radiotherapie speelt een belangrijke rol bij de behandeling van patiënten met deze tumoren; dit betreft ongeveer 6% van de patiëntenpopulatie op een radiotherapie afdeling. Radiotherapie kan de enige behandelingsmodaliteit zijn, maar vaak is er sprake van een multidisciplinaire behandeling, waarbij radiotherapie volgt na chirurgie en/of gecombineerd wordt met chemotherapie (chemoradiatie). Radiotherapie en (concomitante) chemotherapie spelen een belangrijke rol in orgaansparende behandelingsprotocollen. Het effect van ioniserende straling beperkt zich helaas niet tot de maligne cellen; ioniserende straling heeft ook invloed op de cellen van de omgevende gezonde weefsels en dit kan leiden tot acute en late schade. Het hoofd-hals gebied omvat organen en structuren die essentieel zijn voor basale functies, zoals slikken, spreken en ademhaling. Genezing met behoud van een goede kwaliteit van leven, dus een complicatie-vrije overleving, is een van de belangrijkste doelen bij de huidige behandeling van kankerpatiënten. In de radiotherapie heeft de snelle technologische ontwikkeling van de lineaire versnellers en de therapie planning systemen de toepassing en nauwkeurigheid van toediening van hoge bestralingsdoses mogelijk gemaakt. Hooggedoseerde precisie bestraling is binnen het bereik gekomen van vele patiënten. Met deze zogenaamde 3D conformatie radiotherapie (3DCRT) kan de dosisverdeling nauwkeuriger aan het doelvolume (tumor) aangepast worden (conformeren), waardoor een betere sparing van de gezonde weefsels in de directe omgeving van de tumor mogelijk wordt gemaakt.

In dit proefschrift worden de mogelijkheden van 3DCRT met betrekking tot sparing van gezonde weefsels en organen, zoals de grote speekselklieren, onderzocht. Daarnaast worden voorbeelden gegeven van dosis-escalatie zonder toename van toxiciteit. De waarde van andere preventieve maatregelen, zoals de rol van antibiotica in de preventie van bestraling geïnduceerde mucositis, wordt eveneens besproken.

Hoofdstuk 2

Een van de meest frequent optredende, veelal permanente late bijwerking van radiotherapie voor tumoren in het hoofd-hals gebied is xerostomie. Xerostomie is de belangrijkste factor met betrekking tot een verminderde kwaliteit van leven bij patiënten die behandeld zijn voor een hoofd-hals maligniteit. In dit hoofdstuk worden de ernst en de frequentie van

xerostomie en alle daarmee samenhangende bijwerkingen (het zogenaamde droge mond syndroom) geëvalueerd in een groep van 39 radiotherapeutisch behandelde patiënten met een lange overleving. Vierenzestig procent van deze patiënten had permanente klachten varierend van matige tot ernstige xerostomie. De evaluatie werd verricht met behulp van een enquête en een zogenaamde visuele analoge schaal (VAS). Drie vragen, betrekking hebbend op respectievelijk droge mond, eten en spreken, bleken in de multivariate analyse significant voor de mate van xerostomie, zoals uitgedrukt door de VAS-score. Deze drie xerostomie-bepalende vragen en de VAS-score vormen tezamen een eenvoudig meetinstrument voor het analyseren van de subjectieve aspecten van xerostomie.

Hoofdstuk 3 en 4

Standaardisatie van (op CT-gebaseerde) definities van de doelvolumina is een vereiste voor 3DCRT. De planningsprocedure van 3DCRT begint met het minutieus intekenen van de doelvolumina en de kritieke organen en structuren. Vervolgens wordt een dosisverdeling in drie dimensies berekend en aangepast aan de vorm van de ingetekende doelvolumina, waarbij de kritieke structuren zoveel mogelijk gespaard worden.

Bij de behandeling van patiënten met kanker in het hoofd-hals gebied vormen de lymfklieren van de hals een belangrijk doelvolume. Daarom werd als eerste stap ten behoeve van het ontwikkelen van 3DCRT technieken voor hoofd-hals tumoren begonnen met het systematisch bepalen van CT-definities voor het 'clinical target volume' (CTV) van de (niet-) aangedane hals. Het team van het Memorial Sloan Kettering Cancer Center heeft de hals in zes lymfkliemiveaus ('levels') verdeeld; elk niveau bevat een of meer verschillende lymfkliergroepen. De Amerikaanse vereniging voor hoofd-hals chirurgie ('The American Academy of Otolaryngeology-Head and Neck surgery', AAO-HNS) heeft een gestandaardiseerde terminologie voor halsklierdissecties voorgesteld. De chirurgische herkennings-punten van de lymfkliemiveaus I-VI zijn gebruikt als uitgangspunt en vertaald in CT-definities voor de lymfklierregio's 1-6. In hoofdstuk 3 worden deze CT-definities voor het CTV van de klier-negatieve (N0) hals beschreven. Ter vergemakkelijking van het intekenproces bij de invoering van deze CTV-definities op een radiotherapie-afdeling wordt in hoofdstuk 4 een vereenvouding hiervan voorgesteld.

Hoofdstuk 5

Acute, reeds tijdens bestraling optredende complicaties, zijn meestal tijdelijk van aard, maar kunnen wel ongewenste onderbrekingen van de bestralingsbehandeling tot gevolg

hebben. Dit impliceert een nadelig effect op tumorcontrole en overleving. Een voorbeeld van een belangrijke acute bestralings bijwerking is mucositis. Mucositis beperkt de toepassing van geïntensiveerde bestralingsbehandelingen, zoals geaccelereerde fractionering, chemoradiatie en dosis-escalatie. De pathogenese van bestraling geïnduceerde mucositis is complex; cytokinen spelen een belangrijke rol. Aan de micro-organismen en met name aan de aërobe gram negatieve bacteriën (AGNB) wordt een cruciale rol in de pathogenese toegeschreven. Deze hypothese wordt in dit hoofdstuk getest. Het effect van een combinatie behandeling met drie antibiotica (PTA = polymyxine, tobramycine en amphotericine B) op selectieve eliminatie van de AGNB wordt getest in een placebo-gecontroleerde dubbelblind gerandomiseerde studie. Het percentage patiënten met een positieve kweek van AGNB was significant afgenomen in de PTA-groep ($p = 0.01$). Echter, deze afname werd niet weerspiegeld in een verminderd mucositis percentage, noch objectief ($p = 0.33$), noch subjectief ($p = 0.37$). Tenslotte was er wel een significante correlatie aantoonbaar tussen de ernst van de mucositis en het bestraalde mucosa-oppervlak ($p = 0.0001$).

Hoofdstuk 6

Bestralings-geïnduceerde n.opticus neuropathie leidend tot blindheid is een zeldzame maar zeer ernstige late complicatie, die kan optreden bij bestraling van nasopharynx en neusbijholte tumoren. Met de komst van geavanceerde radiotherapie planning systemen is dit een grotendeels te vermijden complicatie. Met de zogenaamde 'beams-eye-view' optie (BEV) van moderne planningssystemen kan de positie van de kritieke structuren en de tumor ten opzichte van de bestralingsvelden zichtbaar worden gemaakt. Hierdoor verkrijgt men het noodzakelijke inzicht, waardoor het mogelijk is om de kritieke structuren adequaat af te schermen. De dosis die in de kritieke structuren komt, kan worden berekend en zichtbaar worden gemaakt als isodose lijnen en/of worden weergegeven in een dosis-volume-histogram (DVH). Aan de hand van een casus wordt in dit hoofdstuk het belang van 3D dosisberekeningen, de BEV-optie en DVH analyse geïllustreerd. Behandeling van een T4N2c nasopharynxcarcinoom met conventionele 2D radiotherapie, leidend tot bestraling geïnduceerde neuropathie van beide nn.optici, wordt gepresenteerd. Heranalyse (mbv CT) bracht aan het licht dat deze complicatie te wijten was aan onvoldoende afscherming van de nn.optici door het ontbreken van CT-informatie.

Hoofdstuk 7 en 8

Voor nasopharynxcarcinomen is een steile dosis-effect relatie met betrekking tot tumorcon-

trole aangetoond. Dit betekent dat in potentie patiënten met een nasopharynxcarcinoom kunnen profiteren van een (dosis) geïntensificeerde behandeling. De patiënt van de in het vorige hoofdstuk beschreven casus werd behandeld volgens een multidisciplinair protocol; de gecombineerde behandeling bestond uit neoadjuvante chemotherapie, uitwendige radiotherapie en 'high dose rate' (HDR) brachytherapie. In hoofdstuk 7 wordt de rol van endocavitaire brachytherapie, als methode voor dosis-escalatie en de rol van chemotherapie bediscussieerd. Voor de vroege stadia van het nasopharynxcarcinoom is uitwendige radiotherapie in combinatie met gefractioneerde HDR brachytherapie de therapie van keuze, resulterend in hoge genezingspercentages. Toevoeging van neoadjuvante chemotherapie wordt aangeraden voor de meer gevorderde stadia. Met stereotactische radiotherapie (SRT) en/of intensiteit gemoduleerde radiotherapie (IMRT) voor die tumoren welke zich uitbreiden in de para-pharyngeale ruimte, kan de dosisverdeling rond het tumorvolume worden verbeterd, zonder de tolerantie van de gezonde weefsels in gevaar te brengen. De afwegingen om te kiezen voor brachytherapie, danwel voor SRT en/of IMRT als conformatie radiotherapie techniek voor de booster bestraling ter plaatse van de nasopharynx, worden in hoofdstuk 8 besproken.

Hoofdstuk 9

IMRT voegt een extra dimensie toe aan 3DCRT middels het variëren van de dosisintensiteit binnen een bestralingsveld. IMRT leidt tot een verbeterde homogeniteit van de dosisverdeling in het doelvolume en tot een beter sparing van de gezonde weefsels. De benodigde intensiteitsprofielen kunnen worden berekend met ofwel gewone of 'inverse' planning systemen. In dit hoofdstuk wordt een niet commerciëel rekenmodel, 'Optimize', voor de berekening van intensiteitsprofielen beschreven. De sparende mogelijkheid van een eenvoudige IMRT techniek op basis van 'Optimize' wordt geëvalueerd in een planningsstudie van larynx- en oropharynxtumoren. Het toevoegen van bundel intensiteits-modulatie (BIM) aan 3DCRT maakte het mogelijk om kleinere marges rond de doelvolumina te gebruiken en resulteerde samen met een scherpere penumbra in betere sparing van beide glandulae parotis.

Hoofdstuk 10

In dit hoofdstuk wordt de klinische introductie van de in het vorige hoofdstuk beschreven ver-eenvoudigde IMRT techniek voor de behandeling van patiënten met een T1-4 N0 larynxcarcinoom beschreven. De speekselklierfunctie werd objectief geanalyseerd door me-

ting van de gestimuleerde totale speekselproduktie ('whole saliva') en subjectief met behulp van een korte enquête en een visuele analoge schaal (VAS). De resultaten van de speekselklierfunctie werden gerelateerd aan de dosis en volume berekeningen van de bestraalde parotiden. De mate van parotis sparing in termen van volume- en dosis-reductie was minder dan op grond van de in hoofdstuk 9 beschreven planningsstudie was verwacht. Voor tenminste de helft van de patiënten was de mate van sparing op grond van recent gepubliceerde drempelwaarden onvoldoende om volledig herstel van de parotisfunctie te garanderen. Ondanks dit resultaat was er bij de meeste patiënten toch nog sprake van een meetbare speekselproduktie. De speekselproduktie correleerde echter niet met de subjectieve klachten van een droge mond en ook niet met de DVH berekeningen van de parotiden. Soortgelijke bevindingen zijn ook door anderen gerapporteerd. Met betrekking tot behoud van orale hygiëne en preventie van xerostomie wordt, in meer recente literatuur, een centrale rol toegeschreven aan de kleine speekselklieren. Ter verbetering van parotissparing met 3DCRT werd de Rotterdamse techniek in een planningsstudie vergeleken met IMRT plannen van 3 andere bestralingsinstituten. Tenslotte, werden voor alle 26 patiënten van de klinische studie, IMRT plannen ontworpen met de inmiddels commercieel beschikbare inverse planning module 'HELIOS'. Zowel met de IMRT plannen van de multi-institutionele planningsstudie als met de 'HELIOS' IMRT plannen was in vergelijking met de gebruikte Rotterdamse 3DCRT techniek een significant betere sparing van de parotiden mogelijk. Echter, in hoeverre optimale sparing van de parotiden ook daadwerkelijk resulteert in vermindering van aan xerostomie gerelateerde klachten, blijft voorlopig nog een punt van discussie.

Hoofdstuk 11

Eén van de problemen die opgelost moet worden ten behoeve van routinematige toepassing van IMRT, is de standaardisatie van behandelingsprotocollen en met name het definiëren van de verschillende tumor doelvolumina. Standaardiseren van intekenprotocollen voor de verschillende tumoren is van cruciaal belang voor de toekomst van de radiotherapie. Bij het intekenen van doelvolumina zal de radiotherapie profiteren van nieuwe functionele afbeeldingstechnieken en andere diagnostische ontwikkelingen. Het registreren en graderen van (radio)therapie gerelateerde bijwerkingen gekoppeld aan DVH berekeningen is essentieel voor het vaststellen van klinisch relevante drempelwaarden en limieten die gebruikt kunnen worden in algoritme gestuurde inverse planningssystemen. Moleculair biologisch onderzoek is noodzakelijk om de pathogenese van bestralings-geïnduceerde

schade nader te verklaren. Daarnaast zal kennis van de DNA herstelmechanismen helpen in het ontwikkelen van klinisch relevante biologische modellen en nieuwe behandelingsstrategieën. De preventie van bestraling geïnduceerde bijwerkingen is afhankelijk van zowel optimale bestralingstechnieken (IMRT, SRT en brachytherapie) en (farmacologische) agentia die selectief kunnen interfereren met bestralingseffecten. De toekomst zal er een zijn van multidimensionale conformatie radiotherapie en dit zal uiteindelijk resulteren in een complicatie-vrije overleving en dus een betere kwaliteit van leven voor patiënten met kanker in het hoofd-hals gebied.

LIST OF ABBREVIATIONS

AAO-HNS	-	American Academy of Otolaryngology Head and Neck Surgery
AF	-	Accelerated fractionation
AGNB	-	Aerobic Gram-negative bacteria
AJCC	-	American joint committee against cancer
AP	-	Antero posterior
BED	-	Biologic effective dose
BED_{10}	-	Biologic effective dose with $\alpha/\beta = 10$
BED_{cor10}	-	Biologic effective dose with $\alpha/\beta = 10$ and corrected for overall treatment time
BEV	-	Beam's eye view
BIM	-	Beam intensity modulation
BT	-	Brachytherapy
BTV	-	Biological target volume
CDDP	-	Cisplatin
CHT	-	Chemotherapy
CRT	-	Conformal radiation therapy
CT	-	Computed tomography
CTV	-	Clinical target volume
2D	-	Two-dimensional
3DCRT	-	Three-dimensional conformal radiation therapy
DFS	-	Disease-free survival
D_{mean}	-	Mean dose
dMLC	-	Dynamic multileaf collimation
DVH	-	Dose volume histogram
E(B)RT	-	External (beam) radiation therapy
ECBT	-	Endocavitary brachytherapy
ENI	-	Elective node irradiation
EORTC	-	European organization for research and treatment of cancer
EPID	-	Electronic portal imaging device
ERD	-	Extensive residual disease
5-FU	-	5 - Fluorouracil
G-CSF	-	Granulocyte colony-stimulating factor

GEE	-	Generalised Estimating Equations
GTV	-	Gross tumor volume
HDR	-	High dose rate
HF	-	Hyperfractionation
ICRU	-	International commission on radiation units and measurements
IL-1	-	Interleukin-1
IMRT	-	Intensity modulated radiation therapy
IRT	-	Interstitial radiation therapy
LC	-	Local control
LDR	-	Low dose rate
LENT	-	Late effects normal tissues
LQ	-	Linear quadratic
LRD	-	Limited residual disease
M+	-	Distant metastasis
MD-CRT	-	Multidimensional conformal radiation therapy
(m)MLC -	-	(mini)Multileaf collimator
MRI	-	Magnetic resonance imaging
NCI	-	National cancer institute
NP	-	Nasopharynx
NPC	-	Nasopharyngeal cancer
NT	-	Normal tissues
NTCP	-	Normal tissue complication probability
OAR	-	Organ at risk
OS	-	Overall survival
OTT	-	Overall treatment time
PD	-	Poorly differentiated
PET	-	Positron emission tomography
PFS	-	Progression-free survival
PG	-	Prognostic group
PP	-	Patient points
PTA	-	Polymyxin E, Tobramycin, Amphotericin B
PTV	-	Planning target volume
QOL	-	Quality of life
RFS	-	Relapse-free survival

RT	-	Radiation therapy / radiotherapy
RTOG	-	Radiation therapy oncology group
SgL	-	Supraglottic larynx
SMART	-	Simultaneous modulated accelerated radiation therapy
SOMA-LENT	-	Subjective objective management analysis – Late effects normal tissues
SPECT	-	Single photon emission computed tomography
SRT	-	Stereotactic radiation therapy
TC	-	Tissue compensator
TCP	-	Tumor control probability
TD_{50}	-	Tolerance dose with a probability of 50% complication
TGFβ	-	Transforming growth factor β
TNFα	-	Tumor necrosis factor α
To	-	Tonsil
Tpot	-	Potential doubling time
TPS	-	Treatment planning system
UD	-	Undifferentiated
UHR	-	University Hospital Rotterdam
UICC	-	Union internationale contre le cancer (International union against cancer)
V_{40}	-	Volume (of normal tissue or tumor) absorbing / receiving more than 40 Gy
VAS	-	Visual Analog Scale
WHO	-	World health organization
WMP-D	-	Well / moderate / poorly differentiated
WS	-	Whole saliva

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CURRICULUM VITAE

Oda Wijers werd op 18 februari 1958 in Den-Haag geboren. In juni 1976 slaagde zij voor het eindexamen Atheneum B aan het van der Putt Lyceum te Eindhoven. Na de middelbare school volgde ze de 3-jarige HBO in-service-opleiding tot operatiekamerassistent, waarvoor zij in september 1979 slaagde. Ze werkte gedurende deze opleiding als leerling O.K.-assistent in het St.Elisabeth Ziekenhuis te Tilburg; het theoretische gedeelte van de opleiding werd verzorgd door het IHBO (Instituut voor Hoger Beroeps Onderwijs) te Eindhoven. In september 1979 begon ze met haar studie Geneeskunde aan de Erasmus Universiteit Rotterdam, waar ze op 21 maart 1986 haar artsexamen behaalde. Van augustus 1986 tot november 1988 werkte zij als arts-assistent-niet-in-opleiding (AGNIO) op de afdeling gynaecologie en verloskunde van het Reinier de Graaf Gasthuis te Delft. Aansluitend begon zij in december 1988 als arts-onderzoeker op de afdeling gastro-enterologie (Hoofd: Prof.dr.G.N.J. Tijtgat) van het Academisch Medisch Centrum te Amsterdam. In samenwerking met de afdelingen gastro-enterologie, gynaecologie (Hoofd: Prof.dr.F.B. Lammes) en radiotherapie (Hoofd: Prof.dr.D. Gonzalez-Gonzalez) deed zij onderzoek naar de waarde van rectale en vaginale endo-echografie bij ondermeer het cervixcarcinoom en recto-(vaginale) fistels. In januari 1993 begon zij als AGNIO op de afdeling radiotherapie van de Dr.Daniel den Hoed kliniek (nu AZR-Daniel; Hoofd en opleider: Prof.dr.P.C. Levendag) te Rotterdam. In juli 1995 begon zij met haar opleiding tot radiotherapeut-oncoloog, die zij op 1 juli 2000 afsloot. Tijdens haar opleiding werd zij betrokken bij de conformatie-werkgroep en met name bij de subgroep die zich bezig hield met de hoofd-hals tumoren. Ze participeerde in verschillende studies van deze werkgroep, waarvan de resultaten materiaal opleverden voor dit proefschrift. Daarnaast werd in samenwerking met de afdeling tandheelkunde onderzoek verricht naar bijwerkingen van radiotherapie, de graderings mogelijkheden en preventieve maatregelen.

Sinds 1 oktober 2000 is zij werkzaam als radiotherapeut-oncoloog in het radiotherapeutisch instituut friesland (RIF) te Leeuwarden (Directeur: G. Botke).

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