Treatment Modalities, Quality of Life and Costs in Head and Neck Cancer

A quest for prioritization

Colophon

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Cover: In 2010, the 'Radiotherapeutisch Centrum Suriname' (RTCS) will open its doors for treatment of cancer patients. It is anticipated that at the same time the short-stay family home of the RTCS will be inaugurated. The painting 'Clairsina' was donated by Sir Roland Richardson, 'the father of Caribbean impressionism', on the occasion of the opening of the family home of the RTCS, the 'Elisabeth Huis - Famiri Oso' in Paramaribo, Suriname. Roland Richardson is considered one of the Caribbean foremost 'en plein air' painters. His famous flamboyant trees symbolize his passion for the brilliant red summer blooms of his home St. Maarten (see also conference room, department of Radiation Oncology, Erasmus MC, Daniel den Hoed Cancer Center).

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Treatment Modalities, Quality of Life and Costs in Head and Neck Cancer

a Quest for Prioritization

Behandelmodaliteiten, kwaliteit van leven en kosten bij hoofdhals kanker

een zoektocht naar prioritering

Proefschrift

Ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

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geboren te Amersfoort

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CHAPTER 1

Introduction

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In their 2009 press report the Central Bureau for Statistics (CBS) of the Netherlands states that in 2008 cancer exceeded cardiovascular mortality for the first time in history [1]. This ranks cancer with about 29% of all deaths as the number one cause of death in the Netherlands (webmagazine 03 February 2009) [2]. It is anticipated that in the next two decades the incidence of malignant tumors will even further increase, annually by 1 to 1,5%. With regard to the incidence of malignant tumors typically seen in the department of radiotherapy, an increase in incidence was seen for the south-western part of the Netherlands of about 5%, mainly due to the increase in treatment options with radiotherapy (more indications and better treatment per indication). Of the newly diagnosed malignancies in the Netherlands, cancer in the head and neck region has an incidence of around 4%, with a male to female ratio of 6 to 1 [1]. Annually, approximately 2000 people develop a tumor in the head and neck, with 600 patients dying of this disease.

Albeit that cancer in the head and neck region is relatively rare, it is associated with a significant amount of morbidity and mortality. This is due to the (locally) destructive character of the disease, to the generally poor condition of the patients often associated with their alcohol abuse, as well as to the morbid effects of some of the aggressive treatment regimes used. In recent years the applied anti-cancer treatment modalities, such as surgery, radiotherapy and chemotherapy have shown a rapid evolution. Many of the innovative treatment approaches in radiotherapy aim for increasing the therapeutic ratio, that is improving the tumor control rate while maximally sparing the normal surrounding tissues and thus limiting the side effects. Examples of developments in radiotherapy in the last decennium are radiobiologically-based modifications of fractionation schedules (altered fractionation), frameless stereotactic radiotherapy (Cyberknife, Gammaknife), IMRT (Intensity Modulated Radiotherapy), Cone-beam CT, proton and charged particle radiotherapy. However, many of these new radiotherapy techniques often translate into an increasing workload and, unavoidably, in higher costs. This is also the case for surgery (advanced reconstructive procedures) and for chemotherapy, think of treatment of systematic modalities (e.g. targeted therapy). Although the newest radiotherapy modalities appear to be expensive due to the required initial investment it must be realized that even the costs for providing a proton facility are far below the research investments made for drug development. An essential difference with drug development is that the efficacy of the innovative radiotherapy treatments is known in advance, leaving only the costs per gained Quality Adjusted Life Year (QALY) to be assessed.

Both aspects, that is the increase in head and neck cancer patients per se and the advances in the applied (and frequently costly) treatment modalities, cause a rapid rise in health care expenses. The latter turns this morbid disease also into an economic issue. Besides direct medical costs, also indirect costs (e.g. costs related to management, depreciation of building), are to be taken into account. Financial resources for medical treatments, in general, are limited at the present time and age. Moreover they are for the near future also somewhat 'unpredictable', given today's (2009) reality, i.e. the global financial crisis, and the fact that as of January 1, 2011, hospitals in the Netherlands will be financed by DBC's[1] (Diagnosis Treatment Combination, comparable to DRG). Thus, given some of the present financial constraints, making choices has already become unavoidable. The oncologist is asked to incorporate costs into the decision making process regarding the disease of his/her individual patient. Hospital organizations are also tasked to take costs into consideration when deciding on new treatment strategies. However, a cost-analysis frequently addresses effectiveness of the treatment, being only one dimension of the problem. Also side effects of cancer treatment should be factored in the equation. Finally, not only the life years gained, but importantly, the quality of life during the years gained, is currently becoming much more of an issue.

This thesis deals with various tumor sites and stages of cancers located in the head and neck region. We have analyzed oropharyngeal cancers (patients with primary tumors of the tonsillar fossa, soft palate, base of tongue and lateral posterior/parapharyngeal wall), cancers of the nasopharynx and cancer of the nasal vestibule. Most of these cancers are treated by organ function preservation therapy protocols; for instance radiotherapy-only for some of the early-staged cancers and limited surgery and/or radiotherapy with or without chemotherapy for the more advanced tumors.
The goal of this thesis is to study the total costs for some of the protocolized routinely executed and new treatment regimes as applied in the Erasmus Medical Center over many years. These costs will be related to the side-effects and quality of life of the individual patients. This gives the possibility to discuss the cost-effectiveness of different treatment options.
From a global economic perspective (macro level), cost effectiveness evaluations can be used to study the treatment efficacy and/or costs related to side-effects, or for reimbursement purposes. From an organizational

1 DBC's are the Dutch synonym for DRG (Diagnosis Related Groups)

perspective (meso level), cost effectiveness evaluation provides an explicit supporting tool to decide whether or not to introduce a new treatment strategy. The active participation of individual physicians (micro level) in cost effectiveness studies is yet, unfortunately, rather limited. Obviously they should have an important role in this area of health care research, because of their clinical knowledge and treatment skills, but also being the initiator of the costs. Translation to the meso- and macro level learns that in order to avoid policy makers and health care insurers unilaterally imposing restrictions on (cancer) care, health care professionals should jointly start helping out how to set priorities in medicine. Some of the studies as presented in this thesis illustrate the benefit of the combined effort of physicians, policy makers and managers, that is to be jointly en route for a more transparent health care system.

All analyses for this thesis were done in conjoint effort with several departments inside and outside the Erasmus MC. The main departments involved were the institute of Medical Technology Assessment of the Erasmus MC, their main activities focuses on conducting applied scientific research in economic evaluation and medical technology assessment (MTA). The Ear, Nose, Throat department and the department of Plastic Surgery participated in the multidisciplinary head and neck tumorgroup and were actively involved in the medical research used in chapters 1 and 7. They also supported us with information for the cost calculations. The department of Medical statistics of the Erasmus MC helped a great deal with all statistical analysis. Finally, some companies (Elekta, Accuray) actively participated in the outline for a paper and the gain for data.

Outline Current Thesis

Chapter 2
This chapter reports on a comparison of local control, survival and functional outcome in patients with cancer of the base of tongue using two different treatment strategies applied in two different clinics, that is the Erasmus MC-Daniel den Hoed Cancer Center and the Free University Hospital Amsterdam.

Chapter 3
To illustrate the effectiveness and extra costs of a second boost of radiation by means of brachytherapy after a curative dose of 70 Gy, the specifics of the Erasmus MC treatment approach for cancer in the nasopharynx have been described in some detail.

Chapter 4
A cost calculation model is presented for two different treatment options (brachytherapy versus surgery); it is illustrated by analyzing the costs for cancer of the tonsillar fossa and/or soft palate.

Chapter 5
The hypothesis that subcutaneously injected amifostine is able to reduce and/or even prevent side-effects and can thus result in a reduction in costs, is tested. It is illustrated by the application of the same cost calculation model as presented in chapter 4 for head and neck cancer patients.

Chapter 6
In chapter 5 the clinical and economic impact is presented for a new treatment approach (Cyberknife) as opposed to a regular treatment strategy (IMRT, brachytherapy). It illustrates how to prioritize treatment strategies in case new treatment options become available.

Chapter 7
In chapter 6 a comparison of costs of three different treatment modalities for oropharyngeal tumors, that is teletherapy, brachytherapy and surgery, is reported, also taking into account the associated costs of complications. Weighted mean costs are presented for all treatment groups.

Chapter 8
The effectiveness, cosmesis and costs for two different treatment strategies, being interstitial radiation therapy or plastic surgery, in nasal vestibule cancer, are analyzed and presented.

Chapter 9
Longitudinal changes in Quality of Life and QALY's (Quality Adjusted Life Years) are presented for two treatment strategies (teletherapy and brachytherapy) in oropharyngeal cancer.

Chapter 10
Chapter 10 deals with the issue when adding a new treatment modality (hyperthermia) to established treatment modes (external beam radiotherapy and brachytherapy). The financial model (chapter 4) is used to 'forecast' whether adding Hyperthermia is cost-effective associated with minimal morbidity.

References
http://www.kwfkankerbestrijding.nl
http://www.CBS.nl

CHAPTER 2

Radical Radiotherapy compared with Surgery for Advanced Squamous Cell Carcinoma of the Base of Tongue

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Brachytherapy, 2004;3(2):78-86.

ABSTRACT

Purpose: This study reports on T3/T4 base of tongue (BOT) tumors treated at the Erasmus MC (Rotterdam) with external beam radiotherapy (EBRT) and brachytherapy (BT). Local control, survival, and functional outcome are compared to results obtained in similar patients treated at the Vrije University Medical Center (VUMC; Amsterdam) by surgery and postoperative RT (PORT).

Methods and Materials: At Rotterdam 46/2 Gy was given to the primary and bilateral neck, followed by an implant using low-dose-rate (24-35 Gy; median 27 Gy), or fractionated high-dose-rate (20-28Gy; median 24Gy). A neck dissection was performed in case of N+ disease. 67% of BOT tumors had a T4 cancer. At Amsterdam surgery followed by PORT 40-70 Gy (median 60 Gy) was performed; 26% BOT tumors were T4. Sex, age and nodal distribution were similar. Actuarial local control and survival were computed. Performance Status Scale (PSS) scores were established. Xerostomia was determined on visual analog scales (VAS).

Results: Local failure at 5-years was 37% (Rotterdam) vs. 9% (Amsterdam) ($p < 0.01$). The overall survival was not significantly different (median 2.5 years vs. 2.9 years, respectively [$p = 0.47$]). The PSS favored BT. Both groups were equally affected by xerostomia.

Conclusion: The 5-year local control was 65% with EBRT and BT. This result is strongly affected by the 4 patients with residual disease after implantation. The Rotterdam patients had more advanced BOT tumors (67% vs. 26% T4), explaining the higher local failure rate. Given the organ preservation properties of radiotherapy-only and the better PSS scores, the jury is still out on the optimal treatment for BOT tumors.

INTRODUCTION

The management of base of tongue (BOT) squamous cell carcinoma (scc) is still controversial. The major treatment options are external beam radiation therapy (EBRT) with or without interstitial radiotherapy (IRT), (hyperfractionated/accelerated) EBRT-alone, or surgery (S) combined with postoperative irradiation (PORT) [1-12]. There is considerable debate as to whether S or radiotherapy (RT) produces better (functional) results, particularly in advanced staged cancers. Other contentious issues for BOT tumors treated with primary RT include the boost technique (external vs. interstitial irradiation), planned neck dissection after previous radiotherapy (RT), and when to use (neo-adjuvant or) concomitant chemotherapy as a standard treatment option [13]. Surgical resection of the BOT carcinoma frequently results in poor swallowing and inadequate speech function. Therefore, at the Erasmus MC (Rotterdam), as of 1985 the treatment of preference has been EBRT to the primary tumor and bilateral neck, followed by a boost by means of brachytherapy (BT) to the BOT. Recently, the Vrije University Medical Center (VUMC, Amsterdam) published results on the outcome of BOT cancer in patients treated with S and PORT [14]. The primary purpose of this article is to evaluate the results of this organ function preservation protocol using EBRT and BT in patients with T3/T4 scc of the BOT. As a secondary endpoint, to put the outcome of the Erasmus MC protocol somewhat more in perspective, loco(regional) control, survival and functional performance scores were compared with similar score functions obtained in patients with advanced cancer of the BOT consistently treated by primary S and PORT at the department of Head and Neck Surgery of the VUMC (Amsterdam).

METHODS AND MATERIALS

Erasmus MC – Daniel den Hoed Cancer Center (Rotterdam)
This study included a total of 88 patients with advanced T3/T4 cancer of the BOT treated between 1980 and 1996. Thirty (34%) were treated at Erasmus MC (Rotterdam), and 58 (66%) at VUMC (Amsterdam). Sixty-four (73%) patients were men, 24 (27% were women. The median age at time of diagnosis was 58 years (range, 33-86). Demographic data of patients are depicted in Table 1. There was no statistically significant difference in sex- and age distribution between both series of patients. The diagnosis was established by joint consultation in the clinic by a radiation oncologist

Table 1: General characteristics of patients treated with T3 or T4 base of tongue tumors treated with primary surgery and primary radiotherapy at Erasmus MC and Vrije University MC

All patients n = 88	Erasmus MC	VUMC	p-value
Number of patients			
- (% of total)	30 (34)	58 (66)	
Sex (% in group)			0.110
- Male	25 (83)	39 (67)	
- Female	5 (17)	19 (33)	
Median age (range)	58 (33-86)	58 (37-75)	0.686
Primary tumor (% in group)			0.001
- T3	10 (33)	43 (74)	
- T4	20 (67)	15 (26)	
Lymph node (% in group)			0.850
- N0	9 (30)	13 (22)	
- N1	5 (17)	16 (28)	
- N2	15 (50)	26 (45)	
- N3	1 (3)	3 (5)	
Stage (% in group)			0.027
- III	4 (13)	21 (36)	
- IV	26 (87)	37 (64)	

and a head-and-neck surgeon, as well as by examination under general anesthesia (including morphological confirmation [biopsy] of the lesion). Ultrasound and, if appropriate, fine needle guided aspiration biopsies of the neck nodes were performed and CT and/or MRI scans of the primary tumor and neck obtained. The primary tumor and neck were (re)staged using the UICC classification system, 1997 edition [15]. Most patients treated at the Erasmus MC (Rotterdam) had a T4 tumor (20 out of 30 [67%]), as opposed to the majority of the patients treated in the VUMC (Amsterdam) having a T3 tumor (43 out of 58 [74%]). This difference in distribution of T-stage was found to be statistically significant ($p<0.01$). Consequently, more patients (87%) treated at Erasmus MC (Rotterdam) had stage IV disease, compared with 64% of the patients treated at the VUMC (Amsterdam).

Thirty patients (10 T3 tumors, 20 T4 tumors) at the Erasmus MC (Rotterdam) with primary scc of the BOT were analyzed in this report for the primary endpoints local control, survival, and functional performance status. Five patients had N1, 15 N2, and one was staged as having N3 disease. According to the treatment protocol used in the Erasmus MC (Rotterdam) at the time, EBRT combined with IRT was considered the first line of treatment. First a custom made head mask was obtained from the mouldroom to immobilize the head of the patient in supine position on the treatment table. After conventional simulation (and at a later stage by means of virtual simulation using a CT-simulator device [AQSim, Philips, Delft, The Netherlands]), the planning target volume (clinical target volume [CTV] + 0.5 cm margin) was planned using a 3D Treatment Planning computer (Cadplan; Varian Inc. Palo Alto, CA).

The dose is prescribed according to ICRU 50 recommendations. The first series of EBRT, using a conventional fraction size of 2 Gy, 5 fractions/week, was delivered by a linear accelerator using a 4 to 8 MV photon beam to the primary site and both sites of the neck to a total dose of 46 Gy. Generally, the PTV was covered by using a simple three-field technique (two parallel-opposed laterals and an abutted low-anterior field without a midline shield). After a total dose of 46 Gy and a rest period of 2-4 weeks, the EBRT was to be followed by implantation of afterloading catheters of the BOT under general anesthesia. In case of N+ disease, in the same operative session a neck dissection of the involved neck was performed. Because bleeding can occur with the removal of the catheters, a tracheotomy was performed in the majority of cases (20 out of 30 patients). The decision to do so is left to the discretion of the brachytherapist and/or surgeon and depends on factors like potential for bleeding (see above), patient's pre- and post-implant clinical condition, site and extent (volume) of implant. The basic principles and

technical aspects of the 3-4 plane BOT volume implant have been published previously [16-19]. From 1985 until 1991, low-dose-rate (LDR) Ir-192 wire sources (radioactivity of approximately 50 mCi/cm) were used in 16 patients. From 1991 onward, LDR was stopped and the remaining 14 implants were radiated according to a so-called fractionated high-dose-rate (fr.HDR) or pulsed-dose-rate (PDR) protocol. Fr.HDR (Ir-192 point source, activity ± 370 GBq, microSelectron HDR), with fraction sizes of 3-4 Gy, 2 fractions per day, minimum 6 h interval between fractions, and total dose of 24-35 Gy (median, 27Gy), was used in 5 patients. PDR (Ir-192 point source, activity ± 37 GBq, microSelectron PDR), with fraction sizes of 1-2 Gy, 8 fractions per day, minimum 3 h interval between fractions, and total dose of 20-28 Gy (median 24 Gy), was used in 9 patients. Patients were seen at follow-up by a radiation oncologist and a head-and-neck surgeon at regular intervals: in the first year every 6 weeks, in the second and third year every 3 months, and subsequently every 6 months.

VU University Medical Center (VUMC, Amsterdam)

The database of advanced BOT cancer in patients treated in the Amsterdam series originates from a previously published paper by Tiwari et al. [14].

For the current report, the medical records of all patients treated between 1980 and 1996 for histologically proven scc of the BOT, were again systematically reviewed, with the relevant findings briefly summarized here. Just as with the Erasmus MC (Rotterdam) series, patients with nonsquamous cell carcinoma, second primaries or those with distant metastases before the start of treatment were excluded from this study. (Re)staging procedures were similar to the ones used in Erasmus MC (see previous section). According to the protocol used at the VUMC (Amsterdam), patients were treated with S and PORT if their general condition allowed for major surgery. Of the 58 patients eligible, 43 (74%) had a T3 tumor, 15 (26%) were staged as T4.

The smaller T3 tumors and those with minimal infiltration were operated upon by partial resection, while the larger T3 tumors with deep infiltration and extension over the midline as well as the T4 tumors were treated with (sub)total excision of the BOT. Thirty-two patients underwent subtotal or total glossectomy.

Defects were reconstructed with a pedicled or a free myocutaneous flap. Finally, after a rest period of 2-6 weeks, EBRT was started. The PTV was covered by using a simple three-field technique (two parallel-opposed laterals and an abutted low-anterior field without a midline shield).

After a total dose of 46 Gy, the fields were taken off-cord and posterior neck supplemented using high-energy electrons (10 MeV) to a cumulative dose of 60-70 Gy. After completion of the treatment protocol, patients were seen at regular intervals (see previous Rotterdam series) at the outpatient clinic of the departments of Otolaryngology-Head and Neck Surgery and Radiotherapy.

Functional Performance

To assess the functional performance, questionnaires were sent in 2002 to all long-term survivors. These questionnaires included the Performance Status Scale for Head and Neck Cancer Patients (PSS) as developed by List et al. [20], and a Visual Analogue Scale for xerostomia. The PSS consists of a number of questions scored on a subjective scale, whereby the patient can be evaluated in terms of daily core activities. The scale was designed to measure the unique disabilities of head-and-neck cancer patients. The major parameters evaluated included the ability to eat in public, understandability of speech, and normalcy of diet (Table 2).

To determine salivary gland function, a visual analogue scale for xerostomia was submitted to all patients as well. This VAS for xerostomia scores the patients' subjective feeling of dryness on a scale of 0 (full saliva, wet) to 10 (complete dryness). A research nurse performed a standardized interview to determine the PSS and VAS scores, 2 weeks after the questionnaires were sent out.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 10.1. To analyze differences in male/female ratio and initial staging of primary tumor and neck, a Pearson chi square was applied. Differences in age distribution were tested using the distribution-free non-parametric Mann-Whitney Test [21]. Survival curves were constructed using the method described by Kaplan and Meier. The statistical significance of the difference between the curves was calculated using the log-rank test. Cumulative incidence rates of local recurrence and disease recurrence (local recurrence, locoregional metastases or distant metastases) were calculated from the time of diagnosis of the primary tumor using actuarial or life table methods [21]. Patients were censored and considered no longer at risk for recurrence of disease if they had died or if they were alive at the end of the observation period without

Table 2: Performance Status Scale for head and neck cancer

Eating in public	
100	No restriction of place, food, or companion (eats out at any opportunity).
75	No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less 'messy' foods, e.g., liquids).
50	Eats only in presence of selected persons in selected places
25	Eats only at home in presence of selected persons
0	Always eats alone
Understandability of speech	
100	Always understandable
75	Understandable most of the time; occasional repetition necessary
50	Usually understandable; face-to-face contact necessary
25	Difficult to understand
0	Never understandable; may use written communication
Normalcy of diet	
100	Full diet (no restrictions)
90	Peanuts
80	All meats
70	Carrots, celery
60	Dry bread and crackers
50	Soft, chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)
40	Soft foods requiring no chewing (e.g., mashed potato, apple sauce, pudding)
30	Pureed foods (in blender)
20	Warm liquids
10	Cold liquids
0	Non-oral feeding (tube fed)

clinical evidence of recurrence of disease. Patients in whom a second primary tumor was detected during follow-up were censored and considered no longer at risk for recurrence of disease from the moment of the diagnosis of the second primary tumor. Differences in overall survival, disease free survival and locoregional recurrence free survival for hospital, male and female, age categories and clinical stage were tested using the univariate Cox regression analysis (proportional hazards model) [21].

RESULTS

Tumor control: Erasmus MC, Rotterdam and VUMC, Amsterdam

Table 3 represents the cumulative frequency of local-, and regional recurrence, as well as distant metastasis, calculated by using the actuarial or life table methods at 1, 2, 3, and 5 years after diagnosis. At 5 years the cumulative incidence of distant metastasis is not very different and relatively high in both treatment groups (30% [RT] vs. 39% [S]; Table 3). This is (partly) reflected in the poor CSS (48% vs. 57%, p=0.16; Figure 1) of the BT group and the S-group. The same was true for disease recurrence, stage for stage (T3 vs. T4) (Table 4). Four patients did not achieve a complete remission after primary RT; these patients were non-salvageable and died within a few weeks or months after primary RT. Locoregional failures were mostly diagnosed in the first 2 years after diagnosis. The local and regional recurrence rate at 5-years in patients treated for their primary cancer with RT compared with patients treated with S and PORT was 37% and 18%, vs. 9% and 12%, respectively. The development of distant metastases in both institutions is 14% vs. 21% at 2 years, cumulating to 30% and 39% at 5-years for the Erasmus MC (radiotherapy) and VUMC (surgery), respectively. Figure 2 depicts the local disease free survival for locally advanced BOT cancer as obtained in both head and neck cancer centers. The local disease free survival was found to be statistically significantly different, in favor of the surgically treated patients (VUMC, Amsterdam) (log rank 12.58, p< 0.01). Disease free survival curves are presented in Figure 3. A statistically significant difference between both treatment groups was found, in favor of the patients treated in Amsterdam (log rank 4.04, p = 0.04). Univariate Cox regression analyses were performed in order to assess the influence of sex, age, T-stage and nodal stage on disease recurrence. Disease free survival was not statistically significantly influenced by these variables. For cause specific survival, no statistically significant difference was found between the treatment groups

Table 3: Cumulative frequency of recurrence using actuarial or life table methods after 1, 2, 3 and 5 years in patients with T3 or T4 base of tongue tumors

	Local recurrence		Regional recurrence		Distant recurrence		Disease recurrence	
	Erasmus MC* %	VUMC %	Erasmus MC %	VUMC %	Erasmus MC %	VUMC %	Erasmus MC* %	VUMC %
one year	32	4	12	6	8	7	38	13
two years	37	9	18	8	14	21	46	30
three years	37	9	18	12	30	21	56	33
five years	37	9	18	12	30	39	56	47

VUMC = Vrije University MC.
* Four patients with residual disease were included in this analysis and considered to have failure.

Table 4: Cumulative frequency of recurrence using actuarial of life table methods after 1, 2, 3 and 5 years according to T-stage.

	Local recurrence		Regional recurrence		Disease recurrence	
T3 tumors	Erasmus MC %	VUMC %	Erasmus MC %	VUMC %	Erasmus MC %	VUMC %
One year	24	5	13	8	33	12
Two years	41	5	32	11	60	29
Three years	41	5	32	15	60	36
Five years	41	5	32	15	73	49
	Local recurrence		Regional recurrence		Disease recurrence	
T4 tumors	Erasmus MC %	VUMC %	Erasmus MC %	VUMC %	Erasmus MC %	VUMC %
One year	17	0	12	0	22	14
Two years	17	21	12	0	36	40
Three years	17	21	12	0	58	40
Five years	17	21	12	0	58	57

VUMC = Vrije University MC.

Figure 1: Cause-specific survival in patients treated by primary radiotherapy (Erasmus MC, Rotterdam) or primary surgery (VUMC, Amsterdam) for T3 or T4 tumors using Kaplan Meier analysis. The thin line represents patients treated in VUMC, the thick line patients treated in Erasmus MC (log-rank 1.97; $p < 0.16$)

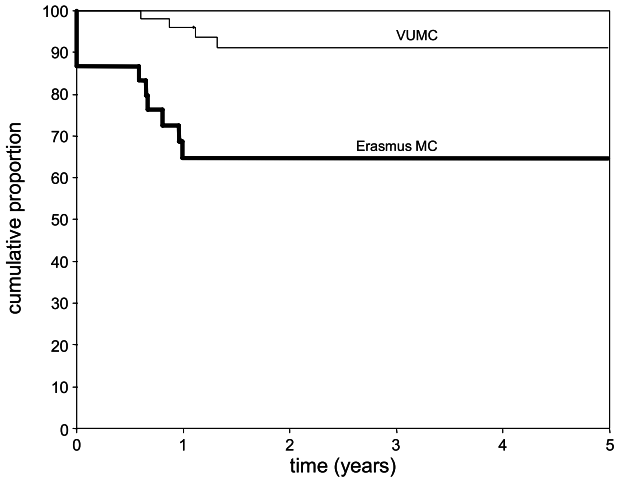
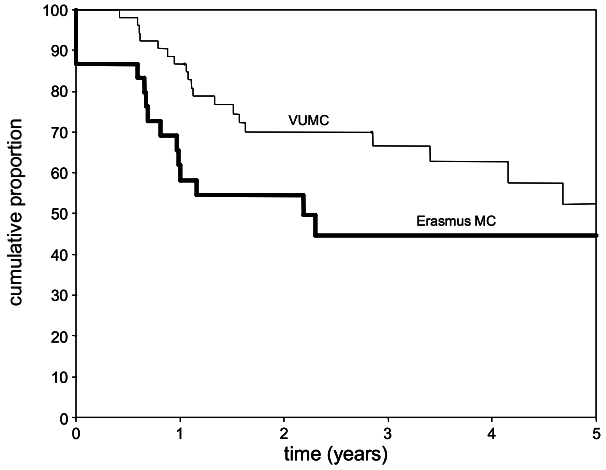


Figure 2: Local disease free survival in patients treated by primary radiotherapy (Erasmus MC, Rotterdam) or primary surgery (VUMC, Amsterdam) for T3 or T4 tumors using Kaplan Meier analysis. The thin line represents patients treated in VUMC, the thick line patients treated in Erasmus MC (log-rank 12.58; $p < 0.01$)



(log-rank 1.97, p 0.16). Cause specific and overall survival curves, constructed by the Kaplan-Meier method, are shown in Figures 1 and 4, respectively. The overall survival curves of both patient populations are almost super-imposable (log-rank 0.52, p = 0.47). Prognostic factors affecting overall survival for all patients were analyzed using univariate Cox regression analysis. Hospital, sex, age, extent of the primary tumor, regional lymph node involvement, and initial stage were not significantly associated with death.

Side-effects and functional outcome parameters

In 12 implanted patients, even at 2-year follow-up, the mucosa of the BOT seemed extremely friable; 2 long-term survivors experienced grade IV dysphagia, necessitating surgical intervention and/or permanent tube feeding [2]. Since we were not able to clinically examine all patients treated by S or BT, questionnaires were sent out in 2002 to all survivors at least 2 years out and NED. Table 5 shows the functional results of the Performance Status Scale (PSS), calculated according to the original proposal of List et al. [20] as well as the VAS scores for xerostomia for both treatment groups. The eating in public subscale assessed the degree to which the patients can eat in the presence of other people. Median scores were 100 in patients treated with primary radiotherapy and 63 in patients treated with primary surgery. Understandability of speech was defined as the patient's subjective awareness of others' ability to understand his or her speech. In patients treated with primary RT, median scores were 88, compared to 75 in patients treated with radical S. The normalcy of diet scale assessed the degree to which the patient was able to eat a normal diet. Ratings were based on the highest ranking of the food the patient was able to eat. Median scores were 100 vs. 40 in patients treated in Erasmus MC (Rotterdam) vs. VUMC (Amsterdam), respectively. Although, overall, the scores are found to be somewhat better in patients treated with primary RT, no significant difference with respect to ability to eat in public (mean scores 78 [Rotterdam] vs. 55 [Amsterdam]), and understandability of speech (mean scores 81 [Rotterdam] vs. 63 [Amsterdam]) were found. The normalcy of diet is significantly better in patients treated in the Erasmus MC (RT) as opposed to the VUMC (surgery) (mean scores 88 vs. 38, respectively [$p < 0.01$]). The median VAS scores for xerostomia were not different in patients treated with radiotherapy (Erasmus MC, Rotterdam) as opposed to primary surgery (VUMC, Amsterdam) (median score 4.7 vs. 4.0).

Figure 3: Disease-free survival in patients treated by primary radiotherapy (Erasmus MC, Rotterdam) or primary surgery (VUMC, Amsterdam) for T3 or T4 tumors using Kaplan Meier analysis. The thin line represents patients treated in VUMC, the thick line patients treated in Erasmus MC (log-rank 4.04; p 0.04)

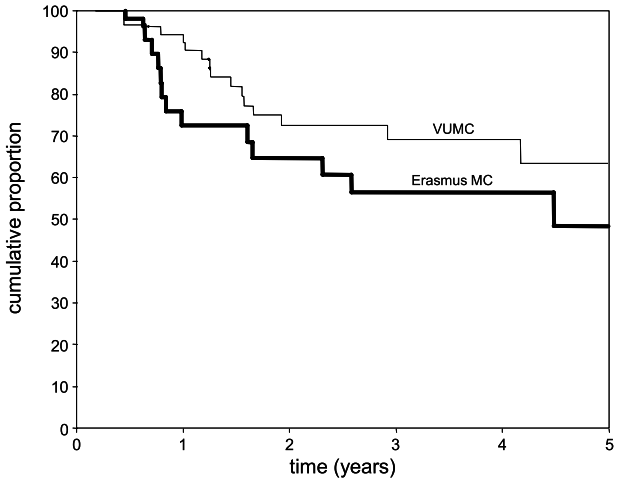


Figure 4: Overall survival in patients treated by primary surgery (VUMC, Amsterdam) or primary radiotherapy (Erasmus MC, Rotterdam) for T3 or T4 tumors using Kaplan Meier analysis. The thin line represents patients treated in VUMC, the thick line patients treated in Erasmus MC (log-rank 0.52; p 0.47)

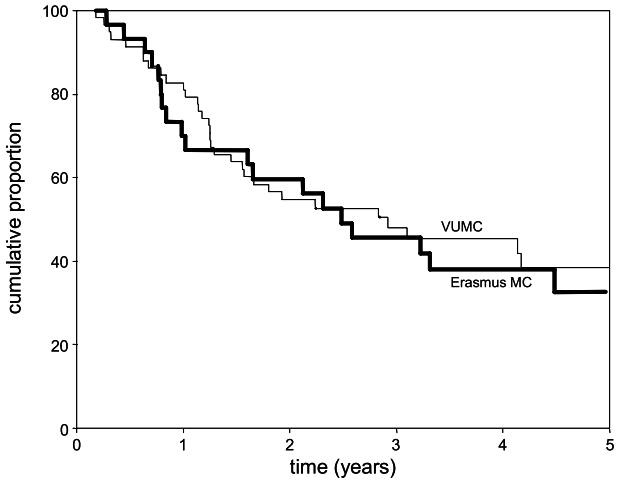


Table 5: Performance Status Scale (PSS) in long-term survivors treated by primary radiotherapy (Erasmus MC)(n = 8) or by primary surgery (VUMC) (n = 14) for base of tongue cancer

	N	Mean	Median	Std dev	p-value (Mann-Whitney test)
Eating in public					0.13
- Erasmus MC	8	78	100	41	
- VUMC	14	55	63	38	
Understandability of speech					0.06
- Erasmus MC	8	81	88	26	
- VUMC	14	63	75	27	
Normalcy of diet					< 0.01
- Erasmus MC	8	88	100	23	
- VUMC	14	38	40	33	
VAS for xerostomia					1.00
- Erasmus MC	7*	3.3	2.0	3.1	
- VUMC	14	3.6	4.0	3.2	

* one value was missing.

DISCUSSION

Head and neck cancer frequently has a morbid character and can be a disabling and disfiguring disease. The major contrasting treatment options for the BOT are primary (hyperfractionated / accelerated) radiotherapy, i.e., external beam with or without interstitial radiation therapy, or surgery combined with postoperative RT. Currently, as is the case for many other advanced head and neck cancers, the role of concomitant chemotherapy is being explored. Finally, although function preservation is generally the preferred treatment, being a rare tumor, the treatment modality of choice in BOT cancer often reflects personal (technical skills) and/or institutional experience.

The objective of this study is to evaluate the results of patients with advanced T3/T4 scc of the BOT, treated consistently with EBRT to the primary and neck, followed by an implant of the primary cancer and a ND for N+ disease. As a secondary endpoint, it tries to put the date in some perspective by comparing the results of EBRT plus BT to S plus PORT. However, the data of this last treatment group are obtained from a series of patients treated at another academic hospital (VUMC, Amsterdam). We fully acknowledge that, given the nonrandomized nature of the data and the retrospective character of the analysis, major limitations exist when trying to compare the tumor control outcome and quality of life of the S-group with the BT-group. But since there are no randomized trials, decision making on the effectiveness of a particular protocol often has to be based, unfortunately, on comparisons with historical controls and/or matched patient populations from other institutions. Fortunately, the patient groups were comparable to a large extent, except for T-stage (Table 1), i.e., in contrast to the patients of the Erasmus MC (Rotterdam) treated by an implant (67% T4), a significantly lower percentage of patients treated at the VUMC (Amsterdam) had T4 disease (26%). So in essence, it remains difficult to discern whether the difference in treatment results is related to patient or treatment modality selection. Both institutions are dedicated centers for head and neck cancer treatment in the Netherlands; however, with a significantly different primary treatment approach for advanced BOT tumors.

The head and neck cooperative group of the Erasmus MC (Rotterdam), in particular with regard to oropharyngeal cancers, has traditionally been oriented towards optimizing organ preservation therapy using radiation as a mainstream therapy modality in early as well as advanced tumors [22,23]. The Department of Head and Neck Surgery of the VUMC has a long standing surgical experience advanced cancers in the head and neck [13,24,25].

The majority of institutions around the world using primary surgery for BOT carcinomas prefer to use this modality in limited staged primaries (T1-3). For example, the percentage of T4 tumors treated by surgery in different institutes varies between 0 and 41%, leaving the more advanced cases for EBRT [8,12,26-28]. This is comparable with the surgical series of the VUMC (33% T4). The percentage of T4 tumors treated with an implant after a first series of EBRT varies, according to the literature, between 0 and 17% [6,11,29,30]. At the Erasmus MC (Rotterdam), 67% of the patients treated by IRT had a T4 staged primary tumor. From these observations, it can be expected that, as a result of the difference in T-stage, obtaining tumor control in advanced primary BOT cancer treated per protocol in Rotterdam (Erasmus MC) by EBRT plus BT and in Amsterdam (VUMC) by S plus PORT, are dissimilar. In fact, better local tumor control was indeed obtained at the VUMC as opposed to the Erasmus MC (at 2-years 91% vs. 63%, respectively). As recently stated by Robbins [31], curing advanced head and neck cancers by combined modality therapy does not imply the battle against these cancers has been won, because the barriers of organ dysfunction, patient co-morbidity, and secondary cancers too often negate therapeutic successes. As a consequence, it remains extremely difficult to demonstrate survival advantages. This is illustrated here again by the cause-specific survival (CSS) at 5-years; due to the force of mortality of distant metastasis (at 4-years more than one fourth of the patients died of metastatic disease in both groups), the CSS was not significantly different for the patients treated by either primary radiation therapy or surgery (at 5-years 48% vs. 57%, respectively, [Figure 1]). This is also true for disease recurrence according to T-stage (T3 vs. T4) (Table 4).

The local control rate for T3/T4 tumors in patients treated with primary radiotherapy seems, compared with the current literature, somewhat less favorable [6,11,29,30]. Most likely, as has been alluded to before, this is the result of the difference in patient selection, i.e. the high number of patients with T4 tumors in the series of the Erasmus MC (Rotterdam). The four patients (13%) having residual disease after the implant should also be factored in.

In retrospect, 2 out of 4 residual disease patients had T4 disease, with implants that would at the present day and age barely be considered optimal in terms of adequate target coverage. In radiotherapy we are in need of better selection criteria when considering patients for large volume implants, and, specifically, better imaging tools to define our target volumes.

We hope that the radiotherapy results can be improved further. Currently, the organ preservation protocol has been modified to some extent: the overall

treatment time is, as with all curative tumors in the head and neck, shortened (6 in stead of 5 fractions/week) and, in case of T3/T4 tumors, the EBRT is given with concomitant chemotherapy (2 courses of concomitant cisplatin). Major emphasis is given to implementing intensity modulated radiotherapy (IMRT) techniques for the first series of EBRT. But it is fair to state that due to the development of new techniques, results can be improved upon in case of S also. For example, at the VUMC, now all defects after surgery for advanced stage base of tongue carcinomas are reconstructed with a vascularized free radial forearm flap or rectus abdominis myocutaneous flap instead of an pedicled pectoralis major myocutaneous flap to improve functional outcome. For better swallowing results, laryngeal suspensions are strictly used in these patients.

The importance of reporting on side-effects and functional performance of our patients after treatment is underlined by our own findings and those reported in the literature. In the analysis by Parsons et al. [12], comparing treatment results form North American academic institutions using S ± RT vs. RT ± ND for cancer of the BOT, local control (79% vs. 76%; p= 0.087), CSS (62% vs. 63%; p= 0.41), and overall survival at 5 years (49% vs. 52%; p = 0.2) were all nonsignificantly different. Severe complications, however, did differ (32% vs. 3.8%; p = < 0.001), with more side effects in the case of surgery. We would not corroborate the findings regarding surgery. However, patients treated with primary radiotherapy fared better in functional outcome in terms of eating in public, normalcy of diet and understandability of speech. In short: with regard to the PSS, 8 out of 8 patients (100%) of the Erasmus MC versus 7 out of 14 (50%) of the VUMC stated they go to a public restaurant regularly to eat and "socialize". With respect to understandability of speech, for 1 patient (13%) of the Erasmus MC as opposed to 5 (29%) of the VUMC, speech comprehension required a major effort on the part of the listener (≤ 50 on the understandability of speech scale).

Twenty-five percent of the patients (2 out of 8) treated by primary RT were eating soft foods at best (≤ 50 on the normalcy of diet scale), compared to 86% [12, 14] of the patients treated by primary S. Mean scores in the radiotherapy subset were comparable with scores in 9 long-term survivors with T3/T4 BOT cancer reported by Harrison et al. [32] and with the 20 long-term survivors with T3/4 BOT reported by Moore and coworkers [33]. The functional outcome in the patients treated with primary S in our group was slightly better than the experience reported by Harrison [32] (5 patients with T3/4 tumors), but slightly worse than the experience with 7 patients with T3 tumors reported by the same institute recently [34].

Scores of xerostomia, using a visual analogue scale, showed that patients treated with radical S fared almost similar as to the patients treated with primary RT-the majority experiencing subjectively some degree of dryness: Erasmus MC, and VAS-xerestomia 3.3 (SD 3.1), and VUMC mean VAS xerestomia, 3.6. (SD 3.1) (Table 5). For certain patients at Erasmus MC with T3/T4 cancers of the BOT, a combination of EBRT and IRT, supplemented by two courses of concomitant chemotherapy is the best treatment modality. Given the treatment techniques and the doses of radiation used at the time in both institutions, albeit in a primary or postoperative setting, this finding can be explained obviously by having surpassed the tolerance of the salivary glands.

Summary

The patients treated with primary S had less advanced disease (33% T4) as opposed to those treated with primary RT (67% T4). Moreover, although in this report the S-group had a better local control rate as opposed to the primary RT group, with both treatment policies overall reasonable locoregional control and survival rates were obtained and both will probably remain to have their (institutional) advocates. The differences in functional outcome as reported in this article could help clinical investigators decide which treatment is to be preferred. In fact, the data presented illustrate the preference of patients for organ preservation therapies; once more it is demonstrated that functional outcome and/or quality of life assessment is essential in determining the final outcome when comparing different treatment strategies. Major improvements in reconstructive surgical procedures also play an important role in benefiting these patients.

Intensity modulated radiotherapy will be implemented routinely to try and diminish side effects such as mucositis and xerestomia and further improve the functional performance of the patients. Given the nonrandomized, retrospective character of the comparison, the jury is still out on the optimal treatment of T3/T4 BOT cancer.

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We appreciate the skills and dedication in patient care of the members of the Head and Neck Cancer Groups in the Vrije University Medical Center, Amsterdam (VUMC) and the Erasmus MC - University Medical Center, Rotterdam. In particular, we would like to acknowledge the research nurse of the Department of Radiation-Oncology of the Erasmus MC, Mrs. Cora Braat, for collecting the functional outcome data.

REFERENCES

1 Foote RL, Parsons JT, Mendenhall WM, Million RR, Cassisi NJ, Stringer SP. Is interstitial implantation essential for successful radiotherapeutic treatment of base of tongue carcinoma? Int J Radiat Oncol Biol Phys 1990;18:1293-1298.

2 Foote RL, Olsen KD, Davis DL, Buskirk SJ, Stanley RJ, Kunselman SJ et al. Base of tongue carcinoma: patterns of failure and predictors of recurrence after surgery alone. Head Neck 1993;15:300-307.

3 Goffinet DR, Harrison LB. 192 iridium implantation of base of tongue carcinoma. Int J Radiat Oncol Biol Phys 1991;21:867.

4 Harrison LB, Sessions RB, Strong EW, Fass DE, Nori D, Fuks Z. Brachytherapy as part of the definitive management of squamous cancer of the base of tongue. Int J Radiat Oncol Biol Phys 1989;17:1309-1312.

5 Harrison LB, Zelefsky MJ, Sessions RB, Fass DE, Armstrong JG, Pfister DG et al. Base-of-tongue cancer treated with external beam irradiation plus brachytherapy: oncologic and functional outcome. Radiology 1992;184:267-270.

6 Harrison LB, Lee HJ, Pfister DG, Kraus DH, White C, Raben A et al. Long term results of primary radiotherapy with/without neck dissection for squamous cell cancer of the base of tongue. Head Neck 1998;20:668-673.

7 Hinerman RW, Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. External beam irradiation alone or combined with neck dissection for base of tongue carcinoma: an alternative to primary surgery. Laryngoscope 1994;104:1466-1470.

8 Machtay M, Perch S, Markiewicz D, Thaler E, Chalian A, Goldberg A et al. Combined surgery and postoperative radiotherapy for carcinoma of the base of radiotherapy for carcinoma of the base of tongue: analysis of treatment outcome and prognostic value of margin status. Head Neck 1997;19:494-499.

9 Mak AC, Morrison WH, Garden AS, Ang KK, Goepfert H, Peters LJ. Base-of-tongue carcinoma: treatment results using concomitant boost radiotherapy. Int J Radiat Oncol Biol Phys 1995;33:289-296.

10 Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Moore-Higgs GJ, Cassisi NJ. Is radiation therapy a preferred alternative to surgery for squamous cell carcinoma of the base of tongue? J Clin Oncol 2000;18:35-42.

11 Puthawala AA, Syed AM, Eads DL, Gillin L, Gates TC. Limited external beam and interstitial 192iridium irradiation in the treatment of carcinoma of the base of the tongue: a ten year experience. Int J Radiat Oncol Biol Phys 1988;14:839-848.

12 Parsons JT, Mendenhall WM, Stringer SP, et al. Squamous cell carcinoma of the oropharynx: Surgery, radiation therapy, or both. Cancer 1994;11:2967-2980.

13 Calais G, Bardet E, Sire C, et al. Radiotherapy with concomitant weekly Docetaxel for stages III/IV oropharynx carcinoma. Results of the 98-02 Gortec Phase II trial. Int J Radiat Oncol Biol Phys 2004;58:161-166.

14. Tiwari RM, van Ardenne A, Leemans CR, Quak JJ, Tobi H, Mehta DM et al. Advanced squamous cell carcinoma of the base of the tongue treated with surgery and post-operative radiotherapy. Eur J Surg Oncol 2000;26:556-560.

15 Sobin LH, ed. TNM UICC/AJCC - Classification of malignant tumours. 5th ed. New York: Wiley-Liss, 1997.

16 Levendag PC, Vikram B, Flores AD, Yin WB. High dose rate brachytherapy for cancer of the head and neck. In: Nag S, editor. High dose rate brachytherapy: a textbook. New York: Futura Publishing Company, Inc.; 1994: 237-273.

17 Levendag PC, van Putten WLJ. Brachytherapy in head and neck cancer: Rotterdam low dose rate experience. In: Martinez AA, Orton CG, Mould RF, editors. Brachytherapy; HDR and LDR. Columbia, USA: Nucletron Corporation; 1990: 325-344.

16 Levendag PC, Nowak PJCM, van der Sangen MJ, Jansen PP, Eijkenboom WMH, Planting AS et al. Local tumor control in radiation therapy of cancers in the head and neck. Am J Clin Oncol 1996;19:469-477.

18 Levendag PC, Keus RB. Radiotherapy in head and neck oncology. In: Jones AS, Philips DE, Hilgers FJM, editors. Diseases of the head and neck, nose and throat. Arnold; 1998: 183-196.

19 Visser AG, van den Aardweg GJ, Levendag PC. Pulsed dose rate and fractionated high dose rate brachytherapy: choice of brachytherapy schedules to replace low dose rate treatments. Int J Radiat Oncol Biol Phys 1996;34:497-505.

20 List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. Cancer 1990;66:564-569.

21 Simpson PM, Spratt JA, Spratt JS. Statistical methods in cancer research. J Surg Oncol 2001;76:201-223.

22 Levendag PC, Schmitz PI, Jansen PP, Senan S, Eijkenboom WMH, Sipkema D et al. Fractionated high-dose-rate and pulsed-dose-rate brachytherapy: first clinical experience in squamous cell carcinoma of the tonsillar fossa and soft palate. Int J Radiat Oncol Biol Phys 1997;38:497-506.

23 Levendag PC, Nijdam WM, Noever I et al. Brachytherapy vs. Surgery in carcinoma of the tonsillar fossa and/or soft palate: Late adverse sequelae and performance status. Can we be more selective and obtain better sparing? Int J Radiat Oncol Biol Phys. In press.

24 Leemans CR, Engelbrecht WJ, Tiwari R, Deville WL, Karim AB, van de, I et al. Carcinoma of the soft palate and anterior tonsillar pillar. Laryngoscope 1994;104:1477-1481.

25 Leemans CR. Surgical management of cancer of the oropharynx. Clin Oncol 1999;11:136.

26 Kraus DH, Vastola AP, Huvos AG, Spiro RH. Surgical management of squamous cell carcinoma of the base of the tongue. Am J Surg 1993;166:384-388.

27 Nisi KW, Foote RL, Bonner JA, McCaffrey TV. Adjuvant radiotherapy for squamous cell carcinoma of the tongue base: improved local-regional disease control compared with surgery alone. Int J Radiat Oncol Biol Phys 1998;41:371-377.

28 Thawley SE, Simpson JR, Marks JE, Perez CA, Ogura JH. Preoperative irradiation and surgery for carcinoma of the base of the tongue. Ann Otol Rhinol Laryngol 1983;92:485-490.

29 Crook J, Mazeron JJ, Marinello G, Martin M, Raynal M, Calitchi E et al. Combined external irradiation and interstitial implantation for T1 and T2 epidermoid carcinomas of base of tongue: the Creteil experience (1971-1981). Int J Radiat Oncol Biol Phys 1988;15:105-114.

30 Lusinchi A, Eskandari J, Son Y, Gerbaulet A, Haie C, Mamelle G et al. External irradiation plus curietherapy boost in 108 base of tongue carcinomas. Int J Radiat Oncol Biol Phys 1989;17:1191-1197.

31 Robbins KT. Barriers to winning the battle with head-and-neck cancer. Int J Radiat Oncol Biol Phys 2002;53:4-5.

32 Harrison LB, Zelefsky MJ, Armstrong JG, Carper E, Gaynor JJ, Sessions RB. Performance status after treatment for squamous cell cancer of the base of tongue - a comparison of primary radiation therapy versus primary surgery. Int J Radiat Oncol Biol Phys 1994;30:953-957.

33 Moore GJ, Parsons JT, Mendenhall WM. Quality of life outcomes after primary radiotherapy for squamous cell carcinoma of the base of tongue. Int J Radiat Oncol Biol Phys 1996;36:351-354.

34 Friedlander P, Caruana S, Singh B, Shaha A, Kraus DH, Harrison LB et al. Functional status after primary surgical therapy for squamous cell carcinoma of the base of the tongue. Head Neck 2002;24:111-114.

CHAPTER 3

Chemotherapy and High–Dose-Rate Brachytherapy in the Management of Advanced Cancers of the Nasopharynx. Clinical Impact of High Technology: is it worth the Cost?

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ABSTRACT

Purpose: The aim of this study was to calculate the costs of chemotherapy and high–dose-rate brachytherapy in advanced-stage nasopharyngeal cancer. It is argued whether the effect of chemotherapy and this type of high-dose, high-precision radiation therapy is worth the costs.

Methods and Materials: Clinical results of stage III–IVB nasopharyngeal cancer in patients treated between 1991 and 2000 are reported. Treatment was broken down into five categories: workup, chemotherapy, preparation of radiation therapy, and application of radiation. For each category, costs were computed. Nasopharyngeal cancer treatment costs were compared with costs previously reported on patients treated for cancers of the oral cavity, larynx, and oropharynx.

Results: With the addition of neoadjuvant chemotherapy and high cumulative doses of radiation (77–81 Gy) with brachytherapy, disease-free survival increased from 48% to 74% (p=0.002), and overall survival increased from 35% to 72% (p=0.005). The Rotterdam protocol has been implemented stepwise: as of 1991, costs per patient increased from €4.521 ($5.023; 2001 exchange rate [December]: 1 Euro ~ 0.88 US$) for conventional external beam radiation therapy to €13.728 ($15.253) in 2000 for combinations of chemotherapy, conventional external beam radiation therapy, and brachytherapy. In case of stereotactic radiotherapy, the cost was €14.516 ($16.495).

Conclusions: Costs for cancer in the nasopharynx vary from €14.528 ($16.509) to €15.316 ($17.405) in case of brachytherapy and stereotactic radiotherapy, respectively, if follow-up costs are added. The treatment cost for other head and neck sites was €21.858 ($24.126). Given the improvement in survival, the sparing capabilities of current high-dose, high-precision radiotherapy techniques, and the favorable cost profile compared with other sites, it is argued that costs should not be considered prohibitive for the introduction of chemotherapy and high–technology-based radiotherapy in advanced nasopharyngeal cancer.

INTRODUCTION

The rationale for the application of high doses of radiation is underscored by dose–tumor effect relationships [1– 10]. Moreover, local control (LC), being one of the most important prognostic factors in nasopharyngeal cancer, has been shown to be an independent prognostic indicator of distant metastasis [9]. Currently a variety of treatment techniques is used in nasopharyngeal cancer to apply highly conformal high doses of radiation to the primary tumor and neck nodes [11–14]. In our institution we have, since 1991, routinely used brachytherapy to boost the dose delivered to the primary tumor site in all stages to 77–81 Gy [15,16]. With this high-dose protocol, we obtained excellent clinical results with radiation therapy alone for T1-2N0/1-staged nasopharyngeal cancer: LC was 97%, and overall survival (OS) was 67% at 3 years. For advanced tumor stages, the combination of radiotherapy and chemotherapy is considered mandatory at present [17–23]. In our cancer center, in stage III–IVB disease, by using neoadjuvant chemotherapy and brachytherapy as a boost (Rotterdam protocol), the disease-free survival (DFS) and OS at 3 years improved from 48% to 74% (p =.002) and from 35% to 72% (p=0.005), respectively (see also "Discussion"). However, it is now well established that the administration of chemotherapy in combination with high cumulative doses of radiotherapy, especially when given in a concurrent fashion, can be associated with (severe) toxicity [24,25]. Given this increased toxicity with combined-modality treatment, the search for optimal sparing (e.g., saliva, mucosa) is of particular relevance for locally advanced nasopharyngeal cancer. With the application of three-dimensional conformal radiation therapy (3DCRT) techniques to the primary tumor and neck nodal regions [26–28], however, sparing of the surrounding critical normal tissues comes within reach. Less optimal results are observed for the poor prognostic subset of patients, that is, T3-4 nasopharyngeal cancer of the well, moderately, and poorly differentiated histologic subtypes; LC and OS were 67% at 3 years [16,29,30]. These results need further improvement. In this respect, in case of T3-4 tumors, it is suggested for the future, with the aim of better target coverage, to boost the primary tumor by means of stereotactic radiation therapy instead of by brachytherapy [12,14,31,32].

Be that as it may, the improvements in LC and OS for stage III–IVB nasopharyngeal cancer with the respective changes in the Rotterdam nasopharyngeal cancer protocol over time heavily relied on the conjoint implementation of chemotherapy and high doses of brachytherapy. Given the up-front limited health care resources, the question can be raised whether the

addition of advanced technology and chemotherapy in treatment modalities is cost-effective. Moreover, clinicians and managers are often unfamiliar with the costs per se generated by these highly sophisticated types of treatments. The aim of this article is to calculate total costs of the different additional steps that evolved over the years in the advanced nasopharyngeal cancer Rotterdam protocol. Detailed computations of the treatment costs for advanced nasopharyngeal cancer patients are presented for the protocol as it is, as well as in anticipation of the steps that will be taken in the immediate future. The costs are related to previous cost computations for various other cancer sites in the head and neck. Finally, the question is raised whether some of the "sacred cows" of radiation oncologists and clinical physicists—the implementation of technology-driven highdose, high-precision radiotherapy techniques—are worth the extra costs.

METHODS AND MATERIALS

Rotterdam nasopharyngeal cancer protocol

For a general overview, the reader is referred to a recently presented detailed analysis of 91 primary nasopharyngeal cancer patients treated routinely by a brachytherapy boost [30]; the protocol and relevant findings are briefly summarized in this article. All patients were jointly seen by the radiation oncologist and ear, nose, and throat surgeon; diagnosis and staging was performed along conventional guidelines and rules of the International Union Against Cancer/American Joint Committee on Cancer classification system, 1997 edition [33–35]. As of 1991, patients with carcinoma of the nasopharynx, irrespective of the differentiation grade, were treated by a combination of external radiation therapy and high–dose-rate endocavitary brachytherapy. External beam radiation therapy was given by using conventional fractionation (2 Gy/d) to a dose of 60 Gy (T1-2a) or 70 Gy (T2b–4). Brachytherapy was applied by means of the silicone Rotterdam Nasopharynx Applicator (Nucletron, Veenendaal, The Netherlands) connected to a computerized afterloading machine (microSelectron high dose rate; stepping 192Ir point source, activity nominally 370 GBq). A boost dose was applied by fractionated high dose rate, with a total dose of 11 Gy (three fractions) or 17 Gy (five fractions). The dose was prescribed according to the International Commission on Radiation Units guidelines (external beam radiation therapy) or anatomically defined points (brachytherapy; see also references 15 and 16). The cumulative dose in the nasopharynx for stage

III–IVB disease was either 77 or 81 Gy. 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, N2-3, or both; stages III– IVB), according to the 1996 Rotterdam guidelines, cisplatin (with or without 5-fluorouracil) neoadjuvant chemotherapy was given per protocol [30]. The Kaplan–Meier method and log–rank tests were used to obtain crude estimates for LC, DFS, and OS for different subsets.

Cost-analysis computation

All hospital costs associated with the treatment of nasopharyngeal cancer were considered [36] on the basis of all resource use, as is required according to the applied protocol. The original nasopharyngeal cancer protocol, designed in 1991, progressed over time, that is, from external beam radiation therapy only (before 1991) to a combined-modality treatment consisting of chemotherapy, 3DCRT, and stereotactic radiation to be implemented as of 2002. Treatment costs were broken down into five categories. All five categories were subdivided into several steps; for each of these steps, costs in Euros (1 Euro ~ 0.88 US$ [exchange rate in December 2001]) were calculated separately. Subsequently, the total costs of the treatment could be computed. The five categories and the incorporated resource use can be summarized as follows (see also Tables 1 and 2).

Category 1: workup—diagnosis and staging

All patients were jointly seen by the radiation oncologist and head and neck surgeon and scheduled for routine clinical workup, including endoscopy, CT scanning, MRI scanning, complete blood chemistry, X-ray film thorax, consultation with the dentist, X-ray film mandible, and consultation with the medical oncologist.

Table 1 Unit prices

Unit prices	Costs in Euros
Outpatient clinic	72
Laboratory blood tests	54
Endoscopy	32
X-ray chest/X-OPG	39
CT or MRI (maximal costs)	191
Admission day	382

Abbreviations:
OPG = orthopantogram.

Category 2: chemotherapy
Tumors of the well, moderately, and poorly differentiated subtype were treated by 6-weekly neoadjuvant chemotherapy courses of cisplatin (70 mg/m2); undifferentiated tumors were treated by three courses of neoadjuvant cisplatin (100 mg/m^2) combined with 5-fluorouracil (1000 mg/m^2), with a 3-week interval. During admission, routine blood tests were performed. During and between the clinical admissions, patients were seen by a medical oncologist and radiation oncologist at the outpatient clinic (four times on average).

Category 3: preparation for radiotherapy
Preparation for conventional external beam radiation therapy (1991 until 2002)
For immobilization purposes, a fixation mask was prepared, and, for simulation, a planning CT scan was taken (AcQSIM; Philips, Delft, The Netherlands). Megavolt imaging was used to verify the accuracy of the beam portal arrangement on the linear accelerator. During treatment, the patient was seen seven times on average at the outpatient clinic by a radiation oncologist. Per protocol, at 46 Gy, an MRI scan was obtained to monitor the initial response to neoadjuvant chemotherapy and radiation therapy.

Preparation for 3DCRT (as of 2002)
First, by using our CT-based protocol for delineation of the clinical target volume (CTV) of the neck nodal regions, the CTVs of the neck, the primary tumor, and the critical structures were contoured [12, 28]. After applying a threedimensional margin to the CTV to arrive at the planning target volume,

a 3DCRT treatment plan was generated by a threedimensional treatment–planning computer system (Cadplan; Varian Dosetek v. 3.1, Espoo, Finland). We recently completed a computer planning study regarding the techniques to be used. That is, class solutions were generated for irradiating the primary neck tumor to highly conformal doses.

Category 4: application of external beam radiation therapy (as of 1991)
The initial part of the radiation treatment consisted of 35 conventional fractions of 2 Gy/d, 5 d/week. As of 2000, all head and neck cancers treated in our institution, nasopharyngeal cancer inclusive, were routinely radiated by using six fractions of 2 Gy/week.

Table 2 Costs and Categories 1 to 5 of the treatment of advanced nasopharyngeal cancer

Category	Costs in Euros
1 Workup: diagnostics and staging	471
2 Chemotherapy	7772
3 Preparation radiotherapy	
3.1.1 Preparation ERT (in case of a BT boost)	992
3.1.2 Preparation ERT (in case of SRT boost)	1650
3.2.1 Preparation 3DCRT (in case of a boost by BT)	1440
3.2.2 Preparation 3DCRT (in case of a boost by SRT)	2098
4 Application ERT	3058
5.1 Application booster dose by BT	987
5.2 Application booster dose by SRT	1117

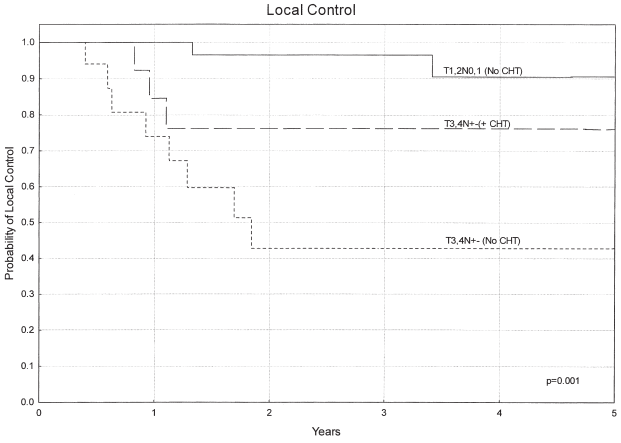
Abbreviations:
EBRT = External Beam Radiation Therapy; SRT = Sterotactic Radiotherapy; BT = Brachytherapy; 3DCRT = Three-dimensional Conformal Radiation Therapy.

Category 5: application of booster dose of radiation
Endocavitary brachytherapy (as of 1991)
According to the Rotterdam protocol, all primary nasopharyngeal cancers analyzed for this article were boosted by brachytherapy to a cumulative dose of 77–81 Gy (the total dose depended on T-stage). As of 2001, only patients staged T1-2a and those with T2b tumors having a good response to a first series of radiation (on the basis of an MRI scan at 46 Gy) were boosted by brachytherapy (see "Rotterdam nasopharyngeal cancer protocol," previously). For the more advanced lesions, see "Stereotactic radiation therapy (as of 2001)," below.

Stereotactic radiation therapy (as of 2001)
As of 2001, T2b tumors with a poor response to a first series of 46 Gy and T3-4 tumors were boosted by stereotactic radiation therapy. For stereotactic radiation therapy, a custom-made mouth bite with the head of the patient fixed in a stereotactic frame, a CT simulation, and an MRI matching procedure were obligatory. Preparation for boosting in case of stereotactic radiation therapy (see 2.5.2) apparently is more time consuming as opposed to the preparatory procedures of brachytherapy (3.1.1). Three-dimensional treatment planning is performed with X-plan (Radionics v. 2.02, Burlington). Four daily fractions of 2.8 Gy were applied.

Costs of treatment for other cancers in the head and neck
To put these data in perspective, the costs generated by the progression in the use of advanced treatment techniques for nasopharyngeal cancer over time were related to the treatment costs of patients with other types of cancers in the head and neck treated in the same institution and the Free University Hospital in Amsterdam. The data on treatment costs for tumors originating in the oral cavity, larynx, and oropharynx were recently reported by van Agthoven et al. [37]. A brief summary of relevant data will be presented in "Results."

Figure 1: Local control of patients with T1-2N0-1 nasopharyngeal cancer (33 patients; at 3 years, 17 were at risk) treated by external beam radiation therapy and brachytherapy. Also depicted are T3-4N± with or without nasopharyngeal cancers treated with radiation therapy without neoadjuvant chemotherapy (no CHT) (18 patients; at 3 years, 2 were at risk) and T3-4N± with or without tumors radiated in conjunction with neoadjuvant chemotherapy (CHT; 15 patients; at 3 years, 5 were at risk).



Unit prices

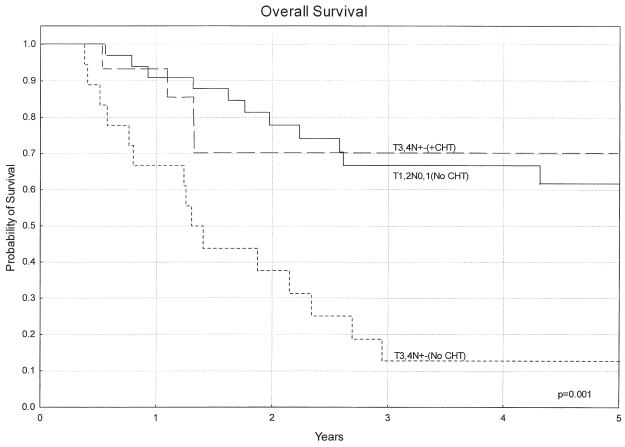
For the most important cost items, unit prices were determined by following the microcosting method reported by Gold et al. [38], which is based on a detailed inventory and measurement of all resources used. These calculations were based on 1998 pricings. The costs of radiotherapy, hospital days, and outpatient visits were divided into direct costs and indirect costs. Direct costs consisted of manpower (doctors, nurses, and so on) and materials (including medical devices). The indirect costs were related to the overhead costs. For radiotherapy, costs of manpower were based on time invested multiplied by salary costs (including wages, social premiums, and fees for irregular working hours). The depreciation of the equipment was based on the purchase price and the depreciation period, divided by the average number of patients treated in 1 year. The cost of other materials (such as molds and catheters) was based on wholesale prices. The costs for diagnosis and staging were based on the Dutch tariff system, and the costs for cytostatics were based on wholesale prices [39].

RESULTS

Clinical results with the Rotterdam nasopharyngeal cancer protocol 1991–2000

This paragraph summarizes briefly the results as recently presented by Levendag et al. [30]. For the radiation part of the treatment, it is of relevance to remember that all patients considered in Figures 1–4 were irradiated with conventional fractionated external beam radiation therapy (70 Gy) and fractionated high–dose-rate brachytherapy (total dose fractionated boost 11–17 Gy). That is, brachytherapy has been the technique used to realize the dose-escalation part above 70 Gy in this series for all T stages. For comparative purposes, for T1-2N0/1-staged tumors and using only high cumulative doses of radiation therapy (77–81 Gy), LC and OS at 5 years were 92% and 62%, respectively (Figures 1 and 2). For T3-4 tumors, the LC and OS at 5 years were 47% and 12% if chemotherapy was not administered, vs. 77% (LC) and 70% (OS) for T3-4 tumors treated with radiation therapy in conjunction with cisplatin-based neoadjuvant chemotherapy (Figures 1 and 2). Figures 3 and 4 depict the DFS and OS of patients treated with doses of 77–81 Gy in combination with neoadjuvant chemotherapy; DFS was 74% and OS was 72% at 5 years.

Figure 2: Overall survival of patients with T1-2N0/1 nasopharyngeal cancer (33 patients; at 3 years, 17 were at risk) treated by external beam radiation therapy and brachytherapy. Also depicted are T3-4N± nasopharyngeal cancers treated with radiation therapy without neoadjuvant chemotherapy (no CHT) (18 patients; at 3 years, 2 were at risk) and T3-4N± tumors radiated in conjunction with neoadjuvant chemotherapy (CHT) (15 patients; at 3 years, 5 were at risk).



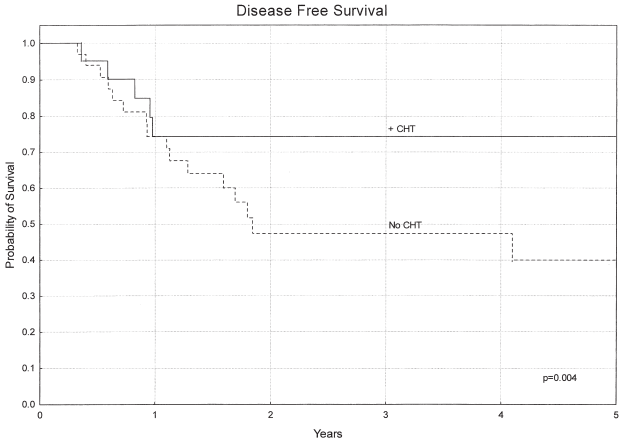
Results of cost analysis

Table 1 shows the most important unit prices. The costs of hospitalization amounted to approximately €382 per day, and the cost of an outpatient visit was €72.

Over the evaluation period 1991–2001, four phases can be studied in the evolution of the Rotterdam protocol for advanced nasopharyngeal cancer. That is, the sequence of major changes started stepwise with the addition of a brachytherapy boost to conventional external beam radiation therapy in 1991 (Phase 1), the implementation of neoadjuvant chemotherapy in 1996 (Phase 1), and, in case of T3-4 tumors, the re-placement of the brachytherapy boost (Phase 2.1) by a boost to be applied by stereotactic radiation therapy (Phase 2.2). Phase 2.2 was implemented at the end of 2001. Finally, as of 2002, neoadjuvant chemotherapy was to be followed by 3DCRT of the neck nodes and primary tumor (replacing the conventional series of external beam radiation therapy to a total dose of 70 Gy; Phase 4) in combination with either a boost by brachytherapy (Phase 4.1) or stereotactic radiation therapy (Phase 4.2), depending on the T stage.

Table 2 depicts the costs of five different categories. These cost categories were used for calculating the total costs per patient for each of the four evolutionary phases (Phases 1–4) in the Rotterdam nasopharyngeal cancer protocol over time. Coming from a single treatment using external beam radiation therapy only (1991) to advanced highdose, high-precision therapy (2002), one can appreciate the substantial accompanying increase in cost from Table 3. The costs of external beam radiation therapy only amounted to approximately €4.521, whereas the anticipated combined-modality treatment as of 2002 by chemotherapy plus 3DCRT plus stereotactic radiation therapy will amount to approximately €14.516.

Figure 3: Patients selected from the nasopharyngeal cancer Rotterdam database 1991–2000, treated by external beam radiation therapy in conjunction with brachytherapy. According to protocol, as of October 1996, stage III–IVB patients were to be treated by neoadjuvant chemotherapy followed by external beam radiation therapy and brachytherapy. Disease-free survival is depicted of nasopharyngeal cancer stage III–IVB patients treated with neoadjuvant chemotherapy (CHT; n=21) vs. nasopharyngeal cancer stage III–IVB patients treated without (no CHT; n=34) neoadjuvant chemotherapy.



DISCUSSION

Clinical results: advanced-stage nasopharyngeal cancer— high-dose, high-precision radiation therapy

LC is one of the most important prognostic factors in nasopharyngeal cancer; it has even been shown to be an independent prognostic indicator of distant metastasis [9]. The rationale for the application of highly sophisticated treatment techniques is underscored by established dose–tumor effect relationships [1–8]. Also, sparing of part of the (critical) normal tissue structures, such as the major salivary glands and mucosa, can be obtained by implementing 3DCRT, intensity modulated radiation therapy (IMRT), or both techniques when irradiating the neck and primary tumor. Finally, for boosting the planning target volume of the primary cancer to even higher cumulative doses (e.g., well over 80 Gy), the best dosimetric results with regard to target coverage and sparing are seen either with brachytherapy for the small lesions (T1-2) or, for the more advanced T3-4 tumors, with stereotactic radiation therapy, IMRT techniques, or both [12,14,31,32].

The combination of radiation therapy and chemotherapy has been shown to be very effective; however, in particular when given in a concurrent fashion, it can be toxic as well [24,25]. We have opted for neoadjuvant chemotherapy; with this combined-modality treatment, results for stage III–IVB nasopharyngeal cancer did improve, with minimal side effects (Figures 3 and 4). In Table 4, comparative data are summarized from three recently reported clinical data sets:

(1) the randomized study by Al-Sarraf et al. [18] for stage III–IV nasopharyngeal cancer disease that used concomitant chemotherapy; (2) the Rotterdam series on stage III–IVB patients [30]; and (3) the findings of the Memorial Sloan-Kettering Cancer Center article by Wolden et al. [40], which studied concomitant chemotherapy in a nonrandomized setting in stage II–IV disease. The results observed at 3 years in the Intergroup 0099 trial and the study of Wolden et al. with respect to LC (90% vs. 84%), progression-free survival (69% vs. 54%), and OS (78% vs. 84%) are in essence not dissimilar to the Rotterdam findings: 86% (LC), 74% (DFS), and 72% (OS). It is anticipated that, because of better target coverage, further improvement can be expected in T3-4 lesions by using stereotactic radiation therapy.

Figure 4: Patients selected from the nasopharyngeal cancer Rotterdam database 1991–2000, treated by external beam radiation therapy in conjunction with brachytherapy. According to protocol, as of October 1996, stage III–IVB patients were to be treated by neoadjuvant chemotherapy followed by external beam radiation therapy and brachytherapy. Overall survival is depicted of nasopharyngeal cancer stage III–IVB patients treated with neoadjuvant chemotherapy (CHT; n=21) vs. nasopharyngeal cancer stage III–IVB patients treated without (no CHT; n=34) neoadjuvant chemotherapy.

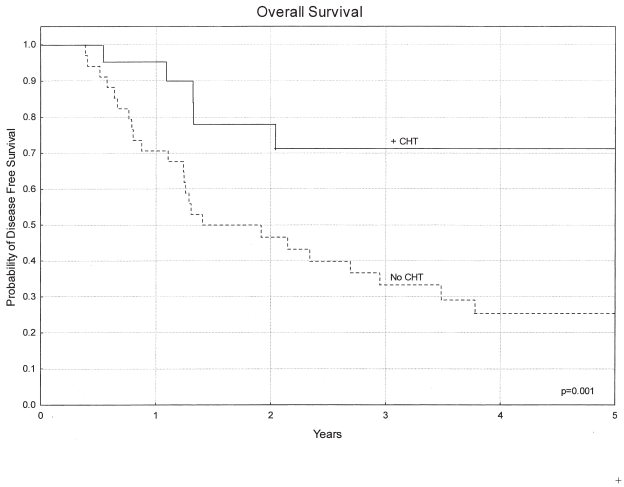


Table 3 Evolution of Rotterdam nasopharyngeal cancer treatment protocol: total cost of each of the various protocol Phases 1–4

Phase	Treatment modality	Time period	Costs in Euros
1	ERT only	Until 1991	4,521
2	ERT + BT	1991–1996	5,508
31	CHT + ERT + BT	1996–2001	13,28
32	CHT + ERT + SRT	2001–2002	14,068
41	CHT + 3DCRT + BT	2002–	13,728
42	CHT + 3DCRT + SRT	2002–	14,516

Abbreviations:
EBRT = External Beam Radiation Therapy; CHT = Chemotherapy; SRT = Stereotactic Radiotherapy; BT = Brachytherapy; 3DCRT = Three-dimensional Conformal Radiation Therapy.

Table 4 Recent studies*

Study	PFS%	*p* Value	OS%	*p* Value
Intergroup 0099, Al-Sarraf *et al.* (18), Stage III–IV				
Conventional ERT 70 Gy (standard)	24	0.001	47	0.005
Exp. (Standard) with concomitant CHT and adjuvant CHT	69		78	
Rotterdam (30), Stage III–IVB	DFS%		OS%	
ERT + BT 78–81 Gy (standard)	48	0.002	35	0.005
Exp. (Standard) with neoadjuvant CHT	74		72	
MSKCC (40), Stage II–IV	PFS%		OS%	
Conventional ERT 70–75.6 Gy in 8 weeks	54	0.01	71	0.04
Exp. Accelerated RT, 70 Gy in 6 weeks + concomitant CHT	66		84	

Abbreviations:
BT = Brachytherapy; RT = Radiotherapy
*Three recent studies are summarized: the randomized Intergroup 0099 (147 stage III–IVB patients), the nonrandomized Rotterdam data (55 stage III– IVB patients), and the nonrandomized Memorial Sloan-Kettering Cancer Center (MSKCC) study (81 stage II–IV patients). DFS = Disease-Free Survival at 3 years according to Kaplan–Meier; PFS = Progression-Free Survival at 3 years according to Kaplan–Meier; OS = Overall Survival at 3 years according to Kaplan–Meier. The experimental treatment arms of the three studies were as follows: I, IG 0099; Al-Sarraf et al.; stage III–IV, 70 Gy external beam radiation therapy (EBRT) plus concomitant and adjuvant chemotherapy (CHT) [18]; II, Rotterdam, Levendag et al., stage III–IVB, neoadjuvant chemotherapy plus external beam radiation therapy (77–81 Gy) [30]; III, MSKCC; Wolden et al., stage II–IV, accelerated external beam radiation therapy (70–75.6 Gy/6 weeks) plus concomitant chemotherapy [40]. Table modified after Levendag et al., 2001 [30].

Results: cost analysis

The introduction of new technologies often leads to additional costs. Although it was not a cost-effectiveness study per se—i.e., no costs per life years were calculated—the effect of the introduction of more advanced technologies on costs and survival has been presented. This study shows that the application of chemotherapy and high-dose, high-precision radiotherapy indeed increases the costs, but a substantial part of the increase is due to the clinical administration of the chemotherapy agents.

In the evolution of the treatment protocol used in our institute, costs increased from €4.521 ($5.023) from before 1991, with conventional external beam radiation therapy only, to €13.728 ($15.253) for advanced stage nasopharyngeal cancer patients treated as of 1996 by a combination of chemotherapy, conventional external beam radiation therapy, and brachytherapy as a boost. In case stereotactic radiation therapy as a booster technique is used in combination with chemotherapy and 3DCRT, the anticipated amount will have increased to €14.516 ($16.495).

In a 1998 survey published in 2001 by van Agthoven et al. [37], costs were analyzed and reported for the treatment of cancers in the oral cavity, larynx, and oropharynx in our institute. As can be seen in Table 5, for the three sites combined (mean), a total of €21.858 ($24.126) for the combined-modality treatment (chemotherapy, radiotherapy, surgery, or a combination of these) was computed. In this amount, the follow-up costs were included up to 2 years of disease-free follow-up. If we are to include comparable costs of 2-year disease-free follow-up (starting after treatment) for our nasopharyngeal cancer patients, an additional amount of €800 has to be included. That is, for nasopharyngeal cancer patients treated according to the Rotterdam protocol (Year 1: two outpatient clinic visits and one MRI; Year 2: five outpatient clinic visits, one chest X-ray, one MRI, and one blood chemistry [thyroxine/thyroid-stimulating hormone]) and corrected for survival (Figure 4), the amount of €800 has to be added to the €13.728 in case of brachytherapy (total, €14.528 [$16.509]) and to the €14.516 in case of stereotactic radiotherapy (total cost, €15.316 [$17.405]).

We can therefore conclude that the costs in advanced nasopharyngeal cancer with sophisticated high-dose, high-precision types of radiation techniques are comparable to or even lower than the costs generated by conventional treatment schemes used in other head and neck cancer sites. Moreover, it is important to note that the contribution of brachytherapy in the dose-escalation part of the protocol is a relatively small component of the total amount (€1.979, $2.198; Table 2). Therefore, our results support the adoption

and use of high-technology-driven treatment strategies in nasopharyngeal cancer.

In summary, in combination with neoadjuvant chemotherapy, the use of high-dose, high-precision brachytherapy delivering cumulative doses of approximately 81 Gy to the nasopharynx has significantly improved local tumor control and OS in stage III–IVB disease. These findings are corroborated by the current literature. The chemotherapy and high technology type of treatment techniques for advanced nasopharyngeal cancer obviously also increase the costs, that is, from €4.521 (before 1991; $5.023) to €14.516 (as of 2002; $16.129) for patients to be treated as of 2002. However, the costs generated by conventional treatment schemes and modalities in other head and neck tumor sites are in a similar range. It is believed that this high-technology type of treatment is effective and worth the extra costs, which should not be considered prohibitive in the treatment of advanced nasopharyngeal cancer and probably in other head and neck sites.

Table 5: Mean costs (in Euros, 1996 price level) of all treatment modalities combined (that is, chemotherapy, conventional external beam radiation therapy, surgery, brachytherapy, or a combination, applied if appropriate according to protocol) up to 2 years disease-free follow-up of patients with primary tumors in the head and neck (category 3): costs were computed for patients treated in the University Hospital Rotterdam or Free University Amsterdam*

Category	Oral cavity costs (Euros)	Larynx costs (Euros)	Oropharynx costs (Euros)	Overall costs (Euros)
1. Outpatient clinic (charges for clinician, follow-up)	3,128	1,868	2,751	2,52
2. Admission days	11,185	6,747	11,122	9,257
3. Treatment modality	7,997	5,775	8,409	7,106
4. Radiology	837	701	1,069	817
5. Other diagnostics	2,278	1,981	2,328	2,158
Total costs	25,425	17,072	25,679	21,858

*Data taken from van Agthoven et al., 2001 [37].

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REFERENCES

1. Teo PML, Leung SF, Lee WY, et al. Intracavitary brachytherapy significantly enhances local control of early T-stage nasopharyngeal carcinoma: The existence of a dose-tumor control relationship above conventional tumoricidal dose. Int J Radiat Oncol Biol Phys 2000;46: 445–458.
2. Syed AM, Puthawala AA, Damore SJ, et al. Brachytherapy for primary and recurrent nasopharyngeal carcinoma: 20 years' experience at Long Beach Memorial. Int J Radiat Oncol Biol Phys 2000;47: 1311–1321.
3. Perez CA, Devineni VR, Marcial-Vega V, et al. Carcinoma of the nasopharynx: Factors affecting prognosis. Int J Radiat Oncol Biol Phys 1992;22:941–947.
4. Wang CC. Improved local control of nasopharyngeal carcinoma after intracavitary brachytherapy boost. Am J Clin Oncol 1991;14:5–8.
5. Bedwinik JM, Perez CA, Keys DJ. Analysis of failure after definitive irradiation for epidermoid carcinoma of the nasopharynx. Cancer 1990;45:2725–2729.
6. Vikram B, Mishra UB, Strong EW, et al. Patterns of failure in carcinoma of the nasopharynx. Int J Radiat Oncol Biol Phys 1985;11: 1455–1459.
7. Mesic JB, Fletcher GH, Goepfert H. Megavoltage irradiation of epithelial tumors of the nasopharynx. Int J Radiat Oncol Biol Phys 1981; 7:447–453.
8. Lee AWM, Chan DKK, Fowler JF. l. Effect of time, dose and fractionation on local control of nasopharyngeal carcinoma. Radiother Oncol 1995;36:24–31.
9. Kwong DLW, Sham JST, Choy D. The effect of loco-regional control on distant metastatic dissemination in carcinoma of the nasopharynx: An analysis of 1301 patients. Int J Radiat Oncol Biol Phys 1994;30: 1029–1036.
10. Lee AW, Poon YF, Foo W, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985: Overall survival and patterns of failure. Int J Radiat Oncol Biol Phys 1992;23:261–270.
11. Chang JT, See LC, Tang SG, et al. The role of brachytherapy in early-stage nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 1996;36:1019–1024.

12. Lagerwaard FJ, Levendag PC, van Nimwegen A, et al. High precision boosting of the nasopharynx: Dosimetric comparison of conventional and conformal radiotherapy techniques. J HK Coll Radiol 2001;4:120–125.
13. Mitsuhashi N, Sakurai H, Katano S, et al. Stereotactic radiotherapy for locally recurrent nasopharyngeal carcinoma. Laryngoscope 1999; 109:805–809.
14. Hunt MA, Zelefsky MJ, Wolden S, et al. Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer. Int J Radiat Oncol Biol Phys 2001;49:623–632.
15. Levendag PC, Peters R, Meeuwis CA, et al. A new applicator design for endocavitary brachytherapy of cancer in the nasopharynx. Radiother Oncol 1997;45:95–98.
16. Levendag PC, Schmitz PIM, Jansen PP, et al. Fractionated high dose-rate brachytherapy in primary carcinoma of the nasopharynx. J Clin Oncol 1998;16:2213–2220.
17. Al-Sarraf M, Pajak TF, Cooper JS, et al. Chemo-radiotherapy in patients with locally advanced nasopharyngeal carcinoma. A Radiation Therapy Oncology Group study. J Clin Oncol 1990;8:1342–1351.
18. Al-Sarraf M, LeBlanc M, Shanker Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer. Phase III randomized Intergroup study 0099. J Clin Oncol 1998;16: 1310–1317.
19. Cheng SH, Jian JJM, Tsai SY, et al. Long-term survival of nasopharyngeal carcinoma following concomitant radiotherapy and chemotherapy. Int J Radiat Oncol Biol Phys 2000;48:1323–1330.
20. Cooper JS, Lee H, Torrey M, et al. Improved outcome secondary to concurrent chemoradiotherapy for advanced carcinoma of the nasopharynx: Preliminary corroboration of the Intergroup experience. Int J Radiat Oncol Biol Phys 2000;47:861–866.
21. Munro AJ. An overview of randomized controlled trials of adjuvant chemotherapy in head and neck cancer. Br J Cancer 1995;72:83–91.
22. Chan ATC, Teo PML, Leung TWT, et al. The role of chemotherapy in the management of nasopharyngeal carcinoma. Cancer 1998; 82(6):1003–1012.
23. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV (> or = N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free

survival. International Nasopharynx Cancer Study Group. VUMCA I trial. Int J Radiat Oncol Biol Phys 1996;35:463–469.
24. Pignon JP, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer. Br J Cancer 1995;72:1062–1063.
25. El-Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. J Clin Oncol 1996;14:838–847.
26. Eisbruch A, Ten Haken RK, Kim HM, et al. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45:577–587.
27. Nowak PJCM, Wijers OB, Lagerwaard FJ, et al. A three-dimensional CT-based target definition for elective irradiation of the neck. Int J Radiat Oncol Biol Phys 1999;45:33–39.
28. Wijers OB, Levendag PC, Tan T, et al. A simplified CT-based definition of the lymph node levels in the node negative neck. Radiother Oncol 1999;52:35–42.
29. Levendag PC, Lagerwaard FJ, Pan de C, et al. High-dose, high-precision treatment options for boosting cancer of the nasopharynx. Radiother Oncol. In press.
30. Levendag PC, Lagerwaard FJ, Noever I, et al. The role of endocavitary brachytherapy with or without chemotherapy in cancer of the nasopharynx. Int J Radiat Oncol Biol Phys 2002;52:755–768.
31. Orecchia R, Redda MG, Ragona R, et al. Results of hypofractionated stereotactic re-irradiation on 13 locally recurrent nasopharyngeal carcinomas. Radiother Oncol 1999;53:23–28.
32. Levendag PC, Lagerwaard FJ, Pan de C, et al. IMRT, stereotactic radiotherapy or brachytherapy following external beam radiotherapy: Target coverage and sparing in early Stage NPC. Presented at ASTRO, Boston, Massachusetts, October 22–26, 2000. Int J Radiat Oncol Biol Phys 2000;48:323–324.
33. Allen PW. Surgical pathology (Chapt. 5). In: Hasselt CA, Gibb AG, editors. Nasopharyngeal carcinoma. 2nd ed. Hong Kong: The Chinese University Press; 1999. p. 69–104.
34. Sanguinetti G, Corvo R. Treatment of nasopharyngeal carcinoma: State of the art and new perspectives [Review]. Oncol Rep 1999;6:377–391.

35. Sobin LH, Wittekind CH. Nasopharynx. In: American Joint Committee on Cancer. Manual for staging of cancer. 5th ed. Philadelphia: Lippincott; 1997. p. 27–30.
36. Drummond M, O'Brien B, Stoddart G, et al. Methods for the economic evaluation of health care programmes (Chapt. 4). Oxford: Oxford University Press; 1997. p. 52–88.
37. van Agthoven M, van Ineveld BM, de Boer MF, et al. The costs of head and neck oncology: Primary tumours, recurrent tumours and long-term follow-up. Eur J Cancer 2001;37(17):2204-2211.
38. Gold M, Siegel J, Russell L, et al. Cost-effectiveness in health and medicine (Chapt. 6). New York: Oxford University Press; 1996. p176–213.
39. Kuy vd A, ed. Pharmacotherapeutical compass 1998. Amstelveen, The Netherlands: Dutch Health Care Board; 1998.
40. Wolden SL, Zelefsky MJ, Kraus DH, et al. Accelerated concomitant boost radiotherapy and chemotherapy for advanced nasopharyngeal carcinoma. J Clin Oncol 2001;19:1105-1110.

CHAPTER 4

Cost analysis comparing Brachytherapy versus Surgery for Primary Carcinoma of the Tonsillar Fossa and/or Soft Palate

∞

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ABSTRACT

Purpose: Locoregional control rates, late normal tissue sequelae, and functional outcome scores, have not been found to be different for tonsillar fossa and/or soft palate tumors treated by either brachytherapy (BT) or surgery in an organ function preservation protocol. For additional prioritizing in clinical decision-making, we focused on a comparison of the full hospital costs of the different treatment options.

Methods and Materials: Between 1986 and 2001, tonsillar fossa and/or soft palate tumors were treated by external beam radiation therapy (EBRT) to the primary tumor and neck, followed by fractionated brachytherapy (BT) to the primary. Neck dissection was performed for node-positive disease (BT-group; 104 patients). If BT was not feasible, resection combined with postoperative EBRT was executed (surgery group; 86 patients). Locoregional control, disease-free survival and overall survival were calculated according to the Kaplan-Meier method. The performance status scales, late side effects and degree of xerostomia have been previously reported. This paper focused on the hospital and follow-up costs for the treatment groups EBRT and BT with or without neck dissection compared with surgery followed by postoperative RT (PORT). Finally, these costs were also computed for future treatment strategies (e.g. better sparing of normal tissues by intensity-modulated RT [IMRT]).

Results: Locoregional control, disease-free survival, and overall survival rate at 5 years for patients treated with EBRT and BT with or without neck dissection vs. surgery plus PORT was 80% vs. 78%, 58% vs. 55%, 67% vs. 57%, respectively. The major late side effect was xerostomia. Dry mouth syndrome affected the BT-group and surgery group equally. The total costs for all treatment groups were €14.262 (BT group), €16.628 (BT plus neck dissection group), €18.782 (surgery plus PORT group), €14.532 (IMRT group) and €16.897 (IMRT plus neck dissection group).

Conclusion: Excellent locoregional tumor control was observed with either modality with no statistically significant differences in the incidence of the most noted side effect xerostomia. The total costs for BT were less than for surgery: €16.628 ($19.452) for EBRT plus BT plus neck dissection vs. €18.782 ($22.074) for surgery plus PORT. To reduce the morbidity of xerostomia we propose to further optimizing our organ function preservation protocol

by implementing IMRT as a more conformal, tissue-sparing RT technique. This is of particular interest because the costs of IMRT plus neck dissection (€16.897; $19.767) were not very different from those for BT plus neck dissection (€16.628, $19.452) and were far less than the costs for surgery.

INTRODUCTION

The management of squamous cell cancer of the oropharynx varies widely from radiotherapy (RT) alone to surgery combined with postoperative RT (PORT)[1-15]. Proponents of RT alone argue that surgical resection of these tumors results in poor swallowing and inadequate speech function, with no difference in tumor control. For this reason, in the Erasmus Medical Center - Daniel den Hoed Cancer Center (Erasmus Medical Center [MC]), the treatment of preference for T1-3N0,+ tonsillar fossa (TF) and/or soft palate (SP) tumors has been external beam RT (EBRT) to the primary tumor and the unilateral or bilateral neck, followed by a boost using brachytherapy (BT) to the primary cancer. Also, according to this organ function preservation protocol, for patients not eligible for BT, surgery followed by PORT, was the first line of treatment [12-14].

Recently, interest has been increasing in reporting secondary endpoints such as acute and late side effects and functional outcome scores for patients with cancer of the head and neck [16,17]. It is now generally agreed on that the outcome of these secondary end points needs to be taken into account when deciding on the best treatment option [5-7]. The results of TF and/or SP tumors treated between 1986 and 2001 in the Erasmus MC by either BT or surgery, were analyzed in detail including locoregional control, disease-free survival (DFS), overall survival, and health related quality of life aspects [14,15]. In this analysis, no statistically significant differences were observed for tumor control, degree of xerostomia, or functional outcome scores for the BT-group vs. the surgery group [14,15].

Another discriminating factor might be the costs related to the treatment modalities per se and to follow up. The aim of the current article is to determine whether one could prioritize the choice of BT vs. surgery for primary tumors located in the TF and/or SP by focusing on the full hospital costs of the patients [19,20].

MATERIAL AND METHODS

Rotterdam organ function preservation protocol

Between 1986 and 2001, as per protocol, stage T1-3N0,+ TF and/or SP tumors underwent EBRT at Erasmus MC to 46 Gy in fractions of 2 Gy per day / 5 days per week to the primary tumor and unilateral or bilateral neck. This series of EBRT was to be followed within 1-3 weeks by a fractionated high-dose-rate (HDR) or pulsed-dose-rate (PDR) BT boost to the primary tumor. At the BT procedure, neck dissection (ND) was performed in case of Node positive disease (BT-group; 104 patients). If BT was technically not feasible (e.g. because of parapharyngeal extension of the primary tumor), combined resection of the primary tumor and neck was done, with surgical reconstruction of the defect. Within 6 weeks, the surgery group (86 patients) underwent postoperative EBRT (PORT) to a dose of 50-70 Gy, depending on the pathology findings.

Pretreatment staging procedures (work-up)

After joint consultation by a radiation-oncologist and head-and-neck surgeon in the outpatient clinic, a general work-up was performed for all patients. This included routine clinical examination, fiber optic endoscopy, routine laboratory tests, chest X-ray, ultrasound examination (ultra-sound-guided fine needle aspiration cytology inclusive, if applicable), CT / MRI of the head and neck, preoperative consultation with the anesthesiologist, and joint examination under general anesthesia in a 1-day admission procedure. All patients were discussed in great detail by the multidisciplinary head and neck tumor board. Finally, before the start of the actual RT, patients were seen by the dentist to receive prophylactic medical dental advice on daily fluoride applications. In both groups, about 57% of the patients also needed some type of prophylactic dental treatment. For all treatment groups, the work-up was assumed to be similar; it was used as one cost component in the cost calculation.

Treatment

For the patients enrolled in the RT arm, the procedural steps in the treatment protocol were as follows. First, the patient was instructed on the pretreatment procedures, as well as on the potential treatment-related side effects. A head and neck fixation mask was then made in a dedicated mouldroom. Subsequently, CT simulation was performed.

After three-dimensional treatment planning (Cadplan, version 3.1.2, Varian-Dosetek, Finland), the dose was prescribed according to the International Commission on Radiation Units and Measurements Report 50 recommendations [18]. The treatment plan was presented to the monodisciplinary tumor board. These steps were the same for all treatment groups and are taken as one cost component in the cost calculation. After the staff members accepted the treatment plan as part of the peer-review process, the target was irradiated with 5 (to 6) daily fractions of 2 Gy per week, with the patient in supine position on the treatment couch of the linear accelerator. Generally a 6 MV photon beam was used for these cancer types. During treatment, the patient was seen on average 4 times by the radiation oncologist on outpatient visits. After 46 Gy (23 sessions), a variable split period was introduced depending on the availability of the integrated brachytherapy unit (IBU) and head-and-neck surgeon (in case of ND). The patient was instructed with regard to the BT procedures in the IBU and on the ward. After introducing BT afterloading catheters under general anesthesia, the implant was simulated in the IBU and a BT treatment plan generated.

After completion of the three-dimensional computer planning procedure, the first fraction was applied in the IBU with the patient still under general anesthesia. Fifty percent of the patients received 20 fractions of 1-2 Gy, 8 times daily (PDR) on average within 7 admission days. The other 50% of the patients received 6 fractions of 3-4 Gy, 2 times daily (fractionated HDR) on average within 4 admission days. The use of these iso-effective schemes (i.e., the choice between fractionated HDR or PDR) depended on the availability of the type of afterloading machine [2]. The cost calculation for the BT group was based on 5.5 admission days. In case of ND, patients are admitted for an average of 8 days, during which the BT fractions were given. Patients of the surgery group were admitted for an average of 14 days. Costs were based on the assumption that 50% of the patients underwent ND and 50% of the patients underwent ND plus reconstruction. These patients were irradiated an average of 31 fractions.

Follow-up

Patients were seen in regular follow-up with standardized clinical and laboratory tests. In year 1, patients had five outpatient clinic visits, including routine clinical examinations. In years 2-4, patients had two follow-up visits, including routine clinical examinations, laboratory tests (blood chemistry and thyroxin, thyroid stimulating hormone), and plain chest X-ray annually. At year 5, patients were seen one time.

Side effects and Performance Status Score

Late side effects were according to the Radiation Therapy Oncology Group criteria [18]. To determine the Performance Status Scale (PSS) scores of long-term survivors, a survey was conducted among patients alive and without evidence of disease (NED) after a minimum of 2 years of follow-up (BT-group: 30, Surgery group: 27)[16,17]. For this purpose, a research nurse interviewed patients regarding eating in public, normalcy of diet and understandability of speech. In the same interview, a Visual Analogue Scale (VAS) was used to determine the VAS score for the degree of xerostomia as experienced by the patients.

Relapse and/or second primary

In case of suspicion for relapse and/or second primary, additional diagnostic procedures were performed (e.g. Xray of the thorax, CT/MRI, endoscopy, blood chemistry) depending on tumor type and location. On average, this was finalized in 2 outpatient clinical visits. Depending on type of relapse, second primary, and/or presence of distant metastasis, either no treatment or (combined) modalities such as surgery, RT, or chemotherapy were implemented to treat the new tumor activity. For this patient category, additional follow-up of five consultations was accounted for in the cost computations.

Cost calculation

This cost analysis was performed from the institutional perspective [22]. In contrast to charges, unit costs are the best estimators of the theoretically proper opportunity costs [22]. For this reason and to facilitate cost comparisons with other countries, we calculated, for the 3 subgroups, (BT, 48 patients; BT plus ND, 56 patients; and surgery plus PORT group, 86 patients), the direct medical costs for the most important items regarding the workup (diagnosis and staging), treatment (preparation treatment, costs for treatment modalities per se, such as teletherapy, brachytherapy, surgery), 5 years of follow-up costs, and costs related to the diagnosis and workup and treatment of a relapse. The direct medical costs were determined by the average unit costs, including overhead costs. To determine these unit costs, we followed the micro-costing method, which is based on a detailed inventory and measurement of resources consumed [23]. The valuation of the resources and overhead costs was determined by the financial data from the Erasmus MC.

Cost calculation of treatment

The number of RT fractions for both teletherapy and brachytherapy used in this article were according to the protocol used (see under 'Treatment'). We estimated the number of admission days on the basis of this protocol. Costs were based on 2001 pricings and stated in Euros (€); for some of the amounts (see 'Discussion'), the Euro was converted to the US dollar to facilitate reading of the manuscript (exchange rate June 2003).

Cost calculation of manpower and materials

Direct costs consisted of manpower and materials. To calculate manpower costs, the time spent for the various procedures in the different subgroups was estimated by the medical disciplines involved. The time invested was multiplied by salary (including wages, social premium and extra fees for irregular working hours). Costs per minute were then calculated under the assumption of 1540 working hours a year [21]. With regard to the specialist, the costs per minute were calculated according to the method as described by Oostenbrink et al. [21], that is, specialist activities were divided into direct and indirect time. The direct time was the time in which both the specialist and the patient were present. This was estimated to be 70% of the specialist's working time. Indirect time was when the patient was not present (e.g. multidisciplinary discussions), and was estimated at approximately 30%. The direct times were therefore multiplied by 1.42 to allow for costs of indirect time. Wholesale prices were used to determine the material costs. A detailed inventory and measurement of materials was executed, on the basis of real use by the department for these patient groups. Also, the costs related to use of equipment and operating room (IBU) were included in the material costs. The costs for diagnosis and staging were based on the Dutch tariff system. All direct costs were multiplied by overhead costs (e.g. depreciation costs of the building, cleaning costs). Overhead costs were based on the relationship between the direct costs of the hospital in total and the costs for administration.

Cost calculation of follow-up and relapse

To calculate the costs for follow-up, first, the DFS for years 1- 5 was calculated according to the Kaplan-Meier method. The costs for follow-up were based on the protocol described above and were corrected for DFS in that year. Relapse costs were based on the actual number of patients in each treatment

group who had renewed tumor activity, whether locoregional relapse, distant metastasis, or second primary tumor. The costs of treatment, additional diagnostic tests, and follow-up were then calculated and averaged for all patients with relapse.

Cost calculation future strategies

To anticipate future protocol modifications in order to better spare the salivary glands and/or the mucosa, additional costs were estimated in case more conformal RT techniques were used, such as Intensity-Modulated RT (IMRT) to 46 Gy in 23 fractions (IMRT plus BT), IMRT to 46 Gy plus stereotactic RT (SRT) or IMRT for the booster dose to the primary tumor in 7 fractions; a combination of IMRT and accelerated RT to > 72 Gy in 42 fractions, and surgery combined with postoperative EBRT (PORT) given using IMRT in 25-35 fractions (50–70 Gy). The cost calculation was based on the same method as described for follow-up and relapse. Manpower costs were based on real time spent to execute IMRT and SRT. Costs for relapse and follow-up were taken from the existing figures of the treatment groups (BT with or without ND and the surgery group).

RESULTS

All patients underwent restaging according to the International Union Against Cancer/American Joint Committee on Cancer Classification system, 2002 edition. The patient and tumor characteristics are summarized in Table 1. The tumor control of patients treated for TF and/or SP tumors at 5-yrs for the 3 treatment groups (BT, BT plus ND and surgery plus PORT) for locoregional control was 87%, 80%, and 78%; for DFS was 57%, 58%, and 55%, and for overall survival was 63%, 67%, and 57%, respectively [13]. The late side effects and PSS scores, have been reported in detail separately [14,15]. In the BT group, 33% developed mucositis (ulceration; with 88% spontaneously healing within 6-8 months). In the surgery group, 21% developed trismus. The most significant late side effect for both modalities was xerostomia, with median VAS scores of 5.6 (BT) and 6 (surgery). No statistically significant differences were observed for the treatment groups BT vs. surgery for the PSS scores eating in public, normalcy of diet and normalcy of speech [14, 15]. In Table 2, the number of patients with renewed tumor activity for the different groups is presented.

The mean total costs of workup and treatment for the treatment groups of EBRT plus BT, EBRT plus BT and ND and surgery plus EBRT are shown in Table 3. The outpatient visits during the workup consisted of one visit (€94,53) by each specialist (radiation oncologist [RO] and head-and-neck surgeon). On average, during treatment, the patients in the BT groups were seen 4 times in the outpatient clinic and the surgery group patients were seen five times. The cost of one admission day is €389,44; the mean hospital stay was 5.5 admission days, 8 days and 14 days for the EBRT plus BT, EBRT plus BT plus ND, and the surgery plus EBRT patients, respectively. Table 4 summarizes the total costs per patient up to 5 years after diagnosis. The relapse costs were calculated for those showing renewed tumor activity (Table 2). For each relapsed patient, first the total costs were calculated separately, with the total amount depending on the modalities used. The total costs were then averaged for each treatment group. The follow-up was according to protocol. Because the DSF was dissimilar for each patient group, the follow-up costs also differed. The total costs for the treatment groups were €14.262 for EBRT plus BT, €16.628 for EBRT plus BT plus ND, and €18.782 for surgery. Table 5 summarizes the future anticipated costs. As shown by the results reported in Table 5, the additional costs of IMRT would be almost negligible. That is, the slightly higher costs were only a result of the higher personnel costs because of the somewhat more laborious preparatory work of the more advanced

Table 1: Patient characteristics

	BT group (n = 104)	Surgery group (n = 86)
Gender (n)		
Male	57 (55)	54 (63)
Female	47 (45)	32 (37)
Age (y)		
Mean Age	57	59
Range	35 – 80	37 – 74
T stage(TNM 2002) (n)		
T1	9	7
T2	72	18
T3	24	61
N stage (n)		
N0	53	20
N1	15	21
N2a	10	8
N2b	14	33
N2c	9	2
N3	3	2

Table 2: Patients with renewed tumor activity by group

	BT (n)	BT+ND (n)	Surgery (n)	Total (n)
Locoregional	4	10	17	31
Distant metastasis	1	3	4	8
Second primary tumor	13	9	18	40
Total	18	22	39	79

Abbreviations:
BT = brachytherapy; ND = neck dissection

Table 3: Mean total costs of workup and treatment per treatment group

Costs	EBRT+BT	EBRT+BT+ND	Surgery+EBRT
Workup (overhead incl.)			
Outpatient visit RO and H&N Surgeon	189,06	189,06	189,06
Endoscopy	106,64	106,64	106,64
X-ray	39,25	39,25	39,25
Ultra sound neck + cytology	132,14	132,14	132,14
CT / MRI	188,40	188,40	188,40
Blood	37,55	37,55	37,55
Preoperative anaesthesiologist consultation	43,78	43,78	43,78
Dental consultation and treatment	193,39	193,39	193,39
One-day admission for biopsy	830,80	830,80	830,80
Total workup	**1.761,01**	**1.761,01**	**1.761,01**
Treatment			
Outpatient visit	166,28	166,28	207,85
Personnel costs surgery	-	-	1.722,30
Material costs (operating room use included)	-	-	3.028,20
Personnel costs preparation EBRT	434,90	434,90	434,90
Material costs preparation EBRT	136,45	136,45	136,45
Equipment costs	235,02	235,02	235,02
Radiation session EBRT	721,83	721,83	1.001,82
Personnel costs preparation BT	184,30	184,30	-
Personnel costs BT surgery	250,65	250,65	-
Material costs (operating room use included)	706,90	706,90	-
Histological examination	40,84	40,84	40,84
Personnel costs neck dissection	-	704,70	-
Material costs neck dissection (operating room use included)	-	1.297,80	-
Overhead of above costs	325,85	660,96	918,02
Radiation session BT (overhead included)	1.031,81	1.031,81	-
Admission days (overhead included)	2.141,92	3.115,52	5.452,16
Total treatment	**6.376,75**	**9.687,96**	**13.177,56**

Abbreviations:
RO = radiation oncologist; H&N surgeon = head-and-neck surgeon; EBRT = external beam radiotherapy; BT = brachytherapy; ND = neck dissection

Table 4: Mean total costs per patient up to 5 years after initial diagnosis

Group	Workup	Treatment	Relapse	5 yrs |Follow-up	Total (Euro's)
EBRT+BT	1.761,01	6.376,75	5.497,98	626,24	14.261,98
EBRT+BT+ND	1.761,01	9.687,96	4.569,15	609,96	16.628,08
Surgery	1.761,01	13.177,56	3.318,47	604,25	18.782,39

Abbreviations:
EBRT = external beam radiotherapy; BT = brachytherapy; ND = neck dissection

Table 5: Mean anticipated future total costs per patient for IMRT (46 Gy) and BT, IMRT (46 Gy) and SRT, IMRT and accelerated RT (70 Gy), and surgery and postoperative IMRT (60 Gy)

Group	Workup	Treatment	Relapse	5 yrs Follow-up	Total (Euro's)
IMRT+BT	1.761,01	6.646,61	5.497,98	626,24	14.531,84
IMRT+BT+ND	1.761,01	9.957,82	4.569,15	609,26	16.897,24
IMRT+SRT/IMRT	1.761,01	3.549,81	5.497,98	626,24	11.435,04
IMRT+SRT/IMRT+ND	1.761,01	9.043,78	4.569,15	609,96	15.983,90
ACC.RT/IMRT	1.761,01	2.770,81	5.497,98	626,24	10.656,04
ACC.RT/IMRT+ND	1.761,01	8.264,78	4.569,15	609,96	15.204,90
S+IMRT	1.761,01	8.657,97	3.318,47	604,25	14.341,70
S+IMRT+ND	1.761,01	13.447,42	3.318,47	604,25	19.131,15

Abbreviations:
IMRT = intensity-modulated radiotherapy; BT = brachytherapy; ND = neck dissection; SRT = stereotactic radiotherapy; ACC.RT = accelerated radiotherapy; S = surgery

IMRT technique. For similar reasons, the SRT fraction costs were €43,35 compared to €31,11 for conventional EBRT fractions.

DISCUSSION

As of 1986, in the Erasmus MC, patients with T1-3 TF and/or SP tumors were treated preferentially by EBRT plus BT (with or without ND). If BT was not feasible, surgery and PORT were used. As shown by the results reported here and by other articles [4,7,8], excellent locoregional tumor control can be achieved. At 10 years, the locoregional control rate was approximately 85%, with no statistically significant difference between RT only and surgery with PORT. The major late adverse side effect was xerostomia, with both groups equally affected. The mean VAS score was 5.5 in the BT-group and 6 in the surgery group. The PSS scores regarding eating in public, normalcy of diet and understandability of speech, were not discriminative for either modality [13]. The results of both treatment groups were highly comparable with regard to the medical and functional outcome. This demonstrates the need for a more distinctive measure for decision-making regarding the choice of treatment modality.

In previous articles we calculated and discussed the costs of head and neck tumors treated by either RT and/or surgery [19,20]. This was done for patients treated by physicians participating in the Rotterdam Cooperative Head and Neck Cancer Group (Erasmus MC) and clinicians of the department of Head and Neck Surgery of the Free University Medical Center in Amsterdam. In general, the costs in both institutions were quite similar. However, the costs of surgical treatment were greater compared with the costs for patients treated by RT only, mainly because of the costs generated by the hospital admission of the surgical patients.

The purpose of this article was to see whether one could use costs as a prioritizing factor in the case of two different treatment options with, in principle, similar outcomes with regard to tumor control, side effects and functional performance. We focused, therefore, on the full hospital costs for BT vs surgery in patients with TF and/or SP tumors. Cost computation methods were similar to those used previously [19,20]. The cost calculation in this paper was based on real patient numbers and the different treatments options used in our institution. However, some numbers had to be estimated, such as the percentage of patients receiving PDR or HDR (which influences slightly the number of admission days), as well as the actual time personnel spent on the

different procedural steps of treatment. Because the complications related to the treatments discussed were relatively minor and, in most cases, healed spontaneously (ulcer) or were treated only with physical therapy (trismus), the costs related to complications were not taken into account. Also, with regard to the potential outcome of future strategies, as an approximation, the tumor control for IMRT, SRT and accelerated RT was considered similar to that for the BT and surgery group.

Another issue related to costs of treatment involved the costs associated with issues such as time missed from work, ability to return to work, and need for social services. In this study, the mean age of the patients was 57 years for the BT group and 59 years for the surgery group (Table 1). For many of these patients, these costs might not have been a relevant issue in the computation of the total costs of treatment [24].

In effect, for the TF and/or SP tumors studied in this paper, using similar calculation methods as previously reported [19,20] and given the approximations (see above), the total costs for EBRT plus BT and BT plus ND were less compared to surgery plus PORT (€14.261,98 and €16.628 vs. €18.782, [Table 4]). The difference was a result of the treatment costs per se, but, in particular, because of the substantially longer hospital stay in case of surgery (Table 3).

It is anticipated that for the curative types of head and neck tumors, such as intermediate stage TF and/or SP tumors, in the near future, the major focus will be on the reduction of side effects, to improve on the therapeutic ratio. Given the late side effects observed for both treatment groups (BT vs. surgery) and, in particular the degree of xerostomia, the organ preservation protocol has been optimized to reduce the dose to the salivary glands and oral mucosa further to obtain better sparing. This was done by introducing IMRT in the first series of 46 Gy. A second future modification could be to replace surgery of the primary tumor with SRT. Finally, the cost computations were performed as if this patient category would have been treated by a well-accepted and very effective accelerated fractionation scheme for head and neck cancer (so-called concomitant boost schedule), delivered by IMRT techniques [25]. The costs of these 3 future strategies were compared with surgery plus PORT, using IMRT (Table 5). The costs for the future strategies hardly seemed to exceed the costs for current treatment modalities, i.e. €16.628 [$19.452] for BT plus ND, €18.782 [$22.074] for surgery and €16.897 [$19.767] for IMRT plus ND.

Conclusion

The results of this article show that costs could potentially be used in decision-making regarding the choice of treatment modality, in particular in the case of equal clinical outcomes for patients treated with RT or surgery. One could question whether any gain can be expected for patients with T1-3 TF and/or SF tumors when treated with more aggressive therapy, given the excellent tumor control in this organ function preservation protocol (locoregional control rate 85% at 10 years). More importantly, additional gain in quality of life can be anticipated when implementing new organ-sparing RT techniques, such as IMRT. When surgery is replaced by SRT and/or accelerated RT schedules, using these IMRT sparing techniques, a gain in the quality of life and effectiveness can be anticipated, apparently at almost equal or even less cost. The cost reduction was mainly of the elimination of, or reduction in, the hospital stay.

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REFERENCES

1. Foote RL, Parsons JT, Mendenhall WM, *et al*. Is interstitial implantation essential for successful radiotherapeutic treatment of base of tongue carcinoma? Int J Radiat Oncol Biol Phys 1990; 18:1293-1298.
2. Foote RL, Olsen KD, Davis DL, *et al*. Base of tongue carcinoma: patterns of failure and predictors of recurrence after surgery alone. Head & Neck 1993;15:300-307.
3. Parsons, JT, Mendenhall WM, Stringer SP, *et al*. Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. Cancer 2002;94:2967-2980.
4. O'Sullivan B, Warde P, Grice B, *et al*. The benefits and pitfalls of ipsilateral radiotherapy in carcinoma of the tonsillar region. Int J Radiat Oncol Biol Phys 2001, 51;332-342.
5. Harrison LB, Zelefsky MJ, Sessions RB, *et al*. Base-of-tongue cancer treated with external beam irradiation plus brachytherapy: oncologic and functional outcome. Radiology 1992;184:267-270.
6. Harrison LB, Lee HJ, Pfister DG, *et al*. Long-term results of primary radiotherapy with/without neck dissection for squamous cell cancer of the base of tongue. Head & Neck 1998;20:668-673.
7. Withers HR, Peters LJ, Taylor JMG, *et al*. Late normal tissue sequelae from radiation therapy for carcinoma of the tonsil: patterns of fractionation, study of radiobiology. Int J Radiat Oncol Biol Phys 1995;33:563-568.
8. Withers HR, Peters LJ, Taylor JMG, *et al*. Local control of carcinoma of the tonsil by radiation therapy: an analysis of patterns of fractionation in nine institutions. Int J Radiat Oncol Biol Phys 1995;33:549-562.
9. Mak AC, Morrison WH, Garden AS, *et al*. Base-of-tongue carcinoma: treatment results using concomitant boost radiotherapy. Int J Radiat Oncol Biol Phys 1995;33:289-296.
10. Mendenhall WM, Stringer SP, Amdur RJ, *et al*. Is radiation therapy a preferred alternative to surgery for squamous cell carcinoma of the base of tongue? J Clin Oncol 2000;18:35-42.
11. Puthawala AA, Syed AM, Eads DL, *et al*. Limited external beam and interstitial 192iridium irradiation in the treatment of carcinoma of the base of the tongue: a ten year experience. Int J Radiat Oncol Biol Phys 1988;14:839-848.
12. Levendag PC, Schmitz PIM, Jansen PP, Senan S, Eijkenboom WMH, Sipkema D, Meeuwis CA, Kolkman-Deurloo IK, Visser AG. Fractionated

High-Dose-Rate and Pulsed-Dose-Rate Brachytherapy: First clinical experience in squamous cell carcinoma of the tonsillar fossa and soft palate. Int J Radiat Oncol Biol Phys 1997; 38: 497-506.

13. Levendag PC, Nijdam WM, Pol van de M, et al. Brachytherapy versus surgery in carcinoma of the tonsillar fossa and/or soft palate: late normal tissue sequelae and performance status. Can we be more selective? Radiotherapy and Oncology 2003; 66: abstract 25, page S10.
14. Pol van de M, Levendag PC, Bree RR, *et al*. Radical radiotherapy compared with surgery for advanced primary squamous cell carcinoma of the base of tongue. Brachytherapy. An International Multidisciplinary Journal, Submitted.
15. Levendag PC, Nijdam WM, Noever I et al. Brachytherapy versus surgery in carcinoma of the tonsillar fossa and/or soft palate: Late Adverse Sequelae and Performance Status. Can we be more selective? Int J Radiat Oncol Biol Phys, in press.
16. List MA, Stracks J, Colangelo L, et al. How do head and neck cancer patients prioritize treatment outcomes before initiating treatment. J Clin Oncol 2000;18:877-884.
17. List M, Ritter-Ster C, Lansky S. A performance status scale for head and neck cancer patients. Cancer 1990; 66: 564-569.
18. International Commission on Radiation Units and Measurements. ICRU Report 50: Prescribing, recording and reporting photon beam therapy. ICRU Publications. Bethesda MD 1993.
19. Levendag PC, Nijdam WM, van Agthoven M, Uyl-de Groot CA. Chemotherapy and high-dose-rate brachytherapy in the management of advanced cancers of the nasopharynx: clinical impact of high technology: is it worth the cost? Brachytherapy 2002; 1: 11-20.
20. van Agthoven M, van Ineveld BM, de Boer MF, *et al.* The costs of head and neck oncology: primary tumours, recurrent tumours and long-term follow-up. European Journal of Cancer 2001; 37: 2204-2211.
21. Oostenbrink JB, Koopmanschap, MA, Rutten FFH. Manual for costing research. Amstelveen. Health Care Board, 2000 (in Dutch).
22. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. New York, Oxford University Press, 1996.
23. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York, Oxford University Press, 1996.

24. Rutten van Mölken MPMH, van Busschbach JJ, Rutten FFH. From costs to effects: a manual for evaluation studies in health care. Maassen, Elsevier Gezondheidszorg, 2000 (in Dutch).
25. Fu KK, Pajak TF, Trotti A, *et.al*. A Radiation Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000; 48:7-16.

CHAPTER 5

Costs of Treatment Intensification for Head and Neck Cancer: Concomitant Chemoradiation Randomised for Radioprotection with Amifostine

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ABSTRACT

Purpose: This study presents an overview of costs of a chemoradiation protocol in Head and Neck Cancer patients and an analysis of whether prevention of acute toxicity with Amifostine results in a reduction of costs.

Material & Methods: Fifty-four patients treated with weekly Paclitaxel concomitant with radiation and randomised for treatment with subcutaneously administered Amifostine (500 mg) and analysed with respect to costs of treatment. Total costs for work-up, treatment and toxicity were calculated per treatment arm.

Results: No significant differences were found between treatment arms in preliminary results regarding response (98%), toxicity and 2-year survival (77%). Average costs for toxicity were €3.789, largely influenced by hospital admissions (€3.013). Total costs for Amifostine administration amounted to €6.495 per patient. The average total costs of treatment were €19.647 versus €13.592 with or without Amifostine, respectively.

Discussion: The applied (subcutaneous) dose of Amifostine appeared to be insufficient for radioprotection and reduction of related costs in the concomitant chemoradiation scheme, whereas total costs increased remarkably. Although it would be accompanied by a further cost raise, applying a higher Amifostine dose might reduce (mucosal) toxicity and therefore in the long run lower related costs for hospital admission and tube feeding.

INTRODUCTION

Current treatment strategies for advanced stage head and neck cancer (H&NC) aim at increased survival and (locoregional) tumor control with organ function preservation implementing multi-modality treatment schedules and altered fractionation schemes. Examples of such approaches include a combination of concurrently applied chemotherapy and radiotherapy [1], reduction of overall treatment time and/or increase of total applied radiation dose [2,3], in some cases followed by a neck dissection [4].

A drawback however is the increased rate of acute toxicity [3,5]. Ways to overcome this (mainly mucosal) toxicity are being explored. For instance, the use of radioprotectors such as Amifostine (Ethyol®, MedImmune Oncology, Gaithersburg, MD) might reduce acute mucositis [6,7] and acute and late xerostomia [8] after (chemo-) radiotherapy.

In an attempt to increase tumor control probability, as of 2000, at the Erasmus MC in Rotterdam, the Netherlands, all patients with a malignancy in the head and neck region are treated with a slightly accelerated fractionation schedule, i.e. 6 fractions of 2 Gy per week. Additionally, selected tumors of the tonsillar fossa, soft palate and base of tongue are boosted using interstitial brachytherapy. Brachytherapy has the advantage of a high tumor dose in a short overall treatment time (e.g. 20 Gy in 4-6 days), without compromising the surrounding normal tissues [9].

In April 2000 a randomized clinical trial for the treatment of stage (II,) III and IVa [10] squamous cell carcinoma of the head and neck (nasopharyngeal carcinoma and N3-disease excluded) was initiated [11]. The chemotherapy agent was Paclitaxel (Taxol®, Bristol-Meyers Squibb, Princeton, NJ). Paclitaxel was applied concurrently with external beam radiation. Patients were randomized for radioprotection with Amifostine or no radioprotection.

This clinical study focused on the radioprotective effect of Amifostine on major salivary glands and mucosal linings (xerostomia, acute mucositis) after subcutaneous (sc) administration. Taking bioavailability into account subcutaneous administration of Amifostine is believed to be as effective as intravenous (iv) administration [12], and moreover, to be less toxic (no allergic reactions, hypotension, nausea and vomiting) [13]. Therefor a reduction of workload and related costs as compared to IV administration can be achieved administering Amifostine sc.

During the past decade, costs for radiotherapy (in H&NC) have increased due to the implementation of 3D-conformal radiotherapy (3DCRT), intensity modulated radiation techniques (IMRT), brachytherapy, stereotactic RT

and combination with chemotherapy [14]. Amifostine treatment is known to be costly. Apart from the costs for medication, chemoradiation increases the rate, severity and duration of acute mucosal toxicity and dysphagia [5,11,15,16]. More patients are being admitted to the hospital due to dehydration, malnutrition and weight loss and therefore become dependent on (gastrostomy catheters for) tube feeding. Complex IMRT plans increase the labor intensity of the treatment planning procedure as well as the treatment delivery time and need for quality assurance [17].
The primary objective of this paper was to compare actual costs of treatment between the two treatment arms of our study, in order to investigate whether the increased costs of chemoradiation would be compensated by a reduction in acute toxicity and related expenses, using Amifostine. The secondary objective was to present a detailed overview of (expected) costs of a concomitant chemoradiation treatment protocol in H&NC patients.

PATIENTS AND METHODS

Study protocol AZR 99220
In this study patients were treated with 4 weekly courses of Paclitaxel 60 mg/m^2 intravenously (iv), concomitant with external beam radiation (46 Gy to primary tumor and bilateral neck nodes [18]). After 46 Gy a booster dose of 26 Gy was applied to the primary tumor (and positive neck nodes). In selected patients (clinical judgement of radiation oncologist) with a tumor located in the tonsillar fossa (TF) and/or soft palate (SP) or base of tongue (BOT) a HDR (High Dose Rate) brachytherapy boost was applied to the primary. In these patients a neck dissection was performed in case of positive neck nodes (N1,2). Patients in this trial were randomized for 500 mg Amifostine SC 15-30 minutes prior to each fraction of radiation (EBRT/BT) or no radioprotection.
Fifty-four patients treated according to the protocol AZR 99220 have been analyzed with respect to the total costs.

Costs
In this cost analysis the institutional perspective was taken, implying that all costs generated in the hospital were calculated, implying that all costs generated in the hospital were calculated [19]. The cost analysis was based on a database with medical procedures, hospital admission days and outpatient visits of all patients.

For the most important items in this database, average unit prices were calculated by a detailed inventory of all resources used. These calculations were based on 2002 unit costs. The costs for radiotherapy, outpatient visits, hospital admissions, neck dissection and implantation consisted of costs for personnel, materials and overhead. Personnel costs included wages, social premiums and fees for irregular working hours of the medical specialists, registrars, nursing staff and administrators. For salary costs see Table 1. Costs of nursing staff and administrators were calculated by dividing their total annual costs by the total annual number of hospital admissions of the department per year. Material costs comprised costs of disposable materials, equipment and nutrition. Overhead costs contained bare hotel costs, laundry and cleaning services and the costs of non-medical departments, like general management, and were fixed at 16.4% of total costs. Costs of less important items (due to low costs or low numbers) were based on the Dutch tariff system (CTG, Central Organ for Pricing in Health Care).
All costs made for diagnosis, staging, work-up and treatment preparations and delivery according to the protocol, as well as costs related to treatment toxicity (during treatment and in 3 months follow up, RTOG acute toxicity phase) were computed (see I – VII). Exchange rate Euro for USD approximately €1 = $1.20 (January 2004).

Table 1: Costs of manpower

Personnel	Salary costs (€ / hr)
Radiation Oncologist (RO)	78
Medical Oncologis (MO)t	78
Head-and-Neck Surgeon (HNS)	78
Anesthesiologist	78
Dentist	48
Medical physicist (MP)	42
Resident (Radiation Oncology)	34
Anesthesiology nurse	27
Operation theatre nurse	26
Radiation technician (RT)	25

I: Diagnosis, staging and work-up

All patients were seen in joint consultation by a radiation oncologist (45 minutes) and a Head-and-Neck Surgeon (45 min) for routine staging and work-up. Diagnosis and staging was established by clinical examination (including fiber optic endoscopy) and examination with biopsy of the primary under general anesthesia. CT- (35% of patients) and/or MRI-scanning (65% of patients) of the head and neck region (weighted cost) and ultrasound guided fine needle aspiration cytology of suspect neck nodes were performed. Clinical work-up consisted of consultation with a Medical Oncologist (20 min), routine blood tests, chest radiography, EKG and pre-operative visit to an anesthesiologist (10 min). An orthopantogram (X-OPG) was performed. Dental examination took 15 minutes for patients with dental prosthesis (43%) and 165 minutes for dentate patients (57%) (weighted costs, including fluoride applications during treatment).

II: Preparation for radiotherapy

External beam radiotherapy (EBRT)

For treatment planning purposes a CT scan (AcQSIM, PQ5000, Philips, The Netherlands), using IV contrast (30 min) was made with the patient in supine treatment position, using a PVC head and neck immobilization cast (210 min). The clinical target volume (CTV) of the primary tumor and bilateral neck nodes [20], as well as the organs at risk (spinal cord, salivary glands) were delineated on 5 mm CT-slices by a resident and corrected by the radiation oncologist in charge (total 90 min). CTV to PTV margin was 5mm. Radiation technicians generated a conformal treatment plan (960 min) using our 3-D treatment planning system CadPlan (Varian-Dosetek, versions 3.1.2 and 6.3.5, Finland). The generated treatment plan was checked and verified by a medical physicist (10 min), a second technician (30 min) and the radiation oncologist (30 min). In case of an external beam booster for pathological neck nodes, the dorsal neck was irradiated using high-energy electron beams (25% of patients; manufacturing of lead inlay 60 minutes, calculation 30 min).

Brachytherapy (BT, n=15)

Patients were admitted to the hospital a day prior to surgery and implantation. In case of positive neck nodes, the Head-and-Neck Surgeon performed a neck dissection (ND, 180 min), in BOT combined with a tracheotomy. In the same session the radiation oncologist implanted the primary tumor with flexible

catheters (90 min). A single plane implant of 2 or 3 catheters for tumors located in the tonsillar fossa and/or soft palate and a volume implant with 9 catheters for base of tongue tumors. Conventional X-rays in AP- and lateral directions were taken for simulation of the catheters (20 min RT, 5 min RO). Treatment planning was performed using Plato BPS (40 min) (Nucletron, Oldelft, Veenendaal, The Netherlands). For dose verification an additional CT-scan was made (30 min).

III: Treatment delivery

EBRT and BT

External beam radiation was slightly accelerated (12 Gy/week). Quality assurance (MegaVolt imaging) was performed during the second fraction of external beam radiation (10 min) and thereafter according to our routine protocol [21]. In case of a brachytherapy boost (with/without ND) 1-2 weeks after finishing 46 Gy EBRT, patients were admitted to the hospital. Six fractions of HDR were given twice daily with a 6-hour interval (total HDR dose 20 Gy). During treatment the radiation oncologist saw the patients in the outpatient clinic weekly (10 min per visit).

Chemotherapy

Before each cycle of chemotherapy, a Medical Oncologist was consulted (10 min) and routine blood tests were performed. Patients were admitted to the daycare center for approximately 4-5 hours: an hour for pre-hydration and anti-emetic treatment and 3 hours Paclitaxel infusion (calculated at 1.8 m^2 mean BSA).

IV: Amifostine

In randomized patients 500 mg Amifostine was administered sc in two 250 mg injections, preferably in the upper arms (by a resident, 10 min).

V: Treatment related toxicity

Costs for hospital admission included use of IV-fluids and medications, as well as salary costs for manpower (medical, administrative and nursing staff). Costs for diagnostic procedures (imaging, cultures) and treatments (e.g. tube feeding, blood transfusions) were computed. Tube feeding was

started if patients were unable to swallow pureed or liquid food and/or weight loss exceeded 5-10% of pre-treatment body weight. When the period of tube feeding was expected to exceed 2-3 weeks, an ultrasound-guided percutaneous gastrostomy catheter was inserted.

VI: Toxicity in acute phase (RTOG, 0-90 days post-treatment)
Admission days, tube feeding, blood transfusions, diagnostic imaging and cultures were analy zed with respect to actual costs.

VII: Routine follow-up on outpatient clinic 0-90 days post-treatment
All patients visited the outpatient clinics of the radiation oncologist, head-and-neck surgeon, dentist and the medical oncologist regularly after finishing chemoradiation treatment (10 minutes per visit).

Statistical analysis
Statistical analysis was performed using SPSS for Windows, version 11.0. Costs were calculated as mean costs per patient. For comparison of treatment arms, the Mann-Whitney U-test was applied, because of the non-parametrical distribution of the cost variables. A significance level of 5% was applied.
Survival was calculated according to Kaplan-Meier. Accordingly, local recurrence free survival (LRFS), regional recurrence free survival (RRFS), distant metastasis free survival (DMFS), disease free survival (DFS) and overall survival (OS) were computed. Calculations were made from the end of RT until latest outpatient-visit, recurrence, distant metastasis or death (whichever occurs first).

RESULTS

Clinical results

For characteristics of the study population see Table 2. Forty-seven patients (87%) finished the prescribed 4 courses of Paclitaxel; in 5 patients (9%) one course had to be delayed due to toxicity. Radiotherapy was given without any treatment interruptions (overall treatment time mean 41 days). Eight percent of Amifostine administrations were accompanied by nausea, in 44% of patients. Two patients (4%) had an anaphylactic reaction to Paclitaxel and/or Amifostine, for which both chemotherapy and Amifostine were discontinued. Due to side effects Amifostine was discontinued in 5 patients (19%).

Although (at the time) maximally sparing radiation techniques (3DCRT and brachytherapy) were used, the toxicity rates were high (Table 3). Preliminary results have been published [22] and presented at ASTRO 2002 (yearly conference of American Society for Therapeutic Radiology and Oncology in New Orleans) [11]. Fifty-three patients (98%) had a complete response on therapy. At 2 years follow up 4, 4 and 7 patients (7%, 7%, 13%) developed a local recurrence, regional recurrence and distant metastasis. Early survival was not significantly different in the 2 treatment arms. LRFS, RRFS, DMFS and OS at 2 years were 77%, 72%, 77%, 70% and 77%, respectively, for the total group.

Analysis of costs

Table 4a and b shows a subdivision of the costs made for diagnosis, staging, treatment delivery, related toxicity and costs during 3 months follow up. For diagnosis and work-up €1.997 was calculated; for preparations for radiotherapy €1.322 and for brachytherapy preparations (e.g. patient information) an additional €73 was required. The implantation of catheters cost €1.299. Chemoradiation (72 Gy) for H&NC amounted to €4.440. A brachytherapy boost and neck dissection added €5.211 and €3.214 respectively (including admission days, see Table 5).

The mean total costs comprised costs for work-up, preparations for radiotherapy, treatment delivery, and treatment related costs. These total costs were weighted costs according to the percentage of patients having been treated with the various types of boosts (external versus brachytherapy with or without a neck dissection and tracheotomy). Total costs of treatment were €19.647 versus €13.592 (with / without Amifostine, $p < 0.0001$). The average total costs for treatment in this study show a difference of €6.055

Table 2: Characteristics of study population

	With Amifostine		Without Amifostine		Total Group	
Primary Tumor Site						
Oral Cavity	1	(4)			1	(2)
Oropharynx	13	(48)	13	(48)	26	(48)
Hypopharynx	7	(26)	6	(22)	13	(24)
Larynx	6	(22)	8	(30)	14	(26)
TNM Stage						
II	2	(7)	1	(4)	3	(6)
III	11	(41)	8	(30)	19	(35)
IVa	14	(52)	18	(67)	32	(59)
Mean Age (years)	59		58		58	
Sex (M :F)	19:8	(70:30)	22:5	(81:19)	41:13	(76:24)
BT Boost	7	(26)	8	(30)	15	(28)
ND after 46 Gy	2	(7)	7	(26)	9	(17)
Total	27	(100)	27	(100)	54	(100)

Numbers between brackets are percentages. BT = brachytherapy; ND = neck dissection.

Table 3: Results on acute toxicity (RTOG)

	With Amifostine	Without Amifostine
Mucositis grade 3 (%)	100	96
Duration (weeks)	8	7
grade 3 – grade 0 (weeks)	10	6
Dysphagia grade 3 (tubefeeding) (%)	85	85
Duration (weeks)	26	24
Hospital admission (%)	81	81
Duration (days)	8	7
Amifostine related nausea		
Patients involved (%)	44	NA
Administrations involved (%)	7.5	NA

Results from start of treatment till 90 days after end of treatment.
Numbers in averages; none are significant. NA = not applicable.

Table 4a: Costs of treatment (in €)

		Costs per "Item"	Total Costs[1]	With Amifostine[2]	Without Amifostine[2]	P-Value[3]
I. Diagnosis and Staging			**1.997**	**1.997**	**1.997**	1.0
Consultation of medical specialists			756			
Radiation Oncologist		95				
Fiber optic endoscopy		107				
Head-and-Neck Surgeon		95				
Fiber optic endoscopy		107				
Medical Oncologist		57				
Dentist (weighted costs)		193				
Anesthesiologist		44				
Laboratory tests		40				
EKG		18				
Diagnostic imaging			411			
CT or MRI (weighted costs)		201				
Ultra Sound Neck (with cytology)		132				
Chest X-ray		39				
Orthopantogram		39				
Examination under general anesthesia			831			
II. Preparations for Therapy[4]				**1.341**	**1.344**	0.8
External Beam RT			1.322			
Radiation Oncologist	130 min	169				
Radiation Technician	1400 min	588				
Medical Physicist	10 min	7				
Materials		136				
Equipment		235				
Brachytherapy: treatment planning			73			
Radiation Oncologist	10 min	13				
Radiation Technician	110 min	46				
Medical Physicist	5 min	4				

III. Delivery of Treatment				**5.808**	**6.760**	
Radiotherapy (personnel, materials, equipment)				1.139	1.141	0.8
36 # EBRT (n=39)	EBRT per #	31	1.116			
23 # EBRT + 6 # HDR (n=15)	HDR per #	79	1.187			
Brachytherapy (implantation +/- ND)			3.735	516	1.011	0.5
Implantation of loops[4]			1.299			
Radiation Oncologist	90 min	117				
Other Personnel[5]	450 min	251				
Equipment (operation room)		649				
Materials (loops)		58				
Histology		41				
Neck Dissection[4] (n=9)			2.436			
Personnel[7]		705				
Equipment (operation room)		1.298				
Materials (tracheotomy)		50				
Histology		41				
Admission for BT +/- ND						
BT only, mean 9 days, incl. ICU (n=6)			3.841	779	1.125	0.7
BT + ND, mean 11 days, incl. ICU (n=9)			4.619	135	189	0.7
Controls on out-patient clinic RO		42[6]	252	239	237	0.8
Concomitant Chemotherapy			3.072	3.000	3.057	
Daycare		56[6]				
Paclitaxel		638[6]		2.646	2.697	0.7
Consultation of MO (incl. laboratory)		74[6]		354	360	0.7
IV. Amifostine (incl. administration by physician)				**6.495**	**0**	<0.0001
36 # EBRT (n=39)		214[6]	7.704			
23 # EBRT + 6# HDR (n=15)			6.206			
V. Toxicity			3.789	**4.006**	**3.491**	
Admission for toxicity during treatment (n=44)			3.013	3.197	2.710	
RT ward (n=44)	per day	389[6]	2.940	3.116	2.683	0.8
ICU (n=3)	per day	729[6]	73	81	27	0.5
Gastrostomy (n=37)		350	240	259	246	0.9
Tube feeding (n=46)		15[6]	285	285	285	1.0
Diagnostic imaging (n=22) (62 procedures)		See I.	60	79	55	0.4
Cultures (n=24)		38	91	110	71	0.3
Blood transfusions (n=13)		186	100	76	124	0.6
Total costs of treatment and toxicity				**19.647**	**13.592**	<0.0001
Total cost of treatment without Amifostine				13.152	13.592	NS[8]

Table 4b: Costs of post-treatment until 90 days after finishing treatment (in €)

	Costs per "Item"	Total Costs[1]	With Amifostine[2]	Without Amifostine[2]	P-Value[3]
VI. Toxicity		**1.776**	**2.111**	**1.203**	
Admission for toxicity (n=8)		780	1.067	159	0.4
Tube feeding (n=43)	15[5]	915	930	900	0.9
Diagnostic imaging (n=22) (38 procedures)	See I.	81	114	92	0.5
VII. Outpatient controls		**316**	**295**	**338**	0.9
Radiation Oncologist	42	151	148	155	0.7
Head-and-Neck Surgeon	42	46	51	44	0.8
Medical Oncologist	42	25	18	36	0.4
Dentist	36	72	63	80	0.2
Other medical specialties	42	22	17	26	0.8
Total costs post-treatment		**2.092**	**2.406**	**1.489**	0.8

Due to rounding of numbers totals may not equal the sum of parts:
Table 4b: The difference between treatment arms in costs of 3 months follow up are strongly influenced by the fact that one patient has been admitted to the hospital for 33 consecutive days. This results in a mean admission of 2.74 versus 0.41 days (with or without Amifostine), although the median admission in both study groups is 0.

[1] Costs are calculated costs for each part of treatment; costs for admission for BT/ND are based on means of involved number of patients; costs for toxicity are based on means of 54 patients (weighted costs).
[2] Weighted costs, based on total costs of patients treated +/- BT, +/- ND, +/- tracheotomy, divided by 27 per treatment arm (+/- A)
[3] P-Value between treatment arms with or without Amifostine.
[4] For total costs 16.4 % overhead is added.
[5] 45 min resident RO; 45 anesthesiologist; 90 anesthesiology nurse; 2x90 operation theatre nurse; 90 anesthesiology nurse for recovery.
[6] Costs per day, per chemotherapy course, per outpatient visit, per Amifostine administration.
[7] 180 min HNS; 180 resident HNS; 90 anesthesiologist; 180 anesthesiology nurse; 2 x 180 operation theatre nurse.
[8] NS = not significant.

Table 5: Calculated and anticipated costs of treatment (in €)

Treatment	Without Amifostine	With 500 mg Amifostine SC		With 875 mg Amifostine SC	
EBRT (36#) with ChT	4.440		12.144		14.444
Chemotherapy	3.072		4.440		4.440
EBRT	1.116	Amifostine (36)	+ 7.704	Amifostine (36)	+ 14.004
Out-patient clinics	252			Reduction in toxicity	- 4.000
EBRT (23#) with ChT + BT (6#)	9.651		15.857		15.432
Chemotherapy	3.072		9.651		9.651
EBRT+BT	1.187	Amifostine (29)	+ 6.206	Amifostine (29)	+ 11.281
Implantation	1.299			Reduction in toxicity	- 4.000
Admission	3.841			Reduction in admission	- 1.500
Out-patient clinics	252				
EBRT (23#) with ChT + BT (6#) + ND	12.865		19.071		18.646
Chemotherapy	3.072		12.865		12.865
EBRT+BT	1.187	Amifostine (29)	+ 6.206	Amifostine (29)	+ 11.281
Implantation	1.299			Reduction in toxicity	- 4.000
Neck dissection	2.436			Reduction in admission	- 1.500
Admission	4.619				
Out-patient clinics	252				

EBRT = external beam radiation; # = fraction; ChT chemotherapy, 4 courses calculated; BT = brachytherapy boost for primary; ND = neck dissection for positive neck nodes in case of BT boost.

Amifostine 500 mg €214 per administration; 875 mg €389.

between treatment arms merely due to the administration of Amifostine in the randomized patients (mean costs of Amifostine administration was €6.495 per patient, calculated mean of 30.41 injections, price per 500 mg vial €201). Without the additional costs for Amifostine, the total expenses in both treatment arms would nearly be equal (€13.152 versus €13.592, P=NS).

In the first 3 months post-treatment the major part of costs consisted of tube feeding (mean 62 and 60 days, with/without Amifostine, P=NS). The mean costs per patient mounted to €1.776; e.g. costs for admissions (€780), tube feeding (€915), and diagnostic imaging (€81). In the two treatment arms patients paid equal number of visits at the outpatient clinics of medical specialties, mean costs €316. The difference in costs in the first 3 months of follow up was not significant.

DISCUSSION

Platinum based chemoradiation is nephrotoxic. Patients need intravenous hyperhydration and monitoring of renal function (resulting in hospital admission during each cycle of chemotherapy). In this clinical trial, Paclitaxel was preferred as chemotherapy agent because of the possibility to treat patients on a daycare (outpatient) basis. Paclitaxel can be given as a 3-hour infusion, on outpatient basis, and is as effective as a 24-hour infusion [23].

If treatment results are improving, the next objective will be improving the patient's quality of life by reducing the acute and late sequelae of treatment, such as mucositis and xerostomia. Patients will probably experience a better quality of life if they have a better ability to eat, to drink and to speak [24]. Furthermore, patients' quality of life will improve if they have a better chance of (disease free) survival. Unfortunately, intensification of treatment increases (mucosal) toxicity [5 25,26].

In this clinical trial, Amifostine was implemented in order to reduce toxicity rates. However, preliminary results showed no differences between treatment arms concerning acute toxicity rates and related treatment costs.

The protective effect of Amifostine on the mucosal linings of the head and neck region is not unequivocal. Large numbers of patients will be needed to provide a reliable answer on the issues of cytoprotection of normal tissues and tumor protection [27].

In our trial, 81% of patients in both treatment arms were admitted to the hospital due to toxicity (e.g. mucositis, dehydration, fever) for 8 days on

average. Eighty-five percent of patients required tube feeding for mean 14 weeks (during RT and up to 90 days post-RT) [11]. The median duration of tube feeding was approximately 6 months.

In a systematic review of 33 randomized trials, Trotti et al. reported 43% grade 3/4 mucositis after chemoradiotherapy. After altered fractionated RT the grade 3/4 mucositis incidence is 57% and 32% hospital admissions. Overall incidence of dysphagia was 56%. In 19% a feeding tube is required [16]. Smith et al. reported 60% of patients still in need for tube feeding >1 year post-chemoradiation [15]. Given these results, one may expect the associated health care costs to increase.

Amifostine 500 mg SC itself costs approximately €214 per administration (€6.495 for a mean number of 30 injections, this study). Without costs for administration of Amifostine, the costs of the patients in our trial amounted to approximately €14.000 on average without significant differences between both study arms.

Few papers report on actual costs for treatment of H&NC patients. Some Dutch studies report on costs of treatment of advanced H&N malignancies. Van Agthoven et al. analyzed costs made for H&NC patients treated with surgery, radiotherapy or a combination in two Dutch university hospitals [28]. In our institute, Nijdam et al. have analyzed costs for treatment of oropharyngeal carcinomas using external beam RT and a brachytherapy boost, with or without a neck dissection [29]. Apparently, in this chemoradiation trial standard costs for preparation and treatment are increased with €1.500, mainly due to a 3 – 4 days longer hospital stay after BT with/without ND following chemoradiation (9 versus 5.5 days for BT, 11 versus 8 days for BT plus ND, ChRT vs RT) (see Table 4a, III).

Levendag et al. have calculated the costs needed for chemotherapy, brachytherapy, 3DCRT and stereotactic radiotherapy in the treatment of nasopharyngeal carcinoma [14]. With respect to chemotherapy treatment, costs are as follows: treatment on a daycare basis costs approximately €56 per day; a hospital admission costs approx. €389 per day (this paper). Six weeks neo-adjuvant hospitalized courses of Cisplatinum for nasopharyngeal cancer cost €7.772 [14], whereas 4 weekly courses of Paclitaxel on a daycare basis cost €3.072 (Table 4a, III). Additional costs for hospitalization, gastrostomy, tube feeding etc. during concomitant chemoradiation mounted up to €3.789 (see Table 4a, V). Total costs of concomitant chemotherapy and toxicity (€6.861) are €1.000 less as compared to the costs of the in-hospital (sequential) treatment schedule (costs for toxicity not mentioned).

Ways to improve clinical and financial results

Amifostine administered SC at a flat dose of 500 mg was not sufficient to prevent high rates and long lasting mucositis grade 3 and inability to swallow solid or liquid food. Alternative ways to control mucosal toxicity have been described with conflicting results. Papers mainly involve dietary and palliative advises. There are few publications on prevention and intervention with strong evidence of efficacy [30, 31]. Biswal et al. have investigated the effect of natural honey on radiation induced mucositis and, interestingly, found a significant reduction (50%) in grade 3/4 mucositis [32].

The lack of differences in this study can be manifold. The applied combination therapy may have caused too many side effects. However, applying a less toxic treatment schedule would probably have influenced the outcome negatively. Although in the presented clinical trial 94% of patients had AJCC stage III or IVa tumor, a premature analysis shows good results. Six weeks post-treatment complete response rate is 98%. Two-year disease free survival is 70% and overall survival is 77% (no difference between treatment arms). Huguenin et al. described a randomized clinical trial for a similar patient group (> 95% stage III, IVa) treated with hyperfractionated RT with or without concomitant cisplatin to a cumulative dose of 200 mg/m^2 [33]. Compared to the presented study, toxicity is reduced (60% grade 3/4 acute mucositis for only 20 days, 50% dysphagia grade 3). Still the frequency of treatment interruptions is much higher (20%, median 4 days, versus none in this study). Moreover, as compared to the presented clinical trial, figures of overall survival and failure rate are less favorable in the Huguenin patients: at 2 years DFS < 50% and OS approximately 60% (versus 70 and 77%).

A second reason for the lack of differences may be due to inadequate dosing of Amifostine. Subcutaneous administration of 500 mg Amifostine is assumed to have a bioavailability equal to 200 mg/m^2 intravenously. This dose was based on a publication by Brizel et al. (200 mg/m^2 IV) with a positive effect on xerostomia, but no significant effect on mucositis [8]. However, patients in the Brizel study received conventional radiation therapy only, while combination therapy is known to be more toxic (mucosae).

For prevention of mucositis and dysphagia in concurrent chemoradiation schemes, a higher dose has been advocated (250-340 mg/m^2, 300 mg/m^2 IV) [6,7]. Buntzel et al. found an 86% reduction in grade 3/4 mucositis and an 80% reduction of grade 3 dysphagia in the patients treated with Amifostine at completion of therapy. Antonadou et al., like in this study, used a weekly concurrent chemoradiation scheme. They found a 60% reduction of grade 4 mucositis in the study group and 73% had a (delayed onset) grade

3 mucositis. In only 14% mucositis grade 3 persisted for more than 4 weeks after treatment. At 8 weeks follow up mucositis had resolved completely in 77% (others only grade 1). Also a 36% reduction of grade 3 dysphagia was found. Only 9% of patients were tubefeeding dependent for more than 4 weeks. At 8 weeks 73% of the study group used a normal diet again.
Based on the described randomized clinical trials, a cautious assumption of 50% reduction of grade 3/4 mucositis and dysphagia grade 3 to a limited period of 6 weeks, would reduce costs both for hospital admissions and tube feeding with approximately 50%. Mean costs for hospital admission were €3.013 during treatment (Table 4a,V) and €780 during 3 months follow up (Table 4b, VI) (total cost €3.793). We found that if patients could only be admitted for insertion of a gastrostomy catheter, the median hospital stay would be 3 days, implying a reduction of 5 days (€2.000, €389 per day). Aiming at 50% reduction of hospital admissions, costs can be reduced by approx. €1.900. Reduction of the duration of tube feeding to approx. 6 weeks would reduce costs even further by €2.100 (20 weeks, €15 per day).
For subcutaneous administration of a dose equal to 300 mg/m^2 IV, one should administer approximately 800 mg flat dose (mean BSA 1.8 m^2 and bioavailability of 70% after SC administration [12]). Commercial vials of Amifostine contain 375 or 500 mg and cost €175 and €201 respectively. Amifostine 875 mg flatdose SC would add €6.300 (EBRT only, 36 administrations, extra costs €175 per vial of 375 mg) or €5.075 (EBRT plus BT, 29 administrations) to the total costs. But as described, a reduction of costs by approximately €4.000 (toxicity and tube feeding) and €1.500 (admission days for BT) should be feasible. Total costs using 875 mg Amifostine would only be increased in the external radiation treatment (see Table 5).

Conclusion
Concomitant chemoradiation for advanced stage head and neck cancer results in high response rates, but also in severe and long lasting (mucosal) toxicity with increase of treatment related expenses. Weekly Paclitaxel 60 mg/m^2 concomitant with 72 Gy in 6 weeks, caused considerable long lasting grade 3 toxicity in 80-100% of patients. Amifostine (500 mg SC daily) was not able to reduce acute toxicity. Costs for (sub)acute toxicity comprised 30% of expenses in both treatment arms. The major cost-initiating factor appeared to be hospital admission. A reduction of admission days and a reduction of incidence and duration of tube feeding might result in reduction of costs.
Based on the literature (Amifostine 300 mg/m^2 IV), subcutaneous

administration of 875 mg Amifostine might result in a reduction of acute (mucosal) toxicity. The extra costs of a 375 mg vial of Amifostine could be balanced by the expected reduction of toxicity.

REFERENCES

1. Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-955.
2. Bourhis J, Audry J, Overgaard J, et al. Meta-analysis of conventional versus altered fractionated radiotherapy in head and neck squamous cell carcinoma (HNSCC): final analysis. Int J Radiat Oncol Biol Phys 2004;60:190-191.
3. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003 [see comments]. Int J Radiat Oncol Biol Phys 2000;48:7-16.
4. Robbins KT, Kumar P, Wong FS, et al. Targeted chemoradiation for advanced head and neck cancer: analysis of 213 patients. Head Neck 2000;22:687-693.
5. El-Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. A meta-analysis of prospective and randomized trials. J Clin Oncol 1996;14:838-847.
6. Antonadou D, Pepelassi M, Synodinou M, et al. Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. Int J Radiat Oncol Biol Phys 2002;52:739-747.
7. Buntzel J, Kuttner K, Frohlich D, et al. Selective cytoprotection with amifostine in concurrent radiochemotherapy for head and neck cancer [see comments]. Ann Oncol 1998;9:505-509.
8. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 2000;18:3339-3345.
9. van de Pol M, Levendag P, Franssen J, et al. Tumor control and functional outcome after radical surgery or interstitial radiotherapy-treatment options in T3/T4 cancer of the base of the tongue. International Journal of Radiation Oncology Biology Physics 2002;54:292-293.

10. TNM Classification of Malignant Tumours. 5th Edition ed. New York: Wiley-Liss; 1997.
11. Braaksma M, Levendag P, De Jonge M, et al. Organ preservation with chemoradiation in advanced head and neck cancer concomitant paclitaxel with or without subcutaneous amifostine prior to radiation preliminary results on toxicity of a randomized clinical trial. Int J Radiat Oncol Biol Phys 2002;54:291.
12. Shaw LM, Bonner HS, Schuchter L, et al. Pharmacokinetics of amifostine: effects of dose and method of administration. Semin Oncol 1999;26:34-36.
13. Rades D, Fehlauer F, Bajrovic A, et al. Serious adverse effects of amifostine during radiotherapy in head and neck cancer patients. Radiother Oncol 2004;70:261-264.
14. Levendag P, Nijdam W, Agthoven van M, et al. Chemotherapy and high-dose-rate brachytherapy in the management of advanced cancers of the nasopharynx: clinical impact of high technology - is it worth the cost? Brachytherapy 2002;1:11-20.
15. Smith RV, Kotz T, Beitler JJ, et al. Long-term swallowing problems after organ preservation therapy with concomitant radiation therapy and intravenous hydroxyurea: initial results. Arch Otolaryngol Head Neck Surg 2000;126:384-389.
16. Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003;66:253-262.
17. Glatstein E. Intensity-modulated radiation therapy: the inverse, the converse, and the perverse. Semin Radiat Oncol 2002;12:272-281.
18. Levendag P, Braaksma M, Coche E, et al. Rotterdam and Brussels CT-based neck nodal delineation compared with the surgical levels as defined by the American Academy of Otolaryngology-Head and Neck Surgery. Int J Radiat Oncol Biol Phys 2004;58:113-123.
19. Drummond M, O'Brien B, Stoddart G, et al. Methods for the economic evaluation of heath care programmes. 1997.
20. Nowak PJ, Wijers OB, Lagerwaard FJ, et al. A three-dimensional CT-based target definition for elective irradiation of the neck. Int J Radiat Oncol Biol Phys 1999;45:33-39.
21. de Boer HC, van Sornsen de Koste JR, Creutzberg CL, et al. Electronic portal image assisted reduction of systematic set-up errors in head and neck irradiation. Radiother Oncol 2001;61:299-308.

22. Braaksma M, Levendag P. Tools for optimal tissue sparing in concomitant chemoradiation of advanced head and neck cancer: subcutaneous amifostine and computed tomography-based target delineation. Semin Oncol 2002;29:63-70.
23. Tishler RB, Busse PM, Norris CM, Jr., et al. An initial experience using concurrent paclitaxel and radiation in the treatment of head and neck malignancies. Int J Radiat Oncol Biol Phys 1999;43:1001-1008.
24. Wijers OB, Levendag PC, Braaksma MM, et al. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. Head Neck 2002;24:737-747.
25. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer [see comments]. N Engl J Med 1998;338:1798-1804.
26. Kaanders JH, van der Kogel AJ, Ang KK. Altered fractionation: limited by mucosal reactions? Radiother Oncol 1999;50:247-260.
27. Brizel DM, Overgaard J. Does amifostine have a role in chemoradiation treatment? Lancet Oncol 2003;4:378-381.
28. van Agthoven M, van Ineveld BM, de Boer MF, et al. The costs of head and neck oncology: primary tumours, recurrent tumours and long-term follow-up. Eur J Cancer 2001;37:2204-2211.
29. Nijdam W, Levendag P, Noever I, et al. Cost analysis comparing brachytherapy versus surgery for primary carcinoma of the tonsillar fossa and/or soft palate. Int J Radiat Oncol Biol Phys 2004;59:488-494.
30. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: part 1, pathogenesis and prophylaxis of mucositis. Head Neck 2003;25:1057-1070.
31. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy. Part 2: diagnosis and management of mucositis. Head Neck 2004;26:77-84.
32. Biswal BM, Zakaria A, Ahmad NM. Topical application of honey in the management of radiation mucositis: a preliminary study. Support Care Cancer 2003;11:242-248.
33. Huguenin P, Beer KT, Allal A, et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. J Clin Oncol 2004;22:4613-4621.

CHAPTER 6

Robotic Radiosurgery vs Brachytherapy as a Boost to Intensity Modulated Radiotherapy for Tonsillar Fossa and Soft Palate Tumors: The Clinical and Economic Impact of an Emerging Technology

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ABSTRACT

As a basis for making decisions regarding optimal treatment for patients with tonsillar fossa and soft palate tumors, we conducted a preliminary investigation of costs and quality of life for two modalities (brachytherapy and robotic radiosurgery) used to boost radiation to the primary tumors following external beam radiotherapy. Brachytherapy was well established in our center; a boost by robotic radiosurgery was begun more recently in patients for whom brachytherapy was not technically feasible. Robotic radiosurgery boost treatment has the advantage of being non-invasive and is able to reach tumors in cases where there is deep parapharyngeal tumor extension. A neck dissection was performed for patients with nodal-positive disease. Quality of life (pain and difficulty swallowing) was established in long-term follow-up for patients undergoing brachytherapy and over a one-year follow-up in robotic radiosurgery patients. Total hospital costs for both groups were computed. Our results show that efficacy and quality of life at one year are comparable for brachytherapy and robotic radiosurgery. Total cost for robotic radiosurgery was found to be less than brachytherapy primarily due to the elimination of hospital admission and operating room expenses. Confirmation of robotic radiosurgery treatment efficacy and reduced morbidity in the long term requires further study. Quality of life and cost analyses are critical to Health Technology Assessments. The present study shows how a preliminary Health Technology Assessment of a new medical technology such as robotic radiosurgery with its typical hypofractionation characteristics might be based on short-term clinical outcomes and assumptions of equivalence.

INTRODUCTION

At the Erasmus Medical Center – Daniel den Hoed Cancer Center (Erasmus MC), for organ preservation purposes, we preferentially use radiation-delivery technologies to treat tonsillar fossa (TF) and soft palate (SP) tumors. For over 10 years we combined external beam radiotherapy (EBRT), most recently using intensity-modulated radiotherapy (IMRT) with a brachytherapy (BT) boost to the primary tumor, along with neck dissection (ND) for nodal-positive (N+) patients. The efficacy, safety, effects on quality of life (QoL) and economic viability of this treatment were established in a series of studies [1-5]. We observed 5-year locoregional control rates of 87% and 80% with EBRT plus BT and EBRT plus BT plus ND, respectively [4]. However, late side effects related to treatment modality were also observed, including an actuarial ulceration rate of 42% with BT (88% of these healed spontaneously), and troublesome xerostomia. The use of IMRT helped reduce this latter effect.

In 2004 we acquired a CyberKnife® (Accuray Incorporated, Sunnyvale, CA) stereotactic robotic radiosurgery (RRS) system, which we began using to deliver radiation boost in certain TF/SP cases, particularly patients with deep parapharyngeal tumor extension where RRS, unlike BT, is able to distribute dose [6,7]. The use of the RRS as an alternative to BT gave us the unique opportunity to assess a new technology based on clinical-, QoL- and economic considerations and compare it to the "gold standard", BT. The CyberKnife (and other radiosurgery devices) is expensive technology; an assessment of its value relative to BT in this context requires a thorough analysis of medical efficacy, complication rates, and QoL effects of both technologies as well as a comparison of their financial costs. In other words, a Health Technology Assessment (HTA) is required. HTAs can inform health policy makers based not only on solid scientific, social, and ethical arguments but also on clear economic benefits to the patient and society.

This paper analyzes clinical endpoints and associated costs of BT and RRS treatment for TF/SP tumors at our institution. Because the application of RRS in this context has occurred only recently, a direct assessment of its long-term benefits and costs relative to BT was not yet possible. However, technical considerations regarding the ability of RRS to distribute radiation to this region in a way that approximates BT, and early clinical results showing comparable clinical efficacy of the technologies, allow us to base this preliminary HTA on assumptions of treatment equivalence. In other words, what we propose here is an HTA model that could be used to assess emerging treatment techniques in general.

MATERIAL AND METHODS

Rotterdam organ function preservation protocol

The protocol at Erasmus MC for the past 10 years for T1-3N0,N+ TF/SP tumors has been a course of external beam radiation to a dose of 46 Gy to the primary tumor and neck. EBRT is followed within 1-2 weeks by a fractionated high-dose-rate (HDR) or pulsed-dose-rate (PDR) BT boost to the primary tumor [4]. For cases of N+ disease, a ND is performed at the time of the BT procedure.

Since March of 2005 a RRS stereotactic radiation boost to the primary tumor for patients with deep parapharyngeal extensions or for other cases otherwise not eligible for BT procedures (Robotic Radiosurgery group) has been performed.

Pre-treatment & staging (work-up)

After joint consultation by a radiation oncologist and a head-and-neck surgeon in the outpatient clinic, a general work-up is performed for all patients. This includes examination, fiber optic endoscopy, routine laboratory tests, chest X-ray, ultrasound examination and CT / MRI scans of the head and neck. For surgical procedures, the anesthesiologist conducted a preoperative consult and monitored the patient during general anesthesia. A dental consult is also performed and before the start of radiation poor dentition is corrected. Finally, each patient's diagnostic results and treatment options are reviewed by the medical professionals during their head and neck tumor board. These elements comprised the *work-up* component of the cost analysis.

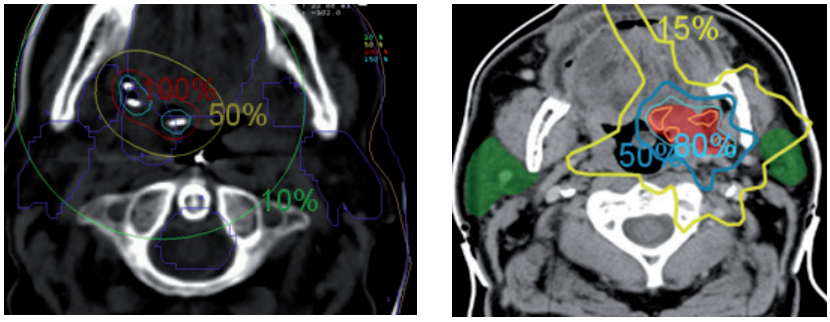
External beam radiotherapy

A head and neck fixation mask is made in a dedicated mouldroom. CT simulation is performed, followed by IMRT treatment planning (Cadplan, version 3.1.2, Varian-Dosetek, Finland). The dose is prescribed, according to ICRU 50 recommendations, to the 95% isodose line (46 Gy in 23 fractions). Normal tissue dose constraints are identified and set in the treatment plan and each treatment plan is presented and reviewed at the radiation oncologists' team (monodisciplinary tumor board). A dose verification computation is performed as a safety check by the physics staff after acceptance by the radiation oncology staff. Finally, the target volume is irradiated with 6 weekly fractions per week. That is one day, 2 fractions with a 6 hour interval; the

4 remaining days one fraction per day. Outpatient follow-up takes place 4-6 times during the course of treatment by the radiation oncologist. The above stated procedures included the *Radiotherapy-IMRT* component of the cost calculation.

Brachytherapy Boost (± Neck Dissection)
After EBRT, two BT dose regimens may be employed depending on the availability of the integrated brachytherapy unit (IBU) and head-and-neck surgeon (in the case of a ND). For both procedures, BT afterloading catheters are introduced under general anesthesia and 3 mm platinum marker seeds are placed to demarcate the CTV. The implant is simulated in the IBU and the dosimetrist generates a 3D-BT treatment plan. The first fraction is applied in the IBU with the patient still under general anesthesia. Fifty percent of BT patients received a total of 20 PDR fractions, 18 fractions of 1 Gy, preceded and followed by a 2 Gy fraction, for a total dose of 22 Gy. This so-called, "24 hour" PDR regimen was applied in an average of 4 consecutive days in the hospital ward. The other half of the BT patients received a HDR regimen of 6 fractions, consisting of 4 fractions of 3 Gy, preceded and followed by a single 4 Gy fraction for a total dose of 20 Gy. This so-called "fractionated high dose rate" regime is delivered in the IBU over an average of 6 days (including the non-treatment delivery weekend). A typical isodose distribution for BT is shown in Figure 1 (left panel). BT treatment, including catheter placement, combined with other hospital-based procedures, including operating room time and materials, ND costs and hospital stay were all combined into the *hospital* component of the cost calculation.

Figure 1: Examples of isodose coverage for TF/SP tumors with HDR-BT (L panel) vs. RRS (R panel)



Robotic Radiosurgery Boost (± Neck Dissection)

Robotic Radiosurgery treatment (RRS) is a hypofractionated stereotactic treatment method, in which a robotically manipulated 6 MeV linear accelerator treats the planning target volume (PTV) non-isocentrically, using collimated beams of varying diameter (0.5 – 6.0 cm). About a hundred beams are selected and applied for a variable duration by the treatment planning program. An inverse-planning algorithm calculates the ideal set of beam positions and intensities to optimize PTV coverage and minimize dose to normal tissue. For RRS treatment, a head cast is made with the patient in the supine position on the treatment table. Three to four fiducial markers are placed under general anesthesia in, or near, the tumor volume at the time of the staging examination. A contrast-enhanced 2 mm sequential slice CT-scan of the treatment volume is obtained. The CTV of the primary target volume is delineated on the CT slices with a 1 cm margin around the GTV. The PTV margin is defined as a 2 mm margin around the CTV. Critical structures are contoured by the radiation oncologist as necessary for appropriate dose limitation. The dose prescribed is 16.5 Gy to the 80% isodose line, that is 5.5 Gy in 3 fractions delivered over 3 days. A typical isodose distribution is shown in Figure 1 (right panel). Real-time kilovoltage X-ray tracking of implanted fiducial markers results in frequent targeting adjustment throughout each treatment session which, in part, produces high system targeting accuracy [6]. Robotic radiosurgery was its own (treatment) component of the cost calculation. If a ND was part of the treatment, then it was included in the hospital component of the cost calculation.

Follow-up

Patients are evaluated at regular follow-up intervals assessed by standardized clinical and laboratory tests. In the first year, patients are seen for five outpatient clinic visits including routine clinical examination. In years 2, 3, and 4, two follow-up visits, including routine clinical examination, laboratory tests (blood chemistry and T4 [TSH]), and annual chest X-Rays. In the fifth year, there is one outpatient clinic visit. All RRS patients have been followed for one year. For the purposes of cost comparison we have assumed that the 5-year follow-up cost for RRS patients will be equal to the 5-year follow-up cost for BT patients. This assumption is based on technical considerations (i.e., the ability of Robotic radiosurgery system to deliver doses and dose distributions that approximate those delivered by BT) and early clinical results showing similar outcomes (see below). The above procedure was the *follow-up* component of the cost calculation.

Relapse and/or second primary

If tumor relapse and/or a second primary are suspected, additional diagnostic procedures are performed (CT/MRI scan, endoscopy, biopsy, blood chemistry, etc.) depending on anticipated tumor type and location. This generally occurs within 2 outpatient visits. Depending on type of recurrence (relapse or second primary) a range of treatments is prescribed (from no treatment to combined modalities including surgery, RT, and chemotherapy). For this patient category an additional follow-up of five consults were included in the cost computations.

Although 5-year actuarial incidence of relapse has been defined and previously reported for our BT patients [4], we have no long-term RRS patient follow-up data so the relapse rate for this group remains undefined. Since RRS dose fractionation is presumed to be as effective as HDR-BT and PDR-BT dose schedules, the RRS relapse rate is presumed to be similar to the BT relapse rate and is taken as one cost component of this analysis.

Cost calculation

This cost analysis was performed from the institutional perspective [8, 9], based on 112 patients (103 treated with IMRT plus BT and 9 treated with IMRT plus RRS). In contrast to charges, unit costs are the best estimators of the real hospital costs [8]. For this reason and to facilitate cost comparison with other countries, we calculated the direct medical costs for the 4 subgroups: 1) IMRT plus BT, 2) IMRT plus BT plus ND, 3) IMRT plus RRS, and 4) IMRT plus RRS plus ND. Costs were specified for workup, treatment, 5-year follow-up and relapse. The direct medical costs were based on average unit costs, including overhead costs. To determine these unit costs, we followed the micro-costing method, which is based on a detailed inventory and measurement of resources consumed (10). The valuation of the resources and overhead costs was based on financial data from our institution. Costs were based on 2001 prices and stated in Euros (€). For some of the amounts (see Discussion section), the Euro is converted to the US dollar (exchange rate January, 2007; 1 Euro = 1.297 dollar).

Cost calculation per treatment group

The cost calculation for the BT group is based on an average of 5.5 hospital in-patient days. In cases of neck dissection, patients are admitted for an average of 8 days during which the BT fractions are given and the patient

can recuperate from the surgical procedure. The cost calculation for the RRS group is based on 3 RRS fractions performed on an outpatient basis. The cost of a fraction includes the robotic system depreciation and maintenance. For RRS patients who undergo a ND, the cost calculation is based on an average of 5 in-patient days for the ND component. ND costs are based on the assumption that 50% of the patients had a ND and 50% of the patients had a ND plus a reconstruction procedure.

Cost calculation - manpower and materials

To calculate manpower costs, time spent for the various procedures in the different subgroups was estimated by the medical specialties involved. Time invested was multiplied by salary costs calculated on a per minute basis, assuming 1540 working hours a year [11]. For medical professionals, the cost per minute was calculated by the method described by Oostenbrink et al. [11], which distinguishes between direct and indirect time. Direct time is when the specialist is with the patient, estimated to be 70% of the specialist's total working time. Indirect time, when the patient is not present, constitutes the remaining 30%. Total manpower costs were computed by multiplying direct time by 1.42, to include the added cost of indirect time.

Wholesale prices were used to determine costs of medical supplies. Supplies were inventoried and an analysis of their rates of use for these patient groups was completed. Costs related to capital equipment use and operating room (IBU) time were added to those costs. The costs for diagnosis and staging were based on the Dutch tariff system. Direct costs were multiplied by overhead. Overhead costs were based on the relationship between total hospital direct costs and administrative costs (building depreciation, device depreciation, etc.). In our RRS cost analysis, we assumed 1410 RRS treatments per year, which translates to 470 RRS patients treated at 3 fractions per patient. Our RRS cost analysis assumes a fully utilized system.

Cost calculation follow-up and relapse

To calculate follow-up costs, disease-free survival (DFS) for years 1 to 5 was calculated for BT patients according to the Kaplan-Meier method. Follow-up costs were based on the protocol described previously and corrected for DFS in that year. Relapse costs were based on the actual number of BT patients who showed renewed tumor activity, whether that be locoregional relapse, distant metastasis or a second primary tumor, as previously reported [3, 4].

The costs of treatment, additional diagnostic procedures and follow-up were totaled and averaged for all patients with a relapse.

Late side effects and Quality of Life for Brachytherapy Patients

QoL and acute/late side effects have been previously studied for BT patients. To assess QoL and late side effects, in 2003 and 2005 we administered a visual analogue scale for xerostomia (VAS xerostomia), a Performance Status Scale (PSS) scores according to List et al. [12, 13] and a questionnaire we devised to assess the severity of xerostomia [14]. The surveys were conducted among patients alive and without evidence of disease (NED) after a 2-year minimum follow-up. In 2005, patients were also assessed using the Euroqol [15], EORTC H&N 35 and QLQC 30 [16] tests.

Acute and Late Side Effects and Quality of Life for Robotic Radiosurgery Patients

To date, we don't have any patients yet with a long enough follow-up to report on late side effects for RRS. QoL was assessed in RRS patients in the same manner as it was in BT patients. Questionnaires were given at the beginning and end of the RRS treatment and at regular intervals, during 3 to 16 months post-RRS.

RESULTS

Number and characteristics of patients treated
This cost analysis was performed from the institutional perspective [8], based on 112 patients (103 treated with IMRT plus BT and 9 treated with IMRT plus RRS). The total number of patients broken down by treatment modality is shown in Table 1.

Survival
Patients treated for TF/SP tumors with BT or BT plus ND showed locoregional tumor control (LRC) of 87% and 80%, disease-free survival (DFS) of 57% and 58%, and overall survival (OS) of 63% and 67% respectively [4]. Due to the short follow-up, there do not yet exist 5-year disease-free survival data for the RRS patient group.

QoL/Toxicity
The severity and recovery of the acute side effects "pain" and "difficulties with swallowing" over time are illustrated in Figures 2A and 2B. Preliminary analysis reveals that RRS patients and BT patients had similar severity of pain and difficulty swallowing post-treatment. These figures suggest the RRS patient's side effects might heal with a slower initial recovery as opposed to BT patients and longer follow-up studies will reveal the trend.

Costs
Costs are shown in Tables 2-7. These include workup costs, individual treatment component costs and aggregate component costs for the BT and RRS groups. Patient groups are designated by their radiotherapy treatment, their boost modality, and whether or not they received a neck dissection. Thus, the four patients groups were designated IMRT plus BT, IMRT plus BT plus ND, IMRT plus RRS, and IMRT plus RRS plus ND.
Table 2 (work-up) shows the individual component cost to be higher (+ €115,60) for the RRS ± ND groups, due to the addition during the examination of the placement of fiducial markers for tracking during RRS treatment. Table 3 details the IMRT treatment costs, which are identical for all treatment groups. The costs of hospitalization are shown in Table 4. In the absence of a ND, BT costs are much higher than RRS, reflecting operating room costs,

Table 1: Patients available for analysis in each study group

	EBRT + BT group	IMRT + RRS
Economic analysis	103	9
Long-term (2-5 yr) QoL analysis	57	0
Short-term (~1 yr) QoL analysis	8	9

Abbreviation
EBRT = External Beam Radiotherapy, BT = Brachytherapy, IMRT = Intensity Modulated Radiotherapy, RRS = Robotic Radiosurgery, QoL = Quality of Life.

Table 2: Total work-up costs for each treatment group (in Euros)

Work-Up component (overhead incl.)	IMRT + BT ± ND	IMRT + RRS ± ND
RO and H&N Surgeon outpatient visits	189,06	189,06
Endoscopy	106,64	106,64
X-ray	39,25	39,25
Ultrasound neck + cytology	132,14	132,14
CT / MRI	188,40	188,40
Blood	37,55	37,55
Anesthesiologist preoperative consult costs	43,78	43,78
Dental consult & treatment costs	193,39	193,39
One-day admission for biopsy	830,80	830,80
Positioning of Fiducials during EGA	-	90,60
Fiducial cost (4 fiducials)	-	25,00
Total work-up	**1.761,01**	**1.876,61**

Abbreviation
IMRT = Intensity Modulated Radiotherapy, BT = Brachytherapy, ND = Neck Dissection, RRS = Robotic Radiosurgery, RO = Radiation Oncologist, H&N = Head and Neck, EGA = Examination under General Anesthesia.

Table 3: Radiotherapy-IMRT costs for each treatment group (in Euros)

Radiotherapy Treatment (IMRT[1])	IMRT + BT ± ND or IMRT + RRS ± ND
Personnel costs: IMRT preparation	650,50
Material costs: IMRT preparation	136,45
Equipment costs	235,02
Overhead: 16.4% of the above costs	167,60
Total IMRT preparation	**1.189,57**
Radiation session IMRT (23 at 31,10 per treatment)	715,33
Electronic Portal Imaging (EPI) (4 per course)	25,20
Outpatient visits (4 at 41,57 per visit)	166,28
Subtotal IMRT	**906,81**
Total IMRT (EBRT)	**2.096,38**

Abbreviation
IMRT = Intensity Modulated Radiotherapy, BT = Brachytherapy, ND = Neck Dissection, RRS = Robotic Radiosurgery, EBRT = External Radiation Therapy.

Table 4: Hospital costs (operating room, brachytherapy catheter placement and treatment, neck dissection, admission days) for each treatment group (in Euros)

Hospital costs (Operating Room, Brachytherapy and/or ND	IMRT + BT	IMRT + BT + ND	IMRT + RRS	IMRT + RRS + ND
Personnel costs: Brachytherapy preparation	184,30	184,30	-	-
Personnel costs: BT surgery	250,65	250,65	-	-
Material costs (OR use included)	706,90	706,90	-	-
Histology	40,84	40,84	-	40,84
Personnel costs: neck dissection	-	704,70	-	704,70
Material costs: neck dissection (including OR use)	-	1.297,80	-	1.297,80
Overhead: 16.4% of the above costs	193,96	529,07	-	335,41
Total OR: BT catheter placement and/or ND	**1.376,65**	**3.714,26**	**-**	**2.378,75**
Radiation session: BT (overhead incl.)	**1.031,81**	**1.031,81**	-	-
Admission days (overhead incl.)	**2.141,92**	**3.115,52**	-	**1.947,20**
Total Hospital: (OR, Radiation session BT and Admission days)	**4.550,38**	**7.861,59**	-	**€4.325,95**

Abbreviation
IMRT = Intensity Modulated Radiotherapy, BT = Brachytherapy, ND = Neck Dissection, RRS = Robotic Radiosurgery, OR = Operating Room.

Table 5: Total Robotic Radiosurgery costs (in Euros)

Robotic Radiosurgery	IMRT+RRS±ND
Treatment preparation/planning (staff)	360,40
Material	136,45
Equipment	235,02
Overhead: 16.4% of above costs	120,03
Total Preparation RRS (incl. materials, equipment)	**851,90**
RRS - SRS[5] session (3 tx at 508,57/tx)	1.525,71
Outpatient visit during RRS SRS (1 visit at 41,57/visit)	41,57
Subtotal Robotic Radiosurgery	**1.567,28**
Total Robotic Radiosurgery	**2.419,18**

Abbreviation
IMRT = Intensity Modulated Radiotherapy, RRS + Robotic Radiosurgery, ND = Neck Dissection, SRS = Stereotactic Radiosurgery.

Table 6: Total work-up and treatment costs for each treatment group (in Euros)

Summary Cost Data	IMRT + BT	IMRT + BT + ND	IMRT + RRS	IMRT + RRS + ND
Total work-up	1.761,01	1.761,01	1.876,61	1.876,61
Total IMRT (EBRT)	2.096,38	2.096,38	2.096,38	2.096,38
Total Hospital: (OR, Brachytherapy and Admission days)	4.550,38	7.861,59	-	4.325,95
Total Robotic Radiosurgery	-	-	2.419,18	2.419,18
Total work-up and treatment	**8.407,77**	**11.718,98**	**6.392,17**	**10.718,12**

Abbreviation
IMRT = Intensity Modulated Radiotherapy, BT = Brachytherapy, ND = Neck Dissection, RRS = Robotic Radiosurgery, EBRT = External Beam Radiotherapy, OR = Operating Room.

Table 7: Weighted total mean costs per patient with tonsil fossa and/or soft palate tumors up to five years from initial diagnosis (in Euros)

Group	Workup	Treatment	Relapse	5 yrs FU	Total
IMRT + BT	1.761,01	6.647,28	5.497,98	626,24	14.532,51
IMRT + BT + ND	1.761,01	9.958,49	4.569,15	609,96	16.898,61
IMRT + RRS	1.876,61	4.516,05	5.497,98*	626,24*	12.517,28*
IMRT + RRS + ND	1.876,61	8.842,00	4.569,15*	609,96*	15.897,72*

Abbreviation
FU = Follow-Up, IMRT = Intensity Modulated Radiotherapy, BT = Brachytherapy, ND = Neck Dissection, RRS = Robotic Radiosurgery, * Cost of relapse management and follow-up assumed identical for BT and Robotic Radiosurgery.

associated materials consumption and hospital admission days required for BT. The requirement of a ND in RRS patients increases costs to near that required for BT alone, but the addition of ND to BT again increases costs above those required for RRS with a ND.

In Table 5 we detail the costs of RRS treatment. RRS treatment sessions themselves are the major constituent of this category, reflecting the depreciation and maintenance costs of the RRS system. Table 6 summates all individual cost components of work-up and treatment for the four different treatment groups, and reveals treatment for the RRS groups to be less costly than for their respective BT counterparts. Total work-up and treatment costs for the respective groups were: €8.408 ($10.905) for IMRT plus BT, €6.392 ($8.290) for IMRT plus RRS, €11.719 ($15.199) for IMRT plus BT plus ND, €10.718 ($13.901) for IMRT plus RRS plus ND. Finally, Table 7 summarizes the mean weighted costs per patient up to 5 years from diagnosis, revealing the comprehensive 5-year cost for the four groups. Per component we multiplied the costs with the number of patients eligible: e.g. in case of BT ± ND a component ND and a component BT was computed. Total costs were then divided by the total number of patients (weighted). These costs are €14.533 ($18.849) for IMRT plus BT, €12.517 ($16.235) for IMRT plus RRS, €16.899 ($21.918) for IMRT plus BT plus ND, and €15.898 ($20.620) for IMRT plus RRS plus ND. This demonstrates a cost saving for the RRS groups compared with their respective BT cohort of patients, particularly in the absence of a ND.

DISCUSSION

We have used robotic radiosurgery to boost radiation dose to TF/SP tumors since 2005. While long-term data and clinical outcomes are not yet available, it is important to assess the cost of this emerging technique, both from an HTA perspective and in order to prioritize treatments in our institution. This analysis required us to make assumptions regarding the therapeutic equivalence of radiation boost by HDR- and PDR-BT and RRS; the latter typically implying the use of a hypofractionated regimen. We make this assumption with confidence based on both the similarities of dose distributions with the two techniques and on early clinical results. Figure 1 illustrates that both techniques are highly conformal, even though RRS was initially used to treat lesions that were not accessible with BT. Early side-effects (pain and dysphagia) were not significantly different. While only a small number of patients have been treated with RRS and follow-up was shorter for these patients, it is important to assess the costs of emerging techniques such as this, even on a preliminary basis, to assure ourselves that they are not wildly divergent from the standard of care. This preliminary analysis of clinical outcomes, QoL, and costs provides assurance that our center has made a rational decision to use RRS in select TF/SP patients. Furthermore, we believe that an analysis such as this can serve as an HTA model for emerging treatment technologies.

Our decision to pursue the RRS-boost approach was based on a decade of experience treating patients with T1-3,N0,N+ TF/SP tumors by EBRT plus BT (± ND) and obtaining good locoregional tumor control. We have also had excellent results with Surgery plus PORT in eligible patients. Published results from our group and others indicate locoregional control rates of approximately 85% at 10 years for both modalities [1,17-19]. EBRT plus BT has proven to result in significantly better Performance Status Scale scores than Surgery in the following categories: understandability of speech, return to normal diet, dental problems, and ability to open mouth (EORTC, QLQC30 and H&N35) [12]. Xerostomia has been the primary long-term morbidity for both groups, as expected, since salivary gland function is directly related to irradiation dose and volume [20].

Our prior findings, showing some acute and late side effects and decreases in functional outcome for these patients, demonstrated a need for additional improvement of the therapeutic ratio [1,2,4,5]. We strive for improved locoregional tumor control with minimal treatment sequelae and lower costs. It was for this reason that the Erasmus MC treatment protocol was altered

in March 2005 to use IMRT in the first series of EBRT (46 Gy). The goal was to enhance bilateral parotid sparing and thus reduce xerostomia. The recent use of robotic radiosurgery as a primary boost treatment in selected patients, to improve CTV coverage compared to BT is expected to reduce the need for Surgery. This will eliminate the need for hospitalization, thus reducing costs and avoiding surgical complications for these cases. Although the number of TF/SP tumors treated with a RRS boost to date is small and has limited follow-up, we are encouraged by the fact that pain and QoL findings approximate those obtained with BT boost (Figure 2).

Figure 2: Acute side effects measured by responses to QoL questionnaires (EORTC H&N35) regarding pain (Figure 2A) and swallowing (Figure 2B) for two treatment schedules: EBRT+BT ['BT'] (red line and red dots) and EBRT+RRS ['RRS'] (blue line). Also shown in the graph are long-term follow-up QoL data (EORTC H&N35) for patients in follow-up cohorts varying from two to five years (o), five to eight years (•) and eight to ten years (■) [4]

Figure 2A

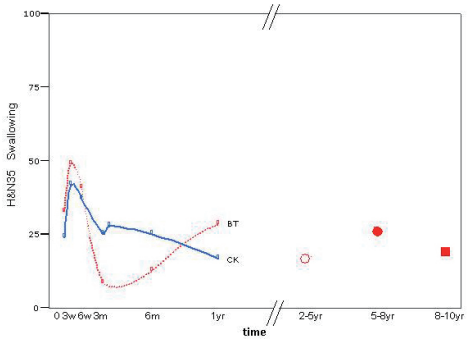
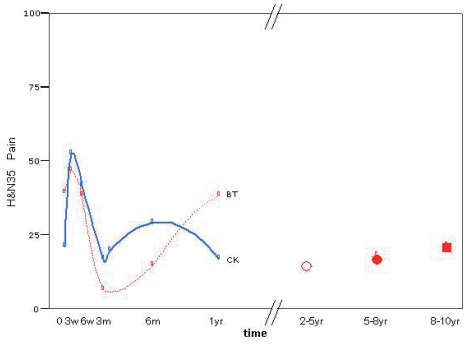


Figure 2B



There are a number of potential clinical advantages of RRS for TF and SP tumors. Foremost is the ability of RRS to cover complex tumor volumes with deep parapharyngeal tumor invasion or tumor extension toward the skull base [6,7]. Performing an extensive BT implant with adequate target coverage for T2-T3 tumors that are bulky and extend deep into the parapharyngeal space can be risky; RRS improves CTV coverage thereby expanding the list of patients who are eligible for radiation alone in our protocol. The ability to adequately cover the target volume with RRS also is affected less by

differences in user experience and technique, whereas those factors can play a significant role in the success of BT. With the BT-like isodose distribution (similar to HDR BT) there is the potential to treat in even fewer fractions because of RRS sharply defines isodose margins and tracking accuracy. Also, PTV margins may conform more tightly to the CTV as compared to other externally delivered boost methods such as IMRT, more effectively minimizing dose to normal tissue and critical structures. However, due to the inaccuracy of tumor target definition on CT resolution, one must appreciate that the requirement for a 2-3 mm PTV margin creates a larger target volume to be covered for RRS as opposed to BT. In BT no PTV margin is used due to the fact that movement of the tumor is paralleled for movement of the catheters. This is for instance significantly different as opposed to the convention that we use for the PTV margin in case of IMRT, being 5 mm. Imaging advances may, in the future, allow us to eliminate or reduce this PTV margin.

In previous papers we reported that the cost of surgical treatment (and PORT) was substantially higher than the cost of radiation therapy alone [21,22]. This was mainly due to the costs of longer hospital stays for surgery patients. We used similar cost computation methods in the current comparison of IMRT plus BT with IMRT plus RRS. Since complications of these treatments are relatively minor and, in most cases, heal spontaneously or are resolved by physical therapy, costs related to complications are only included in cases of hospitalization. In terms of outcome, tumor control in RRS patients was considered to be comparable to that for the BT group. Even though the cost per individual treatment from the RRS device is higher and the work-up charge is slightly higher due to the requirement for fiducial marker placement, we found that the RRS boost treatment groups had the lowest treatment-specific costs (Tables 6 and 7).

Table 4 illustrates that the cost savings for the RRS boost method could be attributed to the complete elimination of operating room costs and items associated with hospitalization for this group. In RRS-boost patients that did require a ND, the cost was also decreased compared with their respective BT boost plus ND group. However, the magnitude of that decrease was smaller, because hospitalization stay and operating room use reemerged as a cost component. Another contributor to RRS cost savings is the ability to hypofractionate the treatment. In our protocol only 3 fractions were required. In reality, the cost savings of the RRS boost technique is larger than demonstrable through a simple RRS vs. BT cost comparison. This is because RRS also replaces primary surgery in some patients in a way that BT cannot, because of its ability to contour full isodose coverage around more complex,

deeply invasive lesions [6,7]. In our prior analysis [4], Surgery plus PORT was even more expensive than EBRT plus BT. Even comparing IMRT alone to RRS, RRS is less expensive; IMRT costs less per treatment than RRS, but this is offset by the requirement for a larger number of IMRT treatments. Hospital costs of IMRT versus IMRT plus RRS-boost regimens could be considered to be equivalent. These costs could favor either approach, depending upon the fractionation schedules selected. However, the mixed IMRT plus RRS approach may still be preferred, both because of the significantly shorter overall treatment time with RRS, which may be biologically advantageous in dealing with accelerated clonogen repopulation, and because of the higher RRS-boost dose conformality to the CTV, due to the smaller CTV→PTV requirement enabled by near real-time RRS tumor tracking.

Conclusion

This analysis indicates that for the TF and/or SP tumors, total costs for IMRT plus RRS were less than IMRT plus BT. Total costs for IMRT plus RRS plus ND were also less than IMRT plus BT plus ND. The primary reason for this difference was the cost of hospitalization and, in the case of BT ± ND, operating room costs. We note that RRS-specific cost savings relative to BT may be understated because RRS may substitute for primary surgery in more patients than BT, which reduces the need for the most expensive treatment, i.e., Surgery plus PORT. Full-dose IMRT as a sole therapeutic approach likely provides a cost reduction comparable to the mixed IMRT plus RRS-boost approach described here, but has the disadvantage of a longer course of therapy and results in a less conformal primary tumor boost.

Early data suggest a somewhat slower recovery of the acute side effects (QoL) for the patients treated by hypofractionated RRS. Longer-term RRS-boost efficacy and morbidity requires additional study.

In this analysis, total hospital costs and QoL data are presented as potential contributory selection factors in deciding between RRS versus BT for this patient group. HTA analyses in highly specialized, rapidly evolving fields with many protocols, criteria, formats and purposes is challenging and may vary geographically and between public and private healthcare systems. Evidence must include clinical and economic endpoints, compared against current *standards of care*. These early results have shown a trend that needs to be confirmed on a larger number of patients followed for at least 5 years. We believe that this type of cross comparison between may serve as a model to evaluate emerging technologies applied to cancers in other clinical sites.

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REFERENCES

1. Levendag P., Nijdam W., Noever I., Schmitz P., van de Pol M., Sipkema D., Braat C., de Boer M., Jansen P. Brachytherapy Versus Surgery in Carcinoma of Tonsillar Fossa and/or Soft Palate: Late Adverse Sequelae and Performance Status: Can We Be More Selective and Obtain Better Tissue Sparing? Int J Radiat Oncol Biol Phys 59:713-724 (2004).
2. Levendag P., Nijdam W., van de Pol M., Noever I. Brachytherapy Versus Surgery in Carcinoma of Tonsillar Fossa and/or Soft Palate: Late Adverse Sequelae and Performance Status: Can We Be More Selective and Obtain Better Tissue Sparing? Radiotherapy and Oncology 66 abstract 25:S10 (2003).
3. Nijdam W., Levendag P., Noever I., Groot C. U., Agthoven M. Cancer in the Oropharynx: Cost Calculation of Different Treatment Modalities for Controlled Primaries, Relapses and Grade III/IV Complications. Radiother Oncol 77:65-72 (2005).
4. Nijdam W., Levendag P., Noever I., Uyl-de Groot C., van Agthoven M. Cost Analysis Comparing Brachytherapy Versus Surgery for Primary Carcinoma of the Tonsillar Fossa and/or Soft Palate. Int J Radiat Oncol Biol Phys 59:488-494 (2004).
5. van de Pol M., Levendag P. C., de Bree R. R., Franssen J. H., Smeele L. E., Nijdam W. M., Jansen P. P., Meeuwis C. A., Leemans C. R. Radical Radiotherapy Compared with Surgery for Advanced Squamous Cell Carcinoma of the Base of Tongue. Brachytherapy 3:78-86 (2004).
6. Chang S. D., Main W., Martin D. P., Gibbs I. C., Heilbrun M. P. An Analysis of the Accuracy of the Cyberknife: A Robotic Frameless Stereotactic Radiosurgical System. Neurosurgery 52:140-146; discussion 146-147 (2003).
7. Yu C., Jozsef G., Apuzzo M. L., Petrovich Z. Dosimetric Comparison of Cyberknife with Other Radiosurgical Modalities for an Ellipsoidal Target. Neurosurgery 53:1155-1162; discussion 1162-1153 (2003).
8. Drummond M., O'Brien B., Stoddart G., Torrance G.: Methods for the Economic Evaluation of Health Care Programmes. New York, Oxford University Press, 1996.
9. Rutten van Mölken M., van Busschbach J., Rutten F.: From Costs to Effects: A Manual for Evaluation Studies in Health Care. Elsevier Gezondheidszorg, 2000 (in Dutch).

10. Gold M., Siegel J., Russell L., Weinstein M.: Cost-Effectiveness in Health and Medicine. New York, Oxford University Press, 1996.
11. Oostenbrink J., Koopmanschap M., Rutten F.: Manual for Costing Research. Amstelveen. Health Care Board, 2000 (in Dutch).
12. List M. A., Ritter-Sterr C., Lansky S. B. A Performance Status Scale for Head and Neck Cancer Patients. Cancer 66:564-569 (1990).
13. List M. A., Stracks J., Colangelo L., Butler P., Ganzenko N., Lundy D., Sullivan P., Haraf D., Kies M., Goodwin W., Vokes E. E. How Do Head and Neck Cancer Patients Prioritize Treatment Outcomes before Initiating Treatment? J Clin Oncol 18:877-884 (2000).
14 Wijers O. B., Levendag P. C., Braaksma M. M., Boonzaaijer M., Visch L. L., Schmitz P. I. Patients with Head and Neck Cancer Cured by Radiation Therapy: A Survey of the Dry Mouth Syndrome in Long-Term Survivors. Head Neck 24:737-747 (2002).
15 Dolan, P. Modelling valuations for the EuroQol health states. Med. Care. 1997;35(11): 1095–1108
16 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 1993;85:365-376 (1993).
17. O'Sullivan B., Warde P., Grice B., Goh C., Payne D., Liu F. F., Waldron J., Bayley A., Irish J., Gullane P., Cummings B. The Benefits and Pitfalls of Ipsilateral Radiotherapy in Carcinoma of the Tonsillar Region. Int J Radiat Oncol Biol Phys 51:332-343 (2001).
18. Withers H. R., Peters L. J., Taylor J. M., Owen J. B., Morrison W. H., Schultheiss T. E., Keane T., O'Sullivan B., van Dyk J., Gupta N., et al. Late Normal Tissue Sequelae from Radiation Therapy for Carcinoma of the Tonsil: Patterns of Fractionation Study of Radiobiology. Int J Radiat Oncol Biol Phys 33:563-568 (1995).
19. Withers H. R., Peters L. J., Taylor J. M., Owen J. B., Morrison W. H., Schultheiss T. E., Keane T., O'Sullivan B., van Dyk J., Gupta N., et al. Local Control of Carcinoma of the Tonsil by Radiation Therapy: An Analysis of Patterns of Fractionation in Nine Institutions. Int J Radiat Oncol Biol Phys 33:549-562 (1995).
20. Kuhnt T., Jirsak N., Muller A. C., Pelz T., Gernhardt C., Schaller H. G., Janich M., Gerlach R., Dunst J. Quantitative and Qualitative Investigations of Salivary Gland Function in Dependence on Irradiation

Dose and Volume for Reduction of Xerostomia in Patients with Head-and-Neck Cancer. Strahlenther Onkol 181:520-528 (2005).

21. Levendag P. C., Nijdam W. M., van Agthoven M., Uyl-de Groot C. A. Chemotherapy and High-Dose-Rate Brachytherapy in the Management of Advanced Cancers of the Nasopharynx: Clinical Impact of High Technology--Is It Worth the Cost? Brachytherapy 1:11-20 (2002).
22. van Agthoven M., van Ineveld B. M., de Boer M. F., Leemans C. R., Knegt P. P., Snow G. B., Uyl-de Groot C. A. The Costs of Head and Neck Oncology: Primary Tumours, Recurrent Tumours and Long-Term Follow-Up. Eur J Cancer 37:2204-2211 (2001).

CHAPTER 7

Cancer in the Oropharynx: Cost Calculation of Different Treatment Modalities for Controlled Primaries, Relapses and Grade III/IV Complications.

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ABSTRACT

Background and Purpose: This paper presents a model for cost calculation using the different treatment modalities for oropharyngeal cancers used in our hospital. We compared full hospital costs, the associated costs of locoregional relapses and/or treatment related grade III/IV complications.

Materials & Methods: Patients with oropharyngeal cancer are treated in the Erasmus MC preferably by an organ function preservation protocol. That is, by external beam radiation therapy followed by a brachytherapy (BT) boost, and neck dissection in case of N+ disease (BT-group: 157 patients). If brachytherapy is not feasible, resection with postoperative radiotherapy (S-group [S=Surgery]: 110 patients) or external beam radiation therapy (EBRT)-alone (EBRT-group: 77 patients) is being pursued. Actuarial locoregional control (LRC), disease free survival (DFS) and overall survival (OS) at 5-years were calculated according to the Kaplan Meier method. The mean costs per treatment group for diagnosis, primary Tx per se, follow-up, (salvage of) locoregional relapse (LRR), distant metastasis (DM), and/or grade III/IV complications needing clinical admission, were computed.

Results: For the brachytherapy-, surgery-, or external beam radiation therapy treatment groups, LRC rates at 5-yrs were 85%, 82%, and 55%, for the DFS, 61%, 48%, and 43%, and for the OS 65%, 52%, and 40%, respectively. The mean costs of primary Tx in case of the BT-group is €13,466; for the S-group €24,219, and €12,502 for the EBRT-group. The mean costs of surgery (the main salvage modality) for a LRR of the brachytherapy group or EBRT-group, were €17,861 and €15,887 respectively. The mean costs of clinical management of grade III/IV complications were €7,184 (BT-group), €16,675 (S-group) and €6,437 (EBRT-group).

Conclusion: The clinical outcome illustrates excellent LRC rates at 5-yrs for brachytherapy (85%), as well as for surgery (82%). The relatively low 55% LRC rate at 5-yrs for external beam radiation therapy probably reflects a negative selection of patients. It is of interest that the total mean costs of patients alive with no evidence of disease are least for the BT-group: €15,101 as opposed to €25,288 (surgery) and €18,674 (external beam radiation therapy). Main underlying cause for the high costs with surgery as opposed to radiotherapy alone is the number of associated clinical admission days, not only during primary treatment, but also at relapse. This might be taken into consideration when treating these patients.

INTRODUCTION

The curative treatment options for squamous cell cancers (scc) originating in the oropharynx differ, depending on institutional (doctors)- and patient preferences. It basically varies from surgery (S) with or without postoperative radiation therapy (PORT), to radiotherapy (RT) alone [3,6,7,13,14,17,18]. RT has been instituted as a sole treatment modality, using different fractionation regimes [3], or combined with a neck dissection (ND) and neo-adjuvant and/or concomitant chemotherapy (CHT)[1]. Also, RT has been effectively applied by means of a linear accelerator only (external beam radiation therapy [EBRT]) or by EBRT in combination with brachytherapy (BT), that is interstitial radiation therapy (IRT) [5-7]. Proponents of RT-alone argue that surgical resection of these tumors can result in depreciation of the swallowing- and speech functions, while in contrast, for S versus RT in terms of tumor control, no difference is observed [6].

To acknowledge the sparing component as well as the application of high doses to a small (boost) volume (dose-effect), a function preserving protocol was designed and initiated in our Institute in 1991, consisting of BT, with S or conventional EBRT [8-11,16]. Eligible for this protocol were patients with 1. early- and intermediate staged (T1-3(4)N0,+) cancers of the tonsil and soft palate (TF and/or SP), and 2. T1-4N0,+ cancers of the base of tongue (BOT). In a recently analyzed subset of patients, that is patients with TF and/or SP tumors treated between 1986 and 2001 in the Erasmus University Medical Center (Erasmus MC) with either EBRT plus BT or S plus PORT, no significant differences were found in tumor control, survival, functional outcome scores, complications, and degree of xerostomia. However, as far as the cost of treatment was concerned, we found that treatment with BT was less expensive in comparison with surgery. Moreover, when surgery is replaced by stereotactic radiotherapy and/or accelerated radiation therapy schedules, using (Intensity Modulating Radiotherapy) sparing techniques, a gain in QoL and effectiveness can be anticipated, apparently at almost equal or even less costs [6,11,15].
In this manuscript, emphasis will be placed on treatment group related costs for cancer of the oropharynx (i.e. BOT included) with regard to the treatment modalities commonly used in our institute, that is BT, S and EBRT (or combinations of these). Costs generated by the treatment of the primary tumor per se, the costs of (salvage of) a locoregional relapse and the costs generated by the (treatment of) serious, that is RTOG Grade III/IV, complications for which hospitalization is needed, were taken into account.

MATERIAL AND METHODS

From 1991 to 2001, 524 primary cancers of the oropharynx were treated in the Erasmus MC. One hundred and eighty patients were excluded from the present analysis because of the tumors being of the non-squamous cell carcinoma (scc) type (n=13), being second primaries (n=48), synchronous primary tumors (n=35), those tumors treated with palliative intent (n=57), and/or in the case of protocol violation (n=27). The remaining 344 patients form the basis of this analysis.

Diagnosis and Treatment

In joint consultation by the radiation oncologist and head-and-neck surgeon, ENT-examination is performed in all patients. That is, diagnostic work-up (CT- / MRI-scans, ultrasound guided fine needle aspiration cytology of potential neck nodes, examination and biopsy under general anesthesia) and dental (prophylactic) care (i.e. in particular institution of prophylactic fluor application) were routinely performed. Based on these findings, patients were discussed in the Rotterdam Head and Neck Cancer Group for staging and choice of best treatment options.

In short: patients of the BT-Group were treated with regard to the BT procedures and ND in the integrated brachytherapy unit (IBU). After introducing BT afterloading catheters under general anesthesia, the implant is simulated in the IBU, and, after digitizing the catheters, a BT treatment plan is generated (PLATO / NPS, Nucletron). The first fraction is applied in the IBU with the patient still under general anesthesia. Patients received 6 fractions of 3 to 4 Gy, 2 times per day, 6-hour interval (fr. HDR; total dose 20 Gy) or 1-2 Gy 8 times per day, 3-hour interval (PDR; total dose 22 Gy). If patients were not suitable candidates to be treated by BT, tumors were either treated by surgery (S-Group) or by EBRT-alone. With regard to the S-Group: In 110 patients the primary tumor was resected and the defect reconstructed, followed by PORT (25-35 fractions depending on pathology report). The 77 patients of the EBRT-group were treated with conventional EBRT-techniques (25-35 fractions, 2 Gy per fraction). For all 3 treatment groups, a ND was performed in case of positive lymph nodes.

Chemotherapy

Patients received neo-adjuvant and/or concomitant chemotherapy (CHT) [1]. Briefly: routine CHT consisted of either three 3-weekly courses of neo-adjuvant Cisplatin plus 5 FU or 6 weekly courses neo-adjuvant Cisplatin or 2 courses Cisplatin concomitant.

Besides routine CHT (per protocol) some of the presently analyzed patients were included in a trial. In the study period the trial AZR-99-220 was running, according to the protocol, patients were to receive concomitant Paclitaxel (60 mg/m^2) on a weekly basis and Amifostine s.c. before every fraction (500mg/fraction) during the EBRT course.

The number of patients who received CHT was relatively small: 23 patients in the BT-group, in the S-group 1 patient and in the EBRT-group 54 patients. The large percentage of patients receiving CHT in the EBRT group reflects the more advanced stage of the patients and in fact could influence the costs of this patient category in particular.

Follow-up

Patients were seen in regular follow-up with clinical (ENT) examination and laboratory tests being executed. Year one: five outpatient visits including routine clinical (ENT) examination, year 2 and 3: two follow-up visits, including again routine clinical ENT examination, blood chemistry, T4, TSH and plain chest X-ray (annually). As from year 4: one outpatient visit annually with routine ENT examination included.

During these visits to the outpatient joint clinic, outcome parameters such as tumor control, side effects and performance were scored.

Relapse and/or complications

In case of a locoregional relapse (LRR) or distant metastasis, additional diagnostic means were used to establish the extent of the disease. Subsequently individualized combinations of CHT, surgery, BT and EBRT were used in order to either cure or palliate the patient.

For details on the treatment mode per se and clinical outcome parameters, the reader is referred to the recent publications on the TF- and/or SP tumors by Levendag et al. (2004) and for the BOT tumors, the paper by Pol et al. (2004) [5,6,15].

Cost calculation

In this paper, the cost analysis is performed from an institutional perspective [2]. For the three treatment groups, direct medical costs generated in the hospital were calculated for:

1. Different options regarding the medical treatment modalities per se (Tx), such as EBRT, BT, S or CHT, including costs for diagnostics;
2. Follow-up (days) from Tx to first event;
3. Treatment modalities used for (salvaging) first event (T1) (such as distant metastases, locoregional relapse or grade III/IV complications needing clinical admission);
4. Follow-up from T1 to the censor date January 1, 2004.

Cost calculation treatment

Patients were analyzed for full hospital costs with the primary having been treated, according to the guidelines of the running protocol at the time, by either one of the three treatment options; that is by EBRT plus BT (BT-Group; 157 patients), S plus PORT (S-Group; 110 patients), or EBRT alone (EBRT-Group; 77 patients).

The initial medical treatment and treatment of the first event (i.e. locoregional relapse and/or distant metastasis) were subdivided in a diagnostic patient part, preparatory part and the treatment itself.

Except for the admission days for examination under general anesthesia (EGA), the work-up for all treatment groups was assumed to be similar; that is, the work-up was used as one fixed cost component in the cost calculation. In contrast, for the preparation phase in case of EBRT and BT, the number of fractions and the number of admission days (in case of BT) were based on real patient data. Outpatient clinic visits during EBRT were included in the treatment and the number is based on the protocol.

The costs of surgery include the use of the operating room and pathology laboratory costs of the biopsy specimen. The number of admission days were based on real numbers and differentiated for by IC/ward.

The costs of CHT consisted of (1) the number of consultations and blood chemistries plus one, (2) the costs of the agents per se and (3) the number of admission days, being on the IC and/or on the regular ward. The costs of the CHT (agents) were based on the price the pharmacy of the hospital has to pay for the medication used.

In case the distant metastasis, complications and/or local relapses occurred within 6 months, costs were attributed to initial treatment. These costs were

calculated until occurrence of a 2nd primary tumor. The costs for a local relapse included the treatment and additional follow-up. In fact, only if the patient was treated with teletherapy or admitted to the hospital for treatment of the distant metastasis and /or complications, costs were taken into account.

Cost calculation follow-up

Follow-up costs were based on real follow-up time, with the number of visits according to protocol. Follow-up was measured from start of treatment to first event or, in case a first event did not lead to death of disease, to the censor date January 1, 2004. In case of a first event (T1), follow-up was again counted from T1 to censor date January 1, 2004 (alive or dead). When a first event occured, the follow-up scheme from the first year after treatment was taken for the cost analysis.

Cost calculation manpower and materials

The use of resources is based on a detailed inventory of the materials used in the department (according to protocol). For the valuation of the resource items, we determined mean unit costs both for direct and indirect patient related activities (meaning the patient being present or not [e.g. administration]). Therefore, we followed the micro-costing method, which is based on a detailed inventory and measurement of resources consumed [4]. In addition, we applied an overhead percentage of 16.4% (amongst others depreciation of the building and costs for administration). The valuation of the resources and overhead costs was based on financial data from the Erasmus Medical Center. Costs were based on 2001 pricings and stated in Euros (€).

Direct costs consisted of manpower costs and material costs. Manpower costs were calculated per minute based on salary costs (including social premium and extra fees for irregular working hours) and under the assumption of 1540 working hours a year [12]. Then minutes spent per discipline (according to protocol) were multiplied by salary per minute. A detailed description of the cost calculation for manpower can be found in the article of Nijdam et al [11].

Material costs were based on wholesale prices, a detailed inventory was made based on real use in the department. Also costs related to use of equipment and OR (IBU) were included in material costs. The costs for diagnosis and staging were based on the Dutch tariff system. Costs of medication, chemotherapy, blood transfusion, tube feeding and hyperbaric O_2 were based

on the charges of the pharmacy/blood bank/hospital (in case of hyperbaric O_2) to the department.

Calculation mean costs
As described in the paragraph of cost calculation, treatment consisted of several components. Per component we multiplied the costs with the number of patients eligible: e.g. in case of BT ± ND a component ND and a component BT was computed. Total costs were then divided by the total number of patients (weighted).

RESULTS

The patient characteristics for the three treatment groups are categorized in Table 1. The BT- and S group show almost equal outcomes on the clinical and functional parameters examined, with regard to tumor control, survival, functional outcome scores, degree of xerostomia and late side effects. This is despite the fact that the BT patients are on average somewhat better of in terms of staging. The EBRT group fares worse due to patient (tumor) characteristics. See e.g. T2/T3 stage Table 1: BT 55%/21%, S 21%/62% and EBRT 12%/30%. However the poorer patient characteristics adversely impact mainly the LRC and DFS. Five years LRC rate was 85% for the BT group, 82% for the S group and 55% for the EBRT-group and DFS was 61%, 48% and 43%, respectively. The Performance Status Scales for Head and Neck cancer patients as developed by List et al. [8], was not significantly different for the 3 treatment groups [6,15]. Similarly, with respect to the Visual Analogue Scales (VAS scores) regarding the problem of xerostomia, no significant difference was observed [6,15] with regard to the late side effects, the BT group experienced more (but reversible) ulceration of the mucosa, the surgery group more (persistent) trismus.
Table 2 denotes a detailed cost-analysis of the different components of the treatment by BT. The same type of calculation was done for the S-group and EBRT-group (results not shown for clarity purposes).
Tables 3-5 show the mean costs for the different parts of treatment and follow-up costs for the BT group, S-group and EBRT-group, respectively. The mean costs shown for the different parts of the treatment are based on consolidation of the detailed components as listed in Table 2. The consolidation

Table 1: Patient characteristics of the brachytherapy (N=157), surgery (N=110) and EBRT group (N=77)

	Brachytherapy-group		Surgery-group		EBRT-group	
Male	98	(62%)	70	(64%)	47	(61%)
Female	59	(38%)	40	(36%)	30	(39%)
Mean Age	56	(34-87)	58	(35-76)	58	(35-76)
T classification (TNM 2002)						
T1	27	(17%)	5	(4%)	4	(5%)
T2	86	(55%)	23	(21%)	9	(12%)
T3	33	(21%)	68	(62%)	23	(30%)
T4a	7	(4%)	11	(10%)	24	(31%)
T4b	4	(3%)	3	(3%)	17	(22%)
Node stage						
N0	70	(44%)	32	(30%)	25	(32%)
N1	22	(14%)	20	(18%)	16	(21%)
N2a	20	(13%)	5	(4%)	2	(3%)
N2b	22	(14%)	44	(40%)	11	(14%)
N2c	17	(11%)	7	(6%)	10	(13%)
N3	6	(4%)	2	(2%)	13	(17%)
Stage (TNM 2002)						
I	7	(5%)	1	(0%)	0	(0%)
II	41	(26%)	12	(11%)	4	(5%)
III	38	(24%)	34	(31%)	18	(23%)
IVa	61	(39%)	58	(53%)	32	(42%)
IVb	10	(6%)	5	(5%)	23	(30%)

Abbreviation
EBRT = External Beam Radiation Therapy

Table 2: Cost analysis of the components used for the brachytherapy-group

	Rate in €
Diagnostics (overhead incl.)	
Outpatient visit	95
Preoperative consultation Anesthesiologist	44
Endoscopy	107
X-ray	39
Ultra sound neck + cytology	132
CT-scan / MRI	188
Bloodchemistry	38
Consultation and treatment dentist	193
Examination under General Anesthesia + Biopsy	655
Admission for biopsy (rate daycare)	176
Admission for biopsy (rate per day on ward)	389
Admission for biopsy (rate per day on IC)	729
Preparation EBRT	
Total preparation BT treatment (one cost component) (including administration, patient instruction, mouldroom, planning CT, planning, finalize planning, mono disciplinary consult and preparation on accelerator)	939
Treatment EBRT	
EBRT per fraction	31
Outpatient visit during treatment	42
Preparation BT Treatment	
Total preparation BT treatment (one cost component) (including administration, patient instruction, implantation catheters, simulation in OR, BT planning and finalize planning and check physics	1.376
Neck Dissection (ND)	
Total Neck Dissection (one cost component) (including staff, use of operating room)	2.378
Treatment BT	
BT per fraction	79
Cost per admission day (rate per day on the ward)	389
Cost per admission day (rate per day on the IC)	729
Chemotherapy (CHT)	
Consults and bloodchemistry (per course)	74
Cost per course (depending on type of CHT)	6 – 638
Cost per admission day (rate per day on the ward)	389
Cost per admission day (rate per day on the IC)	729

Table 2 *(continued)*

Other costs	
Blood transfusion (per packed cell)	186
Tube insertion	350
Tube feeding per day	15
Hyperbaric O2 (30 dives)	6.270
Follow-up	
Outpatient visit	42
X-ray	39
Blood chemistry	38

Abbreviations:
IC = Intensive Care; BT = Brachytherapy; EBRT = Externel Beam Radiation Therapy; OR = Operating Room.

Table 3: Mean costs for the brachytherapy-group (157 patients)

Treatment BT group 1991 – 2001			**Mean costs** (weighted # patients)
Treatment	Diagnostics		€ 2,400
	Chemotherapy		€ 674
	External beam radiotherapy		€ 1,716
	Brachytherapy ± neck dissection		€ 7,518
	Adjuvant costs (med., tube feeding, blood)		€ 1,158
Follow-up	Locoregional relapse (LRR)	(20 patients, 14 months)	€ 225
Period Tx-Event	Distant metastasis (DM)	(9 patients, 20 months)	€ 343
	LRR and DM	(4 patients, 23 months)	€ 324
Event	Locoregional relapse		€ 2,154
	Distant metastasis		€ 694
	Complications with hospital admission (med., tube feeding, blood or hyperbaric O_2)		€ 1,038
Follow-up	Dead of disease	(25 patients, 25 months)	€ 371
Period Event – Dead/Alive	Alive NED	(8 patients, 61 months)	€ 790
No relapse – Dead/Alive	Dead intercurrent	(11 patients, 47 months)	€ 552
	Alive NED	(113 patients, 50 months)	€ 710

Abbreviations:
Med = Medication, NED = No Evidence of Disease

Table 4: Mean costs for the surgery-group (110 patients)

Treatment S group 1991 – 2001			**Mean costs** (weighted # patients)
Treatment	Diagnostics		€ 2,555
	Chemotherapy		€ 52
	Surgery		€ 14,644
	Post operative EBRT		€ 2,168
	Adjuvant costs (med., tube feeding, blood)		€ 4,800
Follow-up	Locoregional relapse (LRR)	(17 patients, 11 months)	€ 187
Period Tx-Event	Distant metastasis (DM)	(12 patients, 15 months)	€ 271
	LRR and DM	(2 patients, 8 months)	€ 159
Event	Locoregional relapse		€ 1,226
	Distant metastasis		€ 671
	Complications with hospital admission (med., tube feeding, blood or hyperbaric O_2.)		€ 1,407
Follow-up	Dead of disease	(28 patients, 16 months)	€ 280
Period Event – Dead/Alive	Alive NED	(3 patients, 38 months)	€ 499
No relapse – Dead/Alive	Dead intercurrent	(11 patients, 32 months)	€ 497
	Alive NED	(68 patients, 56 months)	€ 764

Abbreviations:
EBRT = Externel beam radiation therapy, Med = Medication, NED = No Evidence of Disease

Table 5: Mean costs for the EBRT-group (77 patients)

Treatment EBRT group 1991 – 2001			**Mean costs** (weighted # patients)
Treatment	Diagnostics		€ 2,876
	Chemotherapy		€ 4,440
	External beam radiotherapy		€ 2,331
	Adjuvant costs (med., tube feeding, blood)		€ 2,855
Follow-up	Locoregional relapse (LRR)	(30 patients, 10 months)	€ 161
Period Tx-Event	Distant metastasis (DM)	(0 patients, 0 months)	€ 0
	LRR and DM	(2 patients, 20 months)	€ 216
Event	Locoregional relapse		€ 4,552
	Distant metastasis		€ 25
	Complications with hospital admission (med., tube feeding, blood or hyperbaric O_2.)		€ 3,582
Follow-up	Dead of disease	(25 patients, 12 months)	€ 220
Period Event – Dead/Alive	Alive NED	(7 patients, 37 months)	€ 560
No relapse – Dead/Alive	Dead intercurrent	(11 patients, 18 months)	€ 306
	Alive NED	(34 patients, 52 months)	€ 716

Abbreviations:
EBRT = Externel Beam Radiation Therapy, Med = Medication

is based on real patient data as mentioned in the M&M section. The costs are weighted by number of patients.
Table 6 shows the mean costs for all treatment groups (weighted for number of patients) for the total costs regarding treatment, follow-up (both for follow-up till event and after event, see section M & M), (treatment of) relapse and/or metastasis and treatment of complications needing hospitalization.
Figure 1 presents a summary of the total costs of primary treatment, costs for locoregional relapse and costs related to grade III/IV complications for the 344 oropharyngeal patients per treatment group currently analyzed, not weighted for number of patients.

DISCUSSION

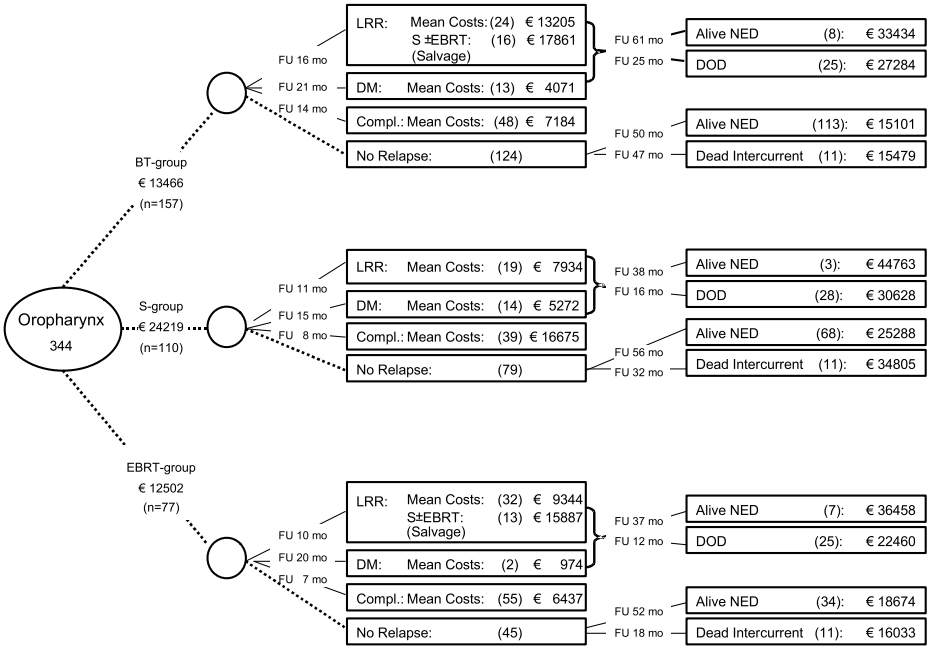
In the Erasmus MC, patients with cancer of the oropharynx are preferably treated with curative intent according to an organ function preservation protocol.
In previous papers by Levendag et al. [6], and Pol et al. [15], tumors of the TF and/or SP [6], and BOT [15] were analyzed for clinical outcome comparing brachytherapy with surgery: basically no difference was observed between the 2 treatment groups. In this paper we calculated full hospital costs for the three treatment modalities most commonly used in our Cancer Center for primary cancers originating in the oropharynx (OPh), that is BT-, S-, or EBRT (with or without chemotherapy). Using OPh cancer in this respect as a computational model for cancer of the head and neck, we analyzed total hospital costs. Besides the costs of the primary treatment, the associated costs of locoregional relapses (LRR) and/or treatment related RTOG grade III/IV complications were also taken into consideration.
For as the 5-years LRC (85%, 82%, and 55%), the DFS (61%, 48%, and 43%) and OS rates (65%, 52%, and 40%) are concerned, no significant difference between the treatment modalities (BT, S and EBRT) was observed. The 55% LRC rate at 5-years for EBRT probably reflects the negative selection of patients undergoing this type of primary treatment within the Erasmus MC protocol.
For example, in the EBRT-group 41 out of 77 (53%) patients had a T4 tumor, as opposed to 14 out of 110 (13%) of the S-group and 11 out of 157 (7%) of the BT-group. It is of interest in this respect that 20% of the costs of the EBRT-group is generated by treatment of the locoregional relapses and/or distant metastases, which is 15% and 6%, respectively, for the BT- and

Table 6: Mean costs all groups, weighted for by number of patients

	Mean costs BT (weighted # patients)	**Mean costs S** (weighted # patients)	**Mean costs EBRT** (weighted # patients)
Treatment	€ 13,466	€ 24,219	€ 12,502
Follow-up	€ 649	€ 607	€ 482
(Treatment of) relapse and/or metastases	€ 2,848	€ 1,897	€ 4,577
Complications	€ 1,038	€ 1,407	€ 3,582*
Mean costs total group	**€ 18,001**	**€ 28,130**	**€ 21,143**

Abbreviations:
BT = Brachytherapy, S = Surgery, EBRT = Externel Beam Radiation Therapy, * Only two patients with significant late side effects needing long lasting treatments

Figure 1: Total costs of primary treatment, relapse and grade III/IV complications for 344 oropharynx patients not weighted for number of patients



LRR = Locoregional Relapse; DM = Distant metastasis; NED = No Evidence of Disease; DOD = Dead of Disease; EBRT = External Beam Radiotherapy; S = Surgery

S-group. As far as treatment for complications is concerned, the costs in the EBRT group were somewhat skewed because of the more advanced stage of the patients in general (e.g. leading to the use of more CHT) and the fact that two patients with significant late side effects needed extremely long lasting clinical treatments because of osteoradionecrosis.

In a previous paper by Nijdam et al. [11], we focused on full hospital costs in patients with TF and/or SP tumors for current treatment strategies (Brachytherapy and Surgery) and future strategies (Intensity Modulated Radiation Therapy, Stereotactic Radiation Therapy and accelerated radiotherapy). The clinical dataset was however limited to patients with relatively small - single plane - implants (TF/SP tumors); also, the role of EBRT was not analyzed. Moreover, the percentage of patients receiving PDR or HDR (which, fortunately, only slightly influences the number of admission days), as well as the actual time the personnel spent on the different procedural steps of treatment was not real time, that is (only) estimated. In contrast, for the current paper, real patient data (numbers) were used. Moreover, in the present analysis, the costs for treatment of complications are also taken into account.

Costs associated with issues such as time missed from work, ability to return to work etc. were not taken into account. Although these costs may be relevant in this patient group, we do not expect differences between the treatment groups. The ability to work will depend more so on the state of disease as opposed to the treatment received. The total mean costs of patients alive NED is least for the BT-group: €15,101 as opposed to €25,288 (S) and €18,674 (EBRT). The 85% LRC rate in the BT-group causes slightly higher follow-up costs in comparison with the other groups. But, as an overriding finding, the initial treatment shows by far the highest costs for patients of the S-group, mainly due to the substantial longer admission period following S. In fact, the mean number of associated clinical admission days in case of a LRR is, for example, 14 days (BT) vs. 21 days (S) and 17 days (EBRT). The same is true for complications: 15 days (BT) vs. 31 days (S) and 14 days (EBRT).

We would like to conclude that, as a rough guideline if the patient seems fit to undergo BT, a reduction in the costs of about €10.000 can be expected (€28.130 as opposed to €18.001). Besides, cost calculations gain in importance given the Dutch desire to gradually change the finance structure of healthcare towards a system in which all healthcare 'products' have been assigned prices on the basis of detailed definitions of these products. The current health care philosophy in the Netherlands, to reduce costs by shortening hospital stay, adds to this discussion.

Summary
In this paper, 344 patients with an oropharyngeal tumor treated between 1991 and 2001 were analyzed for costs. As it seems, if the patient is fit to undergo BT, a reduction in the costs of about €10.000 can be expected. The difference is mainly due to a shorter hospital stay.
We feel that, with the ever constraining budget reductions for health care and the emphasis on efficiency measures to reach that goal, the financial parameter is gaining importance in the treatment armamentarium for these types of cancer.

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REFERENCES

1. Calais G, Bardet E, Sire C, et al. Radiotherapy with concomitant weekly Docetaxel for Stages III/IV Oropharynx Carcinoma. Results of the 8-02 Gortec Phase II trial. Int J Radiat Oncol Biol Phys, 2004;58:161-166.
2. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. New York, Oxford University Press, 1996.
3. Fu KK, Pajak TF, Trotti A, et.al. A Radiation Oncology Group (RTOG) Phase III Randomized Study to Compare Hyperfractionation and Two Variants of Accelerated Fractionation to Standard Fractionation for Head and Neck Squamous Cell Carcinomas: First Report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000; 48:7-16.
4. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in Health and Medicine. New York, Oxford University Press, 1996.
5. Levendag PC, Nijdam WM, van Agthoven M, et al. Chemotherapy and High-Dose-Rate Brachytherapy in the Management of Advanced Cancers of the Nasopharynx: Clinical Impact of High Technology: Is it Worth the Cost? Brachytherapy 2002; 1: 11-20.
6. Levendag PC, Nijdam WM, van de Pol M, et al. Brachytherapy versus Surgery in carcinoma of the tonsillar fossa and/or soft palate: late normal tissue sequelae and performance status. Can we be more selective? Int J Radiat Oncol Biol Phys, 2004; 59: 713-24.
7. Levendag PC, Schmitz PIM, Jansen PP, et al. Fractionated High-Dose-Rate and Pulsed-Dose-Rate Brachytherapy: First Clinical Experience in Squamous Cell Carcinoma of the Tonsillar Fossa and Soft Palate. Int J Radiat Oncol Biol Phys 1997; 38: 497-506.
8. List M, Ritter-Ster C, Lansky S. A Performance Status Scale for Head and Neck Cancer Patients. Cancer 1990; 66: 564-569.
9. List MA, Rutherford JL, Stracks J, et al. Prioritizing treatment outcomes: Head and Neck Cancer Patients Versus Nonpatients. Head & Neck 2004; 26(2):163-170.
10. List MA, Stracks J, Colangelo L, et al. How do Head and Neck Cancer Patients Prioritize Treatment Outcomes Before Initiating Treatment. J Clin Oncol 2000;18:877-884.
11. Nijdam WM, Levendag PC, Noever I, et al. Cost analysis comparing Brachytherapy versus Surgery for Primary Carcinoma of the Tonsillar

Fossa and/or Soft Palate. Int J Radiat Oncol Biol Phys, 2004;59(2):488-494.

12. Oostenbrink JB, Koopmanschap, MA, Rutten FFH. Manual for costing Research. Amstelveen. Health Care Board, 2000 (in Dutch).
13. O'Sullivan B, Warde P, Grice B, et al. The benefits and pitfalls of ipsilateral radiotherapy in carcinoma of the tonsillar region. Int J Radiat Oncol Biol Phys 2001, 51;332-342.
14. Parsons, JT, Mendenhall WM, Stringer SP, et al. Squamous Cell Carcinoma of the Oropharynx: Surgery, Radiation Therapy, or Both. Cancer 2002;94:2967-2980.
15. Pol van de M, Levendag PC, De Bree RR et al. Radical Radiotherapy compared with Surgery for Advanced Squamous Cell Carcinoma of the Base of Tongue. Brachytherapy, In Press, 2004.
16. Van Agthoven M, van Ineveld BM, de Boer MF, et al. The costs of head and neck oncology: primary tumours, recurrent tumours and long-term follow-up. European Journal of Cancer 2001; 37: 2204-2211.
17. Withers HR, Peters LJ, Taylor JMG, et al. Late normal tissue sequelae from radiation therapy for carcinoma of the tonsil: patterns of fractionation, study of radiobiology. Int J Radiat Oncol Biol Phys 1995;33:563-568.
18. Withers HR, Peters LJ, Taylor JMG, et al. Local control of carcinoma of the tonsil by radiation therapy: an analysis of patterns of fractionation in nine institutions. Int J Radiat Oncol Biol Phys 1995;33:549-562.

CHAPTER 8

Interstitial Radiation Therapy for Early Stage Nasal Vestibule Cancer: a Continuing Quest for Optimal Tumor Control and Cosmesis at Low Costs

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ABSTRACT

Introduction: This article reports on the effectiveness, cosmetic outcome and costs of interstitial high-dose-rate (HDR) brachytherapy for early stage cancer of the nasal vestibule proper and/or columella high-dose-rate brachytherapy.

Methods & Materials: Tumor control, survival, cosmetic outcome, functional results, and costs were established in 64 T1/T2N0 nasal vestibule cancers from 1991-2005 by fractionated interstitial radiation therapy (IRT) only. Total dose is 44 Gy: 2 fractions of 3 Gy per day, 6-hour interval, first and last fraction 4 Gy. Cosmesis is noted in the chart by the medical doctor during follow-up, by the patient (visual analogue scale), and by a panel. Finally full hospital costs are computed.

Results: A local relapse-free survival rate of 92% at 5-years was obtained. Four local failures were observed; all four patients were salvaged. The neck was not treated electively; no neck recurrence in follow-up was seen. Excellent cosmetic and functional results were observed. With 10 days admission for full treatment, hospital costs amounted to €5.772 ($7.044).

Conclusion: Excellent tumor control, cosmesis and function of nasal airway passage can be achieved when HDR-IRT for T1/T2N0 nasal vestibule cancers is used. For the more advanced cancers (Wang classification: T3 tumor stage), we elect to treat by local excision followed by a reconstructive procedure. The costs, admission to the hospital inclusive, for treatment by HDR-IRT amounts to €5.772 ($7.044). This contrasts substantially with the full hospital costs when nasal vestibule cancers are treated by plastic reconstructive surgery, being on average threefold as expensive.

INTRODUCTION

The nasal vestibule (NV) is the beginning of the nasal cavity. It is a distinct triangularly shaped space, approximately 1.5 cm in diameter, located in front of the limen nasi. It is defined laterally by the alae with their supporting lateral cartilage, medially by the (partly) membranous septum and the columella, and caudally by the lining of the floor of the nasal cavity. It is covered by skin, which contains numerous hair follicles and sebaceous glands; malignant tumors at this location are essentially of squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) types. Small carcinomas of the NV usually present as asymptomatic (nodular) lesions, often accompanied by excessive crustae formation; tumors rarely advance beyond the anatomic borders of the NV to infiltrate distant anatomical structures like the orbital apex (see below for staging). First-order lymphatic drainage of the NV is essentially to the submandibular and submental nodes; there is also a potential pathway to the facial, pre-auricular and level II nodes. It is generally accepted that NV cancers presenting with synchronous pathological lymphnodes in the neck (N+) carry a grim prognosis. However most authors agree that the overall incidence of regional metastasis at presentation is low, that is, it varies between 5-15%. Moreover, the development of metachronous lymph node metastases during the course of the disease is in approximately the same range. Therefore it is commonly suggested that there is no need for elective neck treatment of the N0 neck in NV cancer. Overviews of several of these issues regarding NV cancer can be found in the literature [1-8].

The T-stage classification according to the American Joint Commission for Cancer (AJCC) classification system (2002 edition for the naso-ethmoidal complex), denotes 4 subsites of the nasal cavity; that is the septum, lateral wall, nasal floor and nasal vestibule [1,9]. T1 corresponds to one subsite with or without bony invasion, T2 to two subsites or involvement of an adjacent region with or without bony invasion, and T3 extends into the medial wall/floor of orbit, sinus complex, palate, cribriform plate, and subcutaneous tissues. Tumors of the T4 category harbor even more advanced lesions, with extensions into the cheek, orbit, nasopharynx, clivus and cranial fossa. During the study period, the other frequently used T-stage classification system for NV cancer, that is the classification according to C.C. Wang [10], was implemented in our institution. It proposes guidelines that are basically very similar to the AJCC for the early T1 an T2 cases: T1 involves one or more sites within the NV proper, T2 extends to one or more adjacent structures, and T3 comprises massive lesions with deep muscle and bone involvement. Surgery

[S; 11,12], brachytherapy [BT; 6,13,14], and external beam radiation therapy only [EBRT; 15,16], and/or a combination of these, are the most commonly used therapy modalities, but no golden standard has been defined so far. In the selection process of the preferred modality, extent of the disease (volume, T-stage) and BT expertise, are important prognosticators [17]. This report first updates tumor control rate and overall survival of a large single institutional experience with early-stage tumors, that is, primary T1/T2N0 cancer of the NV, treated with HDR Interstitial Radiation Therapy (IRT).
A special aim was to assess the cosmetic results and functional nasal sequelae after IRT. This is done for all patients still alive by instructing a panel of non-medical and medical professionals to score the cosmetic result of each of these patients. Also, during an extra outward clinic follow-up session, all patients alive were seen in consultation to score the functional outcome. Finally, to put the IRT technique for NV cancer more in perspective, full hospital costs are computed and compared with costs of other modalities used in NV cancer, such as plastic reconstructive surgery (RS), Moh's surgery (MS), and EBRT.

METHODS AND MATERIALS

Treatment Protocol and Patient Characteristics
The charts were reviewed of all 133 patients treated with radiation therapy between 1991 and 2005 in the Erasmus Medical Center - Daniel den Hoed Cancer Center for BCC or SCC of the NV. Patients were seen in joint consultation by the radiation oncologist and head-and-neck surgeon. Diagnosis was established by clinical examination in the outpatient clinic, and all lesions were biopsied. Ultrasound examination of the neck (and, if appropriate, fine-needle guided aspiration cytology of suspicious lymph nodes) was performed. Staging was done according to the C.C. Wang classification rules [10]. For the purpose of the present investigation, only primary T1/T2N0 NV cancers treated by HDR-IRT, were eligible. In the 15-year time period, 133 patients with NV cancer were treated. Patients with a combination of the following disease or treatment modality characteristics were excluded from the present analysis: patients with N+ disease (29/133 [22%]), T3 tumors (17/133 [13%]), tumors of non-BCC or non-SCC origin (15/133 [11%]), patients treated with EBRT only (19/133 [14%]), or patients treated with a BT mould technique (10/133 [8%]). In summary, of the 133 patients with primary NV cancers, 69 patients treated with radiation therapy were considered

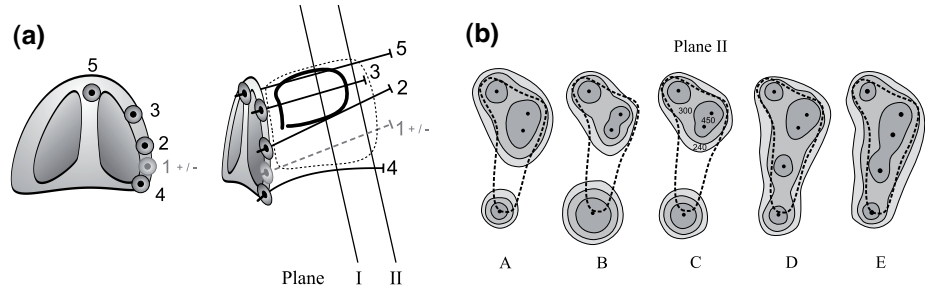
noneligible. Of the 64 (44 T1N0, 20 T2N0), remaining patients, 3 (5%) had BCC and 61 (95%) were of SCC origin; 51 (80%) were of male gender. Mean age was 68, range 46-87 years. Treatment of the primary NV cancer was performed by IRT-only (50 [78%] patients; so-called "nonsurgical" group) or by IRT after an "extensive excision biopsy" had been performed (14 [22%] patients; denoted as "surgical" group).

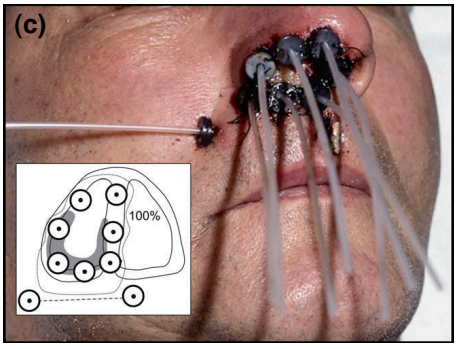
For details regarding of the rationale and interstitial technique per se are referred to in previous papers [6,18]. The total dose of 44 Gy is given in an accelerated fashion; that is 2 fractions of 3 Gy per day in an overall treatment time [OTT] of 10 days. With regard to the technique of this conformal type of radiation therapy: first a needle with outer diameter of 1.5 mm is introduced. Subsequently, after retracting the needle, a plastic afterloading catheter (outer diameter 4 French [1.3 mm]) is inserted in the puncture (guide) channel of the retracted needle. Likewise, general 3-4 (sometimes as many as 7) afterloading catheters are introduced approximately 0.5 cm apart but well into the "heart" of the cancer.

Obviously, the exact configuration and number of catheters are determined by the extent, depth and shape of the lesion. The afterloading tubes are fixed by suturing the buttons to the skin or, more recently, using a heat-sealing technique (Nucletron; catheter ends are heat-sealed flush with the outside of button). The active length is generally about 4 cm. Finally, after dose optimization, the dose is prescribed to dose points 0.5 cm from the implant at source therewith encompassing the full extent of the lesion and eliminating as much dose as possible form the surrounding normal nasal skin and/or mucosal structures (Figure 1c). For that purpose the (optimized) dose is calculated in different planes (e.g., plane I and plane II in Figures 1a, b); in some cases the given dose distribution even necessitates the implant of an extra catheter for adequate dose coverage (see Figure 1b, compare type C with type D and E). Figure 1c depicts a patient with a large implant of the NV and, because of tumor infiltration, an additional catheter for adequate dose coverage was implanted in the lip. The tumor is irradiated by a standardized fractionated HDR protocol: 44 Gy total dose, 3 Gy per fraction, 2 fractions per day, 6 hours interval between the fractions, with the first and the last fraction being 4 Gy [18].

The dose is given by means of a micro-selectron HDR containing an Ir-192 point-source (370 MBq), in conjunction with a PLATO brachytherapy Treatment Planning System. Patients are seen in regular follow-up by the radiation oncologist and head-and-neck surgeon, alternately. In the beginning, these follow-ups occur every 3 months, but at a later stage with 6 months, and up

Figure 1a: Schematic diagram implant of the nasal vestibule. I, II: planes of calculation in periphery of target.
Figure 1b: Five types of dose distributions (A,B,C.D.E) are compared. A: 5 catheters, constant dwell times and dwell positions. B: 4 catheters, dwell times geometrically optimized. C: 4 catheters, optimized on dose points 0.5cm from catheters. D,E: Constant dwell times and dwell positions (D) or optimized implant (E) after implantation of extra (= total of 5) catheters. Fraction size 3 Gy.
Figure 1c: patient with a large implant of the NV and, because of tumor infiltration, an additional catheter for adequate dose coverage, implanted in the lip.

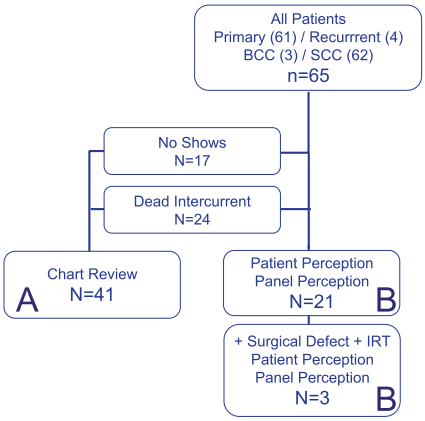




to 1-year intervals. After 5 years of follow-up, patients are dismissed. Actuarial LRFS and overall survival (OS) were computed according to Kaplan-Meier.

Evaluation of cosmesis and nasal function after interstitial radiation therapy
For the current investigation, at one point in time (March 2005) after long follow-up times for the majority of cases, we called upon all patients alive with

Figure 2: Flow diagram Group A and Group B patients. Figure self explanatory; see also text



no evidence of disease (n=40). Twenty patients (58%) showed up (Group B, see also Figure 2). Of these 24 patients; three belonged to the "surgical group" (see before, this section). All patients were seen at the extra outward clinic dedicated to the evaluation of cosmesis and the nasal airway function.
Two groups of patients were indentified: group A and group B. Group B contrasted with group A in that group A (n=41) could only be evaluated by chart review because patients had either died intercurrently (n=24) or did not show up for the extra outward clinic visit (n=17).
Both physician (MD) and patient scored objective and functional study-parameters of the nasal airways function, as being "satisfactory" or "non-satisfactory" (Table 1).
Post-treatment cosmetic outcome is assessed by a panel consisting of non-medical professional workers (n=5) and medical professionals (n=8).
The panelists (data-manager, manager [department of radiation oncology], technician [dental department], medical photographer, secretary, radiation oncologist, resident in training for radiation oncologist, outside physician, two reconstructive surgeons, dermatologist, head-and-neck surgeon) were to score each patient on a 3-point scale: 1 = poor, 2 = moderate, fair, and 3 = good, excellent. For scoring purposes each face, including the upper lip and/or nasal tip (implanted sites) of each patient is represented by six standardized digital photographs on a CD-Rom (Figures 3-8; also column 1, Group B, Table 2). In addition, each patient was asked to mark their appreciation of the cosmetic end-result on a visual analogue scale (VAS),

Table 1: Findings at last follow-up after treatment of nasal vestibule cancer by interstitial radiation therapy*

Objective findings (0% = poorest, 100% = best)	Satisfactory result (%)	Functioning of nasal airways (0% = poorest, 100% = optimal)	Satisfactory result (%)
Dryness	*29**	**Blocked nose**	58
Crustae	*38**	Dry nose	77
Collapse Alae	79	Bloody discharge	77
Fibrosis	83	Speech	77
Erythema mucosa lining	88	Snoring	81
Teleangiectasia mucosa lining	92	Cottle test**	88
Defect nasal septum	96	Nasal whistling	92
Ulcer	96	Extra nasal sounds	92
Defect Alae	100		
Defect/ulcer upper lip	100		

* Only with regard to the objective finding of dryness and crustae of the nose the medical doctors were dissatisfied with the results.
** Cottle test: positive Cottles test, meaning collapse of the nostrils when inhaling.

Table 2: Cosmetic scores after interstitial radiation therapy for nasal vestibule cancer

Scores	Cosmetic results group B			Cosmetic results group A
	Panel CD-ROM	Patient VAS	M.D. chart review	M.D. chart review
Mean score all patients (SD)	2.6. (0.5)		2.9 (0.3)	3 (0)
Mean VAS all patients (SD)		8.7 (2.1)		
Good: 3 (number of Pts. [%])	15 [65]**		18 [90]*	40 [100]
VAS: 7-10 (number of Pts. [%])		18 (86)		
Fair: 2 (number of Pts. [%])	8 [35]		2 [10]	0
VAS: 4-6 (number of Pts. [%])		2 [9]		
Poor: 1 (number of Pts. [%])	0		0	0
VAS: 0-3 (number of Pts. [%])		1 [5]		

Abbreviation:
VAS = Visual Analogue Scale.
* Out of 23 charts, after excluding missing values (3), 18 charts were scored as 'good' (score of 3), that is 90% (score 3).
** 65% of patients score 3 by pane lists.

Figure 3: Figures 3-8 each contain 6 standardized photographs per patient; this way each patient was presented to members of the panel on CD-ROM and allocated a score of '1' (poor), '2' (moderate), '3' (good). This figure is an example of a nonsurgical patient allocated a score of '1' by the panel. Explanation of ' surgical' versus 'nonsurgical': see text

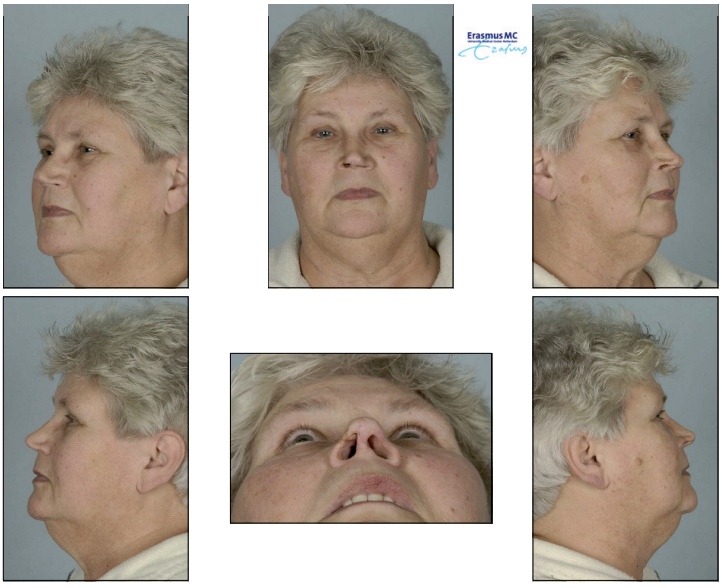


Figure 4: See legend Figure 3: example of a nonsurgical patient allocated a score of '2' (fair, moderate)

Figure 5: See legend Figure 3: example of a nonsurgical patient allocated a score of '3' (good)

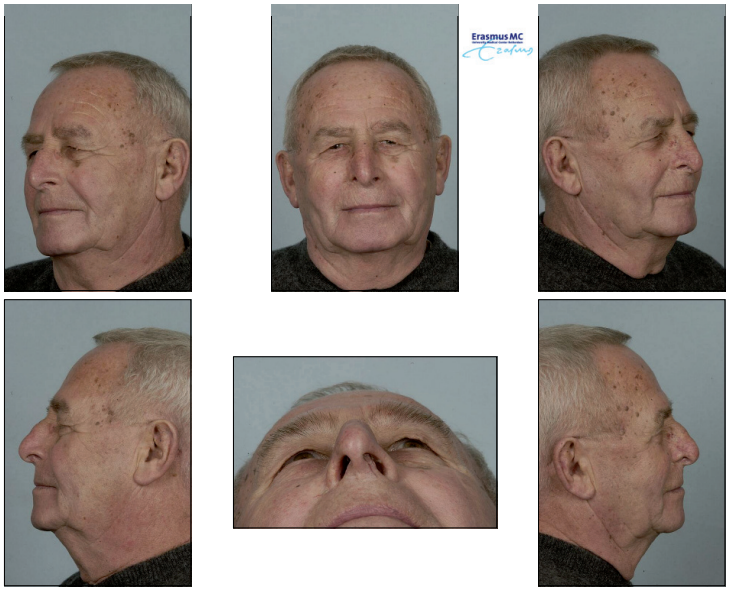


Figure 6: See legend Figure 3: example of a surgical patient allocated a score of '1' (poor)

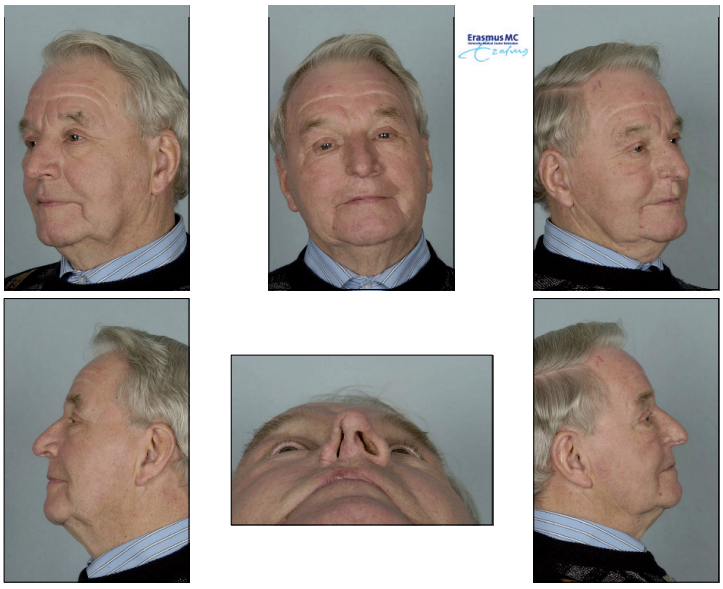


Figure 7: See legend Figure 3: example of a surgical patient allocated a score of '2' (fair, moderate)

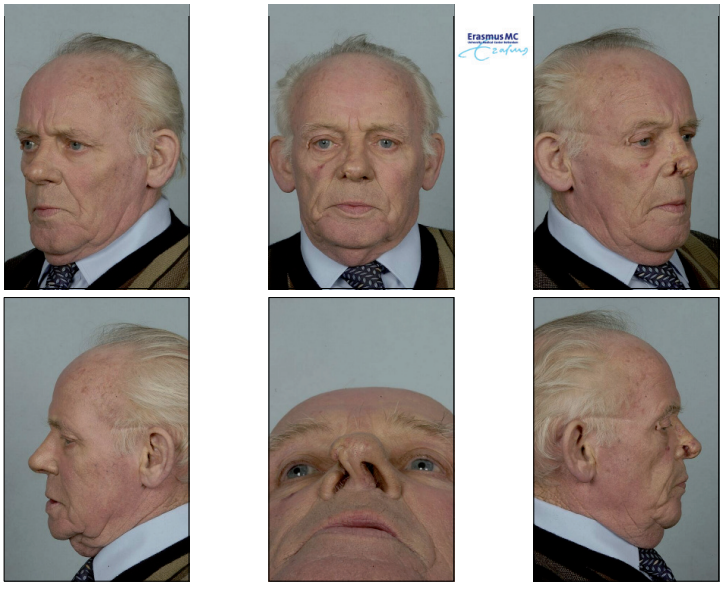
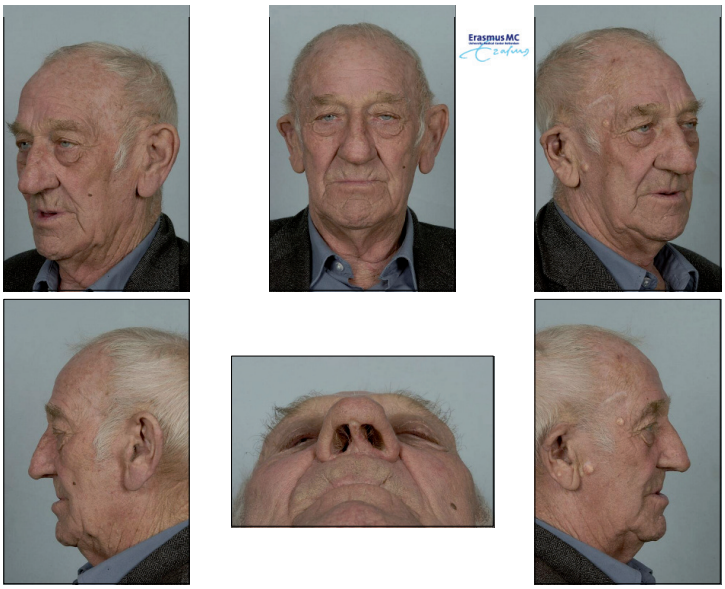


Figure 8: See legend Figure 3: example of a surgical patient allocated a score of '3' (good)



ranging from 1 (minimum) to 10 (maximum), (column 2, Group B, Table 2). Also, the scores of the medical consultant (MD) written in the charts at the last follow-up date, were taken as a cosmetic outcome measure (column 3, Group B, Table 2). Similar findings on cosmetic outcome were retrieved from the charts of Group A (column 4, Group A, Table 2). This last group consisted of the charts of patients that had died because of intercurrent disease (n=24) or were alive but could not be analyzed by the panel because of "no show" for non-tumor-related reasons (n=17) (see also Figure 2).

Total costs of treatment by interstitial radiation therapy

The direct medical costs of IRT of the NV are calculated and summed for the most important items within the work-up (diagnosis and staging) and for the treatment, as well as for the hospital admission. The costs for diagnosis and staging are based on the Dutch Tariff system. The direct medical costs (materials and manpower) are based on average unit costs. To determine the unit costs, we followed the micro-costing method, i.e. a detailed inventory and measurement of resources consumed.

Wholesale prices were used to determine costs of materials. Also costs related to use of equipment and operating room (integrated brachytherapy unit) are included in material costs. The number of radiation sessions for IRT is according to the protocol typically used in case of NV cancer (see before). We also estimated the number of admission days based on this protocol, as was the number of follow-up visits. To calculate manpower costs, the time spend for the various procedures was estimated by the medical disciplines involved. Time invested was multiplied by salary (including wages, social premium and extra fees for irregular working hours). Costs per minute were then calculated under the assumption of 1540 working hours a year. The specialist activities were divided into direct and indirect time. Direct time was estimated to be 70% of the specialist's working time. Indirect time is estimated to be approximately 30%. All direct costs were multiplied by 16,4% to cover overhead costs (e.g. depreciation costs of the building, cleaning costs etc.) The valuation of resources and overhead costs are based on financial data from the Erasmus Medical Center Rotterdam. Costs were based on 2001 pricings and stated in Euros (€); for some of the amounts (see 'Discussion' section), the Euro is converted to the US dollars ($)(exchange rate December 2005). (The cost calculation serves the purpose of comparing the (low) cost of interstitial radiation therapy for early cancers of the NV with costs of other treatment modalities, such as reconstructive surgery [see also the paragraph on cost in the 'Discussion' section]. This relative comparison should also be of interest to readers of other nations given the importance of cost-effectiveness data in the health-care section overall).

RESULTS

Survival

The LRFS and OS rates of patients treated with an interstitial implant for NV cancer (Figure 1c) at 5 years are 89% and 58% for T1 tumors, and 100% and 78% for T2 tumors, respectively. For all 64 tumors combined, these survival rates accumulate to 92% and 59%, respectively. Four patients failed locally; none of the N0 patients experienced a failure in the neck. All four local failures were salvaged.

Nasal airway functions

Detailed examination of the nasal tip and nasal airway functions were scored by the medical specialist and patient, respectively (see Table 1 for study-parameters), at a dedicated last follow-up clinic. Table 1 shows that the great majority of study parameters were considered (scored) "satisfactory" posttreatment by the specialist.

Cosmesis

All 23 patients were presented in a standardized fashion (6 photographs per patient) to 13 panel members on a CD-ROM. Examples of the so-called "non-surgical" group of patients (n=20) are shown by Figure 3 (score 1; poor), Figure 4 (score 2; fair), and Figure 5 (score 3; good). The "surgical group" of patients (n=3) is shown in Figure 6 (poor), Figure 7 (fair), and Figure 8 (good). In summary, 65% of the patients were scored by the 13 panel members having an "excellent" or "good" result (score 3) in terms of cosmesis after IRT of the NV. Moreover, 90% of the cases were appreciated in the chart by the physician at last follow-up as "good" (maximum score 3).

Total costs of treatment by IRT

The total hospital costs are divided in costs for diagnosis and staging (Table 3) and IRT brachytherapy including admission days (Table 4). In case the patient (tumor) is implanted and treated as an outpatient, the admission amounts to only 2 days with the IRT-brachytherapy given twice daily. Most patients, however, preferred clinical admission during treatment. For a full clinical treatment, the number of admission days is 10.

Table 3: Hospital costs for diagnosis and staging NV cancers

	COSTS
Diagnostics / Staging	Euro
Consultation Radiation Oncologist	95
Consultation head-and-neck Surgeon	95
Radiograph Thorax	39
Blood Chemistry	38
Pre-operative consultation Anesthesiologist	44
Grand (Consultation) rounds	0
Subtotal (Euro)	310
(US Dollars)	$372

Table 4: Hospital costs related to IRT for NV cancers

	COSTS
Brachytherapy / Clinical Admission	Euro
Patient Education	
Anesthesiology	
Simulation (Integrated Brachytherapy Unit)	
Brachytherapy PLATO treatment planning system	
Total Preparation brachytherapy + personnel	46
Total Preparation surgery / anesthesiology + personnel	101
Material (catheters)	30
Operating Room	216
Overhead 16.4%	64
$Subtotal_2$ preparation, equipment, materials, personnel	457
$Subtotal_3$ radiation fraction # 14 (Euro 79 / fraction)	1.111
$Subtotal_4$ Admission days # 2 (Euro 389 / day)	779
$Subtotal_{1+2+3+4}$ Outpatient Therapy	2. 657
(US Dollars)	$3.227
$Subtotal_5$ Admission Days # 10 (Euro 389 / day)	3.894
$Subtotal_{1+2+3+5}$ Inpatient	5.772
(US Dollars)	$7.011

Abbreviations:
IRT = Interstitial Radiation Therapy; NV = nasal vestibule; # = number of fractions

DISCUSSION

Surgery and radiotherapy may provide similar chances for cure in NV cancers. Primary local control (LC) rates have been variably reported. Data on external beam radiation therapy (EBRT) and BT show an LC of approximately 79-95% [5,6,15]. For EBRT alone they amount to 77-86% [7,10], and for primary surgery the data are in essence comparables to primary EBRT [11,19,20]. Detailed objective reports on results concerning cosmetic sequelae and nasal airway function posttreatment are, however, frequently absent or biased; the choice of modality and results often seem to depend on the specialty of the physician in charge of the patient. The purpose of this article is to report on the results of fractionated HDR-IRT to a total dose of 44 Gy for T1/T2N0 SCC or BCC tumors of the NV. Over many years, this protocol has proven to be a straightforward, simple, reliable, and effective treatment approach in controlling NV tumors. A LRFS rate of 92% at 5 years was obtained. The four local failures observed over time were salvaged. Moreover, the neck was not treated electively; this policy has been proven right because no neck recurrences were seen during follow-up. Given the proximity of major and minor salivary glands to the clinical target volume, and to part of the upper neck and not having to treat the lymph nodal regions electively by radiation, safe-guards the patient from serious potential side effects such as xerestomia. Importantly, at this time and ages, not only the locoregional failure rates are important; many physicians now try to obtain good tumor control in combination with optimal quality of life for their patients. This means that good cosmetic outcome and preservation of the (functions of the) nasal airway passages are becoming of paramount importance as well. Finally, with the severe budget constraints and deficits present in many of the major hospitals, the preferred modality should be at low cost without compromising the efficacy and the quality of the treatment.

When comparing the notes in the charts of group B patients still alive and seen in the last follow-up with charts of group A patients (no show or dead of intercurrent disease), it can be concluded that the IRT technique produces excellent cosmetic outcomes across the board (100% maximum score of 3, Table 2).

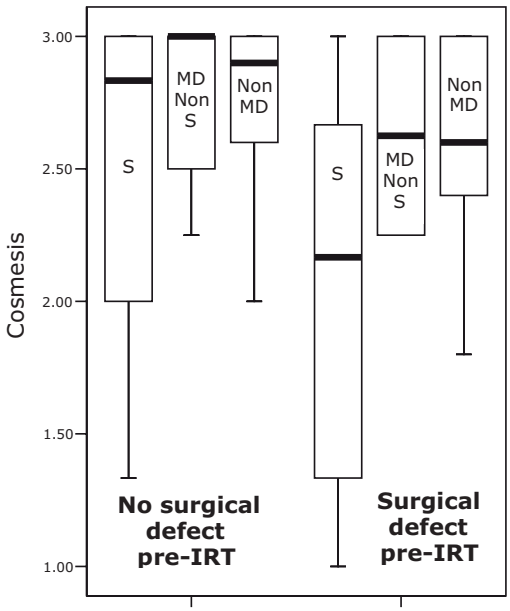
What was achieved in group B? In the majority of patients, panel scores were "good to excellent" (65% maximum score of 3; Table 2). Similarly, "good" (VAS scores 7-10) cosmetic outcome can be observed in the majority (86%) of cases when looking at patient appreciation; overall, a mean score of 8.7

on a scale of 10 (Table 2) was found. Also, the functional aspects of the nasal cavity passage after IRT are excellent (see Table 1).

Of interest is the difference between the "non-surgical" group (20 patients) and "surgical" group scores (3 patients with extensive biopsies) when taking into account the profession of the panelist (Figure 9). Although the question posed was to objectify the cosmetic result by scoring the effect of IRT per se, surgeons appreciated the cosmetic results of the "surgical" patients as being worse, probably biased because of the presence of a surgical defect (Figure 9). It demonstrates to some extend the difficulties encountered when trying to objectively score cosmesis.

Lastly, when computing the cost (diagnosis and staging [€310, $372], IRT [€1.568, $1.905] and admission 10 days [€3.894, $4.730]), implantation

Figure 9: Box-plot of panel scores of patients with nasal vestibule cancer of either the 'nonsurgical' group or 'surgical' group, respectively. Both groups were scored by members of the panel being medical doctors (surgeons and nonsurgeons) or nonmedical doctors. The good rating overall is apparent. It is interesting that the median score on cosmesis is lower for the surgeons scoring the patients of the surgical group as opposed to the other medical doctors or nonmedical doctors of the panel scoring the patients of both (surgical and nonsurgical) groups



of these cancers is really at relatively low costs (€5.772, $7.044). This is particularly true if the patient is willing to go home and return to the IRT unit twice daily on an outpatient basis for actual treatment. In that case, the cost of 8 days' admission can be saved; total remaining cost is €2.657 ($3.227). These data are on costs by interstitial radiation therapy. Obviously, in case of EBRT, the amounts will be different. Due to the number of fractions in case of EBRT, the price will increase. However, this will be cancelled out because EBRT is usually given on an outpatient basis. A detailed discussion on BT vs. EBRT in terms of cost has been presented by Nijdam et al. [21].
In our view the more diffuse and advanced lesions (T3-stage C.C. Wang, T3T4 stage AJCC 2002) are more difficult to cure with IRT alone. Probably wide excision and reconstructive surgery in combination with EBRT has more to offer in these cases in terms of local tumor control. We are presently evaluating a series of patients treated in a similar time frame with reconstructive surgery post wide excision and performed in one or multiple sessions (mean, 3) compared with the current series (this article), the patient population [22] is more advanced, with 14 out of 34 (47%) being a recurrent lesion and only 5 of 34 (15%) being a T1/T2N0 tumor. Not surprisingly, the latter treatment (reconstructive surgery, in 6 cases combined with Moh's surgery) is at a much higher cost (€15.000; ($18.181) in these 34 patients, mainly due to the multistep procedure.

Conclusion

Excellent tumor control rates, good cosmetic results, and optimal nasal function at relatively low cost can be achieved when using IRT only for early T1/T2N0 NV cancers. Elective treatment of the neck is not warranted. Although not the topic of the present paper, we feel reconstructive surgery should be the modality of choice for the more advanced lesions [22].

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REFERENCES

1. De Vita VT, Hellman S, Rosenberg SA, editors. Cancer, principles & practice of oncology. 7th edition. Philadelphia: Lippincott, Williams & Wilkins, 2005. p. 713-721.
2. Horsmans JDJ, Godbalie C, Jorgensen KE, et al. Squamous Cell Carcinoma of the Nasal Vestibule. Rhinology 1999; 37: 117-121.
3. Johansen LV, Hjelm-Hansen M, Andersen AP. Squamous cell carcinoma of the nasal vestibule. Treatment results. Acta Radiol Oncol. 1984; 23: 189-192.
4. Kagan AR, Nussbaum H, Rao A, et al. The management of carcinoma of the nasal vestibule. Head and neck surgery 1981; 4: 125-128.
5. Langendijk JA, Poorter R, Leemans CR, et al. Radiotherapy of squamous cell carcinoma of the nasal vestibule. Int J Radiat Oncol Biol Phys 2004;59(5):1319-1325.
6. Levendag PC, Pomp J. Radiation Therapy of squamous cell carcinoma of the nasal vestibule. Int. J Radiat Biol Phys 1990;19:1363-1367.
7. Mendenhall WM, Stringer SP, Cassisi N, et al. Squamous cell carcinoma of the nasal vestibule. Head & Neck 1999;21:385-393.
8. Wong CS, Cummings BJ. The place of radiation therapy in the treatment of squamous cell carcinoma of the nasal vestibule: A review. Acta Oncol 1988;27:203-208.
9. TNM AJCC classification system; edition 2002. Nasal Cancers.
10. Wang CC. Treatment of carcinoma of the nasal vestibule. Cancer 1976;38:100-106.
11. Patel P, Tiwari R, Karim AB, et.al. Squamous cell carcinoma of the nasal vestibule. J Laryngol Otol 1992;106:332-336.
12. Weinberger JM, Briant TD, Cummings BJ, et al. The role of surgery in the treatment of squamous cell carcinoma of the nasal vestibule. J Otolaryngol 1988;17:372-375.
13. Evensen EF, Jacobsen AB, Tausio E. Brachytherapy of squamous cell carcinoma of the nasal vestibule. Acta Oncol 1996;35:Suppl 8:87-92.
14. Chassagne D, Wilson JF. Brachytherapy of carcinoma of the nasal vestibule. Int. J of Radiation Biol Phys 1984;10:761.
15. Mazeron JJ, Chassagne D, Crook J, et al. Radiation therapy of carcinomas of the skin of nose and nasal vestibule: A report of 1676 cases by the Groupe European de Curietherapie. Radiother Oncol 1988;13:165-173.

16. Mendenhall NP, Parsons JT, Cassisi NJ, et al. Carcinoma of the nasal vestibule treated with radiation therapy. Laryngoscope 1987;97: 626- 632.
17. Wong CS, Cummings BJ, Elhakim T, et al. External irradiation for sqaumous cell carcinoma of the nasal vestibule. Int. J of Radiat Biol Phys 1986;12:1943-1946.
18. Kummer E, Rasch C, Keus RB, et al. T Stage as prognostic factor in irradiated localized squamous cell carcinoma of the nasal vestibule. Head & Neck 2002;24:268-273.
19. Levendag PC, Schmitz PIM, Jansen PP. Fractionated high-dose-rate and pulsed-dose-rate brachytherapy: First clinical experience in squamous cell carcinoma of the tonsillar fossa and soft palate. Int J Radiat Oncol Biol Phys 1997;38:497-506.
20. Goepfert H. The vex and fuss about nasal vestibule cancer [editorial comment]. Head & Neck 1999;21:383-384.
21. Nijdam WM, Levendag PC, Noever I et al. Cost analysis comparing brachytherapy versus surgery for primary carcinoma of the tonsillar fossa and/or soft palate. Int J Radiat Oncol Biol Phys 2004;159:488-494.
22. Mureau MAM, Moolenburgh SE, Levendag PC, et al. Aesthetic and functional outcome following nasal reconstruction. Plastic Reconstr Surg 2006;submitted.

CHAPTER 9

Longitudinal Changes in Quality of Life and Costs in Long-term Survivors of Tumors of the Oropharynx treated with Brachytherapy or Surgery

∞

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ABSTRACT

Purpose: Based on earlier studies we were interested if longitudinal assessment of quality of life and costs in long-term survivors of oropharyngeal cancers treated with external beam radiation therapy and brachytherapy or surgery and postoperative radiotherapy showed a change in quality of life over the years. Besides we were curious how much the costs per life year and the Quality Adjusted Life Years would be for this patient group.

Methods & Materials: Performance status scales eating in public, understandability of speech, normalcy of diet, xerostomia and ability to swallow were determined in 2003 and 2005. In 2005, EORTC QLQ-C30, EORTC H&N35, and Euroqol questionnaires were also measured. Costs and Quality Adjusted Life Years were calculated.

Results: Eating in public, Understandability of Speech, and Normalcy of Diet significantly differed in favor of brachytherapy. Surgical patients experienced more speech, teeth and opening mouth problems. Mean costs and Quality Adjusted Life Years for brachytherapy were €16.112 and €56.060 and for surgery €26.590 and €93.275.

Conclusion: Quality of Life scores don't change over time. Due to the number of admission days, surgery is more costly. Difference in costs for Quality Adjusted Life Years in favor of brachytherapy was found.

INTRODUCTION

The curative treatment options for squamous cell cancers (scc) originating in the oropharynx differ, depending on institutional (doctors)- and patient preferences. It basically varies from surgery with or without postoperative radiation therapy (PORT), to radiotherapy (RT) alone [1-8]. RT has been instituted as a sole treatment modality, using different fractionation regimes [1], or combined with a neck dissection (ND) and neo-adjuvant and/or concomitant chemotherapy [8]. Also, RT has been effectively applied by means of a linear accelerator only (external beam radiation therapy [EBRT]) or by EBRT in combination with brachytherapy (BT), that is interstitial radiation therapy (IRT)[2,3,9]. Proponents of RT-alone argue that surgical resection of these tumors can result in depreciation of the swallowing- and speech functions, while in contrast, for surgery versus RT in terms of tumor control; no difference is observed [2].

In our institute, a function preserving protocol was designed and initiated in 1991, consisting of conventional EBRT and BT, or with surgery and PORT [10]. Eligible for this protocol were patients with 1. early- and intermediate staged (T1-3(4)N0,+) cancers of the tonsil and soft palate, and 2. T1-4N0,+ cancers of the base of tongue (BOT). In a recently analyzed subset of patients, that is patients with Tonsillar Fossa and/or Soft Palate tumors treated between 1986 and 2001 in the Erasmus University Medical Center (Erasmus MC) with either EBRT plus BT or surgery plus PORT, no significant differences were found in tumor control, survival, functional outcome scores, complications, and degree of xerostomia. However, as far as the cost of treatment was concerned, we found that treatment with BT was less expensive in comparison with surgery. In the future, however, a gain in Quality of Life and effectiveness can be expected given the current rapid development in relevant technology that enables the implementation of (even better) sparing techniques. These sophistication in technology undoubtedly increase the total costs of future treatments [2,10,11].

In a recent article [12], costs of cancer of the oropharynx with regard to the three treatment modalities, that is BT, surgery and EBRT were reported. In this analysis costs, generated by the treatment of the primary tumor per se, the costs of (salvage of) a locoregional relapse and the costs generated by the (treatment of) serious, that is RTOG Grade III/IV and complications for which hospitalization is needed, were calculated.

In the above-mentioned analysis, we found no difference in quality of life for the three treatment groups according to the Performance Status Scales (PSS) for Head and Neck cancer patients as developed by List et al. [13-15]. The object of this study is to see whether patients showed a change in quality of life over the years and how much the costs per life year would be for this patient group.
In this analysis, we will emphasize the QoL scores measured by standard queries and a Visual Analogue Scale for xerostomia. The queries used are PSS scores according to List, the European Organization for Research and Treatment of Cancer (EORTC)-Quality of Life Questionnaire (QLQ-C30), the EORTC Head and Neck (H&N35) module, and the Euroqol (EQ-5D). The health state measured in the EQ-5D was used to be able to calculate the costs per quality adjusted life year (QALY) for these patientgroups.

MATERIAL AND METHODS

Patient eligibility and procedure
The protocol at the time was as follows: because of organ function preservation, patients with Tonsillar Fossa (TF) and Soft Palate tumors (SP) (T1-T3) and tumors of the Base of Tongue (BOT) (T1-T4) were preferentially treated by EBRT (46 Gy) and BT as a boost. If neck nodes are present, a neck dissection is performed. For those patients not eligible for BT (deep parapharyngeal space invasion or extension of the tumor in the lateral and posterior pharyngeal wall or simply patient refusal) surgery and PORT was the treatment of choice. From 1991-2001, 254 patients with TF and/or SP, and BOT tumors, were treated by organ function preservation therapy, using EBRT and BT. Hundred and ten patients not suitable for BT were treated by a combined resection with PORT.
Among all patients ≥ 2 years and < 10 years alive and with no evidence of disease (NED) with tumors of the TF/SP (98 patients) and BOT (21 patients), a Quality of Life (QoL) survey was conducted in 2003. For that purpose, two groups were studied: group I with TF/SP/BOT tumors treated by a BT boost (75) and group II with TF/SP/BOT tumors treated by surgery and PORT (44). The first object of the study was to determine the performance status scales (PSS) scores. In addition, symptoms related to xerostomia and the (in)ability to swallow were measured by standardized queries and a visual analogue scale ("VASxero").
In 2005 the survey was repeated among patients fulfilling the criteria. In

addition to the PSS, in 2005 the EORTC QLQ-C30, the H&N35 and the EQ-5D questionnaires were sent. Technical help of a research technician was offered to every patient. After answering of the queries was completed, questionnaires were returned in the majority of cases within one month.

Diagnosis, treatment, follow-up and relapse and/or complications

In joint consultation by the radiation oncologist and head-and-neck surgeon, a thorough Ear Nose Throat (ENT)-examination is performed in all patients. Based on the criteria mentioned previously, patients underwent either BT as a boost after EBRT or surgery. Patients were seen in regular follow-up with clinical (ENT) examination and laboratory tests being executed. Year one: five outpatient visits including routine clinical (ENT) examination, year two and three: two follow-up visits, including again routine clinical ENT examination, blood chemistry, T4, TSH and plain chest X-ray (annually) were performed. As from year four: one outpatient visit was executed annually with routine ENT examination included.

In case of a locoregional relapse or distant metastasis, additional diagnostic means were used to establish the extent of the disease. Subsequently individualized combinations of chemotherapy (as of the year 2000), surgery, BT and EBRT were used in order to either cure or palliate the patient.

The protocol for oropharyngeal patients in the Erasmus MC is described earlier. For a detailed description the reader is referred to Levendag et. al [2].

Measures QoL

Five questionnaires were used to define Quality of Life: The List Performance Status Scale scores, the EORTC QLQ-C30, EORTC H&N35, EQ-5D and an in-house developed Visual Analogue Scale (VASxero). All questionnaires were sent to patients at least 2 years NED.

Performance Status Scale by List. The PSS [13-15] consists of three subscales: eating in public, understandability of speech, and normalcy of diet. Scales are scored from 0 to 100, with higher scores representing better performance, defined as better day-to-day functioning in the specified area.

EORTC QLQ-C30: The EORTC QLQ-C30 [16] is a cancer specific self-report questionnaire and incorporates a range of QoL issues. The QLQ-C30 contains five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting), a global QoL score and

six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

EORTC H&N35: The EORTC-H&N35 [17,18] is a site-specific module designed to assess QoL in head and neck cancer patients, varying in disease stage and treatment modality. It incorporates seven multiple-item scales and assesses symptoms of pain, swallowing ability, sense (taste/smell), speech, social eating, social contact and sexuality. Also included are eleven single-item scales, which survey the presence of symptomatic problems associated with amongst others teeth, mouth opening, dry mouth, sticky saliva, coughing, feeling ill. For the H&N35, a high score indicates more problems (there are no function scales in which high scores would mean better functioning).

The scales and single-item variables of the QLQ-C30 and H&N35 questionnaires were linearly transformed into a score from 0 to 100. A high score for a functional scale and for the global QoL scale represents a better level of functioning, whereas a high score for a symptom scale or a single item-scale denotes a high level of symptoms/problems.

EuroQol (EQ-5D): The EuroQol questionnaire exists of two parts. The first part is a generic five-dimensional questionnaire, the EQ-5D. Five items are asked for: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This profile can be transformed to a value given by the general public: the $EQ\text{-}5D_{index}$ [19]. The second part of the EuroQol questionnaire is a visual analogue scale, the EQ_{VAS}, which represents the patient's judgment of his own health state.

VASxero: This in house developed questionnaire has been described previously [20]. In this analysis, we asked for specific xerostomia related issues and, in particular, the consequences of xerostomia on speech, swallowing, eating and dentition. In addition, patients were asked to indicate the overall severity of their xerostomia problem on the linear visual analogue scale. This is a 10-point scale where zero equals no complaints and 10 reflect severe complaints of a totally dry mouth (see appendix I for detailed questions).

Appendix I: Detailed questions of the in-house developed questionnaire by Wijers et.al

1. Do you have a dry mouth problem since RT?
    a. No
    b. More complaints than before RT
    c. Considerably more complaints than before RT
    d. Always a dry mouth since RT

2. Do you need to sip water to facilitate eating?
    a. No
    b. Sometimes, depending on quality of food
    c. Frequently, more often than before RT
    d. Always since RT

3. Do you drink to facilitate speaking?
    a. Never
    b. Sometimes
    c. Regularly
    d. Always (even when speaking)

4. Do you wear dental prothesis?
    a. No
    b. Yes

5. Did you develop caries/poor dentition after RT?
    a. Never
    b. Sometimes, but the same as before RT
    c. Frequently, more often than before RT
    d. Many teeth deteriorate after RT to such an extend that most of them have to be extracted?

6. Do you have pain when swallowing?
    a. Never
    b. Sometimes
    c. Regularly
    d. Always

7. Did you use painkillers?
    a. No
    b. Yes

8. Did you use drip-feed?
    a. No
    b. Yes

9. Visual Analog Scale dry mouth.
   Score between 0 and 10.

10. Visual Analog Scale painful mouth.
    Score between 0 and 10.

Statistic analysis

Data were analyzed with the statistical package StataCorp 2003 (Stata Statistical Software: release 8.0. College Station, TX: Stata Corporation). The QLQ-C30 and the QLQ-H&N35 were analyzed according to the scoring manual of the EORTC. Outcomes were summarized with median values and tested between groups using the Mann-Whitney test.

The simultaneous effect of time from diagnosis till answering the queries, age, total dose, sex, T-classification, N-classification, trismus, necrosis (ulcer) and modality on the five queries was determined by ordinary multivariate regression analysis and Wald's test (significance was assumed when $p \leq 0.05$).

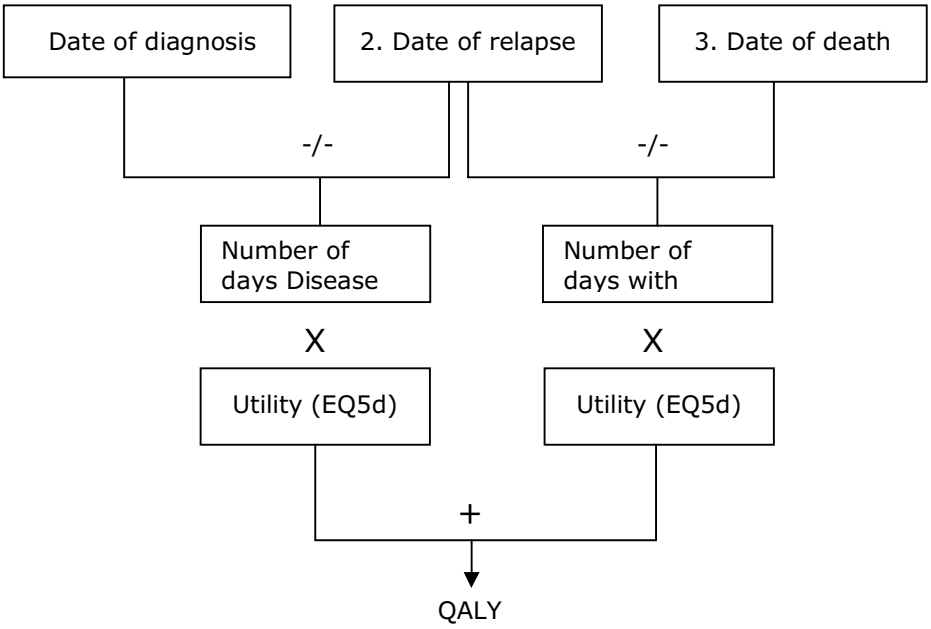
Cost calculation

Patients were analyzed for full hospital costs with the primary (and neck) having been treated, according to the guidelines of the running protocol at the time. The cost analysis is performed from an institutional perspective [21]. In contrast to charges, unit costs are the best estimators for the costs [21]. For the two treatment groups, direct medical costs (including follow-up and relapses and/or complications which needed admission) generated in the hospital per modality were calculated for all steps of the protocol. The initial medical treatment and treatment of the first event (i.e. locoregional relapse and/or distant metastasis) were subdivided in a diagnostic patient part, preparatory part and the treatment itself. The costs of surgery include

the use of the operating room and pathology laboratory costs of the biopsy specimen. The number of admission days were based on real numbers and differentiated for by IC/ward. The use of materials is based on a detailed inventory used in the department (according to protocol). Wholesale prices were used to determine the costs of materials. The costs for diagnosis and staging were based on the Dutch tariff system.
For the valuation of the resource items, we determined mean unit costs both for direct and indirect patient related activities (meaning the patient being present or not [e.g. administration]) according to the micro-costing method [22]. Manpower costs were calculated by time spent (per minute) for the various activities per treatment, multiplied by salary costs [23]. In addition, we applied an overhead percentage of 16.4% (amongst others depreciation of the building and costs for administration). The valuation of the resources and overhead costs was based on financial data from the Erasmus Medical Center Rotterdam. Costs were based on 2001 pricings and stated in Euros (€). For a detailed description of the cost calculation the reader is referred to Nijdam et. al. [10,12].

Calculation costs per life year
For the calculation of costs per life year we used the cost calculation as mentioned above as a base, using the actual survival data for this patient group, which has been reported earlier [10,12]. To determine costs per life year one needs (1) date of diagnosis, (2) date of relapse, and (3) date of death. The subtraction of (2) minus (1) is number of disease-free days, these are multiplied by the utility measure (health state on a range from 0 to 100). The subtraction of (3) minus (2) leads to number of days with relapse, which we also multiplied by the utility measure. These utility outcomes were added. See Figure 1.
Patients lost to follow-up were not taken into account. To compare total costs of both treatment groups (patients treated between 1986 and 2001 inclusive), five-year follow up costs were calculated.
Secondly we calculated the costs per patient per year. To define the costs per year; treatment costs were attributed to year of diagnosis. Costs for relapse / complications per patient were divided by the number of years the relapse / complication lasted and the costs were attributed to the year treatment took place. Costs for follow-up were calculated per year (or months) according to protocol.

Figure 1: Calculation of quality adjusted life years including 5 yrs follow-up (QALY)



RESULTS

The patient characteristics for the three treatment groups are categorized in Table 1. Sex and mean age did not differ much between the two groups, the larger proportion of T1 and T2 in the BT group and T3 in the surgery group reflects the inclusion criteria for both treatments.

In 2003, the List survey and the in-house developed survey were conducted for the first time [2,20]. The PSS scores of the BT and surgery group showed no significant difference for Eating in Public ($p = 0.97$); Normalcy of Diet ($p = 0.89$), and Normalcy of Speech ($p = 0.34$). The median visual analog score for xerostomia was 5.5 (range, 0–10) for the BT group and 6 (range, 2–10) for the surgery group. No statistically significant differences were noted in questions 1 and 4 of the xerostomia-related questions between the BT and surgery group.

The group of 75 BT patients consists of 48 patients completing one questionnaire (either the one in 2003 or 2005) and 27 patients completing the questionnaires of 2003 as well as of 2005. For the surgery group 22 patients completed one questionnaire (either 2003 or 2005) and 22 patients completed the questionnaires both in 2003 and 2005.

Results for 2005 (total response rate 96%) showed a significant difference for Understandability of Speech ($p = 0.0002$) and Normalcy of Diet ($p = 0.05$) between the BT (score = 100 and 80 respectively) and the surgery group (score = 75 and 50 respectively), where 100 is best.

The questions on the QLQ-C30 and EQ-5d showed no significant difference comparing the median values between the two treatments. For the H&N35, Speech Problems ($p = 0.02$), Teeth Problems ($p = 0.03$) and Opening Mouth ($p = 0.002$) showed significant difference between the two groups in favor of the BT group (0 vs. 11, 0 vs. 33 and 0 vs. 67 respectively where 100 is most unfavorable). See Table 2.

The median visual analog score for xerostomia was 4.5 (range, 0-10) for the BT group and 5.0 (range, 0-10) for the surgery group.

Parameters significantly affecting the mean QoL scores for the List survey and in-house developed survey for all patients are shown in Table 3.

As mentioned before, 48 patients in group I and 22 patients in group II completed two questionnaires in 2003 and 2005. 27 patients (56%) in group I and 22 (100%) patients in group II returned both questionnaires. Neither of the PSS scores showed a significant result per treatment in time, nor between the treatments in time.

Mean costs for the different groups are shown in Figure 2. The mean costs

Table 1: Patient characteristics of the BT (N=75), and Surgery group (N=44)

	Brachytherapy-group	**Surgery group**
Male	43 (57%)	28 (64%)
Female	32 (43%)	16 (36%)
Mean Age	56 (min 34 - max 78)	59 (min 38 - max 74)
Tonsil and/or Soft Palate	57 (76%)	41 (93%)
BOT	18 (24%)	3 (7%)
T classification (TNM 2002)		
T1	13 (17%)	3 (7%)
T2	44 (59%)	12 (27%)
T3	14 (19%)	27 (61%)
T4a	3 (4%)	2 (5%)
T4b	1 (1%)	0 (0%)
Node classification		
N0	35 (47%)	18 (41%)
N1	8 (11%)	9 (20%)
N2a	12 (16%)	3 (7%)
N2b	13 (17%)	12 (27%)
N2c	6 (8%)	2 (5%)
N3	1 (1%)	0 (0%)
Classification (TNM 2002)		
I	2 (3%)	0 (0%)
II	21 (28%)	6 (14%)
III	16 (21%)	21 (48%)
IVa	34 (45%)	17 (38%)
IVb	2 (3%)	0 (0%)

Table 2: Median values and P-values for all questions of the QLQ-C30, H&N35 and EQ-5D for patients treated with brachytherapy (BT) (N= 75) and surgery (S) (N= 44)

Variable name	BT-group	S-group	P-value
QLQ-C30			
Functional scales (100 = favorable)			
Physical functioning	87	80	0.42
Role functioning	83	67	0.76
Emotional functioning	92	92	0.85
Cognitive functioning	83	100	0.41
Social functioning	100	100	0.81
Symptom scales (100 = unfavorable)			
Fatigue	33	22	0.64
Nausea and vomiting	0	0	0.51
Pain	17	17	0.76
Single items (100 = unfavorable)			
Dyspnea	0	0	0.82
Insomnia	0	0	0.64
Appetite loss	0	0	0.92
Constipation	0	0	0.75
Diarrhea	0	0	0.71
Financial difficulties	0	0	0.64
Global Health status	75	67	0.76

Table 2 *(continued)*

H&N35			
Multiple item scales (100 = unfavorable)			
Pain	8	25	0.09
Swallowing	17	25	0.14
Senses problems	0	17	0.91
Speech problems	0	11	**0.02**
Trouble social eating	8	17	0.13
Trouble social contact	0	7	0.07
Less sexuality	0	17	0.37
Single item scales (100 = unfavorable)			
Teeth	0	33	**0.03**
Opening mouth	0	67	**0.002**
Dry mouth	67	33	0.89
Sticky Saliva	33	33	0.98
Coughing	33	0	0.36
Feeling ill	0	0	0.27
Pain killers	0	0	0.35
Nutritional supplements	0	0	0.77
Feeding tube	0	0	0.85
Weight loss	0	0	0.20
Weight gain	0	0	0.79
EQ-5D *(100 = favorable)*			
Mobility	100	100	0.40
Self care	100	100	0.87
Daily activities	100	100	0.74
Pain / complaints	50	50	0.44
Mood	0	0	0.78
Health state	75	75	0.87

Table 3: Parameters affecting the mean QoL scores of the different surveys for all patients

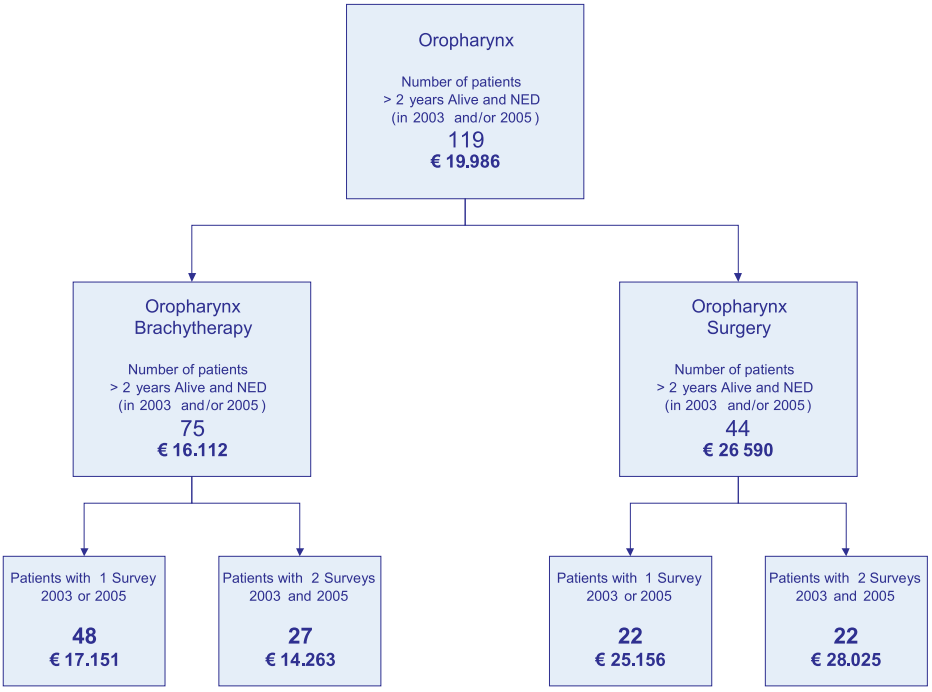
	Tdiag-quer	Age	Total dose	Sex	T-class.	N-class.	Trismus	Necrosis	Modality
Wijers et al.									
Dry mouth			0.03						
Dental prothesis							0.02		
Dentitian				0.009					
Pain swallowing							0.007		
VAS dry mouth						0.002 (N1)			
List et al.									
Eating in public									0.006
Understandability of speech				0.04					< 0.001
Normalcy of diet			0.03						0.003
QLQ-C30									
Health state							0.04		
Physical functioning		<0.001							
Emotional functioning				0.04					
Social functioning							0.03		
Pain		0.03							
Constipation							0.008		0.02
Diarrhea				0.04					

Tdiag-quer = Time between diagnosis and answering the queries; T-class = T-Classification

Table 3 *(continued)*

H&N35						
Swallowing					0.004	
Senses problems				0.001 (N3)		
Speech problems					0.01	0.02
Social eating				< 0.001 (N3)	< 0.001	
Social contact						0.01
Less sex	0.01					
Teeth	0.046					
Opening mouth					0.003	
Dry mouth				0.02 (N2)		
Nutritional supplements		0.04				
Weight loss		0.02	0.02	< 0.001 (N2)		
EQ-5D						
Mobility	0.005					

Figure 2: Mean costs (including follow-up and costs for relapses and/or complications) for patients with oropharyngeal cancer treated by either brachytherapy (N=144) or surgery (N=110) and ≥ 2 and <10 years alive NED. Whether the patient answered to one questionnaire (2003) or two questionnaires (2003, 2005) is dependent on the amount of time in follow-up



of a patient treated with BT are €16.112 and the mean costs for a patient treated with surgery is €26.590.

The costs per life year are €56.060 (5 years follow up included) for BT patients, and €93.275 (5 years follow up included) for surgery patients.

DISCUSSION

In the Erasmus MC, patients with cancer of the oropharynx are preferably treated with a curative intent according to an organ function preservation protocol. However, given the fact that both patient groups have right, almost similar, local control rates (80%-90%) and the majority of patients can be treated by organ preservation we feel comfortable to date with this protocol.
In previous papers by Levendag et al. [2,9], Nijdam et al. [10,12] and Wijers et al. [20] tumors of the TF and/or SP and BOT were analyzed for clinical outcome comparing BT with surgery: basically no difference was observed between the 2 treatment groups. Additionally full hospital costs (including associated costs of locoregional relapses and/or treatment related RTOG grade III/IV complications) were calculated for primary cancers originating from the oropharynx, and treated by BT, surgery, or EBRT [with or without chemotherapy]. We summarized that with equal functional outcome and equal QoL scores, costs can be of additional value when prioritizing treatment modalities. A saving of €10.000 per weighted patient when treating a patient with an oropharyngeal tumor with BT instead of surgery is possible.
In the above-mentioned analysis, we found no difference in QoL for the three treatment groups according to the PSS for Head and Neck cancer patients as developed by List et al. [13-15]. We were interested if patients showed a change in QoL over the years and how much the costs per life year and the QALY would be for this patient group.

The QoL surveys of this paper show that item for item the median scores did not significantly change in time. Also Fang [24] did not find any difference in mean scores of QoL scales in patients with Head and Neck cancer, except for problems of social eating, teeth, dry mouth and sticky saliva. The findings of this study, where patients were at least 2 years NED, are also in agreement with those of Hammerlid [25]; the largest changes in QoL for Head and Neck patients are seen within the first year of treatment. She concluded that Health related QoL in Head and Neck cancer patients remained almost unchanged between one and three years after diagnosis, except for the H&N35 pain assessment.
We found that parameters significantly affecting the mean QoL scores for the List survey and in-house developed survey were total dose, trismus, and modality, for the QLQ-C30 trismus and for the H&N35 age, total dose, N-classification, trismus and modality. In the EQ-5D only age had an effect

on the mobility score. So QoL is affected by modality and site related parameters.

With regard to the costs, we earlier found the mean costs for BT patients were €16.112, and for the surgery group €26.590, this is mainly due to the higher number of admission days in case of surgery. We do have to keep in mind however, that with the current protocol there is a slight bias towards BT being more frequently used in the somewhat smaller T-stages (as opposed to Surgery).

We also calculated costs per quality adjusted life year. A QALY incorporates both qualitative and quantitative improvements in life. When used across a wide range of diseases, comparisons may be made between diseases so that eventually rational decisions about health care allocation can be made. In this study, we found the costs per QALY were €56.060 (including 5 years follow up) for BT patients and €93.275 (including 5 years follow up) for surgery patients.

Critique related to the use of QALY'S in economic evaluations regards for instance which cut-off point is to be used [26]. To compare the results of different treatment modalities, in the Netherlands momentarily a 'threshold level' of €80.000 per QALY is suggested [27]. When roughly comparing the QALY'S for patients with oropharyngeal tumors treated with BT compared to this threshold level we can conclude it is worthwhile investigating costs, QoL and QALY for cancer patients treated with radiotherapy.

Conclusion

This paper shows that PSS scores, xerostomia scores and QoL scores on the EORTC QLQ-C30, H&N35 and EQ-5D did not significantly change in time for patients with oropharyngeal cancer between patients ≥ 2 and <10 years alive NED. Parameters affecting QoL of this group seem to be modality related and site specific (e.g. BT more ulceration, surgery more trismus, and for both modalities the dry mouth syndrome). Due to the number of admission days, surgery is more expensive as opposed to BT. With regard to the QALY's; we found a difference in favor of BT. As of 2007, the Dutch Hospitals will be financed by cost prices per treatment (comparable with the Diagnosis Related Group [DRG] system) negotiated by insurance companies. We feel it would be of interest not just to negotiate in the future on cost prices but also add information regarding qualitative and quantitative QoL aspects per diagnosis related group. Another interesting subject is the comparison of costs and reimbursement rate in the Netherlands and between different countries. Further study on these subjects is needed.

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REFERENCES

1. Fu KK, Pajak TF, Trotti A, et.al. A Radiation Oncology Group (RTOG) Phase III Randomized Study to Compare Hyperfractionation and Two Variants of Accelerated Fractionation to Standard Fractionation for Head and Neck Squamous Cell Carcinomas: First Report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000; 48:7-16.
2. Levendag PC, Nijdam WM, van de Pol M, et al. Brachytherapy versus Surgery in carcinoma of the tonsillar fossa and/or soft palate: late normal tissue sequelae and performance status. Can we be more selective? Int J Radiat Oncol Biol Phys, 2004; 59: 713-24.
3. Levendag PC, Schmitz PIM, Jansen PP, et al. Fractionated High-Dose-Rate and Pulsed-Dose-Rate Brachytherapy: First Clinical Experience in Squamous Cell Carcinoma of the Tonsillar Fossa and Soft Palate. Int J Radiat Oncol Biol Phys 1997; 38: 497-506.
4. O'Sullivan B, Warde P, Grice B, et al. The benefits and pitfalls of ipsilateral radiotherapy in carcinoma of the tonsillar region. Int J Radiat Oncol Biol Phys 2001, 51;332-342.
5. Parsons, JT, Mendenhall WM, Stringer SP, et al. Squamous Cell Carcinoma of the Oropharynx: Surgery, Radiation Therapy, or Both. Cancer 2002;94:2967-2980.
6. Withers HR, Peters LJ, Taylor JMG, et al. Late normal tissue sequelae from radiation therapy for carcinoma of the tonsil: patterns of fractionation, study of radiobiology. Int J Radiat Oncol Biol Phys 1995;33:563-568.
7. Withers HR, Peters LJ, Taylor JMG, et al. Local control of carcinoma of the tonsil by radiation therapy: an analysis of patterns of fractionation in nine institutions. Int J Radiat Oncol Biol Phys 1995;33:549-562.
8. Calais G, Bardet E, Sire C, et al. Radiotherapy with concomitant weekly Docetaxel for Stages III/IV Oropharynx Carcinoma. Results of the 8-02 Gortec Phase II trial. Int J Radiat Oncol Biol Phys, 2004;58:161-166.
9. Levendag PC, Nijdam WM, van Agthoven M, et al. Chemotherapy and High-Dose-Rate Brachytherapy in the Management of Advanced Cancers of the Nasopharynx: Clinical Impact of High Technology: Is it Worth the Cost? Brachytherapy 2002; 1: 11-20.
10. Nijdam WM, Levendag PC, Noever I, et al. Cost analysis comparing Brachytherapy versus Surgery for Primary Carcinoma of the Tonsillar

Fossa and/or Soft Palate. Int J Radiat Oncol Biol Phys, 2004;59(2):488-494.

11. Pol van de M, Levendag PC, De Bree RR et al. Radical Radiotherapy compared with Surgery for Advanced Squamous Cell Carcinoma of the Base of Tongue. Brachytherapy, 2004; 3: 78-86.
12. Nijdam WM, Levendag PC, Noever I, et al. Cancer in the oropharynx: cost calculation of different treatment modalities for controlled primaries, relapses and grade III/IV complications. Radiother Oncol, 2005;77(1):65-72.
13. List M, Ritter-Ster C, Lansky S. A Performance Status Scale for Head and Neck Cancer Patients. Cancer 1990; 66: 564-569.
14. List MA, Rutherford JL, Stracks J, et al. Prioritizing treatment outcomes: Head and Neck Cancer Patients Versus Nonpatients. Head & Neck 2004; 26(2):163-170.
15. List MA, Stracks J, Colangelo L, et al. How do Head and Neck Cancer Patients Prioritize Treatment Outcomes Before Initiating Treatment. J Clin Oncol 2000;18:877-884.
16. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 1993;85:365-376.
17. Bjordal K, Hammerlid E, Ahlner-Elmqvist M et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. J Clin Oncol. 1999;17(3):1008-19.
18. Bjordal K, Kaasa S. Psychometric validation of the EORTC Core Quality of Life Questionnaire, 30-item version and a diagnosis-specific module for head and neck cancer patients. Acta Oncol. 1992;31(3):311-21.
19. Dolan, P. Modelling valuations for the EuroQol health states. Med. Care**.** 1997;35(11): 1095–1108.
20. Wijers OB, Levendag PC, Braaksma MM, et al. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. Head Neck 2002;24 (8):737-47.
21. Drummond MF, O'Brien BJ, Stoddart GL, et al. Methods for the Economic Evaluation of Health Care Programmes. New York, Oxford University Press, 1996.
22. Gold MR, Siegel JE, Russell LB, et al. Cost-effectiveness in Health and Medicine. New York, Oxford University Press, 1996.

23. Oostenbrink JB, Koopmanschap, MA, Rutten FFH. Manual for costing Research. Amstelveen. Health Care Board, 2000 (in Dutch).
24. Fang FM, Chien CY, Kuo SC, et al. Changes in Quality of life of head-and-neck cancer patients following postoperative radiotherapy. Acta Oncologica. 2004;43(6): 571-578.
25. Hammerlid E, Silander E, Hörnestam L, et al. Health-related quality of life three years after diagnosis of head and neck cancer-a longitudinal study. Head & Neck. 2001;23(2): 113-125.
26. Evans C, Tavakoli M, Crawford B. Use of Quality Adjusted Life Years and Life Years Gained as Benchmarks in Economic Evaluations: A Critical Appraisal. Health Care Management Science. 2004;7:43-49.
27. The Council for Public Health and Health Care (Raad voor de Volksgezondheid & Zorg). Advice on sensible and enduring healthcare ('Zinnige en duurzame zorg'). June 2006 (in Dutch).

CHAPTER 10

Hyperthermia as a Radiosensitizer in Patients with Head and Neck Cancer: is there a Financial Incentive?

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ABSTRACT

Purpose: In the Erasmus MC - Daniel den Hoed Cancer Center, patients with oropharyngeal cancer are routinely treated with external beam radiotherapy (EBRT) in combination with a brachytherapy boost (BT) or (robotic frameless) stereotactic radiation (SRT). Despite good local tumor control (80% at 5 years), 20-40% of the patients develop severe late side effects (xerostomia, dysphagia). It has been demonstrated that adding Hyperthermia (HT) offers an enhancement of radiation effectiveness. Thus, hypothetically, adding HT to RT offers a way to reduce the physical RT dose. Maintaining the same biological RT-dose provides potentially the same treatment outcome, but with a lower degree and number of side effects. Assuming these benefits, this paper investigates the financial consequence of adding HT to EBRT in head and neck cancer.

Material and Methods: Total hospital costs were calculated for two potential treatment groups. One group consisted of patients treated by EBRT and BT; with HT given concomitant with BT. In the other group HT is given in conjunction with EBRT.

Results: Treatment with BT is most expensive because of neck dissection and admission days. Overall, HT is more expensive as EBRT, mainly due to equipment costs and the personnel costs, i.e. costs related to preparation and treatment.

Conclusion: This study indicates that, due to the anticipated fewer side-effects and increased QoL, concomitant HT given in combination with BT or EBRT for patient with H&N cancer is still economically beneficial.

INTRODUCTION

In the Erasmus MC - Daniel den Hoed Cancer Center (Erasmus MC), the treatment of preference for T1-3N0,+ tonsillar fossa (TF), soft palate (SP) tumors and tumors of the base of the tongue (BOT) is EBRT for the primary tumor and (unilateral or bilateral) neck, followed by a brachytherapy boost (BT) of the primary cancer. Also, for patients non eligible for BT (e.g. patient refusal or technical reasons), according to the organ function preservation protocol, surgery (S) followed by postoperative radiotherapy (PORT) is the first alternative treatment [1-3]. Treatment of advanced tumors in the Head and Neck (H&N) though remains complex because of the technical limitations in case of BT [4]. The current radiochemotherapeutic (RCT) regimes in cancer of the H&N result in a 5-year survival rate of 65% as opposed to 20% in the past [4-6]. However, the toxicity related to the RCT regimes is a major issue [7]. The early and late side effects, xerostomia and dysphagia, are often closely correlated, leading to serious difficulties in speech and eating [8, 9]. Several Phase III trials [10-15] have demonstrated the efficacy of adding HT to either RT or chemotherapy (ChT) in terms of local tumor control and/or survival rates. In addition, these studies showed little clinically relevant extra HT toxicity and, moreover, no enhancement of the commonly observed RT or ChT toxicity: a unique feature in cancer treatment!

We recognize that this paper on exploitation of the radiosensitizing effects of HT [16] could be seen as old wine in new bottles. In contrast to the wealth of literature concerning HT of tumors located on the surface and in the pelvic region, the reported data on HT in H&N cancer has been very scanty so far; even though some of the reports, like the one on HT for neck nodes of Valdagni [14] were very promising. A major drawback to apply hyperthermia more centrally in the neck was the lack of adequate heating equipment. Therefore, we feel that the availability of a novel applicator that enables one to heat tumors in anatomically complex areas as the H&N, could open new strategies for the clinical application of HT.

In this paper some of the rationales underpinning the HT protocols currently in use in Rotterdam are discussed. It is anticipated that HT, being a potent non-toxic modality, will reduce the radiation induced side-effects (when used with lower doses of radiation) or increase the effectiveness of the combined modality treatment (when added to the standard RT dose)[13].

Moreover, it is anticipated that this can be accomplished at relatively overall low costs. To demonstrate this, the paper focuses on the inventory of the costs

increase due to HT-treatment with the newly designed H&N HT applicator as well as estimated savings due to reduced hospitalization costs associated with care related to toxicity. The inventory is up to 3 months follow-up.

MATERIAL AND METHODS

The basis of this study is the standard Rotterdam radiation protocol. For these conventional radiation treatment modalities, the costs are known [17, 18]. Next, we replace some EBRT/BT fractions by HT, assuming that the thermal enhancement effect (TER 1.5) will cause the total biological RT-dose to remain the same. Subsequently, we describe the treatment procedure of HT and associated cost calculations in detail. Finally, this analysis results in an overall cost price for the new EBRT ± BT + HT protocols and provides the possibility to balance the increased treatment costs versus the costs associated with treatment of side-effects and potential economical benefits of a higher QoL.

Rotterdam EBRT/BT protocol

From 1986, as per protocol, T1-3N0/+ TF and/or SP tumors are radiated in the Erasmus MC to a dose of 46 Gy EBRT in fractions of 2 Gy per day / 5 days per week to the primary tumor and (unilateral or bilateral) neck. This series of EBRT is to be followed within 1-3 weeks by a fractionated high-dose-rate (HDR) or pulsed-dose-rate (PDR) brachytherapy (BT) boost to the primary tumor. At the time of the BT procedure, a neck dissection (ND) is performed in case of N+ disease. If BT is technically not feasible, a combined resection of the primary tumor and neck is executed. Postoperative EBRT is to be performed, within 6 weeks to a dose of 50-70 Gy. In case of reirradiation, or for those patients with tumors surrounded by critical normal tissues, radiation induced side-effects can be dose limiting. Moreover, for patients treated by radiation according to the standard protocol (EBRT 46 Gy and BT), recently late side-effects such as dysphagia, were observed in a substantial number (± 20%) of these patients [8]. To prevent this type of late side-effects to occur, the radiation oncologist has two options. He may choose to either lower the dose of radiation per se as a single modality treatment, with the risk of poorer treatment outcome, or combine a lower dose of radiation with a, preferably non-toxic, radiosensitizer. This is where hyperthermia can be introduced in clinical treatment. This renewed interest

emerged in our institution with the recent introduction of the HYPERcollar hyperthermia applicator [19-24].

TER determination and new protocols including HT

Because of the novelty of the treatment, the thermal enhancement ratio (TER) has not been established as yet [25]. This TER is, amongst others, dependent on tumor location, quality of heating and "fractionation" scheme. Because it is uncertain what the actual TER will be, a conservative estimation (1.5) is used from the range of values found in the literature for all tumor sites combined (between 1.2 and 5) [26].

The new protocols including HT are described in Table I. Depending on the protocol hyperthermia is added from 3 to 5 sessions and as frequent as every day to once a week. The maximum thermal enhancement of the RT-dose (i.e. 12 Gy) is calculated for RT with the Cyberknife (six fractions of 6Gy) combined with four HT-sessions.

Hyperthermia treatment procedure

Work-up Hyperthermia: All clinical information is already obtained by the radiation oncologist. Extra costs made by the radiation oncologist are implantation of afterloading catheters to insert the temperature probes during the treatment. If HT is combined with BT, obviously the costs of the catheter implantation are low, as they are included in the BT part.

Hyperthermia treatment: A standard H&N radiotherapy contrast enhanced CT-scan is used to segment all tissues. This segmentation, along with a Computer Aided Design (CAD) implementation of the applicator, is imported in SEMCAD X[1], the hyperthermia treatment planning platform, that is used to calculate the optimum treatment settings [24].

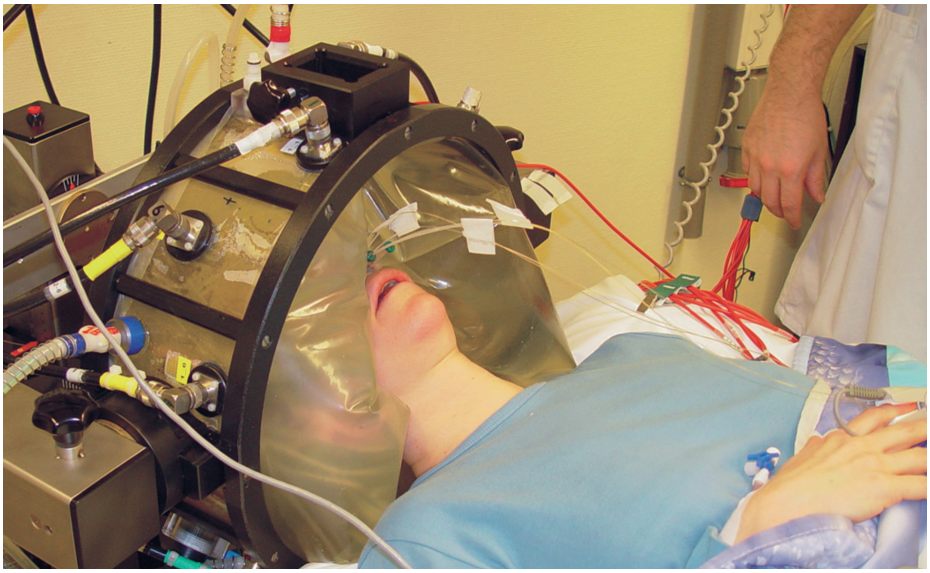
The patient is placed on a comfortable bed (Figure 1). Next, thermometry probes are placed within the implanted afterloading catheters and the HYPERcollar is placed around the target volume. After the water bolus is filled with water (kept at constant temperature), RF-power is increased until tolerance: 40°C in CNS, 43°C in other normal tissues or the occurrence of a hot spot at a site without thermometry, as indicated by the patient. When (one of) the tolerance limits results in inadequate intratumoral temperatures, phase and amplitude settings are adjusted according to pre-treatment

1 SEMCAD X: the Simulation platform for Erasmus MC, Antenna Design and Dosimetry, Smith and Partner Engineering AG, http://www.semcad.com.

Table 1: Summary phase I/II HT protocols

Treatment type	Dose schedule EBRT	Dose schedule HT	RT Equivalence (BED)	RT + HT Equivalence
Primary radiation				
EBRT only	35 x 2 Gy 6 fractions per week	5 sessions 1 session per week	70 Gy	≥ 75 Gy
EBRT + BT boost	23 x 2 Gy + 6 x 3 Gy	3 sessions during BT 1 session per day	64 Gy	≥ 73 Gy
Reirradiation				
EBRT	33 x 1.8 Gy 1 session per week	5 sessions	59.4 Gy	≥ 63.9 Gy
Frameless stereotactic radiation (Cyberknife)	6 x 6 Gy 2 weeks	4 sessions 2 sessions per week	36 Gy	≥ 48 Gy

Figure 1: Positioning of the patient in the HYPERcollar



planning findings. During the 3 treatment sessions, each lasting 1 hour; a medical doctor, a technician and a physicist stay with the patient in the treatment room. With growing experience, we anticipate that the demand on personal attendance *during* treatment will reduce, we foresee to one technician.

Follow-up Hyperthermia: There is no separate follow-up for the hyperthermia treatment. Patients are seen in regular follow-up by the radiation oncologist and ENT surgeon and standardized clinical and laboratory tests will be executed. We accounted for 1 follow-up visit after three months.

Cost calculation

This cost analysis was performed from the institutional perspective [27]. In contrast to charges, unit costs are the best estimators of the theoretically proper opportunity costs (the value of the next best alternative forgone as the result of making a decision) [27]. We calculated the costs of treatment for an initial and a recurrent tumor in the H&N. As HT can be combined with EBRT as well as with the BT part of the treatment (somewhat depending on the location of the tumor), we have calculated the costs for both schedules: 1) EBRT+BT+HT and 2) EBRT+HT. For these combinations, the direct medical costs were based on average unit costs, including overhead costs. To determine these unit costs, we followed the micro-costing method, which is based on a detailed inventory and measurement of the resources consumed [28]. The costs for diagnosis and staging are based on the Dutch tariff system. In case these tariffs were not present, the tariff was indexated. The valuation of the resources and overhead costs (16.4%) was based on financial data from the Erasmus MC.

Cost calculation treatment

The cost calculation for EBRT (including frameless stereotactic radiation) and BT is described earlier [17,18,29] and corrected for 2007 pricings.

The number of radiation fractions for teletherapy, brachytherapy and hyperthermia used in the clinic are depending on the protocol used. On average, we opt for 4 (range 3-5) HT sessions. In case of invasive thermometry we added one extra (BT) fraction to take into account the costs for invasive thermometry. Costs were based on 2007 pricings and stated in Euros (€).

Cost calculation manpower and materials

Direct costs consist of manpower and materials. To calculate manpower costs, time spent for the various procedures in the different subgroups was estimated by the professional disciplines involved. Time invested was multiplied by salary (including wages, social premium and extra fees for irregular working hours). Costs per minute were then calculated under the assumption of 1540 working hours a year [30]. Costs were calculated for both direct and indirect (tumorboard meeting etc) activities. Wholesale prices were used to determine costs of materials. A detailed inventory and measurement of materials was executed, based on real use by the department for these patient groups. Also costs related to use of equipment and OR (IBU) are included in material costs. All direct costs were multiplied by overhead costs (e.g. depreciation costs of the building, cleaning costs). Overhead costs are based on the relationship between direct costs of the hospital in total and costs for administration.

In case of the HT prices, costs related to equipment costs and quality assurance are based on 80 patients per year. This is currently the maximum number of patients referred for treatment with this hyperthermia 433 MHz device.

For real pricings we have estimated the market value of the HYPERcollar. The costs were calculated with depreciation of the system over 10 years, based on 80 patients per year. Service costs are estimated at 6% of the purchase price.

RESULTS

For each of the four protocols (Table I) we have calculated in a stepwise fashion the total hospital costs (Table II-V), that is, for these groups, the direct medical costs, including overhead costs. As mentioned before, calculation of these costs is based on a detailed inventory and measurement of resources consumed [28]. The number of radiation fractions for teletherapy, brachytherapy and hyperthermia used in clinic are depending on the protocol used.

Table 2: Primary radiation by EBRT (35 x 2 Gy) + HT (5 sessions/ 1 session per week)

	EBRT costs		HT costs
Workup (overhead included)		*Workup (overhead included)*	
Outpatient visit RO and H&N Surgeon	288,30	Outpatient visit	113,14
Endoscopy	117,95		
X-ray	48,31		
Ultra sound neck + cytology	133,16		
CT-scan / MRI (50%-50%)	138,96		
Blood	43,88		
Preoperative consultation Anaesthesiologist	74,14		
Consultation and treatment dentist	242,65		
One-day admission for biopsy	997,66		
Total workup	**2.085,01**	**Total workup**	**113,14**
Treatment (overhead included)		*Hyperthermia treatment (overhead included)*	
-		Planning-CT	134,12
Personnel costs preparation EBRT	901,58	Personnel costs preparation	1.260,57
Material costs preparation EBRT	175,68	Material costs treatment	4.463,95
Equipment costs	302,59	Equipment costs	3.098,68
Radiation session EBRT (35x)	1.226,40	Hyperthermia session (5x)	3.716,85
Outpatient visits (7x)	498,61	Quality Assurance	164,64
Total treatment	**3.104,86**	**Total treatment**	**12.838,81**
Follow-up (overhead included)		*Follow-up Hyperthermia (overhead included)*	
Outpatient visit (1x)	71,23	Outpatient visit (1x)	18,86
MRI	143,79	Letter to referrer	37,71
Total follow-up	**215,02**	**Total follow-up**	**56,57**
Total treatment EBRT	**5.404,89**	**Total treatment HT (65%)**	**13.008,52**
Total treatment ERT and HT	**18.413,41**		

Abbreviations for all tables:
RO = Radiation Oncologist; H&N Surgeon = Head and Neck Surgeon; EBRT = External Beam Radiation Therapy; HT = Hyperthermia; BT = Brachytherapy

Table 3: Primary radiation by EBRT (23 x 2 Gy) + BT (6 x 3 Gy) + HT (3 sessions/1 session per day during BT)

	EBRT costs		BT costs		HT costs
Workup (overhead included)		*Workup*		*Workup (overhead included)*	
Outpatient visit RO and H&N Surgeon	288,30			Outpatient visit	113,14
Endoscopy	117,95				
X-ray	48,31				
Ultra sound neck + cytology	133,16				
CT-scan / MRI (50%-50%)	138,96				
Blood	43,88				
Preoperative consultation Anaesthesiologist	74,14				
Consultation and treatment dentist	242,65				
One-day admission for biopsy	997,66				
Total workup	**2.085,01**			**Total workup**	**113,14**
EBRT treatment (overhead included)		*BT treatment (overhead included)*		*HT treatment (overhead included)*	
				Planning-CT	134,12
Personnel costs preparation	901,58	Personnel costs neck dissection	1.091,60	Personnel costs preparation	1.260,57
Material costs preparation		Material costs neck dissection (use operating room included)	1.671,97	Material costs treatment	2.678,37
		Histology	37,25		
		Total Neck Dissection	**2.800,82**		

Table 3 *(continued)*

Equipment costs	302,59	Material costs BT (use OR included)	1.031,63	Equipment costs	3.098,57
		Personnel costs preparation BT	376,61		
Radiation session EBRT (23x)	805,92	Radiation session BT (6)	1.050,01	HT session (3x)	1.832,60
Outpatient visits (5x)	356,15	Admission days	2.209,24	Quality Assurance	164,26
Total treatment	**2.541,92**	**Total treatment**	**4.667,49**	**Total treatment**	**9.168,49**
Follow-up (overhead included)		*Follow-up Brachytherapy (overhead included)*		*Follow-up Hyperthermia (overhead included)*	
Outpatient visit (1x)	71,23	-	-	Outpatient visit (1x)	18,86
MRI	143,79	-	-	Letter to referrer	37,71
Total follow-up	**215,02**			**Total follow-up**	**56,57**
Total treatment EBRT	**4.841,95**		**7.465,31**	**Total treatment HT (38%)**	**9.338,20**
Total treatment EBRT+BT+HT	**21.645,46**				

Table 4: Reirradiation by EBRT (33 x 1.8 Gy) + HT (5 sessions/1 session per week)

	EBRT costs		HT costs
Workup (overhead incl.)		*Workup (overhead incl.)*	
Outpatient visit RO and H&N Surgeon	288,30	Outpatient visit	113,14
Endoscopy	117,95		
X-ray	48,31		
Ultra sound neck + cytology	133,60		
CT-scan / MRI (50%-50%)	138,96		
Blood	43,88		
Preoperative consultation Anaesthesiologist	74,14		
Consultation and treatment dentist	242,65		
One-day admission for biopsy	997,66		
Total workup	**2.085,01**	**Total workup**	**113,14**
Treatment (overhead incl.)		*Hyperthermia treatment (overhead incl.)*	
		Planning-CT	134,12
Personnel costs preparation EBRT	901,58	Personnel costs preparation	1,260,57
Material costs preparation EBRT	175,88	Material costs preparation	4.463,95
Equipment costs	302,59	Equipment costs	3.098,57
Radiation session EBRT (33x)	1.156,32	Hyperthermia session (5x)	3.716,83
Outpatient visits (7x)	498,61	Quality Assurance	164,26
Total treatment	**3.034,78**	**Total treatment**	**12.838,30**
Follow-up Hyperthermia (overhead incl.)		*Follow-up Hyperthermia (overhead incl.)*	
Outpatient visit (1x)	71,23	Outpatient visit (1x)	18,86
MRI	143,79	Letter to referrer	37,71
Total follow-up	**215,02**	**Total follow-up**	**56,57**
Total treatment EBRT	**5.334,81**	**Total treatment HT (64%)**	**13.008,01**
Total treatment EBRT and HT	**18.342,82**		

Table 5: Reirradiation by frameless stereotactic radiation (6 x 6 Gy) + HT (4 sessions/1 session per week)

	Reirradiation costs		Hyperthermia costs
Workup (overhead incl.)		*Workup (overhead incl.)*	
Outpatient visit RO and H&N Surgeon	288,30	Outpatient visit	97,20
Endoscopy	117,95		
X-ray	48,31		
Ultra sound neck	133,16		
CT-scan	134,12		
MRI	143,79		
Blood	43,80		
Preoperative consultation Anaesthesiologist	74,14		
Consultation and treatment dentist	242,65		
Four-days admission for biopsy and consultation rounds	997,66		
Total workup	**2.222,88**		**113,14**
Treatment Stereotactic Radiotherapy (overhead incl.)		*Hyperthermia Treatment (overhead incl.)*	
		CT	134,12
Personnel costs preparation EBRT	607,02	Personnel costs preparation	1.260,57
Material costs preparation EBRT	175,88	Material costs preparation	3.571,16
Equipment costs	302,59	Equipment costs	3.098,57
Radiation session EBRT (6x)	3.059,88	Hyperthermia session (5x)	3.716,83
Outpatient visit (3x)	213,69	Quality Assurance	164,26
Total treatment	**4.358,86**	**Total treatment**	**11.945,51**
Follow-up (overhead incl.)		*Follow-up Hyperthermia (overhead incl.)*	
Outpatient visit (1x)	71,23	Outpatient visit (1x)	18,86
MRI	143,79	Letter to referrer	37,71
Total follow-up	**215,02**	**Total follow-up**	**56,57**
Total treatment EBRT	**6.797,76**	**Total treatment (58%)**	**12.115,22**
Total treatment EBRT + HT	**18.912,98**		

DISCUSSION

It is obvious that the radiosensitizing effect of HT can be of use in reirradiation as well as in primary treatment. We have therefore designed a number of protocols. As the main purpose of the paper is on costs, we have summarized the HT protocols in Table 1. In short, we have two protocols for reirradiation and two for primary radiation. As HT can be combined with EBRT as well as with the BT part of the treatment, we have calculated the costs for both conditions ± HT. In calculating the biological equivalent RT dose, it is anticipated that the hyperthermia treatment sensitizes only for the radiation dose(s) given on the same day. In case of BT, the HT is given at 3 consecutive days between the two daily fractions of BT, hence both fractions are sensitized. In case of EBRT, HT is given once a week during 5 weeks and immediately after the radiotherapy dose. Hence only 5 fractions of EBRT are sensitized. As explained before a conservative value for the TER of 1.5 is used to calculate the enhancement of the RT dose for each RT-fraction combined with a HT fraction.

Based on the above mentioned assumption the total costs for the two potential treatment groups (four protocols) were calculated to assess economical consequences of adding hyperthermia. The results of these calculations demonstrate variations up to €4.500 depending on the protocol used. Treatment with BT is most expensive because of neck dissection and hospital admission days. Overall, HT is more expensive as EBRT, mainly due to the personnel costs regarding preparation and treatment and the equipment costs. At present, far less patients for HT are treated then for teletherapy (TT), so equipment costs per HT patient are still high. In the future, when more patients are being treated by HT, these costs will decrease. Hence, the current calculations represent a ceiling level. The total hospital costs (EBRT + HT) were respectively (1) primary radiation (35x2 Gy) + HT: €18.413, HT treatment costs were €13.008 (Table 2), (2) primary radiation + BT boost + HT: €21.645, HT costs were €9.338 and BT costs €4.667 (Table 3), reirradiation (33x1.8 Gy) + HT: €18.342, HT costs were €13.008 (Table 4) and reirradiation Cyberknife: €18.912, HT costs were €12.115 (Table 5).

Earlier, we stated that concomitant HT given in combination with BT or EBRT for patients with H&N cancer is economically beneficial due to the anticipated fewer side-effects and increased QoL. To support this expectation that, due to lower toxicity of the radiotherapy (lower dose), total care costs will be

reduced in the follow-up years, below we motivate the performance of a clinical study on the potential of reducing side-effects in H&N cancer by adding HT to the current treatment protocols:

Earlier [29], we calculated the costs for grade III/IV complications and relapses for patients treated with Surgery, BT or EBRT. To compare the results (which were based on 2001 pricings) to our findings today we multiplied the costs by the regular index figures from 2002. For treating a patient with dysphagia, the indexation resulted in €7.823. Note that these costs are comparable to the costs of a HT treatment. Hence, the investment for the HT treatment seems worthwhile, because with apparently the same costs, a higher Quality of Life for the patient is achieved. Instead of treating a patient for dysphagia (including all discomfort), the patient can be treated beforehand to avoid the probability to develop a lower QoL due to dysphagia.

A further justification to verify our hypothesis in a clinical study is also provided by the results reported in a recent study by Levendag et al. [8], which investigated the complaints on swallowing in 81 patients. This study revealed that, with an increase of every additional 10 Gy, the probability of dysphagia increases with 19%. Thus, again adding a modality, i.e. hyperthermia, that enables a lower radiotherapy dose with similar tumor control, is expected to lead to a lower percentage of toxicity and thus complications.

The emphasis on QoL is also an important one. Recently [31], we calculated costs and QALY´s (Quality Adjusted Life Year), in long term survivors from oropharyngeal cancer, that were treated, amongst others, with BT. A QALY incorporates both qualitative and quantitative improvements in life. When used across a wide range of diseases, comparisons may be made between diseases (and their treatment). In our publication, mean costs per year for long term survivors from oropharyngeal cancer treated with BT, were €17.827 (2007 indexation). The costs per QALY were €61.260 (2007 indexation). We expect that adding HT will result in less complaints, resulting in a higher QoL, measured by the EQ-5D (which is used to calculate the costs per QALY), resulting in less costs per QALY. In the end, this will lower the costs for health care in total.

In summary, given the anticipated minor extra toxicity of the additional HT [15] and the potential reduction of the side effects in the most commonly used radiation therapy regime in our institution (18 Gy BT as opposed to 20-22 Gy), we anticipate that the additional costs for HT will be compensated fully by reduced costs for treatment of complications in the follow-up years. We consider this a good motivation to perform a study to calculate avoidable costs and QALY's.

Conclusion

From the literature search it is apparent that RT in combination with HT is an effective treatment with minimal morbidity for (recurrent) H&N tumors. Given the recent introduction of the HYPERcollar, new protocols on the combination of HT and RT have been developed and a cost analysis is presented for four different protocols. From the cost analysis, given the small variations per protocol, it seems warranted to study the radiosensitizing effects of HT in primary as well as in recurrent H&N cancer in detail.

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REFERENCE

1. Levendag PC, Schmitz PIM, Jansen PP, Senan S, Eijkenboom WMH, Sipkema D, Meeuwis CA, Kolkman-Deurloo IK, Visser AG. Fractionated High-Dose-Rate and Pulsed-Dose-Rate Brachytherapy: First Clinical Experience in Squamous Cell Carcinoma of the Tonsillar Fossa and Soft Palate. Int J Radiat Oncol Biol Phys 1997; 38: 497-506.
2. Levendag PC, Nijdam WM, Noever I, Schmitz P, Pol van de M, Sipkema D, Braat C, de Boer M, Jansen P. Brachytherapy versus Surgery in carcinoma of the tonsillar fossa and/or soft palate: late normal tissue sequelae and performance status. Can we be more selective? Radiotherapy and Oncology 2003; 66: abstract 25, page S10.
3. Pol van de M, Levendag PC, Bree RR, Franssen JH, Smeele LE, Nijdam WM, Janssen PP, Meeuwis CA, Leemans CR. Radical Radiotherapy compared with Surgery for Advanced Primary Squamous Cell Carcinoma of the Base of Tongue. Brachytherapy. An International Multidisciplinary Journal, 2004;3(2):78-86.
4. Conley BA. Treatment of advanced head and neck cancer: what lessons have we learned? J Clin Oncol 2006; 24:1023-1024. Editorial.
5. ElSayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region: a meta-analysis of prospective and randomized trials. J Clin Oncol 1996; 14: 838-847.
6. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 2000; 355: 949-955.
7. Trotti A. Toxicity in head and neck cancer: a review of trends and issues. Int J Rad Oncol Biol Phys 2000; 47: 1-12.
8. Levendag PC, Teguh DN, Voet P, van der Est H, Noever I, de Kruijff WJ, Kolkman-Deurloo IK, Prevost JB, Poll J, Schmitz PI, Heijmen BJ. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. Radiother Oncol. 2007 Oct;85(1):64-73.
9. Van der Zee J. Heating the patient: a promised approach? Ann Onc 2002; 13:1173-1184.
10. Van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with

radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. Lancet 2000; 355:1119-1125.

11. Colombo R, Da Pozzo LF, Salonia A, Rigatti P, Leib Z, Baniel J, Caldarera E, Pavone-Macaluso M. Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. J Clin Oncol 2003; 21:4270-4276.
12. Jones E, Thrall D, Dewhirst MW, Vujaskovic Z. Prospective thermal dosimetry: the key to hyperthermia's future. Int J Hyperthermia 2006; 22:247-253.
13. Horsman MR, Overgaard J. Hyperthermia: a potent enhancer of radiotherapy. Clin Oncol (R Coll Radiol). 2007 Aug;19(6):418-26. Review.
14. Valdagni R, Amichetti M. Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymph nodes in stage IV head and neck patients. Int J Radiat Oncol Biol Phys. 1994 Jan 1;28(1):163-9.
15. Zee van der J, Vujaskovic Z, Kondo M, Sugahara T. The Kadota International Forum 2004 – Clinical group consensus. Int J Hyperthermia 2008, 24, 111-122.
16. Kampinga HH. Cell biological effects of hyperthermia. Int J Hyperthermia. 2008 January;24(1).PartII.A:126-34.
17. Paulides MM, Vossen SHJA, Zwamborn APM, Van Rhoon GC. Theoretical investigation into the feasibility to deposit RF energy centrally in the head and neck region. Int Rad Onc Biol Phys 2005, 63, 634–642.
18. Paulides MM, Wielheesen DHM, Van der Zee J, Van Rhoon GC. Assessment of the local SAR distortion by major anatomical structures in a cylindrical neck phantom. Int J Hyperthermia 2005, 21, 382–400.
19. Paulides MM, Bakker JF, and Van Rhoon GC. A head and neck hyperthermia applicator: experimental phantom verification and FDTD model. Int J Rad Oncol Biol Phys 2007, 68, 612–620.
20. Paulides MM, Bakker JF, Zwamborn APM, and Van Rhoon GC. A head and neck hyperthermia applicator: theoretical antenna array design. Int J Hyperthermia 2007, 23:59 – 67.
21. Paulides MM, Bakker JF, Chavannes N, and Van Rhoon GC. A patch antenna design for a phased-array head and neck hyperthermia applicator. IEEE BME 2007, 54, 11, 2057-2063.

22. Paulides MM, Bakker JF, Neufeld E, van der Zee J, Janssen PP, Levendag PC, van Rhoon GC. The HYPERcollar: a novel applicator for hyperthermia in the head and neck. Int J Hyperthermia 2007 Nov;23(7):567-76.
23. Overgaard J. The current and potential role of hyperthermia in radiotherapy. Int J Rad Oncol Biol Phys 1989, 16(3):535-49.
24. J Van der Zee. Heating the patient: a promising approach? Ann Onc 2002, 13: 1173–1184.
25. Nijdam WM, Levendag PC, Noever I, Uyl-de Groot CA, van Agthoven M. Cost analysis comparing brachytherapy versus surgery for primary carcinoma of the tonsillar fossa and/or soft palate. Int. J. Rad Onc Biol Phys, 2004 Jun 1;59(2):488-94.
26. Nijdam W, Levendag P, Fuller D, Schulz R, Prevost JB, Noever I, Uyl-de Groot C. Robotic radiosurgery vs. brachytherapy as a boost to intensity modulated radiotherapy for tonsillar fossa and soft palate tumors: the clinical and economic impact of an emerging technology. Technol Cancer Res Treat. 2007 Dec;6(6):611-20.
27. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. New York, Oxford University Press, 1996.
28. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in Health and Medicine. New York, Oxford University Press, 1996.
29. Nijdam W., Levendag P., Noever I., Groot C. U., Agthoven M. Cancer in the Oropharynx: Cost Calculation of Different Treatment Modalities for Controlled Primaries, Relapses and Grade III/IV Complications. Radiother Oncol 77:65-72 (2005).
30. Oostenbrink JB, Koopmanschap, MA, Rutten FFH. Manual for costing Research. Amstelveen. Health Care Board, 2000 (in Dutch).
31. Nijdam WM, Levendag PC, Noever I, Schmitz PIM, Uyl - de Groot, CA. Longitudinal Changes in Quality of Life and Costs in Long-term Survivors of Tumors of the Oropharynx treated with Brachytherapy or Surgery. Brachytherapy 2008 Oct-Dec;7(4):343-50.

CHAPTER 11

Discussion and Summary

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DISCUSSION AND SUMMARY

Introduction

In 2008, the Council for Public Health and Health Care (RVZ) recommended the Dutch Government on how to regulate the ever-increasing costs of health care in the Netherlands. It was argued that health care organizations should aim for more efficiency. Therefore, the role of quality parameters in financing hospitals was emphasized. Hospitals should be paid not only by the number of treatments, but also the quality of medical care should be taken into account. The Council foresees that this could result in a reduction of the health care expenses because of a decrease in (costs of) complications, recurrences, and hospital stay. They also stated that costs should be diminished by raising the productivity in health care. One of the possibilities mentioned was the use of technology. The Health Council of the Netherlands reported that investing in technology will increase the total costs of health care but will reduce unit costs, thus being an effective instrument.

Tumors in the head and neck are infrequent; however, the aggressive nature of some of the combined modality treatment approaches of these cancers is associated with significant morbidity and therefore could serve as a role model in studying parameters such as the aforementioned effectiveness, costs, and quality of the treatment. Radiation therapy is used as a single modality or in combination with other treatment modes, such as surgery, chemotherapy and hyperthermia. Radiation therapy perse can be divided in external beam radiotherapy and (endocavitary or interstitial) brachytherapy. This thesis focuses on costs- and quality of life (QoL) relationships for patients treated for early-, intermediate- or advanced staged primary cancers in the head and neck with combinations of external beam and/or brachytherapy and/or surgery and/or chemotherapy.

Tumor control and costs in early- and intermediate staged tumors

With regard to brachytherapy, good results have been obtained for early-staged cancers: this is exemplified by cancer in the nasal vestibule treated by brachytherapy only. A local relapse-free survival of 92% at 5-years was obtained (chapter 8). Post-treatment cosmetic outcome was assessed by a panel consisting of non-medical workers and medical professionals. In summary, the great majority of the patients was scored as ‘excellent’ or ‘good’ in terms of cosmesis.

With regard to the intermediate-staged group: for tonsillar fossa (TF) and/or soft palate (SP) tumors surgery was compared to radiation therapy (using brachytherapy [BT] as a booster dose after external beam radiation therapy [EBRT]). Excellent locoregional control was obtained in T1-T3 tumors: at 5 years a locoregional control rate of 84% (EBRT plus BT group) vs. 78% (surgery plus PORT group) was found (chapter 4). Adverse late side effects were not negligible; however no significant differences were observed with regard to the degree of xerostomia and functional outcome for the BT-group vs. the surgery-group Therefore, it was hypothesized that costs related to the treatment modalities per se and to follow up, might be (another) discriminating factor. A cost calculation model was therefore developed.
The aim of chapter 4 is to see whether one could prioritize the choice of BT as opposed to surgery for primary tumors located in the TF and/or SP by focusing on the full hospital costs of the patients. From the analysis it was observed that the total costs for BT were less as opposed to surgery: €16.628 ($19.452; EBRT plus BT plus ND) vs. €18.782 ($22.074; surgery plus PORT).

Tumor control and QoL in advanced staged tumors
Good local control rates by BT can even be seen in some of the more advanced tumors, for example cancers of the base of tongue. Pol et.al published the results of T3, T4 tumors of the base of tongue treated in Rotterdam (by RT only) or in Amsterdam (by surgery and PORT), demonstrating a local failure rate at 5-years of 37% (Rotterdam) vs. 9% (Amsterdam) ($p < 0.01$) (chapter 2). Interestingly enough, the overall survival was not significantly different (median 2.5 years vs. 2.9 years, respectively [$p = 0.47$]). Moreover, the quality of life of the patients, measured by the performance status scales of List et al., favored EBRT combined with a BT boost. Both groups were equally affected by xerostomia. A second example is given in chapter 3, that is early stages of cancer of the nasopharynx (T1, T2) are boosted after 70 Gy by endocavitary brachytherapy (or stereotactic radiotherapy) with an excellent local control rate and minimal morbidity: 92% at 5 yrs.

Late side-effects and Quality of Life (QoL)

In the patients with oropharyngeal cancer, late side effects were observed. In radiotherapy, the most significant treatment modality related side effect is xerostomia, with median VAS scores of 5.6 (BT) and 6 (surgery). In the surgery + postoperative radiotherapy group, 20% of the patients developed some degree of trismus. No differences were observed for the treatment groups brachytherapy and surgery with regard to the Performance Status Scale Scores (PSS) eating in public, normalcy of diet and normalcy of speech. From the data analyzed in chapters 1 to 3 it is obvious that besides the good locoregional control rates and the limited side-effects, QoL plays an important role when objectivating the results of different treatment modalities. We were therefore interested if longitudinal assessment of QoL in long-term survivors showed a change in QoL over the years. For patients with cancer in the oropharynx the performance status scales eating in public, understandability of speech, normalcy of diet, xerostomia and ability to swallow were determined in 2003 and 2005. Additionally, in 2005, the response to the questionnaires EORTC QLQ-C30, EORTC H&N35, and Euroqol were studied. It is of interest that regarding the scales eating in public, understandability of speech, and normalcy of diet patients treated with brachytherapy were least affected. Surgical patients experienced more speech-, teeth- and opening mouth problems as opposed to brachytherapy patients. The outcome of QoL surveys published in chapter 9 show that item for item the median scores did not significantly change over time. This observation is corroborated by the literature. For example, Fang et al. did not find any difference in mean scores of QoL scales in patients with head and neck cancer, except for problems of social eating, teeth, dry mouth and sticky saliva. The findings of this study were also in agreement with those of Hammerlid et al.; she concluded that health related QoL in head and neck cancer patients remained almost unchanged between one and three years after diagnosis.

Technology: investment in new equipment

In 2004, the department of Radiation Oncology of the Erasmus MC acquired the CyberKnife® (Accuray Incorporated, Sunnyvale, CA), a robotic frameless stereotactic radiosurgery system (SRS) capable of delivering (hypo)fractionated radiation to clinical (moving) targets throughout the body with high accuracy. In March 2005, the use of the CyberKnife (CK)

was initiated. A clinical example of patients treated with a Cyberknife boost is tonsillar fossa/soft palate carcinoma (chapter 6). This was typically the case in patients with tumors deeply infiltrating the parapharyngeal space where the CK, unlike brachytherapy, is able to deliver focused radiation to virtually any anatomical location, while simultaneously sparing closely adjacent radiosensitive structures. The use of the CK as an alternative to BT gives one the unique opportunity to assess a new technological device based on clinical-, QoL- and economic considerations by subsequently comparing it to BT, being the "gold standard" in the Erasmus MC. With regard tot the execution of the treatment, a head cast is made with the patient in the supine position on the treatment table. Fiducial markers are placed under general anesthesia in, or near, the tumor volume at the time of the staging examination. Currently however, this so-called 'tracking' on fiducial markers is in Head and Neck cancer replaced by tracking on the stable Base of Skull, so no markers are involved. Contrast-enhanced 2-mm CT-slices with a 16 slice CT-scanner are obtained. The dose is prescribed to the planning target volume (PTV) to the 80% isodose line: 5.5 Gy in 3 fractions over 5 days was applied per protocol. Real-time kilovoltage X-ray tracking of implanted fiducial markers, results in continuous targeting with adjustment throughout each treatment session. This produces a high system targeting accuracy. Both techniques (CK and BT) are highly conformal. In radiotherapy, complications and clinical outcomes are closely linked to the dose of radiation to the treated volume, and the 'spared' normal surrounding critical tissues. One can postulate equivalence of the techniques and clinical outcomes by evaluating both the technical features of CK versus BT, and the early clinical results. With the BT-like isodose distribution, seemingly similar to high-dose-rate BT, there is the potential for even fewer fractions because of the CK's sharply defined isodose margins and tracking accuracy. In other words, smaller target volumes because of smaller (PTV) margins in case of Cyberknife as opposed to EBRT in general. If one considers the benefit of a smaller number of fractions, this type of investment is even more worthwhile, as its hypofractionation might even be cost-effective (see below).

Sparing: adjuvant therapy: Amifostin

For patients with advanced staged head and neck cancer, chemoradiation and/or altered radiation therapy schedules can result in increased locoregional control. A drawback however is the associated morbidity.

These (mucosal) side-effects are sometimes radiotherapy dose-limiting and therefore preferably, need to be prevented. This can be done in multiple ways: one way that has been explored in the Erasmus MC at the time is the implementation of radioprotectors such as Amifostin (Ethyol®, Med Immune Oncology Gaithersburg MD). A randomized trial for treatment of stage III and IVA squamous cell carcinoma of the head and neck (nasopharynx carcinoma excluded) was initiated in 2000. All patients received Paclitaxel (Taxol®, Bristol Meyers Squibb, Princeton, NJ) concurrently with external beam radiation. Patients were randomized for Amifostin subcutaneously (sc) administered. The outcome of the trial was negative, meaning that there is no beneficial effect of amifostin sc (chapter 5). Evident from the trial was that the radiation therapy fractionation schedule (slightly accelerated) in combination with Paclitaxol, had a severe impact on the mucosal linings and swallowing muscles (dysphagia). More patients were admitted to the hospital as customarily seen in this patient category. This trial demonstrated again the toxicity problems associated with chemoradiation and thus the consequential financial aspects were evident.

Sparing: adjuvant therapy: Hyperthermia

Another way to enhance the radiation effectiveness and to reduce the radiotherapy toxicity is the addition of Hyperthermia. Chapter 10 describes the HYPERcollar. This device is based on dynamic SAR scanning and developed in the department of Radiation Oncology of the Erasmus MC. It has been demonstrated that adding hyperthermia (HT) offers an enhancement of radiation effectiveness. Thus, hypothetically, adding hyperthermia to radiotherapy offers a way to reduce the physical radiotherapy dose. Maintaining the same biological radiotherapy dose provides potentially the same treatment outcome, but with a lower degree and number of side effects. Assuming these benefits, this paper investigates the financial consequence of adding hyperthermia to EBRT in head and neck cancer. This study indicated that, due to the anticipated fewer side-effects and increased QoL, concomitant hyperthermia given in combination with BT or EBRT for patient with head and neck cancer can be economically speaking beneficial.

Cost computation and prioritization

In discussing optimal treatment regimens and/or prioritizing the different treatment options, cost calculations are often missing, and should play a more formal role. In this thesis, cost calculations and quality adjusted life years (QALY) were studied for patients with similar types of tumors treated with different modalities. For example, in chapter 4 the cost analysis for BT was compared to costs of surgery for carcinoma of the tonsillar fossa (TF) and soft palate (SP). It focuses on hospital- and follow-up (FU) costs for the treatment groups external beam radiotherapy (EBRT) only and BT ± neck dissection (ND) as opposed to surgery followed by postoperative radiotherapy (PORT). In chapter 4 these costs were also computed for advanced treatment strategies (e.g. IMRT). Total costs for EBRT plus BT and BT plus ND were less as opposed to Surgery plus PORT: €14.261,98 and €16.628 as opposed to €18.782. The difference was due to treatment costs per se, but in particular because of the substantial longer hospital stay in case of surgery. With regard to future modalities, the additional costs of IMRT are almost negligible. That is, the slightly higher costs are only due to the higher personnel costs because of the somewhat more laborious preparatory work of the more advanced IMRT technique. Finally, in chapter 7, the costs for TF and/or SP tumors were studied.

The cost analysis was performed from the institutional perspective. In contrast to charges, unit costs are the best estimators of the theoretically proper opportunity costs. For this reason and to facilitate cost comparison with other countries, we calculated for the 3 subgroups, that is BT (48 patients), BT plus ND (56 patients) and the surgery plus PORT group (86 patients), direct medical costs for the most important items regarding the workup (diagnosis and staging), treatment (preparation treatment, costs for treatment modalities per se, such as teletherapy, brachytherapy, surgery), 5 years follow-up costs and costs related to the development (and treatment) of a relapse. The direct medical costs were based on average unit costs, including overhead costs. To determine these unit costs, we followed the micro-costing method, which is based on a detailed inventory and measurement of resources consumed.

The valuation of the resources and overhead costs was based on financial data from the Erasmus Medical Center Rotterdam. Direct costs consist of manpower and materials. To calculate manpower costs, time spent for the various procedures in the different subgroups was estimated by the medical disciplines involved. Time invested was multiplied by salary (including wages, social premium and extra fees for irregular working

hours). Costs per minute were then calculated under the assumption of 1540 working hours a year. With regard to the specialist, the costs per minute were calculated according to the method as described by Oostenbrink et al., that is, specialist activities were divided in direct and indirect time. Direct time is the time in which both specialist and patient are present. This was estimated to be 70% of the specialist's working time. Indirect time is when the patient is not present (e.g. multidisciplinary discussions), and is estimated to be approximately 30%. The direct times were therefore multiplied by 1.42 to allow for costs of indirect time. Wholesale prices were used to determine costs of materials. A detailed inventory and measurement of materials was executed, based on real use by the department for these patient groups. The use of equipment and operating room are included in material costs. The costs for diagnosis and staging are based on the Dutch tariff system. All direct costs were multiplied by overhead costs (e.g. depreciation costs of the building, cleaning costs). Overhead costs are based on the relationship between direct costs of the hospital in total and costs for administration.

To calculate costs for follow-up, first disease free survival (DFS) for year 1 to 5 was calculated according to the Kaplan-Meier method. Costs for follow-up were based on protocol and was corrected for DFS in that year. Relapse costs were based on the actual number of patients in each treatment group who showed renewed tumor activity, being a locoregional relapse, distant metastasis or second primary tumor. The costs of treatment, additional diagnostics and follow-up included, were then calculated and averaged for all patients with a relapse.

Prioritization: conditions and chances

As far as the cost of treatment was concerned, we found, with taking radiation therapy as a role model, that BT is advantageous (local control, cosmesis, organ function preservation) for early (example nasal vestibule) and even some of the more advanced tumors (T3, T4, BOT tumors) and was less expensive then surgery. Moreover, in the future, a gain in QoL and effectiveness can be expected given the current rapid development in relevant technology that enables the implementation of (even better) sparing techniques. As stated by the Health Council of the Netherlands, prioritization in treatment of patients with head and neck cancer should also be based on quality- and financial aspects. At this moment, hospitals in the Netherlands are gradually moving to another finance system. Ultimately, as of 2011

(as is now foreseen), Dutch hospitals will totally be paid in so-called DBC's (Diagnose Behandel Combinatie = Diagnosis Treatment Combination). At the moment, already 34% of the DBC's is subject to market forces, meaning that hospitals have to compete with each other with regard to quality and price. The effects are already substantial; in the last six months, several hospitals got themselves into severe financial problems.

Nowadays, Dutch society (Government, Netherlands Health Care Inspectorate, patients groups, newspapers) emphasizes the value of quality indicators, but financial parameters are hardly found. One of the challenges in the Dutch health care system is how to integrate these parameters given the current change in the finance system and the increase in multidisciplinary care.

The Health Council of the Netherlands published in 2008 'Searchlight on Radiotherapy. A vision for 2015'. Up to now, in the Netherlands, hospitals that want to practice radiotherapy, need a license from the minister of health. The minister's decision is based on the Law on Specialized Medical Interventions (WBMV), which sums up the criteria (e.g. volume, minimum quality requirements, catchment area needed) that centers must comply with in order to qualify for this license. In essence it means that, based on a specific Planning document ("Planningsbesluit") that regulates the capacity, so far, the minister ultimately decides whether to admit a new center for radiotherapy in the Netherlands. The actual Planning document expired in 2005, so the Council advised the government on how radiotherapy capacity should be regulated until 2015. The Health Council foresees, based on epidemiological and demographic trends, an increase in the demand of radiation treatments from 60.000 in 2005 till 79.000 in 2015. Together with the shift towards more complex and labor-intensive treatments, treatment- and staff capacity should increase with 50% (based on 2005) in 2015. In order to allow for these high capital costs to be financed, one obviously needs rigid financial criteria reflecting (cost) effectiveness.

Another important advice of the Council is on lifting the Planning document. The Council states that "deregulation (lifting the licensing requirement) can only be implemented in a responsible way after a comprehensive quality assurance system (including accreditation and a priori quality audit of centers) has been put into place. This will require a transitional period of about three to four years, during which the current legislation (licensing system) should stay in force". This also means that in the end the radiotherapy centers have to compete on quality and price because the DBC's (former paragraph) will fall under the so-called B-segment with prices being subject to competitive (market) forces.

Summary

With head and neck cancer as a role model, this thesis shows that costs could potentially be used in decision-making regarding the choice of treatment modalities, in particular in the case of equal clinical outcome for patients treated by radiotherapy or surgery. This is particularly important to realize since currently the financing structure of the health care system in the Netherlands is changing. Hospitals in the Netherlands are gradually moving to another finance system, i.e. in 2011, Dutch hospitals will totally be paid in so-called DBC's ("Diagnose Behandel Combinatie" = Diagnosis Treatment Combination). Another important advice of the Health Council is on lifting the Planning document. But the Council clearly states that "deregulation" (lifting the licensing requirement) can only be implemented in a responsible way after a comprehensive quality assurance system (including accreditation and a priori quality audit of centers) has been put into place". This calls for transparency in costs and quality of care.

DISCUSSIE & SAMENVATTING

Introductie
In 2008 heeft de Raad voor de Volksgezondheid (RVZ) de Nederlandse regering geadviseerd over hoe de toenemende kosten van de Nederlandse gezondheidszorg beter beheerst zouden kunnen worden. Één van de aanbevelingen was dat gezondheidszorginstellingen meer doelmatig moeten gaan werken. Daarbij moeten kwaliteitsindicatoren een belangrijke rol spelen. De Raad stelt dat instellingen niet alleen betaald moeten worden voor de hoeveelheid zorg die ze leveren, maar dat ook de kwaliteit van zorg hierin meegenomen moet worden. De Raad geeft aan dat dit volgens haar kan leiden tot een reductie in de uitgaven voor gezondheidszorg door een daling van (de kosten van) acute en later in het verloop optredende complicaties, recidieven en opnames. De Raad geeft aan dat kosten ook moeten kunnen dalen door de productiviteit in de zorg te verhogen door in technologie te investeren. Hierdoor zouden de overall kosten toenemen, maar de kosten per behandeling afnemen, waardoor dit een effectief instrument zou kunnen zijn.

Hoofdhals tumoren zijn niet de meest voorkomende tumoren, maar vereisen vaak (een combinatie van) agressieve modaliteiten die echter ieder voor zich ook tot een significante morbiditeit kunnen leiden. Dit is één van de redenen dat hoofdhals tumoren in dit proefschrift als model genomen zijn om effectiviteit, kosten en kwaliteit van verschillende behandelingen met elkaar te vergelijken. Radiotherapie kan als enige behandeling aangeboden worden, maar ook in combinatie met andere behandelingen, zoals chirurgie, chemotherapie en hyperthermie. Radiotherapie zelf kent verschillende toepassingsvormen, namelijk teletherapie en (endocavitaire- of interstitiële) brachytherapie. Dit proefschrift richt zich op kosten en Kwaliteit van Leven (KvL) voor patiënten met vroege, intermediaire en late tumorstadia die met een combinatie van radiotherapie en/of chirurgie en/of brachytherapie en/of chemotherapie behandeld zijn.

Tumorcontrole en kosten in vroege en intermediaire tumoren
Voor 'early-staged' (vroege) tumoren zijn met brachytherapie goede resultaten bereikt. Een voorbeeld hiervan zijn vestibulum nasi tumoren met een 5-jaars 'local relapse-free survival' van 92% (hoofdstuk 8). Een panel bestaande uit medewerkers zonder medische achtergrond en

met medische achtergrond is gevraagd de cosmetische uitkomst na de behandeling te scoren. Samenvattend is de overgrote meerderheid van de patiënten als 'uitstekend' of 'goed' beoordeeld in termen van cosmetiek.
Tonsillar Fossa (keelamandel) en soft palate (weke verhemelte) tumoren zijn voorbeelden van tumoren die wel als 'intermediair' geclassificeerd worden. Hier wordt chirurgie vergeleken met radiotherapie (met een brachytherapie boost volgend op de teletherapie). Zeer goede lokale regionale controle werd behaald in T1-T3 tumoren: de 5-jaars lokale regionale controle was 84% (teletherapie met brachytherapie) versus 78% in de groep patiënten die geopereerd was en postoperatief werd nabestraald (hoofdstuk 4). Ondanks ernstige late bijwerkingen, zijn er geen significante verschillen gevonden met betrekking tot xerestomie (droge mond) en 'functional outcome scores' (functionaliteit) voor de brachytherapie groep in vergelijking met de chirurgie groep. Om deze reden is in dit proefschrift de hypothese onderzocht of kosten van de behandeling en follow-up een andere (toegevoegde) discriminerende factor kunnen zijn in de keuze voor een bepaalde behandeling. Hiervoor is een kostprijsmodel ontwikkeld.
Het doel van hoofdstuk 4 is te laten zien of het mogelijk is de keuze voor brachytherapie of chirurgie voor tonsillar fossa (keelamandel) en soft palate (weke verhemelte) tumoren mede te laten bepalen door de kosten van behandeling. Berekend is dat de totale kosten voor brachytherapie minder waren dan voor chirurgie, namelijk €16.629 ($19.452; teletherapie en brachytherapie en halsklierdissectie) versus €18.782 ($22.074; chirurgie en postoperatieve bestraling).

Tumorcontrole en Kwaliteit van Leven (KvL) in uitgebreide tumoren
Goede lokale controle wordt ook bereikt bij grotere tongbasis tumoren die behandeld zijn met uitwendige radiotherapie in combinatie met brachytherapie. Pol et.al. heeft resultaten laten zien van T3 en T4 tongbasis tumoren die of behandeld waren in Rotterdam (alleen radiotherapie en een halsklierdissectie in geval van positieve klieren in de hals) of in Amsterdam (chirurgie en postoperatieve radiotherapie). 37% van de Rotterdamse patiënten versus 9% van de Amsterdamse patiënten kregen na 5 jaar een lokaal recidief ($p<0.01$) (Hoofdstuk 2). De 'overall survival' was statistisch gezien echter niet verschillend (mediaan 2.5 jaar tegenover 2.9 jaar [$p=0.47$]). Ook bleek dat de kwaliteit van leven van patiënten, gemeten door de 'Performance Status Scale' (functionele

vragenlijst) van List, groter was bij de patiënten die teletherapie met een brachytherapie boost hebben gehad. Beide groepen hadden wel evenveel last van een xerestomie (droge mond).

Bijwerkingen en Kwaliteit van Leven (KvL)
Bij patiënten met tumoren van de oropharynx komen de volgende behandelgerelateerde bijwerkingen voor: 33% van de patiënten die met brachytherapie zijn behandeld hebben mucositis op de plek waar de implantatie heeft plaatsgevonden (88% geneest vanzelf na 6-8 maanden), bij chirurgie zegt 21% van de patiënten enige mate van beperking te hebben van het openen van de mond (trismus). Droge mond is de meest voorkomende en vervelende bijwerking; de mediane VAS-score was 5.6 (brachytherapie) en 6 (chirurgie). Bij de vragen van de 'Performance Status Scale' die vroegen naar 'eating in public' (eten met andere mensen), 'normalcy of diet' (normaal kunnen eten) en 'normalcy of speech' (normaal kunnen praten) werden geen verschillen gevonden tussen beide groepen patiënten. De resultaten die gepresenteerd zijn in de hoofdstukken 2 t/m 4 laten zien dat naast goede lokale controle en minimale bijwerkingen, ook KvL een belangrijke rol speelt bij het objectiveren van resultaten van verschillende behandelingen. Een volgende voor de hand liggende vraag was of de KvL in de tijd zou veranderen. Voor patiënten met oropharynx tumoren zijn daarvoor in een longitudinale setting vragen van de 'Performance Status Scale' gesteld. Daarnaast is longitudinaal gekeken naar het optreden van xerestomie en moeilijkheden met slikken. Deze vragen zijn eveneens gesteld in 2003 en 2005. Ook zijn in 2005 de EORTC-QLQC30, de EORTC H&N 35 en de Euroqol afgenomen. Wat opviel was dat 'eten met andere mensen' (eating in public), 'duidelijk kunnen praten' (understandibility of speech) en 'normaal kunnen eten' (normalcy of diet) significant verschilden, in die zin dat patiënten die behandeld waren met brachytherapie hier het minste last van hadden. Chirurgische patiënten hadden meer spraak- en tandproblemen en hadden problemen met het openen van de mond. De KvL scores uit dit hoofdstuk (Hoofdstuk 9) laten zien dat de mediane scores door de tijd heen niet verschillend zijn. Deze bevinding komt ook overeen met de literatuur. Fang et.al. vonden geen verschil in gemiddelde KvL scores bij patiënten met kanker in het hoofdhals gebied, behalve bij 'problemen met eten met anderen', 'tanden', 'droge mond' en 'sticky saliva'. De gegevens uit dit onderzoek komen ook overeen met de

bevindingen van Hammerlid et.al; zij concludeerde dat KvL scores in deze groep patiënten vrijwel niet veranderden tussen het eerste en derde jaar na de diagnose.

Technologie: investeren in nieuwe apparatuur

In 2004 heeft de afdeling Radiotherapie van het Erasmus MC een Cyberknife ® (firma Accuray in Sunnyvale, CA) aangeschaft, dit is een robot met een stereotactisch radiochirurgie systeem (SRS) die ge(hypo)fractioneerd bestraling af kan geven, daarbij met zeer grote nauwkeurigheid corrigerend voor bewegingen van de tumor. In maart 2005 werd de Cyberknife in gebruik genomen voor Tonsillar Fossa / Soft Palate tumoren waarvoor het technisch of medisch niet mogelijk was deze met een brachytherapie boost te behandelen (Hoofdstuk 6). Dit is met name het geval bij patiënten met tumoren die diep infiltreren in de parapharyngeale ruimte en waar de Cyberknife (i.t.t. brachytherapie) niet invasief en heel precies (zonder omliggende structuren te raken) op bijna elke plaats in het lichaam zijn dosis af kan geven. Het gebruik van de Cyberknife als escape voor brachytherapie gaf de mogelijkheid om een nieuwe techniek op basis van klinische, KvL en financiële indicatoren te vergelijken met brachytherapie, de 'gouden standaard behandeling' in het Erasmus MC. Om de behandeling uit te kunnen voeren wordt eerst een masker gemaakt van het hoofd van de patiënt die op de rug op de behandeltafel ligt. Onder (soms) algehele anesthesie worden markers ingebracht in of dicht bij de tumor op het moment dat de patiënt toch voor zijn stagieringsonderzoek (tumoruitbreiding) onder algehele narcose op de operatietafel wordt onderzocht. Vervolgens wordt om de 2 mm een CT coupe (met gebruikmaking van i.v. contrast) gemaakt van het te bestralen gebied. De dosis wordt bepaald voor het doelgebied waar 80% van de straling moet komen: protocollair werd 5.5 Gy in 3 fracties gegeven (gedoseerd op de 80% isodose lijn), verdeeld over 5 dagen. Gedurende de Cyberknife behandeling worden door middel van röntgenfoto's de markers voortdurend gevolgd, waarbij het systeem zichzelf voortdurend corrigeert (robotfunctie) in geval van niet voorziene afwijkingen van het oorspronkelijke bestralingsplan. Overigens wordt het algemene principe zoals hiervoor beschreven, namelijk het zg 'tracken' op markers, juist in geval van stereotactische bestralingen van hoofdhals tumoren weinig toegepast. Bij hoofdhals tumoren vindt tracking met behulp van het Cyberknife meestal plaats door identificatie van bepaalde

botstructuren in de schedelbasis (vanwege de goede zichtbaarheid van deze in de nabijheid gelegen structuren). Zowel met het Cyberknife als bij de brachytherapie worden zeer conformele dosisberekeningen bereikt. In het algemeen kan gesteld worden dat mede door het gebruik van kleine CTV en PTV marges, maximale sparing kan worden bereikt. Immers, complicaties en klinische resultaten (lokale tumorcontrole) worden in hoge mate bepaald door de dosis die wordt afgegeven in het doelgebied en door de mate waarin omliggende kritische structuren gespaard kunnen worden. Dit betekent, dat in vergelijk met de conventionele uitwendige radiotherapie, bij eenzelfde tumor (GTV) kleinere doelvolumes (PTV) bestraald worden. Wordt hierbij ook het lagere aantal fracties betrokken, dan lijkt deze investering kosteneffectief te kunnen zijn.

Sparen door middel van adjuvante therapie: Amifostine

Chemotherapie, al dan niet in combinatie met gehyperfractioneerde- of geaccelereerde radiotherapeutische bestralingsschema's kan voor patiënten met grote hoofdhals tumoren een betere lokale controle opleveren. Echter, bijwerkingen van deze veelal ook toxische combinaties zijn vaak dosis-limiterend. Één van de manieren die in het Erasmus MC is onderzocht is het geven van radioprotectors, zoals subcutaan Amifostine (Ethyol®, Med Immune Oncology Gaitherburg MD). De gedachte daarbij was dat het antitumor effect van radiotherapie niet zou optreden, maar wel selectieve bescherming zou geven van structuren zoals de speekselklieren. In 2000 is een gerandomiseerd onderzoek gestart voor plaveiselcelcarcinoom van het hoofdhals gebied (met exclusie van nasopharynx tumoren). Alle patiënten kregen Paclitaxol (Taxol®, Bristol Meyers Squibb, Princeton, NJ) afwisselend met teletherapie. Patiënten werden gerandomiseerd voor subcutane toediening van Amifostine. Het onderzoek had een negatieve uitkomst, dat wil zeggen dat de toediening van Amifostine geen voordelig effect had (Hoofdstuk 5). Wat sterk naar voren kwam was dat een (iets geaccelereerde) bestraling in combinatie met Paclitaxol, een ernstige bijwerking op de slijmvliezen en slikspieren gaf (dysphagia). Daarnaast waren er meer ziekenhuisopnames in deze groep. Dit onderzoek onderstreept de toxiciteit die met chemotherapie samenhangt en direct (grotere) financiële gevolgen heeft.

Sparen door middel van adjuvante therapie: Hyperthermie
Een andere mogelijkheid om de effectiviteit van bestraling te vergroten is door middel van Hyperthermie. In Hoofdstuk 10 wordt de HYPERCOLLAR beschreven. Dit apparaat is gebaseerd op de principes van dynamische SAR scanning en is ontwikkeld op de afdeling Radiotherapie van het Erasmus MC. Het is aangetoond dat door Hyperthermie analoog aan de bestraling te geven, dit de effectiviteit van de bestraling verhoogt. Het effect dat bereikt zou moeten worden is dat de af te geven 'fysieke' bestralingsdosis naar beneden kan worden bijgesteld. Doordat de 'biologische' dosis hetzelfde blijft, zou dit tot dezelfde medische effectiviteit moeten leiden, maar met minder (in aantal en gradatie) bijwerkingen. Uitgaande van deze positieve veronderstellingen, beschrijft dit hoofdstuk de financiële gevolgen van het toevoegen van hyperthermie aan de teletherapiebehandeling voor hoofdhals patiënten. Uit het onderzoek blijkt dat, uitgaande van de genoemde veronderstellingen (minder bijwerkingen en hogere kwaliteit van leven), concomitante hyperthermie in combinatie met brachytherapie of teletherapie voor patiënten met hoofdhals kanker ook financieel gezien de investering waard is.

Kostenberekening en prioritering
Bij discussie over de meeste effectieve behandeling waarbij uit verschillende behandelingen een keuze kan worden gemaakt, worden kosten vaak niet meegenomen. In dit boekje zijn kosten en 'Quality Adjusted Life Years' (QALY's) bestudeerd voor patiënten met gelijksoortige tumoren in het hoofdhals gebied, maar die op verschillende manieren zijn behandeld. In Hoofdstuk 4 bijvoorbeeld, zijn de kosten voor brachytherapie vergeleken met chirurgie voor tonsillar fossa (keelamandel) en soft palate (weke verhemelte) tumoren. De ziekenhuis- en follow-up kosten zijn berekend voor 2 groepen patiënten, waarvan de ene groep behandeld is met teletherapie en brachytherapie met halsklierdissectie en de andere groep met chirurgie en postoperatieve radiotherapie.
In Hoofdstuk 4 zijn ook de kosten berekend voor meer geavanceerde behandelingen, zoals Intensiteitsgemoduleerde radiotherapie (IMRT). De kosten voor teletherapie en brachytherapie en brachytherapie en halsklierdissectie kwamen lager uit dan die voor chirurgie en postoperatieve bestraling: €14.261,98 en €16.628 versus €18.782. Het verschil zit in de behandelkosten, namelijk in de langere opnameduur voor patiënten die geopereerd waren. Het financiële verschil met de

toekomstige behandelingen, zoals IMRT, zijn praktisch te verwaarlozen. De kosten zijn iets hoger, maar dit wordt veroorzaakt door hogere personele kosten omdat de planning voor deze behandelingen meer arbeidsintensief is. In hoofdstuk 7 tenslotte zijn de totale kosten voor tonsillar fossa (keelamandel) en soft palate (weke verhemelte) berekend, dat wil zeggen inclusief recidieven en bijwerkingen.
Uitgangspunt voor de kostenberekeningen was het instellingsperspectief. Daarbij is niet uitgegaan van de lasten maar van daadwerkelijke kosten. Om daarnaast de vergelijking met andere landen mogelijk te maken, zijn voor 3 subgroepen, namelijk brachytherapie (48 patiënten), brachytherapie en halsklierdissectie (56 patiënten) en chirurgie en postoperatieve bestraling (86 patiënten), de directe medische kosten berekent, onderverdeeld naar stadia in de behandeling, zoals voorbereiding (diagnose stellen), behandeling (voorbereiding op de behandeling en de behandeling zelf), kosten voor 5 jaar follow-up en kosten gerelateerd aan (de behandeling) van een recidief. Deze kosten zijn gebaseerd op de kosten per kleinste eenheid, inclusief een percentage voor overhead. Om tot kosten per eenheid te komen, zijn op het laagste niveau de kosten berekend, door per stap gedetailleerd na te gaan wat er verbruikt werd. Alle berekeningen zijn gebaseerd op financiële data uit het Erasmus MC. De directe kosten bestaan uit personeels- en materiële kosten. Voor de personele kosten is de personele inzet van alle betrokken disciplines per stap in de behandeling berekend. De gespendeerde tijd werd vermenigvuldigd met het bruto salaris incl. werkgeverslasten en onregelmatigheidstoeslag. De kosten per minuut zijn vervolgens berekend door uit te gaan van 1540 werkbare uren per jaar. Voor de berekening van de personeelskosten van de medisch specialisten is gebruik gemaakt van de berekening zoals Oostenbrink et.al. die beschreven heeft; de inzet van de medicus is verdeeld in directe en indirecte tijd. Directe tijd is tijd die besteed wordt waarbij de patiënt lijfelijk aanwezig is. Dit is geschat op ongeveer 70% van de tijd. Bij indirecte tijd is de patiënt niet aanwezig (bv multidisciplinaire besprekingen), dit is ongeveer 30% van de tijd. De directe tijd is met 1.42 vermenigvuldigd om vervolgens tot de indirecte tijd te komen. Om de materiële kosten te berekenen is gedetailleerd geïnventariseerd welke materialen gebruikt zijn voor deze patiëntgroepen. De kosten voor diagnostiek en stagering zijn gebaseerd op het Nederlandse tarievenstelsel. Alle directe kosten zijn gecorrigeerd voor overhead (dit zijn gebouwgebonden kosten, schoonmaakkosten etc). De overheadkosten zijn gebaseerd op de verhouding tussen alle

directe en indirecte (bv voor gebouwen, schoonmaak, management, administratie) ziekenhuiskosten.
Om de follow-up kosten te berekenen, is uitgegaan van ziektevrije overleving voor de eerste 5 jaar berekend via de Kaplan-Meier methode. De kosten voor follow-up zijn berekend volgens protocol en gecorrigeerd voor de ziektevrije overleving.
De recidiefkosten zijn berekend door per behandelgroep het daadwerkelijke aantal patiënten te nemen die opnieuw kanker hebben gekregen, of dat nu een lokaal recidief was, een metastase of een tweede primaire tumor. De kosten voor behandeling, aanvullende diagnostiek en follow-up zijn voor deze patiënten berekend en 'verdeeld' over alle patiënten die opnieuw kanker hebben gekregen.

Prioritering: voorwaarden en kansen
Voor zover het behandelkosten betreft, hebben we aangetoond dat, uitgaande van radiotherapie als voorbeeld, brachytherapie meer voordelen (lokale controle, cosmetisch, orgaansparend) biedt bij vroege (vestibulum nasi) en soms bij grote tumoren (T3, T4 en mondboden tumoren) en goedkoper is. Verwacht wordt dat deze voordelen in de toekomst verder toenemen als de technologie (met als doel [nog betere] sparende technieken) verder zal verbeteren. Zoals door de Gezondheidsraad ook aangehaald, zou prioritering voor een bepaalde behandeling ook gebaseerd moeten zijn op kwaliteits- en kostenaspecten. Momenteel verandert het financieringssysteem voor de gezondheidszorg in Nederland. Zoals het er nu uitziet zal in 2011 de gezondheidszorg gefinancierd worden door DBC's (Diagnose Behandel Combinatie). Momenteel is 34% van de DBC's onderhevig aan marktwerking, dit betekent dat ziekenhuizen moeten concurreren op kwaliteit en prijs. De effecten zijn goed merkbaar; in de laatste maanden is een aantal ziekenhuizen in de financiële problemen gekomen.
Tegenwoordig wordt in Nederland (regering, inspectie, patiëntgroeperingen en kranten) het belang van kwaliteitsindicatoren sterk benadrukt, maar financiële indicatoren zijn nog vrij schaars. Eén van de uitdagingen voor de Nederlandse gezondheidszorg zal zijn om, gezien de financiële veranderingen en toenemende multidisciplinaire zorg, deze indicatoren te integreren.
De Gezondheidsraad publiceerde in 2008 het rapport 'De Radiotherapie belicht. Een vooruitblik tot 2015'. Tot op heden hebben ziekenhuizen die

radiotherapie aan willen bieden een vergunning nodig van de Minister van Volksgezondheid, Welzijn & Sport. De Minister beslist op basis van de WBMV (Wet Bijzondere Medische Verrichtingen), die aangeeft aan welke criteria (bv grootte, minimaal aantal behandelingen, adhaerentiegebied) ziekenhuizen moeten voldoen om in aanmerking te komen voor een vergunning voor radiotherapie. In wezen betekent het dat, gebaseerd op het Planningsbesluit wat de capaciteit reguleert, de minister uiteindelijk bepaalt of een nieuwe afdeling Radiotherapie wordt toegelaten. Het huidige Planningsbesluit loopt tot 2005, de Gezondheidsraad heeft dus geadviseerd hoe in de toekomst om te gaan met regulering van de capaciteit. De Gezondheidsraad voorspelt op basis van epidemiologische en demografische trends een toename in de vraag naar radiotherapie behandelingen van 60.000 in 2005 tot 79.000 in 2015. Samen met de ontwikkeling naar meer complexe en arbeidsintensieve behandelingen, betekent dit dat de behandelcapaciteit en formatie medewerkers ten opzichte van 2005 met 50% moet toenemen. Om ervoor te zorgen dat deze uitbreidingen ook gefinancierd kunnen worden, zijn er duidelijk financiële indicatoren nodig om de kosteneffectiviteit te bepalen.
Een ander belangrijk advies van de Gezondheidsraad is om het Planningsbesluit op te heffen. De Gezondheidsraad geeft aan dat de planning van radiotherapie alleen op een verantwoordelijke manier aan het veld overgelaten kan worden als hier een samenhangend kwaliteitssysteem (inclusief accreditatie en een a priori kwaliteitsaudit) voor in de plaats komt. De voorbereiding en implementatie hiervan vraagt 3 tot 4 jaar. Tot die tijd zou het Planningsbesluit gehandhaafd moeten worden. Dit betekent uiteindelijk dat ook radiotherapie centra moeten concurreren op DBC's die, zo is de verwachting, uiteindelijk in het B-segment (onderhevig aan marktwerking) zullen gaan vallen.

Samenvatting

Deze thesis laat zien dat, met als voorbeeld hoofdhalstumoren, kosten een rol zouden kunnen spelen in de keuze voor een bepaalde behandeling als de medische uitkomst van de behandelingen, namelijk chirurgie en radiotherapie, gelijk is. Dit is met name belangrijk omdat de financieringsstructuur van de gezondheidszorg in Nederland aan het veranderen is. Ziekenhuizen zullen langzamerhand op een andere manier worden bekostigd. In 2011 is het doel dat ziekenhuizen bekostigd worden op basis van DBC's (Diagnose Behandelcombinatie). Een ander

belangrijk advies van de Gezondheidsraad is om het Planningsbesluit Radiotherapie op te heffen. De Gezondheidsraad geeft daarbij wel gelijk aan dat deregulering alleen op een verantwoordelijke manier plaats kan vinden als er een samenhangend kwaliteitsborgingsysteem (incl. accreditatiecriteria en audits tussen centra) geïmplementeerd is. Dit vraagt om transparantie van kosten en kwaliteit van zorg.

CURRICULUM VITAE

Wideke M. Nijdam was born in Amersfoort on June 16, 1967. After following secondary school in Hilversum she went to Utrecht for her bachelor in Nursing (HBO-V, 1985-1989). In 1989 she moved to Maastricht to study Health Sciences at Maastricht University, with subspecialisation Business and Economics. She graduated in 1993. From June 1994 until March 2009 she worked at the Erasmus MC – Daniel den Hoed Cancer Center in Rotterdam, first as a trainee, lately as a staff manager of the departments of Radiation Oncology, Oncologic Surgery, Pathology and the Audiovisual Department. As from April 1 2009, she is working in the Onze Lieve Vrouwe Gasthuis in Amsterdam as manager of the Operating Rooms, Daycare and Anesthesiology.

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Lieve Miek; je bent een geweldige (lieve) zus. Altijd vroeg je hoe het ging, eerst met het onderzoek, toen met het schrijven en de 'praatjes' en op het laatst wat we aan zouden trekken vandaag. Gelukkig heb ik nu weer meer tijd om 'dagjes' af te spreken en te gaan eten bij elkaar. Ik hoop dat we dat nog vaak zullen doen.

Lieve pa en ma, zonder jullie steun had ik hier nooit gestaan. Om van de zorg maar niet te spreken. Steeds meer kom ik erachter hoe essentieel een

stabiele, goede en liefdevolle opvoeding is. Aan dat alles heeft het mij nooit ontbroken. Ik ben nog trotser op jullie dan jullie op mij(n promotie)! Dank jullie heel veel voor alles.