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Costs of treatment intensification for head and neck cancer: Concomitant chemoradiation randomised for radioprotection with amifostine

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Abstract

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 to costs. Fifty-four patients treated with weekly paclitaxel concomitant with radiation were 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.

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.

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.

Keywords: Chemotherapy; Radiotherapy; Chemoradiation; Costs; Radioprotection; Amifostine; Head and neck cancer

1. Introduction

Current treatment strategies for advanced stage head and neck cancer (H&NC) aim at increasing survival and (locoregional) tumour control with organ function preservation by 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]; and 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.

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In an attempt to increase tumour control probability, as of year 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 tumours of the tonsillar fossa, soft palate and base of tongue are boosted using interstitial brachytherapy. Brachytherapy has the advantage of a high tumour 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 randomised 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 randomised 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 or 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.

2. Patients and methods

2.1. 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 tumour and bilateral neck nodes [18]). After 46 Gy a booster dose of 26 Gy was applied to the primary tumour (and positive neck nodes). In selected patients (clinical judgement of radiation oncologist) with a tumour 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 randomised for 500 mg amifostine sc 15–30 min prior to each fraction of radiation or no radioprotection.

Fifty-four patients treated according to the protocol AZR 99220 have been analysed with respect to the total costs.

2.2. Costs

In this cost analysis the institutional perspective was taken, 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

Table 1
Costs of manpower

Personnel	Salary costs (€/h)
Radiation oncologist (RO)	78
Medical oncologist (MO)	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

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).

2.3. Diagnosis, staging and work-up (I)

All patients were seen in joint consultation by a radiation oncologist (45 min) 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 min for patients with dental prosthesis (43%) and 165 min for dentate patients (57%) (weighted costs, including fluoride applications during treatment).

2.4. Preparation for radiotherapy (II)

2.4.1. External beam radiotherapy (ERT)

For treatment planning purposes a CT scan (AcQ-SIM, 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 tumour 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 5 mm. 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 min, calculation 30 min).

2.4.2. 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 tumour with flexible catheters (90 min). A single plane implant of 2 or 3 catheters for tumours located in the tonsillar fossa and/or soft palate and a volume implant with 9 catheters for base of tongue tumours. 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).

2.5. Treatment delivery (III)

2.5.1. ERT 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 ERT, patients were admitted to the hospital. Six fractions of HDR were given twice daily with a 6-h interval (total HDR dose 20 Gy). During treatment the radiation oncologist saw the patients in the outpatient clinic weekly (10 min per visit).

2.5.2. 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 h: an hour for pre-hydration and anti-emetic treatment and 3 h paclitaxel infusion (calculated at 1.8 m^2 mean BSA).

2.6. Amifostine (IV)

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

2.7. Treatment related toxicity (V)

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.

2.8. Toxicity in acute phase (RTOG, 0–90 days post-treatment) (VI)

Admission days, tube feeding, blood transfusions, diagnostic imaging and cultures were analysed with respect to actual costs.

2.9. Routine follow-up on outpatient clinic 0–90 days post-treatment (VII)

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 min per visit).

2.10. Statistical analyses

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 occured first).

3. Results

3.1. 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%).

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.

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, respectively. Early survival was not significantly different in the 2 treatment arms. LRFS, RRFS, DMFS, DFS and OS at 2 years were 77%, 72%, 77%, 70% and 77%, respectively, for the total group.

3.2. Analysis of costs

Table 4(a) and (b) shows a subdivision of the costs made for diagnosis, staging, treatment delivery, related

Table 3
Results on acute toxicity according to RTOG, from start of treatment until 90 days post-treatment

	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 4
(a) Costs of treatment, (b) costs of post-treatment until 90 days after finishing treatment

		Costs per "Item"	Total costs[a]	With amifostine[b]	Without amifostine[b]	*P*-value[c]
(a)						
I. Diagnosis and staging			*1997*	*1997*	*1997*	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[d]				*1341*	*1344*	0.8
External beam RT			1322			
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				*5808*	*6760*	
Radiotherapy (personnel, materials, equipment)				1139	1141	0.8
36 # ERT ($n = 39$)	ERT per #	31	1116			
23 # ERT + 6 # HDR ($n = 15$)	HDR per #	79	1187			
Brachytherapy (implantation ± ND)			3735	516	1011	0.5
Implantation of loops[d]			1299			
Radiation oncologist	90 min	117				
Other personnel[e]	450 min	251				
Equipment (operation room)		649				
Materials (loops)		58				
Histology		41				
Neck dissection[d] ($n = 9$)			2436			
Personnel[g]		705				
Equipment (operation room)		1298				
Materials (tracheotomy)		50				
Histology		41				
Admission for BT ± ND						
BT only, mean 9 days, incl. ICU ($n = 6$)			3841	779	1125	0.7
BT + ND, mean 11 days, incl. ICU ($n = 9$)			4619	135	189	0.7
Controls on out-patient clinic RO		42[f]	252	239	237	0.8
Concomitant chemotherapy			3072	3000	3057	
Daycare		56[f]				
Paclitaxel		638[f]		2646	2697	0.7
Consultation of MO (incl. laboratory)		74[f]		354	360	0.7
IV. Amifostine (incl. administration by physician)				*6495*	*0*	<0.0001
36 # ERT ($n = 39$)		214[f]	7704			
23 # ERT + 6# HDR ($n = 15$)			6206			
V. Toxicity			3789	*4006*	*3491*	
Admission for toxicity during treatment ($n = 44$)			3013	3197	2710	
RT ward ($n = 44$)	per day	389[f]	2940	3116	2683	0.8

Table 4 (*continued*)

		Costs per "Item"	Total costs[a]	With amifostine[b]	Without amifostine[b]	*P*-value[c]
ICU ($n = 3$)	per day	729[f]	73	81	27	0.5
Gastrostomy ($n = 37$)		350	240	259	246	0.9
Tube feeding ($n = 46$)		15[f]	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				*€ 19647*	*€ 13592*	<0.0001
Total cost of treatment without amifostine				13152	13592	NS[h]
(b)						
VI. Toxicity			*1776*	*2111*	*1203*	
Admission for toxicity ($n = 8$)			780	1067	159	0.4
Tube feeding ($n = 43$)		15[e]	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			*€ 2092*	*€ 2406*	*€ 1489*	0.8

Due to rounding of numbers totals may not equal the sum of parts.

(b) 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.

[a] 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).

[b] Weighted costs, based on total costs of patients treated ± BT, ±ND, ±tracheotomy, divided by 27 per treatment arm (±A).

[c] *P*-value between treatment arms with or without amifostine.

[d] For total costs 16.4% overhead is added.

[e] 45 min resident RO; 45 anesthesiologist; 90 anesthesiology nurse; 2×90 operation theatre nurse; 90 anesthesiology nurse for recovery.

[f] Costs per day, per chemotherapy course, per outpatient visit, per amifostine administration.

[g] 180 min HNS; 180 resident HNS; 90 anesthesiologist; 180 anesthesiology nurse; 2×180 operation theatre nurse.

[h] NS not significant.

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 between treatment arms merely due to the administration of amifostine in the randomised 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.

4. Discussion

Platinum based chemoradiation is nephrotoxic. Patients need intravenous hyperhydration and monitoring of renal function (resulting in hospital admission during

Table 5
Calculated and anticipated costs of treatment

Treatment	Without amifostine	With 500 mg amifostine sc		With 875 mg amifostine sc	
ERT (36#) with ChT	€ 4440		€ 12144		€ 14444
Chemotherapy	3072		4440		4440
ERT	1116	Amifostine (36)	+7704	Amifostine (36)	+14004
Out-patient clinics	252			Reduction in toxicity	−4000
ERT (23#) with ChT					
+BT (6#)	€ 9651		€ 15857		€ 15432
Chemotherapy	3072		9651		9651
ERT + BT	1187	Amifostine (29)	+6206	Amifostine (29)	+11281
Implantation	1299			Reduction in toxicity	−4000
Admission	3841			Reduction in admission	−1500
Out-patient clinics	252				
ERT (23#) with ChT					
+BT (6#) + ND	€ 12865		€ 19071		€ 18646
Chemotherapy	3072		12865		12865
ERT + BT	1187	Amifostine (29)	+6206	Amifostine (29)	+11281
Implantation	1299			Reduction in toxicity	−4000
Neck dissection	2436			Reduction in admission	−1500
Admission	4619				
Out-patient clinics	252				

ERT 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.

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-h infusion, on outpatient basis, and is as effective as a 24-h 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 tumour 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 randomised trials, Trotti and colleagues 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 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 analysed costs made for H&NC patients treated with surgery, radiotherapy or a combination in two Dutch university hospitals [28]. In our institute, Nijdam has analysed 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+ND, ChRT *versus* RT) (see Table 4, III).

Levendag and colleagues 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 approximately € 389 per day (this paper). Six weeks neo-adjuvant hospitalised courses of Cisplatinum for nasopharyngeal cancer cost € 7.772 [14], whereas 4 weekly courses of paclitaxel on a daycare basis cost € 3.072 (Table 4, III). Additional costs for hospitalisation, gastrostomy, tube feeding and others during concomitant chemoradiation mounted up to € 3.789 (see Table 4, 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).

4.1. 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 and colleagues 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 tumour, 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 describe a randomised 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% in this trial).

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 (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 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, 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 randomised 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 4,V) and € 780 during 3 months follow up (Table 4, 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 (ERT only, 36 administrations, extra costs € 175 per vial of 375 mg) or € 5.075 (ERT + BT, 39 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).

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 pac-

litaxel 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.

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