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ORIGINAL ARTICLE

Definitive radiochemotherapy with weekly cisplatin in patients with head and neck cancer; single institution outcome analysis

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Summary

Purpose: *The objective of this study was to evaluate the feasibility, toxicity and efficacy of definitive radiochemotherapy with weekly cisplatin in head and neck cancer in a single institutional setting.*

Methods: *Previously untreated patients with stage II-IV head and neck cancer were included. Radiotherapy consisted of 70 Gy/7 weeks/35 fractions. All patients received concurrent cisplatin 40 mg/m^2 weekly.*

Results: *Between 2/2002 and 8/2009, 148 consecutive patients (WHO ≤ 2, male to female ratio 6/1, median age 56 years) were treated. The mean follow-up was 40 months. Tumors of the oropharynx were the most frequent (46%) and stage IV predominated (80%). Eighty-nine percent of the patients had received the full radiation treatment as planned. Omission of weekly cisplatin occurred frequently, mainly because of hematological toxicity. Only 64% of the patients completed at least 5 cycles of chemotherapy. Grade 3/4 mucosal toxicity developed in 32% of the patients. The late toxicities were acceptable: 74% of the patients were able to eat solid food during the 1st post-treatment year, 4 patients were not able to swallow at all during the 1st post-treatment year, requiring thus permanent feeding tube. Five cases of osteoradionecrosis of the mandible were reported. Three-year overall survival, locoregional control, time to progression and disease free survival were 34, 60, 52 and 29%, respectively.*

Conclusion: *Definitive radiochemotherapy with weekly cisplatin was toxic, with high rate of morbidity and mortality in this patient population. Five weekly cycles of 40 mg/m^2 cisplatin seem to be the dose limit for most patients. Three-year survival was significantly reduced despite the promising high initial response and locoregional control.*

Key words: cisplatin, concomitant chemoradiotherapy, head and neck cancer, radiochemotherapy

Introduction

Approximately two-thirds of patients with head and neck cancer are those with locally or locoregionally advanced disease with poor prognosis. The initial treatment approaches for these tumors include surgery with postoperative radio (chemo) therapy or definitive radiotherapy combined with chemotherapy or with targeted biological therapy. The choice of therapeutic modality depends on patient factors, primary site, clinical stage, resectability of the tumor, as well as institutional experience. The goals of a treatment include maximizing tumor control while maintaining function and quality of life. Unfortunately, there is a high tendency to recurrences and the long-term overall survival remains poor despite aggressive treatment.

Radiochemotherapy is now a standard component of a therapeutic algorithm in patients with squamous cell carcinoma of the head and neck. Simultaneous application of both treatment modalities offers the opportunity to enhance the effects of radiation on tumor cell kill and overcome radioresistance as well as to allow the elimination of a potential systemic micrometastatic disease. Several meta-analyses have shown that radiochemotherapy prolongs survival in patients with head and neck cancer as compared with radiotherapy alone [1-6]. The individual patient data meta-analysis MACH-NC [7] shows 19% reduction in the risk of death after ad-

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dition of chemotherapy to radiotherapy, which corresponds with an absolute improvement of 6.5% in overall survival at 5 years. This benefit was mainly due to an improvement in the locoregional control and only had a marginal effect on distant metastases.

Despite the benefits of radiochemotherapy, this treatment also carries risks of severe local and systemic toxicities.

The optimal regimen of chemotherapy is still unknown. Cisplatin is a potent radiosensitizer, most commonly used for radiochemotherapy. The optimal scheduling of cisplatin and radiation has not been established. Various schedules have been investigated. The dose of cisplatin has ranged from three-weekly high-dose [8] to weekly intermediate-dose [9] or daily low-dose [10]. Currently, the most widely used regimen is 100 mg/m^2 cisplatin every 3 weeks during radiotherapy. This regimen is associated with severe side effects, such as nephrotoxicity, ototoxicity, neurotoxicity and gastrointestinal toxicity, as well as severe mucositis, which make radiochemotherapy suitable only for patients with normal renal parameters and good performance status. A randomized trial comparing the effectiveness of three-weekly and weekly schedule of cisplatin has not been published. Small retrospective studies comparing the two regimens did not produce clear results [11,12].

The aim of this article was to report the results of adding monochemotherapy with cisplatin to definitive radiation in patients with locoregionally advanced disease. Instead of the most frequently used 3-weekly cisplatin, we used a weekly cisplatin schedule at a dose of 40 mg/m^2.

Methods

The purpose of the study was to determine the efficacy of definitive radiochemotherapy with weekly cisplatin in a group of consecutive patients with head and neck cancer treated at the Institute of Radiation Oncology Prague. The endpoints included compliance and toxicity of radiochemotherapy, initial response, overall survival, locoregional control, time to progression and disease free survival.

Eligibility criteria

Eligible patients had to have a previously untreated, histologically proven carcinoma arising from the head and neck area, with stage II-IV, and without distant metastases. Patients were required to have a Karnofsky performance status ≥ 70% and adequate organ function: granulocyte count ≥ 1,5.10^9/l, platelet count ≥ 100.10^9/l, hemoglobin ≥ 90 g/l, creatinine clearance ≥ 60 ml/min, aspartate and alanine aminotransferase ≤ 3× upper limit of normal (ULN) and total bilirubin ≤ 3× ULN. All patients signed an institutional review board-approved informed consent form.

Surgery

Surgery was accepted as a diagnostic intervention. Patients with surgery limited to neck dissection without resection of the primary tumor were also included to the study.

Radiotherapy

All patients underwent a treatment simulation in supine position. Patient's fixation was achieved using individualized thermoplastic masks. A planning-CT scan was performed. The treatment was performed with linear accelerator with a nominal photon beam energy of 5-6 MeV. 2D, 3D and intensity modulated radiation treatment (IMRT) techniques were allowed. The planned total dose was 70 Gy to the known site of disease, in 2 Gy fractions delivered 5 times weekly for 7 weeks.

Chemotherapy

Patients were scheduled to receive cisplatin (40 mg/m^2) once weekly, administered concurrently with radiation. All patients were receiving adequate hydration and antiemetic agents. Prophylactic antiemetics consisted of setron antiemetics, dexamethasone and metoclopramide. Assessment of hematological and renal parameters was performed before each chemotherapy cycle. Seven courses of chemotherapy were planned in total. If the patients experienced significant hematological toxicity, nephrotoxicity or deterioration in performance status during treatment, chemotherapy was temporarily interrupted and restarted later when possible. Patients with nasopharyngeal carcinoma were scheduled to receive adjuvant chemotherapy with 3 courses of cisplatin and 5-fluorouracil after completion of radiochemotherapy.

Supportive care

Feeding tube insertion was recommended before or at the beginning of treatment. Percutaneous endoscopic gastrostomy tube was preferred. Defined enteral feeding was initiated at a weight loss of 5% from the initial pretreatment weight. Prophylactic mouth washes were recommended. Radioprotection with subcutaneous amifostin was allowed when significant portions of both parotid glands were included in the radiation port (with the exception of IMRT). Patients were admitted to hospital for the whole course of treatment with a possibility of weekends and bank holidays leaves.

Treatment-related toxicity

Acute radiation toxicities were scored using the Radiation Therapy Oncology Group criteria, and toxicities attributed to chemotherapy were graded according to the National Cancer Institute Common Toxicity Criteria. Toxicity assessment was repeated weekly throughout the whole course of radiochemotherapy. Late radiation toxicities were evaluated using the Radiation Therapy Oncology Group / European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme more than 90 days after the end of radiation treatment.

Follow-up

Patients were evaluated 4 weeks after the completion of the whole treatment and then every 3 months for the first year, every 4 months for the second year, every 6 months for the next 3 years, and then annually. Visits were performed at the Institute of Radiation Oncology by an otorhinolaryngologist and a radiation oncologist.

Initial response

Initial response was evaluated according to the WHO crite-

ria ≤ 3 months after termination of the whole treatment. Priority of response assessment was, first pathologic, then clinical and radiographic; a pathologic complete response overruled partial clinical or radiographic response.

Long-term results definitions

Overall survival was defined as the time to death from any cause. Locoregional control was defined as the time to the first local or regional recurrence. Time to progression was defined as the time to the first local, regional or distant failure. Disease free survival was defined as the time to a recurrence at any site or death from any cause without detectable disease.

Statistical analysis

The potential follow-up was calculated as the time between the start of radiochemotherapy and the closeout date (August 31, 2009) for all patients, regardless of their vital status. All time-to-event analyses used the Kaplan-Meier product-limit method, with 95% confidence intervals (CIs). Comparison of toxicities between IMRT and non-IMRT techniques were tested for significance with Fisher's exact test. $P<0.05$ was considered as statistically significant.

Results

We analysed 148 consecutive patients (WHO ≤ 2, male to female ratio 6/1, median age 56 years, range 19-76) with a histologically proven locally advanced carcinoma of the head and neck treated at the Institute of Radiation Oncology between February 2002 and August 2009. The most frequent localization was the oropharynx (46%). Stage IV predominated (80%). Neck dissections were performed in 11 patients before radiochemotherapy. Eighty-nine percent of the patients were either current smokers or ex-smokers. Daily consumption of alcohol was noted in 61% of the patients. The patient sociodemographic and tumor-specific characteristics are presented in Tables 1 and 2. The mean duration of follow up at the time of analysis (August 2009), regardless of the patients' vital status, was 40 months (median 30, range 4-93), and the mean duration of follow-up of surviving patients was 30 months (median 23, range 4-86).

Table 1. Patient and disease characteristics

Characteristics	*N*	*%*
Age, years, median (range)	56 (19-76)	
Gender		
Male	127	86
Female	21	14
Smoking history		
Smoker or exsmoker < 5 years	112	76
Exsmoker ≥ 5 years	19	13
Never smoked	17	11
Consumption of alcohol		
Daily	91	61
Occasional	47	32
Abstinence	9	6
Unknown	1	<1
Primary site		
Oropharynx	68	46
Nasopharynx	25	17
Larynx	23	16
Hypopharynx	17	11
Oral cavity	8	5
Others	7	5
TNM stage		
II	7	5
III	23	16
IVA	96	65
IVB	22	15
Histological type		
Squamous cell carcinoma	135	91
Undifferentiated carcinoma	8	5
Carcinosarcoma	2	1
Others	3	2
Grade		
Well differentiated	17	11
Moderately differentiated	62	42
Poorly differentiated	53	36
Unknown	16	11

Table 2. TN classification

Patients, N (%)	*T1*	*T2*	*T3*	*T4*	*Total*
N0	0 (0)	3 (2)	3 (2)	15 (10)	21 (14)
N1	4 (3)	5 (3)	4 (3)	12 (8)	25 (17)
N2	5 (3)	13 (9)	18 (12)	50 (34)	86 (58)
N3	1 (<1)	0 (0)	2 (1)	13 (9)	16 (11)
Total	10 (7)	21 (14)	27 (18)	90 (61)	148 (100)

Protocol compliance

The median total dose of radiation was 70 Gy (range 26-74, mean 68.32). The radiation treatment techniques varied depending on the time period of treatment: 2D radiotherapy with 2 lateral opposite wedged fields and a direct posterior field with central shielding block protecting the spinal cord (n=53; 36%), conventional 3D-conformal radiotherapy (n=39; 26%) and IMRT (n=56; 38%). Eighty-nine percent of the patients received the full radiation treatment as planned. Reasons for premature termination of radiotherapy included patient's death during treatment in 12 patients and deterioration of performance status in 2 patients; another 2 patients decided to discontinue treatment after 68 Gy for personal reasons. In 33% of the patients the total treatment time was prolonged for more than 3 days. In total, 717 courses of concomitant chemotherapy were applied. The median number of chemotherapy courses was 5 (range 1-8). Of the 148 patients, 94 (64%) received at least 5 courses, and only 26 (18%) received all 7 courses of chemotherapy. The most frequent reason for early ces-

sation of concomitant chemotherapy was hematological toxicity (38%). Other reasons are listed in Table 3.

Acute toxicity

Acute grade 3/4 mucositis was reported in 32% of the patients (IMRT vs. non-IMRT=18 vs. 40%; p=0.006), acute grade 3/4 dermatitis in 17% (IMRT vs. non-IMRT=15 vs. 17%; p=0.654) and acute grade ≥2 salivary gland toxicity in 61% (IMRT vs. non-IMRT=50 vs. 67%; p=0.039). Three cases with serious laryngeal oedema required tracheostomy. Median weight loss during treatment was 8 kg (10.7% of the pretreatment weight). Thirty-eight percent of the patients were fully dependent on a nutritional support with a feeding tube in some part of the treatment, and 34% of the patients were able to swallow liquid at most. Only 11 patients (7%) were able to eat solid food during the whole treatment course. Hematologic toxicity was relatively frequent; grade 3/4 neutropenia occurred in 24% of the patients. Four cases with febrile neutropenia were recorded. Renal toxicity and the emetic potential of cisplatin were mild in general. Tables 4 and 5 summarize the acute treatment toxicities. Twelve deaths were recorded during treatment. The most frequent cause of death was bronchopneumonia in 4 patients, followed by pulmonary embolism in 3 patients. The other causes of death during treatment were heart failure (1 patient), peritonitis (2 patients), stroke 1 (patient) and unknown (1 patient).

Late toxicity

Late toxicities were mild, predominantly subcutaneous fibrosis and xerostomia. Of the patients 74% were able to eat solid food 1 year post-treatment, 4 patients developed aphagia requiring permanent feeding tube. Five cases of osteoradionecrosis of the mandible were reported 1 - 43 months after radiochemotherapy. All cases of osteoradionecrosis occurred in patients who had received 70 Gy and had initial stage IV disease. Two cases were treated conservatively with hyperbaric oxygen therapy, 3 cases were treated surgically. Two patients died due to arterial bleeding from the head and neck area without having documented recurrence. Table 6 summarizes the late toxicities of the treatment. Tracheostomy was present in 22% of the patients one year after the treatment termination and in 17% of the patients one year later.

Initial response

The response rate after the whole treatment was 83%. Complete remission was recorded in 104 (70%) patients and 19 (13%) patients had partial remission (Table 7). Persistent disease was detected in 31 patients

Table 3. Reasons for termination of concomitant chemotherapy

Reason	*Patients, N*	*%*
Hematological toxicity	56	38
Renal toxicity	27	18
In-field radiation toxicity	10	7
Fatigue	9	6
Gastrointestinal toxicity	5	3
Infection	5	3
Death	5	3
Refusal	3	2
Premature termination of treatment	1	<1
Others	1	<1
All courses of chemotherapy	26	18
Total	148	100

Table 5. Hematological acute toxicities

Grade	*Leukocytes N (%)*	*Granulocytes N (%)*	*Hemoglobin N (%)*	*Platelets N (%)*
0	22 (15)	49 (33)	16 (11)	102 (69)
I	27 (18)	29 (20)	58 (39)	26 (18)
II	48 (32)	34 (23)	62 (42)	11 (7)
III	44 (30)	30 (20)	10 (7)	7 (5)
IV	7 (5)	6 (4)	2 (1)	2 (1)
IMRT vs. non-IMRT	p=NS	p=NS	p=NS	p=NS

For abbreviations see footnote of Table 4

Table 4. Non hematological acute toxicities

Grade	*Mucositis N (%)*	*Skin N (%)*	*Salivary gland N (%)*	*Eye N (%)*	*Ear N (%)*	*Larynx N (%)*	*Pharynx N (%)*	*Upper GI N (%)*	*Renal N (%)*	*Nausea/vomiting N (%)*
0	0 (0)	1 (1)	6 (4)	128 (86)	113 (76)	81 (55)	11 (7)	2 (1)	63 (43)	90 (61)
I	10 (7)	49 (33)	52 (35)	18 (12)	29 (20)	45 (30)	31 (21)	12 (8)	54 (36)	39 (26)
II	91 (61)	74 (50)	90 (60)	2 (1)	6 (4)	14 (10)	50 (34)	82 (56)	28 (19)	15 (10)
III	46 (31)	20 (14)	–	0 (0)	0 (0)	5 (3)	56 (38)	52 (35)	3 (2)	4 (3)
IV	1 (1)	4 (3)	0 (0)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)
IMRT vs. non-IMRT	p=0.06	p=NS	p=0.030	p=0.088	p=0.001	p=0.005	p=NS	p=NS	p=NS	p=NS

GI: gastrointestinal tract, NS: non significant, IMRT: intensity modulated radiotherapy

Table 6. Late toxicities (%)

Grade	*Year*	*Mucositis*	*Skin*	*Subcutaneous*	*Salivary gland*	*Eye*	*Larynx*	*Brain*	*Spinal cord*
II	1	4	2	38	36	0	6	0	0
	2	6	2	32	45	0	0	0	0
III	1	0	0	2	7	0	0	0	0
	2	0	0	6	9	0	0	0	0
IV	1	0	0	0	0	1	0	0	0
	2	0	0	0	0	2	2	0	0
IMRT vs. non-IMRT		NS	NS	NS	NS	NS	NS	NS	NS

For abbreviations see footnote of Table 4

≤ 3 months after the termination of radiochemotherapy (11 local, 7 regional, 9 both local and regional, 4 distant).

Locoregional control

Forty-six cases of locoregional failure were detected, and 27 of them were persistent locoregional disease at the end of radiotherapy (11 local, 7 regional, 9 both local and regional); in 19 patients locoregional recurrence during follow-up were recorded (13 local, 1 regional, 3 both local and regional, 2 both locoregional and distant). The majority of locoregional failures happened in patients with initial stage IV (80%). The median time to detection of a recurrence was 9 months (range 5-66). The majority of locoregional failures (84%) were detected up to 2 years post-treatment. The estimated 3-year locoregional control rate was 60% (95% CI 49-71; Figure 1).

Salvage treatment for locoregional failures

From 44 patients with failures restricted to the head and neck area, only 7 (16%) underwent salvage surgery. Other types of salvage treatment included reirradiation in 4 patients and palliative chemotherapy in 12 patients. Twenty-one patients received symptomatic care only.

Time to progression

Thirteen patients experienced distant failures (all with initial stage IV). The median time to detection of distant metastasis was 6 months (range 1-21). All distant failures were detected up to 2 years post-treatment. Lung metastases were the most common (69%). Together with locoregional failures, the total number of failures was 57. The estimated 3-year time to progression was 52% (95% CI 41-62; Figure 2).

Table 7. Initial response

Initial response	*Patients, N*	*%*
CR	104	70
PR	19	13
SD	6	4
PD	6	4
Unknown	13	9
Total	148	100

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

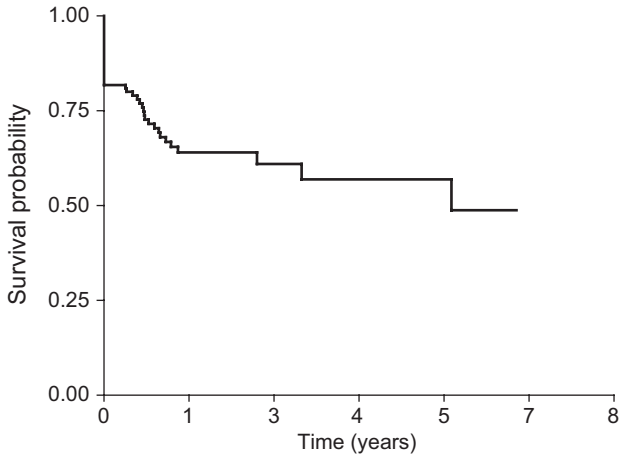

Figure 1. Kaplan-Meier estimate of locoregional control.

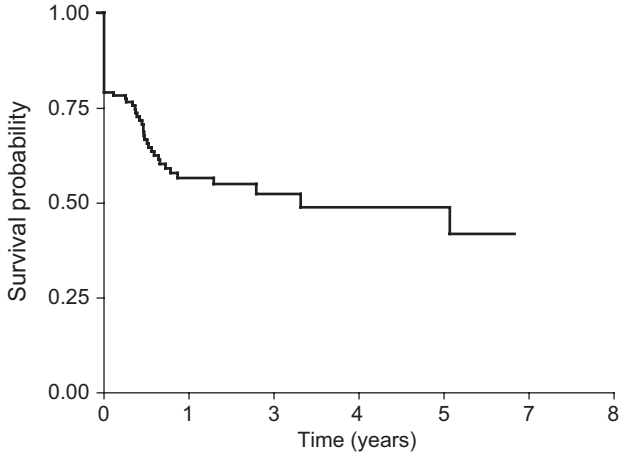

Figure 2. Kaplan-Meier estimate of time to progression.

Overall survival

Eighty-three of 148 patients had died at the time of the analysis. Twelve patients died during treatment. Seventy-one patients died between the date of termination of treatment and the closeout date; 39 of them died due to recurrence or progression of the disease. Three patients died due to toxicity of radiochemotherapy, 1 patient died due to progression of another primary tumor. In the remaining cases no direct relationship between cause of death and tumor or treatment-related complications of radiochemotherapy was found. The estimated 3-year overall survival was 34% (95% CI 25-44; Figure 3).

Disease free survival

The estimated 3-year disease free survival was 29% (95% CI 20-38; Figure 4).

Discussion

Herein we presented the results of a definitive radiochemotherapy schedule in a group of patients with advanced head and neck cancer. Instead of the most frequently used 3-weekly cisplatin, we applied the weekly cisplatin schedule.

In our study 89% of the patients received the full dose of radiotherapy. Compliance to concomitant chemotherapy was poor. Only 64% of the patients completed at least 5 cycles of chemotherapy (≥ 200 mg/m^2 cumulative dose). All 7 cycles were completed by only 18% of the patients. The main reason for a discontinuation of chemotherapy was the frequent high-grade hematological toxicity associated with the weekly administration of cisplatin which is likely to have affected the overall results.

Concomitant chemotherapy markedly increases the incidence of early and late toxicity. Severe mucositis affected 32% and severe dermatitis 17% of our patients. These results are in concordance with literature. Geeta et al. in a retrospective comparison of weekly and 3-weekly cisplatin in combination with radiation reported grade 3/4 mucositis in 28% and grade 3/4 dermatitis in 16% of patients in the arm with weekly cisplatin [11]. Severe late dysphagia affects 40-50% of patients treated with radiochemotherapy [13-15]. We observed severe dysphagia (grade ≥ 3) in 10% of 96 patients, evaluated in the first year post-treatment with 4 patients fully dependent on feeding tube. This is lower than the number given in published works [16,17]. Whether this is due to the use of IMRT in some patients or to lower late toxicity of weekly cisplatin it is hard to conclude from this study. In the Geeta et al. study, the 3-weekly schedule of cisplatin was associated with a higher rate of pharyngeal toxicity [11].

The estimated 3-year overall survival was 34%. This result is worse compared with the results in the majority of randomized trials, despite the relatively satisfactory 3-year locoregional control rate. It has to be mentioned that patients treated in the routine clinical practice may differ from patients included in clinical trials, where very distinctive inclusion criteria are often applied. Study populations tend to be biased towards younger, healthier, and more educated patients. This tendency in patient selection for clinical trials implies that real treatment results may be substantially worse. We evaluated a consecutive group of patients. As a result, our study included patients who could not pass through a sieve of inclusion criteria used in clinical trials, including patients with second tumors, patients with serious comorbidities, as well as patients with less willingness to cooperate in the treatment procedures and follow-up. All these conditions coupled with a high

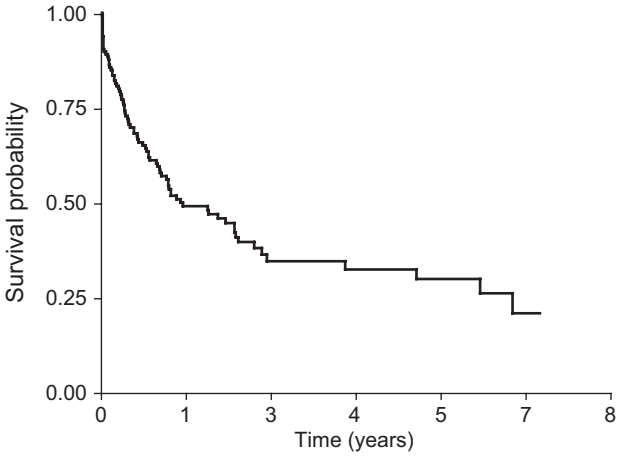

Figure 3. Kaplan-Meier estimate of overall survival.

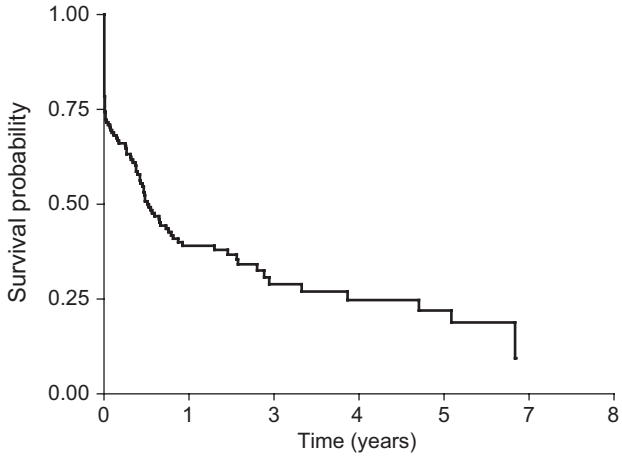

Figure 4. Kaplan-Meier estimate of disease free survival.

proportion of patients with very advanced disease (stage IV 80%, multiple nodal metastases 62%) and with a high percentage of patients burdened by autodestructive lifestyle, signals clearly an unfavorable prognosis. For one third of patient deaths we were not able to find a direct relationship between cause of death and tumor or radiochemotherapy-related complications. This indicates the high rate of non-cancer related mortality in our group of patients. Langenberg et al. evaluated the treatment results in a group of 87 consecutive patients who underwent "standard" radiochemotherapy (70 Gy external radiation with 3 cycles of 3-weekly cisplatin). In that study 91% of the patients received the full dose of radiotherapy. With a median follow-up of 17 months the 2-year overall survival was 44% [18]. These results are similar to the results obtained in our study.

Definitive radiochemotherapy with weekly cisplatin is toxic, with a high rate of morbidity and mortality. Overall survival was significantly reduced despite the promising high initial response and satisfactory locoregional control. The high mortality rate points to the need of more accurate selection of patients for this intensified regimen. Some aspects may favor the weekly schedule of cisplatin compared to the standard 3-weekly regimen: low acute nephrotoxicity, low emetic potential and mild late toxicity of radiochemotherapy with weekly cisplatin. Unfortunately, hematological toxicity with weekly cisplatin is frequent and 5 weekly cycles of 40 mg/m^2 cisplatin seem to be the dose limit for most of the patients.

References

1. Munro AJ. An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cancer. Br J Cancer 1995; 71: 83-91.
2. 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.
3. Pignon JP, Bourhis J, Domenge C et al. Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: Three meta-analysis of updated individual data. Lancet 2000; 355: 949-955.
4. Browman GP, Hodson DI, Mackenzie RJ et al. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: A systematic review of the published literature with subgroup analysis. Head Neck 2001; 23: 579-589.
5. Langendijk JA, Leemans CR, Buter J et al. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. J Clin Oncol 2004; 22: 4604-4612.
6. Budach W, Hehr T, Budach V et al. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer 2006; 6: 28.
7. Pignon JP, Le Maitre A, Maillard E et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009; 92: 4-14.
8. Al-Sarraf M, Pajak TF, Marcial VA et al. Concurrent radiotherapy and chemotherapy with cisplatin in inoperable squamous cell carcinoma of the head and neck: An RTOG study. Cancer 1987; 59: 259-265.
9. Sharma A, Mohanti BK, Thakar A et al. Concomitant chemoradiation versus radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: final results of a phase III trial. Proc Am Soc Clin Oncol 2007; 25: 306 (abstr 6030).
10. Jeremic B, Shibamoto Y, Milicic B et al. Hyperfractionated radiation therapy with or without concurrent low dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: A prospective randomized trial. J Clin Oncol 2000; 18: 1458-1464.
11. Geeta SN, Padmanabhan TK, Samuel J et al. Comparison of acute toxicities of two chemotherapy schedules for head and neck cancers. J Can Res Ther 2006; 2: 100-104.
12. Uygun K, Bilici A, Karagol H et al. The comparison of weekly and three-weekly cisplatin chemotherapy concurrent with radiotherapy in patients with previously untreated inoperable non-metastatic squamous cell carcinoma of the head and neck. Cancer Chemother Pharmacol 2009; 64: 601-605.
13. Eisbruch A, Lyden T, Bradford CR et al. Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2002; 53: 23-28.
14. Nguyen NP, Moltz CC, Frank C et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. Ann Oncol 2004; 15: 383-388.
15. Koiwai K, Shikama N, Sasaki S et al. Risk factors for severe dysphagia after concurrent chemoradiotherapy for head and neck cancers. Jpn J Clin Oncol 2009; 39: 413-417.
16. Machtay M, Moughan J, Trotti A et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008; 26: 3582-3589.
17. Chen AM, Li BQ, Jennelle RL et al. Late esophageal toxicity after radiation therapy for head and neck cancer. Head Neck 2010; 32: 178-183.
18. Langenberg M, Terhaard CHJ, Hordijk GJ et al. Simultaneous radio- and chemotherapy for squamous cell carcinoma of the head and neck in daily clinical practice: 5 years experience in a University Hospital. Clin Otolaryngol Allied Sci 2004; 29: 729-734.