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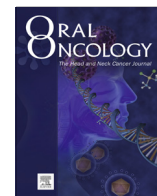
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A comparison of weekly versus 3-weekly cisplatin during adjuvant radiotherapy for high-risk head and neck cancer



Sjoukje F. Oosting^{a,*}, Tom W.W. Chen^b, Shao H. Huang^c, Lisa Wang^d, John Waldron^c, Ralph Gilbert^e, David Goldstein^e, Gyorgy B. Halmos^f, Max J.H. Witjes^g, Jourik A. Gietema^a, Brian O'Sullivan^c, Johannes A. Langendijk^h, Lillian L. Siu^b, Aaron R. Hansen^b

^a Department of Medical Oncology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

^b Division of Medical Oncology and Hematology, University of Toronto, Princess Margaret Cancer Center, 610 University Ave, Toronto, ON M5G 2M9, Canada

^c Department of Radiation Oncology, University of Toronto, Princess Margaret Cancer Center, 610 University Ave, Toronto, ON M5G 2M9, Canada

^d Department of Biostatistics University of Toronto, Princess Margaret Cancer Center, 610 University Ave, Toronto, ON M5G 2M9, Canada

^e Department of Otolaryngology and Head and Neck Surgery, University of Toronto, Princess Margaret Cancer Center, 610 University Ave, Toronto, ON M5G 2M9, Canada

^f Department of Otolaryngology and Head and Neck Surgery, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

^g Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

^h Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

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SUMMARY

Objectives: To compare cumulative cisplatin dose and toxicity between patients who received 3-weekly versus weekly cisplatin during adjuvant radiotherapy for high-risk head and neck squamous cell carcinoma (HNSCC).

Materials and methods: Consecutive HNSCC patients with involved resection margins and/or extra-capsular extension in two tertiary cancer centers with different institutional practices were identified. Cumulative cisplatin dose was calculated and information on toxicity reviewed and compared between patients who received 3-weekly versus weekly cisplatin.

Results: Of 270 high risk patients, 60 received 3-weekly 100 mg/m² and 48 received weekly 50 mg/m² cisplatin during adjuvant radiotherapy (60–66 Gy in 30–33 fractions). Fourteen patients received other chemotherapy schedules and 148 received no chemotherapy. Mean cumulative cisplatin dose was 199.4 mg/m² (standard error (SE) 5.4) in 3-weekly versus 239.8 mg/m² (SE 11.0, $P = 0.001$) in weekly treated patients. Cumulative cisplatin ≥ 200 mg/m² was given to 67.7% of patients in the 3-weekly cohort and 85.2% ($P = 0.039$) in the weekly cohort. The rate of feeding tube dependency 6 months after treatment, osteoradionecrosis, neutropenic fever, and persistent renal function decline were not statistically different.

Conclusions: About one half of high-risk HNSCC patients are not eligible for cisplatin during postoperative radiotherapy. Patients treated with weekly 50 mg/m² cisplatin received a higher cumulative dose with comparable toxicity as patients who received 3-weekly 100 mg/m² cisplatin. Efficacy and applicability to the frequently used weekly 40 mg/m² schedule remains to be evaluated.

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Introduction

Patients with head and neck squamous cell carcinoma (HNSCC) treated with primary surgery have a very high risk of recurrence if resection margins are positive and/or if there is extra-capsular extension of lymph node metastases. Combined analysis of two

phase 3 studies demonstrated that these patients derive benefit from adding high dose cisplatin (100 mg/m² at day 1, day 22 and day 43) to adjuvant radiotherapy with regard to loco-regional control, disease free and overall survival [1–3]. The combination of adjuvant radiotherapy and high dose cisplatin induces significant acute and long term toxicity, and even in a trial setting only 61% and 64% of the patients could complete 3 cycles of chemotherapy [1,2].

As an alternative, a weekly lower dose cisplatin schedule has been used, based on the assumption that a weekly regimen is less toxic and equally effective as 3-weekly high dose cisplatin. One

* Corresponding author at: University Medical Center Groningen, Department of Medical Oncology, DA11, PO Box 30.001, 9700 RB Groningen, The Netherlands. Tel.: +31 50 3612821; fax: +31 50 3614862.

E-mail address: s.oosting@umcg.nl (S.F. Oosting).

small trial demonstrated a survival benefit of adding weekly cisplatin to postoperative radiotherapy [4]. However, weekly and 3-weekly cisplatin plus radiotherapy have not been compared directly in a randomized and adequately powered study. A single institution retrospective comparison of weekly ($n = 53$) versus 3-weekly cisplatin ($n = 51$) showed a trend for improved survival with 3-weekly high dose cisplatin. However, patients who received weekly cisplatin were older, had a lower rate of human papillomavirus (HPV) related tumors and a higher number of smoking pack-years, which are well known adverse prognostic factors [5]. These differences likely result from selection bias of less fit patients to receive the weekly schedule.

We therefore aimed to compare patient cohorts from 2 tertiary care centers where one center routinely treats high-risk HNSCC patients postoperatively with 3-weekly high dose cisplatin and the other center routinely gives weekly cisplatin. If weekly cisplatin is better tolerated than 3-weekly cisplatin, this might be reflected by a higher cumulative cisplatin dose in patients treated with a weekly schedule. We aimed to compare the cumulative cisplatin dose and toxicity between patients treated with a weekly schedule and patients treated with the high dose 3-weekly schedule.

Patients and methods

Study design, patients and treatment

For this retrospective cohort study all consecutive patients with HNSCC of the oral cavity, larynx, hypopharynx and oropharynx who underwent primary surgery and had positive resection margins (<1 mm) and/or extra-capsular extension of lymph node metastasis who started adjuvant radiotherapy between March 1st, 2005 and December 12th, 2012 at Princess Margaret Cancer Center (PM, Toronto, Canada) and between December 15th, 2008 and July 15th, 2013 at the University Medical Center Groningen (UMCG, The Netherlands) were included. Information on disease characteristics, treatment details and acute and late toxicity were extracted from prospective institutional databases and supplemented by reviewing electronic patient records [6,7]. For patients who received adjuvant radiotherapy alone, the reasons for not having chemotherapy were collected. Patients who received adjuvant radiotherapy at PM with up to 3 cycles of 3-weekly 100 mg/m² cisplatin and patients treated at the UMCG who received up to 7 weekly cycles cisplatin 50 mg/m² were included for cumulative chemotherapy dose and toxicity comparisons. The weekly dose of 50 mg/m² was chosen as institutional practice because this allows a cumulative dose of 300 mg/m² to be reached, which was the target dose in the landmark studies [1,2]. Patients who tolerated treatment well were offered a seventh cycle during the last week of radiotherapy. For both cisplatin schedules, patients were admitted overnight for equivalent hydration regimens. All patients received 3000–4000 mL of normal saline with magnesium and potassium supplementation and were premedicated with a 5-HT₃ receptor antagonist, a neurokinin-1 receptor antagonist and dexamethasone.

Patients treated at PM received postoperative intensity-modulated radiotherapy (IMRT) as previously described [8]. High-risk patients treated at UMCG received IMRT with a simultaneous integrated boost technique. Patients received 66 Gy in 2 Gy fractions on high risk areas (lymph node areas with extracapsular extension and/or positive surgical margins), 59.4 Gy in 1.8 Gy per fraction on the intermediate risk areas (e.g. lymph node areas with positive nodes without extracapsular extension) and 52.8 Gy on the elective nodal areas.

All patients treated with 3-weekly high-dose cisplatin underwent prophylactic percutaneous endoscopic gastrostomy (PEG)

feeding tube insertion, unless contraindicated or refused by the patient. In the weekly cisplatin cohort, all patients treated between December 2008 and December 2009 received a PEG tube. Thereafter standard treatment policy was changed and only patients with swallowing problems or significant weight loss before start of chemoradiotherapy received a PEG feeding tube. In the remainder of the weekly cohort a nasogastric feeding tube was placed during treatment if the caloric intake by mouth was insufficient.

This study was approved by the PM Institutional Review Board. In the UMCG a consent waiver was granted for this retrospective chart review.

Study endpoints and data analyses

The primary endpoint of the study was the cumulative cisplatin dose, defined as the total dose in mg/m² that a patient received during the course of adjuvant radiation. Secondary endpoints included the rate of tube feeding dependence at 6 months after chemoradiotherapy; the rate of osteoradionecrosis of the jaw after treatment; the rate of neutropenic fever during treatment; the worst change of serum creatinine according to the common terminology criteria for adverse events version 4.0 (CTCAE 4.0); and the change in body weight during treatment. For comparisons of endpoints and clinical characteristics between patients treated with weekly and 3-weekly cisplatin, the means of continuous variables were compared using two-sample *t*-tests and the frequency of categorical variables were compared using the chi-squared test or Fisher's exact test, whenever appropriate. Odds ratios and corresponding *p*-values were calculated using the binary logistic regression model.

The efficacy outcome was reported as the 1-year recurrence rate including type of recurrence for each group. No formal statistical testing was carried out to compare the clinical outcomes because this was a retrospective review with significant clinical heterogeneity between the two groups. All analyses were performed with SPSS version 19 (IBM, Chicago, IL).

Results

In total, 270 HNSCC patients with high risk features were identified. Out of 178 patients from PM, 104 (58%) received postoperative radiotherapy only. Likewise, 44 (48%) out of 92 UMCG patients did not receive chemotherapy (Fig. 1). The most frequently documented reasons for withholding chemotherapy were age, poor performance, cardiovascular morbidity and patient refusal (Table 5). Wound healing problems were mentioned as a contraindication for chemotherapy in 7 (4%) PM and 6 (7%) UMCG patients. Fourteen PM patients were excluded from the cumulative dose and toxicity comparisons because of treatment with weekly cisplatin ($n = 11$) or carboplatin ($n = 1$), or disease recurrence before start of chemoradiotherapy ($n = 2$).

Chemoradiotherapy comparison cohorts

Sixty patients were treated with 3-weekly high dose cisplatin and 48 patients received weekly 50 mg/m² cisplatin during adjuvant radiotherapy. The groups were balanced for age, sex and T-classification but not for tumor site, N-classification, smoking status, WHO performance status and type and extent of surgery (Table 1). All patients were treated with intensity modulated radiation therapy (IMRT). All patients except for one in the 3-weekly cohort completed radiotherapy. Patients treated with 3-weekly cisplatin received 60–72 Gy in 30–36 fractions.

All except one patient in the weekly cisplatin cohort received 66 Gy in 33 fractions (Table 2).

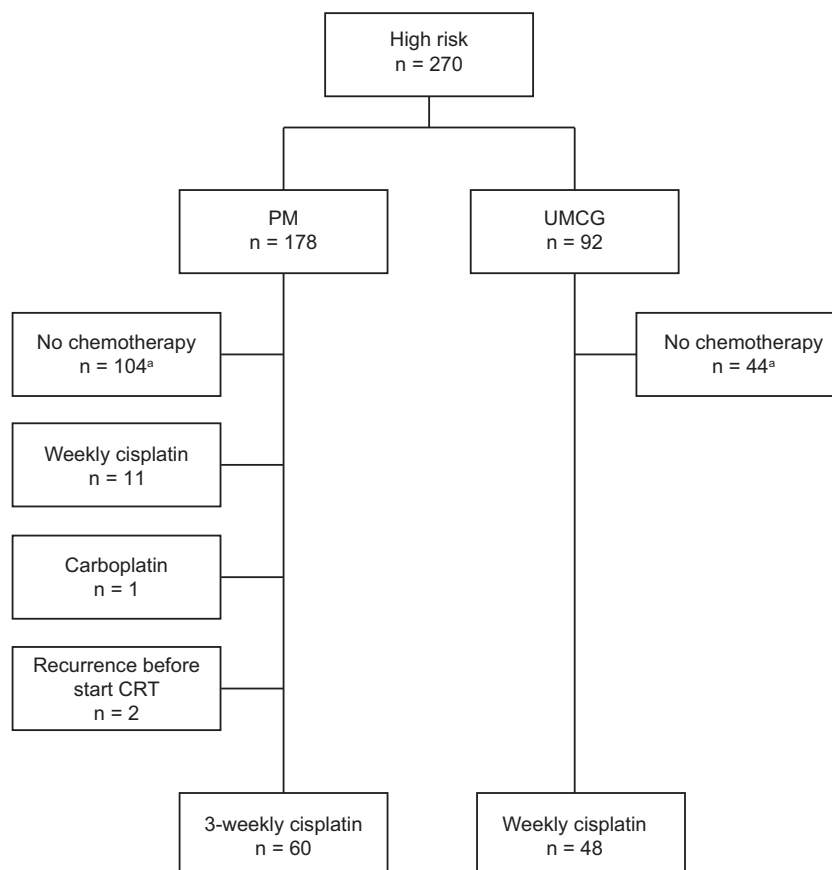


Fig. 1. Study flow diagram.

Cumulative cisplatin dose

The mean cumulative cisplatin dose was higher in patients treated with weekly cisplatin (239.8 mg/m², standard error (SE) 11.0) compared to patients treated with the high dose 3-weekly regimen (199.4 mg/m² SE 5.4, $P = 0.001$). Also the percentage of patients who received a cumulative cisplatin dose ≥ 200 mg/m² was higher in the weekly cohort (85.2%) than in the 3-weekly cohort (67.7%, $P = 0.039$). There was no significant interaction between RT dose schedule, cisplatin regimen, and the cumulative mean cisplatin dose ($p = 0.34$).

Treatment morbidity

The toxicity rates between patients treated with the 3-weekly and weekly regimens were similar (Table 3). Of all weekly treated patients, 40% completed treatment without tube feeding. Six months after completion of chemoradiotherapy, 18% of the patients treated with 3-weekly cisplatin and 10% of the patients treated with weekly cisplatin were feeding tube dependent (odds ratio (OR) 2.1, $P = 0.19$, Table 3).

Mean weight loss was higher in the 3-weekly (7.0%, SE 0.64) compared to the weekly cisplatin cohort (2.7%, SE 0.61, $P < 0.0001$). The rate of neutropenic fever was low and not significantly different between treatment cohorts (Table 3).

The baseline creatinine value was compared with the highest creatinine value between start and 6 weeks after treatment for each patient, and no grade 4 and only one case of grade 3 renal toxicity in both cohorts was found. In the weekly cohort, more grade 1 and 2 renal toxicity was found (Table 3), however for weekly treated patients more creatinine measurements were available. Six weeks after completion of treatment, grade 1 renal toxicity was

present in 2 patients of the 3-weekly cohort and 3 patients of the weekly cohort. Only one patient of the 3-weekly cohort had permanent grade 2 renal toxicity.

Osteoradionecrosis occurred in 3 patients (5%) in the 3-weekly cisplatin cohort and in 6 patients (13%, $P = 0.18$) in the weekly cisplatin cohort. The cumulative cisplatin dose was similar in patients with and patients without osteoradionecrosis.

Recurrence rate

For the 3-weekly cisplatin cohort the median follow-up was 28.3 months (range 1.2–94). Nineteen patients (32%) had a recurrence of whom 16 relapsed within one year after completion of treatment (Table 4). For the weekly cisplatin cohort, median follow-up was 35.7 months (range 4.7–60). Eleven patients (23%) had a recurrence of whom 6 within one year. The predominant pattern of relapse in both cohorts was distant failure.

Discussion

This is the first study comparing resected, high-risk HNSCC patients who received adjuvant chemoradiotherapy at 2 tertiary care centers with different institutional practices. We found that the weekly regimen allowed for more cisplatin to be delivered during radiation, without evidence of added toxicity. The vigorous hydration regimen with weekly overnight admission may have contributed to the tolerability.

There is limited data to support alternative regimens in the adjuvant setting other than high dose 3-weekly cisplatin combined with radiation [4,5,9–18]. A small prospective randomized study comparing weekly and 3-weekly cisplatin combined with radiation in the post-operative setting reported that patients treated with

Table 1
Demographic and clinicopathological characteristics.

Variable	3-weekly cisplatin N = 60		Weekly cisplatin N = 48		P value
	N	%	N	%	
Sex					0.65
Male	40	67	30	63	
Female	20	33	18	37	
Age, mean (range)	55.5	(22–74)	56	(27–68)	0.77
Tumor site					0.013
Oral cavity	49	82	29	60	
Oropharynx, (p16 pos/neg/UK)	2 (1/0/1)	3	6 (1/5/0)	13	
Larynx	8	13	6	13	
Hypopharynx	1	2	7	15	
Surgery type					0.013
Partial/hemiglossectomy	26	44	10	21	
Total glossectomy	1	2	0	0	
Mandibulectomy marginal	6	10	6	13	
Mandibulectomy continuity	2	3	9	19	
Floor of mouth resection	10	17	3	6	
Oropharynx resection	5	8	5	10	
Laryngectomy	8	13	13	27	
Maxillectomy	2	3	2	4	
Surgery extent					0.007
Primary closure	11	19	13	27	
Pedicled flap	5	8	2	4	
Soft tissue free flap	30	51	15	31	
Composite free flap	12	20	8	17	
Skin graft/obturator prosthesis	1	2	10	21	
T classification					0.50
1	12	20	7	15	
2	20	34	12	25	
3	5	8	7	15	
4	23	38	22	46	
N classification					0.015
0	7	12	15	31	
1	8	13	11	23	
2a	2	3	1	2	
2b	27	45	15	31	
2c	16	27	5	10	
3	0	0	1	2	
Stage					0.36
I/II	5	8	4	8	
III	7	12	10	21	
IVa	43	72	33	69	
IVb	5	8	1	2	
High risk factors					0.001
ECE only	33	55	10	21	
Involved margin only	15	25	27	56	
ECE + involved margin	12	20	11	23	
Smoking pack years ≥ 10					0.11
Yes	37	62	38	79	
No	17	28	6	13	
Unknown	6	10	4	8	
ECOG performance status					0.012
0	24	40	29	60	
1	33	55	11	23	
2	3	5	2	4	
Unknown	0	0	6	13	

pos = positive, neg = negative, UK = unknown, ECE = extracapsular extension of lymph node metastases, ECOG = Eastern Cooperative Oncology Group.

the weekly regimen had more frequent and more severe mucositis but similar hematologic and renal toxicity [9]. This trial used a weekly 40 mg/m² cisplatin dose and the authors suggested that the increased toxicity was due to lower compliance with treatment protocols in the weekly cohort and better post-chemotherapy care in the 3-weekly cohort. The mean cumulative dose was similar (208.5 mg/m² for 3-weekly cisplatin and 200.4 mg/m² for weekly cisplatin) but the percentage of patients who received a cumulative dose ≥ 200 mg/m² was higher in the 3-weekly cohort (88.5%) than

in the weekly cohort (62.5%) which is in contrast with our results. There is however no evidence that a threshold of 200 mg/m² cisplatin is clinically relevant in the postoperative setting.

Several single center experiences of weekly versus 3-weekly cisplatin concurrent with radiotherapy have been reported in HNSCC patients in the adjuvant setting alone or in the adjuvant and definitive setting combined, with weekly cisplatin doses ranging from 25 to 40 mg/m² [5,10–12]. In contrast to our results, patients treated with the weekly schedule received lower mean

Table 2
Treatment characteristics.

Variable	3-weekly cisplatin N = 60		Weekly cisplatin N = 48		P value
	N	%	N	%	
Cumulative cisplatin (mg/m ²), mean (SE)	199.4	(5.4)	239.8	(11.0)	0.001
Cumulative cisplatin ≥200 mg/m ²	41	67.7	41	85.2	0.039
IMRT	60	100	48	100	
RT dose schedule					0.001
66 Gy in 33 fractions	42	70	47	98	
>66 Gy in 33–36 fractions	11	18	1	2	
60 Gy in 30 fractions	7	12	0	0	

SE = standard error, IMRT = intensity modified radiotherapy.

cumulative cisplatin doses than patients treated with 3-weekly high dose cisplatin [5,10,11]. This is probably due to selection bias where unfit patients, who are less likely to complete the intended treatment schedule, received the weekly regimen. In contrast, in our study the weekly cohort more often had ECOG performance status zero (60% with 13% missing data) compared to the 3-weekly cohort (40%) which could have influenced tolerability of cisplatin in favor of the weekly regimen.

Despite a lower rate of feeding tube use during treatment, weight loss was less in patients treated with weekly cisplatin in our study. However, we cannot exclude that differences in radiation fields and doses influenced the ability to maintain oral intake and weight. In a single center retrospective study feeding tube insertion was performed in 90% of 3-weekly treated patients and 41% of weekly treated patients, but in contrast to our results more weekly treated patients experienced ≥10% weight loss [12]. Another retrospective comparison of weekly versus 3-weekly cisplatin during definitive radiotherapy, reported no difference in the rate of tube feeding during treatment and dependency on tube feeding at 3 and 12 months after treatment [19]. Furthermore, in the small randomized controlled trial reported by Bachaud et al. one out of 30 patients in the postoperative chemoradiotherapy arm required permanent gastrostomy for tube feeding and one additional patient a permanent liquid diet, compared to 3 out of 26 patients who required a permanent liquid diet in the postoperative radiotherapy alone arm [4].

Table 3
Treatment morbidity.

Variable	3-weekly cisplatin N = 60		Weekly cisplatin N = 48		OR	95% CI	P value
	N	%	N	%			
Feeding tube dependent					2.1	0.69–6.71	0.19
6 months after CRT							
Yes	11	18	5	10			
No	43	72	42	86			
Unknown or dead	6	10	1	2			
Osteoradionecrosis					0.37	0.08–1.56	0.15
Yes	3	5	6	13			
No	57	95	42	88			
Neutropenic fever					0.25	0.03–2.53	0.25
Yes	1	2	3	6			
No	61	98	45	94			
CTCAE creatinine change					NA		0.09
Gr 1	6	10	12	25			
Gr 2	0	0	3	6			
Gr 3	1	2	1	2			
Weight change during CRT (%), mean (SE)	–7.0	(0.64)	–2.7	(0.61)			<0.001

CRT = chemoradiotherapy, OR = odds ratio, CI = confidence interval, CTCAE = common toxicity criteria for adverse events version 4.03, SE = standard error.

Table 4
Recurrence pattern per treatment group.

Variable	3-weekly cisplatin N = 60		Weekly cisplatin N = 48	
	N	%	N	%
Median follow-up time in months (range)	28.2	(1.2–94)	35.7	(4.7–60)
Recurrence	19	32	11	23
Locoregional only	7	12	3	6
Distant only	8	13	6	13
Locoregional + distant	4	7	2	4
Recurrence within one year	16	27	6	13

The low rates of neutropenic fever and grade 3 renal toxicity that we found are in line with other studies [1,2,9,11,15,19]. The percentage of osteoradionecrosis was higher in the weekly group although the difference was not statistically significant. A likely explanation is the higher rate of mandibulectomy in the weekly compared to the 3-weekly cohort (32% versus 13%), which may be an important risk factor for development of osteoradionecrosis [20,21]. Another independent risk factor is radiotherapy dose to the bone [20,21]. In the weekly cohort, more patients had involved margins (79% versus 45%) and received 66 Gy to the area of the primary tumor. The influence of concomitant chemotherapy on development of osteoradionecrosis is unclear. A systematic review reported that the rate of osteoradionecrosis following chemoradiation was 6.8% compared to 7.4% for conventional radiotherapy and 5.2% for IMRT [22]. How the chemotherapy schedule impacted on this was not determined.

The prevalence and the severity of other clinically relevant toxicities such as mucositis, dysphagia, ototoxicity and neurotoxicity could not reliably be assessed due to the retrospective nature of our study. Several other studies showed higher percentage of severe mucositis in patients treated with weekly cisplatin compared to patients treated with 3-weekly cisplatin [9–12]. However, our data on weight loss and tube feeding dependence do not suggest excess mucositis and acute dysphagia in the weekly cohort.

The patients included in this retrospective cohort study were representative of the typical HNSCC population. For different reasons, around half the patients with high risk HNSCC did not receive adjuvant chemoradiotherapy. Age and performance status were

Table 5

Main reasons^a for not giving chemotherapy to high-risk HNSCC patients during radiotherapy.

Reason	PM	UMCG
	Number of patients	
Age >70 years	39	17
Poor performance	17	7
Cardiovascular co-morbidity	13	9
Declined by the patient	17	2
Wound healing problems	7	6
Active inflammatory disease/infection	3	5
Neurological co-morbidity	2	3
Diminished renal function	3	1
Felt to be not indicated	6	0
Non-compliant/alcohol use	5	0

CRT = chemoradiotherapy, PM = Princess Margaret Cancer Center, UMCG = University Medical Center Groningen.

^a Limited to reasons that were documented in at least 4 patients, one patient could have more than 1 reason.

the main reasons for patients not receiving chemotherapy, and this was true at both institutions. The high percentages of co-morbidities and poor performance status were likely related to the etiological risk factors tobacco and alcohol use in HNSCC patient population. Two patients with oropharyngeal carcinoma, one in each cohort, had a p16 positive tumor. In oropharyngeal cancer, p16 protein expression is a reliable surrogate marker of human papillomavirus (HPV) infection and an established prognostic factor. Compared to North America, the incidence of HPV related oropharyngeal cancer in the Netherlands is low [23]. For non-oropharyngeal HNSCC, p16 expression also appears to be associated with favorable outcome, but the difference between p16 positive and p16 negative patients is less pronounced and the positivity rate is lower compared to oropharyngeal cancer [24]. Also correlation with HPV is less clear, therefore p16 is not recommended for routine use in non-oropharyngeal HNSCC.

This study was not powered to evaluate the efficacy of the weekly versus 3-weekly cisplatin regimen. The rate of relapse was reported but not compared, and no conclusions can be drawn on efficacy because of significant differences between the patient cohorts. In general, it is unclear if cumulative cisplatin dose in the adjuvant setting impacts on relapse rate and survival. In the Radiation Therapy Oncology Group 95-01 trial, patients were randomized between radiotherapy alone and radiotherapy plus concurrent 3-weekly high dose cisplatin after surgery [2]. The patients who completed the intended 3 cycles of chemotherapy had similar loco-regional control as the whole group assigned to chemoradiotherapy. A retrospective study of 3-weekly cisplatin 75 mg/m² during postoperative radiotherapy could not demonstrate a relationship between the number of chemotherapy cycles and survival [18]. However, a better overall survival was demonstrated in patients who received a cumulative cisplatin dose ≥ 240 mg/m² in a study with weekly and 3-weekly cisplatin combining adjuvant and definitive chemoradiotherapy [10]. A recent systematic review suggested a linear association between overall survival and cumulative cisplatin dose during definitive radiotherapy which was independent of chemotherapy schedule [25].

The choice of optimal adjuvant treatment will be a balance between toxicity and efficacy. An alternative chemotherapy schedule that has equivalent clinical outcomes to 3-weekly high dose cisplatin but has fewer acute and late side effects would be preferable. Important limitations of our retrospective study are imbalances between treatment groups with regard to tumor site, N-stage, type and extent of surgery and consequently radiotherapy fields, performance status and distribution of pathological high-risk features. Because of these differences and low number of patients no conclusions can be drawn about efficacy. Furthermore,

information on important toxicities such as mucositis was not available. To address this a prospective randomized trial is required. Since October 2012 a randomized phase II/III study (JCOG1008) in Japan has been evaluating non-inferiority of weekly cisplatin (40 mg/m², 7 cycles) compared with 3-weekly cisplatin (100 mg/m², 3 cycles) for postoperative high-risk HNSCC patients [26]. The primary objective of the phase II portion is treatment completion and for the phase III part overall survival is the primary endpoint. Until the results of this study are known, high dose 3-weekly cisplatin combined with radiation for resected high risk HNSCC remains the standard of care supported by level I evidence.

Conclusion

This retrospective comparison has demonstrated that around one half of high-risk HNSCC patients are not eligible for cisplatin during postoperative radiotherapy. Weekly 50 mg/m² cisplatin permits a higher cumulative dose to be delivered with no evidence of excess toxicity compared to 3-weekly 100 mg/m² cisplatin during postoperative radiotherapy. Efficacy remains to be determined and it is unclear if this data is applicable to the 40 mg/m² weekly cisplatin schedule, which is a commonly used alternative to high dose 3-weekly cisplatin.

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Conflict of interest statement

None declared.

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