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PHASE III STUDY OF RADIATION THERAPY WITH OR WITHOUT CIS-PLATINUM IN PATIENTS WITH UNRESECTABLE SQUAMOUS OR UNDIFFERENTIATED CARCINOMA OF THE HEAD AND NECK: AN INTERGROUP TRIAL OF THE EASTERN COOPERATIVE ONCOLOGY GROUP (E2382)

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Abstract

Purpose—The Head and Neck Intergroup conducted a Phase III randomized trial to determine whether the addition weekly cisplatin to daily radiation therapy (RT) would improve survival in patients with unresectable squamous cell head-and-neck carcinoma.

Methods and Materials—Eligible patients were randomized to RT (70 Gy at 1.8–2 Gy/day) or to the identical RT with weekly cisplatin dosed at 20 mg/m². Failure-free survival (FFS) and overall survival (OS) curves were estimated with the Kaplan-Meier method and compared with the log rank test.

Results—Between 1982 and 1987, 371 patients were accrued, and 308 patients were found eligible for analysis. Median follow-up was 62 months. The median FFS was 6.5 and 7.2 months for the RT and RT + cisplatin groups, respectively ($p = 0.30$). The p value for the treatment difference was $p = 0.096$ in multivariate modeling of FFS (compared to a $p = 0.30$ in univariate analysis). Expected acute toxicities were significantly increased with the addition of cisplatin except for in-field RT toxicities. Late toxicities were not significantly different except for significantly more esophageal (9% vs. 3%, $p = 0.03$) and laryngeal (11% vs. 4%, $p = 0.05$) late toxicities in the RT + cisplatin group.

Conclusion—The addition of concurrent weekly cisplatin at 20 mg/m² to daily radiation did not improve survival, although there was evidence of activity. Low-dose weekly cisplatin seems to have modest tumor radiosensitization but can increase the risk of late swallowing complications.

Keywords

Randomized; Cisplatin; Unresectable; Weekly cisplatin; Late complications

INTRODUCTION

Over the past 20 years, multiple randomized trials (1–4) and meta-analyses (5, 6) have supported the conclusion that radiotherapy (RT) intensification improves local-regional disease control and survival in the management of locally advanced head-and-neck squamous cell carcinomas. This may be achieved with altered fractionated RT (2) or with the addition of concurrent chemotherapy (1, 3). Not only is the spectrum and magnitude of acute toxicities increased, but it is now clear that treatment intensification increases late swallowing complications (7–9). No randomized trials have defined the optimal treatment intensive regimen, although meta-analysis and consensus expert opinion have favored platinum chemoradiation, typically with cisplatin dosed at 100 mg/m² every 3 weeks (10).

Now that the improved prognosis of human papillomavirus–associated oropharyngeal carcinomas has become accepted (11, 12), attention has focused on developing risk-adapted deintensified therapies in the hope of reducing the long-term toxicities of concurrent chemoradiation strategies in this patient population. This issue is also relevant in patients of advanced age. Meta-analysis has demonstrated that the survival gains achieved with treatment intensification (5, 6) are attenuated with advancing age, which is also an independent risk factor for late swallowing toxicity when these patients are treated with chemoradiation (7, 8).

These considerations have placed a greater emphasis on the potential activity of alternative platinum chemoradiation approaches in the hope of establishing regimens with improved toxicity and tolerability profiles. Weekly cisplatin schedules have been proposed not only for improved tolerability but to reduce both acute and late toxicities. This practice has been based on little evidence guiding the appropriate weekly dose of cisplatin that should be used. We report the results of a previously completed and unreported randomized trial conducted through the Head and Neck Intergroup, asking whether or not weekly cisplatin at a dose of 20 mg/m²/week was effective.

METHODS AND MATERIALS

Patients

Study eligibility included patients with biopsy-proven head-and-neck squamous cell or undifferentiated carcinoma, technically unresectable American Joint Committee on Cancer 1980 clinical Stage III or IV with no distant metastasis. This trial, to our knowledge, represented the first clinical trial that established a systematic criterion for unresectability to ensure a homogeneous study population. The criteria for unresectability were identical to E1392 (13). All anatomic sites of the head and neck were included. This included nasopharyngeal carcinomas but restricted to T3/4 or N2/3 disease only. At the initiation of the trial, from November 1982 to August 1983, patients with an incomplete resection and gross residual tumor were permitted to enroll in the absence of documented distant disease. After August 1983, these patients were excluded.

Eligibility also required an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3 and adequate hematologic, hepatic, and renal function. Exclusion criteria included existing cardiac conditions, pregnancy or lactation in women, prior treatment with RT or chemotherapy, and any prior or synchronous malignancy.

This study was conducted under the auspices of ECOG, Southwest Oncology Group (SWOG), and Radiation Therapy Oncology Group (RTOG) and was approved by the individual institutional review boards of all participating institutions.

Randomization

On study entry, eligible patients were stratified by PS (0–1 vs. 2–3), primary tumor stage (T1–3 vs. T4) and nodal stage (N0–1 vs. N2–3). Patients were randomized (ECOG central randomization desk) using permuted blocks within strata using dynamic institutional balancing (14). Patients were assigned to once daily RT or to RT plus concomitant cisplatin dosed at 20 mg/m² per week (Fig. 1).

Radiation

Treatment was delivered with either cobalt teletherapy or a linear accelerator (up to 6 MV) with a standard three-field bilateral neck beam arrangement. The primary lesion was treated with a generous margin, typically 2–3 cm. Each field was treated daily, 5 days a week. Off spinal cord field reductions were used with additional field reductions left to the discretion of the treating radiation oncologist. The prescribed dose to the primary lesion and involved nodal disease was 68–76 Gy. Uninvolved areas were electively treated to 50–55 Gy. The low anterior cervical neck was prescribed 50 Gy (at D_{max}) unless gross disease was initially present, and the dose was then boosted to 70 Gy. The daily fraction was 1.8–2 Gy and 1.8 Gy in the RT and RT + cisplatin arms, respectively.

Chemotherapy

In the RT + cisplatin arm, concurrent single-agent cisplatin, 20 mg/m² intravenously, was administered on Days 1, 8, 15, 22, 29, 36, and 43 of the radiation schedule. Cisplatin was administered within 2 hours after the scheduled RT. Aggressive hydration and antiemetic therapy was used with the cisplatin administration. Cisplatin dose modifications were defined for nadir or treatment-day leukopenia or thrombocytopenia and for any nephrotoxicity. Dose modification for mucositis or any local-regional complications was left to the discretion of the treating physician.

Endpoint definition

At the time of the study, complete response (CR) was defined as complete disappearance of all detectable tumor lasting for at least 4 weeks. Partial response (PR) was defined as a reduction of at least 50% of the product of the longest perpendicular diameters of the tumor with no new area of malignant disease appearing for at least 4 weeks. Stable disease was defined as less than 25% increase in measurable disease with no significant deterioration in PS by greater than one level caused by disease progression. Disease progression was defined as an increase in a measurable lesion by greater than 25% or the appearance of new areas of malignancy or deterioration in PS resulting from malignancy. Disease response was assessed weekly during radiation, then monthly during the first year of follow-up, and then every 3 months thereafter.

The major endpoint of the study was failure-free survival (FFS) measured from the date of randomization to the first evidence of progression, relapse, or death. Additional endpoints included the overall survival (OS) measured from the date of the randomization to the date of death or the last date the patient was known to be alive. Secondary endpoints for analysis included tumor response, acute toxicities, and late toxicities as measured on the Radiotherapy Long Term Follow-up Form. Two additional acute effects, laryngeal edema and nutritional toxicity, were also evaluated using the Head and Neck Radiation Therapy Form.

Statistical analysis

The accrual goal for this study was 300 patients (150 patients in each arm), which was needed to detect an increase of 50% in median survival between the two arms with an 80% power using a one-sided log-rank test with an overall Type I error of 0.05. This was based on an expected median survival of 13 months in the control arm. An accrual rate of 75 patients/year was projected. The FFS and OS curves were estimated with the Kaplan-Meier method and compared with the log rank test. The proportional hazards model was used to adjust for variables simultaneously when assessing FFS or OS. Fisher's exact test was used to compare a dichotomous endpoint. For ordered contingency tables (*i.e.*, toxicity grade by treatment), the two-sample Wilcoxon midrank test was used. The logistic model was used to adjust for one or more explanatory variables simultaneously when assessing response. For both the logistic and the proportional hazards model, a stepwise regression approach was used. The original analysis design was performed on an as-treated basis.

RESULTS

From November 23, 1982, to June 12, 1987, a total of 371 patients were accrued to the study. The number of patients accrued from ECOG, RTOG, and SWOG was 173, 114, and 84 patients, respectively. The study was administered and analyzed by ECOG. Of the 371 patients randomized, 63 (17%) were excluded from the primary analyses. Eighteen patients did not receive protocol therapy, and an additional 45 patients were found to be ineligible. Reasons included findings of inadequate hematologic and renal function, resectable disease, nonsquamous histology, and a second primary malignancy with or without metastases. A total of 308 (83% of the total randomized) was eligible for analysis. Table 1 summarizes the number of eligible and analyzable patients. Median follow-up for these patients was 62 months.

The clinical characteristics of the 308 analyzable patients are presented in Table 2. There were some imbalances with the RT + cisplatin group: a higher number of patients with age >65, weight loss 10% in the previous 6 months, >40 pack-years exposure to smoking, well or moderate cell differentiation, and nonnasopharyngeal primary tumors. These imbalances contributed to a bias against the RT + cisplatin treatment group with the as-treated analysis.

Overall, the addition of weekly cisplatin did not significantly increase both FFS and OS. The Kaplan-Meier estimates of the probability of being failure free (FFS) and remaining alive (OS) are presented in Figs. 2 and 3, respectively. The median FFS was 6.5 and 7.2 months for the RT and RT + cisplatin groups, respectively ($p = 0.30$). An intent-to-treat analysis demonstrated no difference (data not shown). Univariate analysis demonstrated that a poorer FFS was associated with several factors: more smoking exposure ($p = 0.002$), greater alcohol consumption ($p = .003$), ECOG PS 2–4 ($p < 0.001$), better cell differentiation ($p = 0.007$), higher stage ($p = 0.003$), and nonnasopharynx primary site ($p = 0.002$). The final multivariate analysis is summarized in Table 3. The p value for the treatment difference was $p = 0.096$ in this model (compared to $p = 0.30$ in the univariate analysis).

The median survival was 13.3 and 11.8 months for the RT and RT + cisplatin groups, respectively ($p = 0.81$), also not significantly different with an intent-to-treat analysis (data not shown). Univariate analysis demonstrated that a poorer OS was associated with several factors: white race ($p = 0.04$), greater smoking exposure ($p = 0.002$), greater alcohol consumption ($p < 0.001$), ECOG PS 2–4 ($p < 0.003$), better cell differentiation ($p = 0.034$), higher stage ($p = 0.021$), and nonnasopharynx primary site ($p = 0.001$). Multivariate analysis demonstrated no significant treatment effect ($p = 0.60$) (Table 3).

Tumor response reported by treatment group is summarized in Table 4. Overall, 39% of patients had a CR, and 34% achieved a PR, for a total response rate of 73%. There was no difference in the CR rate by treatment group ($p = 0.64$). There was a significant difference in the overall response rate by treatment group in favor of the RT + cisplatin group (79% vs. 67%, $p = 0.03$). Factors associated with a poorer overall response rate (CR + PR) by univariate analysis included worse PS (*i.e.*, ECOG PS 1–3, $p = 0.02$) and no prior surgery ($p = 0.03$). Multivariate modeling demonstrated that treatment (RT + cisplatin, $p = 0.03$), better PS (*i.e.*, ECOG PS 0, $p = 0.04$), and prior surgery ($p = 0.03$) were all independently associated with a higher probability of achieving a response.

Table 5 summarizes the acute toxicities observed. The addition of weekly cisplatin significantly increased the frequency and severity of nausea/vomiting ($p < 0.001$) and of neurologic ($p = 0.002$), renal ($p < 0.001$), and hematologic toxicities ($p < 0.001$). Respiratory acute toxicities were increased in the RT + cisplatin group. The increased frequency of toxicities was primarily mild to moderate in severity. Toxicities within the radiation fields did not seem to be increased. Additional evaluation for laryngeal edema and nutritional toxicity was also evaluated with different grading schemas (Table 5). The addition of weekly cisplatin also did not significantly increase the spectrum and the severity of any of these toxicities. When each patient was classified by the worst grade of any type of toxicity, the treatment groups were comparable ($p = 0.21$).

Compliance was not measured other than a global evaluation for compliance to the treatment protocol on the Case Evaluation Form. The noncompliance was 16% (25/159) in the RT group compared to 32% (47/149) in the RT + cisplatin group. The number of cycles of cisplatin administered was not available.

Table 6 summarizes the late toxicities observed. Late toxicities were recorded on the Radiotherapy Long Term Follow-up Form. None of the late toxicities evaluated were significantly different except for two toxicities ($p = 0.57$). Both esophageal (9% vs. 3%, $p = 0.03$) and laryngeal (11% vs. 4%, $p = 0.05$) late toxicities were more prevalent in the RT + cisplatin group.

DISCUSSION

The optimal dose for cisplatin radiosensitization is unclear, though a target cumulative dose of at least 200 mg/m² is commonly advocated but is without much supportive evidence (15). Studies using the 100 mg/m² × 3 regimen consistently show that about 70% of patients receive all three doses. Several reports have therefore questioned whether this high-dose bolus schedule is optimal (1, 13, 16). Hence, a fundamental but unanswered question is whether or not comparable cisplatin radiosensitization may be achieved with alternative schedules, such as weekly cisplatin, which may be better tolerated, improving compliance and achieving cumulative doses that approach 300 mg/m² (15, 17–20).

The results reported here constitute part of the early efforts to determine whether cisplatin was an effective radiosensitizer and whether survival could be improved in a homogeneously defined unresectable study population with a poor prognosis. Comparable eligibility criteria were used to define the subsequent Intergroup Phase III trial E1392 (excluding nasopharyngeal carcinoma), which demonstrated superior disease-free survival and OS with the concurrent administration of 100 mg/m² scheduled bolus cisplatin (13). Not only did E2382 permit nasopharyngeal carcinomas, but ECOG PS 2 and 3 patients compared to the now favored PS 0–1 for many clinical trials. These inclusion criteria account for the statistical significance of cell differentiation and PS seen in the univariate and multivariate analyses. Despite this, comparable results in the RT control arm in E1392

(13) and E2382 were observed (median survival: 12.6 months and 13.3 months, respectively) confirming the homogeneity and poor prognosis of the unresectable cohort.

Though they must be interpreted with caution, the superior survival results seen with concurrent cisplatin at 100 mg/m² for three cycles in contrast to the marginal activity with 20 mg/m² for seven weekly cycles ($p = 0.09$) are consistent with the notion that cisplatin radiosensitization may be more dependent on the total dose delivered than on the schedule. Effective tumor radiosensitization with weekly doses of cisplatin may likely necessitate doses greater than 20 mg/m².

The evidence to support the use of higher weekly cisplatin doses is largely inferred. For definitive nonnasopharyngeal head-and-neck squamous cell carcinoma, several small retrospective reports have described the results with weekly cisplatin at 30 mg/m² (19) and 40 mg/m² (15, 18, 20), suggesting that weekly cisplatin is active. Comparisons to every-3-week high-dose cisplatin have been reported because of changes in institutional practices, with comparable local-regional disease control rates observed at weekly doses of 33–40 mg/m² (17) or 40 mg/m² (18). Lower rates of nausea and vomiting and nephrotoxicity (18) and significantly higher cumulative doses were achieved with weekly cisplatin dosing, resulting in 65% of patients receiving 200 mg/m² (18). However, lower cumulative doses with cisplatin dosed at 40 mg/m²/week have been reported (15). The use of weekly cisplatin 40 mg/m² as an effective radiosensitizer is also supported by level 1 evidence from clinical trials of endemic nasopharyngeal carcinoma (21, 22) and cervical carcinoma (23). Improved tolerance with higher rates of completed cycles and less dose reduction have been observed at weekly doses of 40 mg/m² for nasopharyngeal (22) and cervical (23) carcinomas, with no evidence of increased late effects (23).

Although more effective tumor radiosensitization likely requires weekly doses greater than 20 mg/m², this dose was sufficient to significantly increase the risk of late laryngeal (11% vs. 4%) and esophageal (9% vs. 3%) toxicities. The low survival rates observed in this study may contribute to an underreporting of these late toxicities and suggest that this risk may be even higher. In as much as the current paradigm associates chronic oxidative stress with the development of radiation-induced fibroproliferative normal tissue injury (24), these observations suggest that even low weekly doses of cisplatin may be detrimentally contributing to non-selective oxidative injury of the normal tissues. Cisplatin not only induces DNA crosslink damage but can induce 8-OHdG moieties, reflecting its ability to increase oxidative stress to the cell with its cytotoxicity reduced by antioxidant therapy (25). Cancer cells have also been shown to have a greater antioxidant capacity in adaptation to the intrinsic oxidative stress of cancer progression (26).

Hence, weekly cisplatin at 20 mg/m² may not offer the selective radiosensitization that was initially hoped for. It is unclear whether modern conformal radiation techniques, capable of limiting the radiation dose to threshold levels associated with injury to normal swallowing organs (27–29), may allow for more effective combination with higher weekly doses of cisplatin.

CONCLUSION

In summary, this Intergroup trial demonstrated that concurrent weekly cisplatin at a dose of 20 mg/m² did not significantly improve upon the results seen with daily RT to 70 Gy. Although acute toxicities within the radiation field are not significantly increased, the risk of late swallowing toxicities is increased. Higher and potentially more effective weekly doses of cisplatin may pose similar risks and should be considered in future designs of clinical trials.

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Fig. 1.
Study schema.

Fig. 2.
Failure-free survival by treatment.

Fig. 3.
Overall survival by treatment.

Table 1

Study population

Eligibility	Radiation	Radiation + cisplatin (20 mg/m ² /wk)	Total
Randomized	185	186	371
Excluded	8 [*]	10 [†]	18
Ineligible	18	27	45
Eligible for analysis	159	149	308

^{*} Patient refusal ($n = 5$), died before treatment ($n = 1$), received nonprotocol treatment ($n = 1$), could not be positioned for radiation therapy ($n = 1$).

[†] Patient refusal ($n = 4$), died before treatment ($n = 3$), elected non-protocol treatment ($n = 1$), decreased serum creatinine and creatinine clearance ($n = 1$).

Table 2

Patient characteristics

Characteristic	Radiation (<i>n</i> = 159)	Radiation + cisplatin (20 mg/m ² /wk) (<i>n</i> = 149)
Age (y)		
<65	114 (72%)	99 (64%)
65	45 (28%)	54 (36%)
Median	60	61
Range	(19–85)	(20–81)
Sex		
M	133 (84%)	117 (79%)
F	26 (16%)	32 (21%)
Race		
White	122 (77%)	115 (77%)
Nonwhite	37 (23%)	34 (23%)
Weight loss (previous 6 mo)		
0%	46 (29%)	46 (31%)
1–9%	38 (24%)	26 (17%)
10%	63 (40%)	70 (47%)
Unknown	12 (8%)	7 (5%)
Smoking history		
Never	16 (10%)	6 (4%)
Pipe or cigar only	7 (4%)	11 (7%)
Cigarette: <20 pack/y	7 (4%)	9 (6%)
Cigarette: 20–40 pack/y	47 (30%)	38 (26%)
Cigarette: >40 pack/y	78 (49%)	80 (54%)
Unknown	4 (3%)	5 (3%)
Performance status		
0	42 (26%)	33 (22%)
1	81 (51%)	87 (58%)
2	29 (18%)	23 (15%)
3	7 (4%)	6 (4%)
Cell differentiation		
Well	16 (10%)	28 (19%)
Moderate	79 (50%)	80 (54%)
Poor/undifferentiated	48 (30%)	32 (21%)
Unknown	16 (10%)	9 (6%)
T stage		
0	2 (1%)	0 (0%)
1	5 (3%)	3 (2%)
2	14 (9%)	12 (8%)
3	49 (31%)	45 (30%)
4	89 (56%)	89 (60%)

Characteristic	Radiation (n = 159)	Radiation + cisplatin (20 mg/m ² /wk) (n = 149)
N stage		
0	39 (25%)	32 (22%)
1	17 (11%)	24 (16%)
2	32 (20%)	27 (18%)
3	71 (45%)	66 (44%)
Stage		
III	23 (14%)	21 (14%)
IV excluding T4 N3	97 (61%)	89 (60%)
T4 N3	39 (25%)	39 (26%)
Prior surgery		
No	121 (76%)	108 (72%)
Yes	38 (24%)	41 (28%)
Primary site		
Nasopharynx	25 (16%)	16 (11%)
Oral cavity	43 (27%)	51 (34%)
Oropharynx	48 (30%)	37 (25%)
Larynx	7 (4%)	14 (9%)
Hypopharynx	30 (19%)	27 (18%)
Other	6 (4%)	4 (3%)

Table 3

Multivariate proportional hazards model for failure-free survival (FFS) and overall survival (OS)

Covariate	Unfavorable category	<i>p</i> value
Proportional hazards model for FFS		
Treatment	Radiation	0.096
Performance status	2, 3	0.0002
Alcohol	Yes	0.02
Site	Non-nasopharynx	0.003
Stage	T4 N3	0.009
Proportional hazards model for OS		
Treatment	Radiation + cisplatin (20 mg/m ² /wk)	0.60
Performance status	2, 3	<0.001
Weight loss	Yes	<0.001
Sex	Male	0.002
Age (y)	65	0.005

Table 4

Best tumor response by treatment group

Response rate	Radiation	Radiation + cisplatin (20 mg/m ² /wk)	Total	<i>p</i> value
CR	59 (37%)	60 (40%)	119 (39%)	0.64
PR	48 (30%)	57 (39%)	105 (34%)	
CR + PR	67%	79%		
No change	12 (8%)	11 (7%)	23 (7%)	
Progressive disease	33 (21%)	14 (9%)	47 (15%)	
Unevaluable	7 (4%)	7 (5%)	14 (5%)	0.03
Total	159 (100%)	149 (100%)	308 (100%)	

Abbreviations: CR = complete response; PR = partial response.

Table 5

Acute adverse effects

Toxicity	Treatment	Grade					Lethal	p value
		None	Mild	Mod	Sev	LT		
Nausea/vomiting	RT	84%	7%	8%	1%			<0.001
	RT + P	40%	24%	34%	3%			
Diarrhea	RT	94%	3%	3%				0.45
	RT + P	91%	7%	2%				
Infection	RT	85%	6%	9%	1%			0.11
	RT + P	79%	5%	13%	3%	1%		
Hemorrhage	RT	97%	1%	1%	1%			0.80
	RT + P	97%	3%					
Skin/mucosa	RT	11%	23%	46%	20%	1%		0.22
	RT + P	15%	25%	41%	18%	1%		
Neurologic	RT	94%	3%	4%				0.002
	RT + P	82%	11%	7%	1%			
Respiratory	RT	97%	3%					0.01
	RT + P	90%	7%	2%		1%		
Genitourinary	RT	87%	11%	1%	1%			<0.001
	RT + P	70%	28%	2%	1%			
Hematologic	RT	58%	30%	9%	4%			<0.001
	RT + P	29%	37%	23%	10%	1%		
Renal	RT	91%	6%	3%				0.27
	RT + P	87%	9%	3%	1%			
Other	RT	48%	20%	24%	6%	1%	1%	0.92
	RT + P	48%	22%	21%	7%		1%	
Worst	RT	4%	10%	53%	31%	1%	1%	0.21
	RT + P	2%	11%	47%	36%	3%	1%	
Laryngeal edema *			0	1	2	3	4	
	RT		65%	18%	14%	3%		0.72
	RT + P		66%	19%	10%	4%	1%	

Toxicity	Treatment	Grade										p value
		None	Mild	Mod	Sev	LT	Lethal					
Nutritional [†]	RT	0	1	2	3	4	5	6	7	8	0.29	
	RT + P	38%	8%	24%	14%	3%	8%	1%	4%	1%		
		34%	7%	21%	21%	1%	8%	2%	3%			

Abbreviations: Mod = moderate; Sev = severe; LT = lethal; RT = control arm treated with radiotherapy and concurrent cisplatin (P).

* Laryngeal edema grading: 0 = none, 1 = mild, 2 = moderate, 3 = moderate to severe with deterioration of voice, 4 = requires tracheostomy.

[†] Nutritional acute toxicity grading: 0 = none, 1 = regular diet, 2 = soft diet, 3 = liquid diet, 4 = intravenous fluids, 5 = nasogastric tube, 6 = hyperalimentation, 7 = gastrostomy, 8 = hospitalization required.

Table 6

Late adverse effects

Late effect	Radiation	Radiation + cisplatin (20 mg/m ² /wk)	<i>p</i> value
Skin	21%	15%	0.18
Mucous membrane	28%	22%	0.29
Subcutaneous tissue	11%	13%	0.60
Esophagus	3%	9%	0.03
Larynx	4%	11%	0.05
Other	13%	16%	0.52