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Weekly Chemotherapy with Radiation versus High-Dose Cisplatin with Radiation as Organ Preservation for Patients with HPV Positive and HPV Negative Locally Advanced Squamous Cell Carcinoma of the Oropharynx (SCCOP)

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Abstract

Background—Optimal treatment for locally advanced SCCOP is not well defined. Here we retrospectively compare survival and toxicities from two different organ preservation protocols.

Methods—The matched dataset consisted of 35 patients from each trial matched for age, stage, smoking, and tumor HPV status. Patients on University of Michigan Cancer Center (UMCC) trial 9921 were treated with induction chemotherapy followed by high-dose cisplatin and radiation in

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responders, or surgery in non-responders. Patients on UMCC trial 0221 were treated with weekly carboplatin and paclitaxel and radiation.

Results—Survival was comparable for both studies and did not differ significantly across each trial after stratifying by HPV status. Grade 3 and 4 toxicities were more frequent in UMCC 9921. At 6 months post-treatment, G-tube dependence was not statistically different.

Conclusions—These data suggest that survival outcomes in patients with locally advanced SCCOP are not compromised with weekly chemotherapy and RT, and such treatment is generally more tolerable.

Keywords

chemoradiation; oropharynx; HPV; weekly; toxicity

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) accounts for approximately 3–4% of all new cancer diagnoses each year (1E). Approximately 49,260 new cases of SCC of the oral cavity, oropharynx, and larynx were diagnosed in the United States in 2010 (2), and approximately 60% of these patients present with locally advanced disease (2). Such patients are primarily treated with combined chemoradiotherapy (CRT) as a means of organ preservation (3, 4). In particular, definitive CRT offers excellent survival and functional results for patients with squamous cell carcinoma of the oropharynx SCCOP, especially those with human papillomavirus (HPV)-positive disease (5). As the number of HPV-related oropharynx cancers continues to rise, there is growing concern that this patient population is perhaps being overtreated. Work is currently underway to find treatment strategies that provide excellent survival but with lesser toxicity.

Cisplatin based CRT regimens remain standard of care for the majority of patients with locally advanced SCCOP (3, 4). Carboplatin has been used alone or in combination with other cytotoxic chemotherapies in conjunction with radiation to treat oropharynx SCC with outcomes similar to those of cisplatin-based regimens, although no large randomized studies have compared the efficacy of carboplatin and radiation with that of high-dose cisplatin and radiotherapy. (6–8) Studies combining weekly platinum and taxanes with radiation demonstrate similar efficacy to high-dose cisplatin-containing regimens, but again such combinations have not been compared head-to-head. These weekly chemoradiotherapy strategies do, however, appear to be more tolerable than their high-dose platinum counterparts. (9–11)

To evaluate for efficacy and tolerability, we compared a weekly carboplatin- and paclitaxel-radiotherapy regimen against a chemoselection regimen utilizing high-dose cisplatin and radiotherapy following one cycle of induction chemotherapy.

Materials and Methods

Patient populations

We retrospectively conducted pairwise matching of patients from two prospective, single arm phase II trials that employed different treatment strategies for stage III/IV SCCOP (UMCC trial 9921 and UMCC trial 0221). Our goal was to compare survival outcomes and toxicities of these treatment strategies. Both protocols enrolled patients with histologically confirmed, previously untreated stage III or IV SCCOP, who were candidates for treatment with curative intent. All patients had a Karnofsky performance status of at least 60%. UMCC 9921 protocol enrolled only patients who were candidates for complete surgical resection, while UMCC 0221 eligibility did not require surgical resectability. However, our analysis only included those patients who were deemed surgically resectable.

Treatment Protocols

The schemata for both trials is shown in Figure 1. UMCC 9921 trial (6) enrolled patients from January 1, 2000 through November 30, 2002. It employed chemoselection with one cycle of induction chemotherapy (IC) with 5-fluorouracil at 1,000mg/m²/day by continuous infusion, days 1 through 5, plus either cisplatin at 100 mg/m² (n=31) or carboplatin (n=4) dosed at an area under curve (AUC) of 6, on day 1. Subjects were then assessed by direct laryngoscopy three weeks after IC. Responders (patients with greater than 50% reduction in bidimensional product of the primary tumor area on direct laryngoscopy) were then treated with definitive concurrent chemoradiation (CRT) utilizing intensity-modulated radiation therapy (IMRT) in daily 2-Gy fractions 5 days a week to a total of 70 Gy to areas of gross disease. Radiation was administered concurrently with cisplatin (100mg/m²) or carboplatin (AUC 6) on days 1, 22, and 43. Tissue volumes at risk of harboring subclinical disease received 59–63 Gy at 1.7–1.8/fraction. Non-responders (patients with 50% or less reduction in bidimensional product of the primary tumor area) underwent definitive surgery followed by adjuvant radiation (66Gy). Eight weeks after completion of CRT direct laryngoscopy was performed. Patients without residual disease were offered adjuvant paclitaxel (two cycles at 175 mg/m² every 21 days). Those with residual disease underwent surgical resection of the primary tumor with an ipsilateral neck dissection. Cervical lymph nodes of 3 cm or greater at time of diagnosis were among the indications for planned neck dissection (6). Post-therapy evaluations consisted of clinical exams every 6–8 weeks and PET-CT imaging at 3 and 12 months. UMCC 0221 trial (9) employed IMRT (70Gy delivered in 2Gy fractions over 7 weeks) concurrently with weekly chemotherapy, carboplatin (AUC 1) plus paclitaxel (30 mg/m²). IMRT planning objectives included sparing of the swallowing structures (i.e. pharyngeal constrictor muscles, esophagus, glottic and supraglottic larynx, major salivary glands and oral cavity). Post-therapy evaluations consisted of clinical exams every 6–8 weeks and PET-CT imaging at 3 and 12 months.

HPV testing

HPV testing on pre-treatment biopsies was performed using HPV PCR-MassArray, which detects and identifies 15 high-risk HPV subtypes using type-specific, multiplex, competitive PCR and single base extension followed by MALDI-TOF Mass Spectrometry analysis, as previously described (12).

Statistical Analysis

Propensity score matching of patients treated on these two protocols yielded 35 pairs of subjects (70 subjects) matched for age, clinical stage, smoking status (never smoked, past smoker, or current smoker) and tumor HPV status. Primary end points were overall survival (OS), defined as duration of survival from date of enrollment to date of death from any cause, and disease-specific survival (DSS), which was defined as time from enrollment to date of death from local recurrence, distant metastasis, or treatment-related mortality. Deaths from other causes were treated as censored observations for DSS analysis. Kaplan-Meier estimates were calculated for OS and DSS. The results from univariate Cox proportional hazards models and multivariable Cox models chosen from a backward selection process are presented here. The matched datasets were adjusted using multivariate statistics and cluster analyses to account for the correlated nature of the matched pairs. Secondary endpoints included treatment-induced toxicities and persistent gastric (G)-tube use beyond 6 months. Generalized estimating equations (GEE) models were employed to analyze these dichotomous outcomes adjusting for the matched nature of the dataset. Adjusted analysis was performed for the matched design and obtained similar results to unadjusted analysis. For all statistical analyses, a p-value of less than 0.05 was considered significant. Of the patients treated on 9921 protocol, three underwent early surgery due to the failure of induction chemotherapy. The analysis shown in this paper includes all patients; a sensitivity analysis removing the 3 surgery patients is described as well.

Both UMCC 9921 and UMCC 0221 trials were reviewed and approved by the institutional IRB, and were in accordance with the Helsinki Declaration of 1975 as revised in 1983.

Results

Comparability of Matched Patients

Survival outcomes and toxicities were compared amongst the two trials. To assure a meaningful comparison, we matched patients by study cohort for age, smoking status, and tumor HPV status. In total, 70 patients (35 from each trial) were matched. The patients were well balanced between the 0221 and 9921 cohorts (Table 1). All patients included in the analysis had an ECOG performance status of 0 or 1, but there were more ECOG 0 patients in the 9921 than the 0221 group (ECOG 0, 86% vs. 63%; ECOG 1, 14% vs. 37%, $p=0.05$). Both groups enrolled predominantly male patients, although the proportion of females was higher in the 9921 trial (29% vs. 9%, $p=0.03$). Three patients in the 9921 group failed induction chemotherapy and therefore required early surgery.

Survival Outcomes

In the univariate analysis (Figure 2A), survival at 36 months was superior in the UMCC 0221 group compared to the UMCC 9921 group (88% vs. 71%, hazard ratio, 0.35, 95% confidence interval 0.14 – 0.89). However, this difference was not confirmed on multivariate analysis (Table 2). Another factor that predicted improved survival in the univariate, but not the multivariate analysis, was past smoker vs. current smoker status (HR, 0.083, 95% CI 0.012 – 0.59). Our analysis confirmed that HPV-positive status was associated with superior survival (multivariate model, HR 0.26, 95% CI 0.09 – 0.72). DSS at

3 years was superior in the UMCC 0221 group in the univariate (97% vs. 81%), but not within the multivariate analysis (Figure 2B). The favorable prognostic value of HPV-positive status was seen for patients in both study cohorts (Figure 3). Comparing HPV+ve patients in both protocols, a trend toward an association between improved survival and UMCC0221 protocol was observed within the HPV+ve group ($p=0.06$). The best survival was seen in HPV-positive patients in UMCC 0221, while the worst survival was observed in HPV-negative patients treated on UMCC 9921 ($p=0.01$). Previously published analyses reported 70.4% OS and 75.8% DSS rates at 4 years in UMCC9921. At a median follow-up of 36 months, 3-year disease-free and locoregional recurrence-free survivals were reported as 88% and 96%, respectively in UMCC0221. Exclusion of the 3 patients on 9921 protocol who underwent early surgery did not affect the overall survival outcomes (data not shown).

Comparison of Toxicities

Toxicities (all grades) were overall more prevalent in the 9921 group with the exception of weakness/fatigue, which was somewhat more frequent in the 0221 group (54% vs. 40% respectively, $p=0.09$). (Table 3). Among grade III and IV toxicities, leukopenia, neutropenia and mucositis were more prevalent in the 9921 group.

Persistent G-tube dependence for longer than 6 months was seen more often in the 9921 than the 0221 patients, albeit it was not statistically significant (26% vs. 6%, $p=0.05$). This did not vary by HPV status (Table 4). When the 3 early surgery patients from 9921 protocol were excluded from analysis, the difference across protocols became statistically significant ($p=0.04$).

Discussion

Weekly administration of platinum-based chemotherapy with radiation, while potentially allowing for lower toxicity (13), has not been established as standard of care for patients with locally advanced SCC of the head and neck. Furthermore, there are no randomized trials demonstrating the benefit of taxane-based chemoradiotherapy regimens, with or without platinum, over bolus regimens of cisplatin with radiation or even radiotherapy alone. Our center has studied methods of organ preservation in oropharynx cancer patients utilizing both a standard, high-dose cisplatin chemoradiation regimen and a weekly carboplatin and paclitaxel chemoradiation regimen, both with similar outcomes. Given the lack of randomized data comparing weekly to bolus-dose platinum chemoradiotherapy regimens, we elected to compare these two trials to evaluate efficacy and toxicity. The results of our pairwise-matched analysis are interesting, as they imply that our less toxic organ preservation approach with weekly chemotherapy and radiation provides similar clinical efficacy to that of high-dose cisplatin and radiation.

Bolus-dose cisplatin chemoradiation regimens incur significant toxicities (14–16), while , weekly chemoradiation is better tolerated overall, with lower incidence of side effects, as seen in our study and other trials utilizing weekly chemoradiotherapy (10, 11, 17, 18). Radiation therapy contributes extensively to the toxicity observed in these patients; however, weekly chemotherapy itself is usually well tolerated. We specifically report on long-term G-tube dependence, as this is a major impediment to regaining quality of life for

many patients with head and neck cancers. In our experience, there was a decreased long-term G-tube dependence with weekly chemoradiotherapy.

Although our data is not randomized or prospective, our findings are important as we are the first to report outcomes of a comparison of a weekly versus a bolus-dose chemoradiotherapy regimen for locally advanced SCCOP. Since the ideal weekly regimen has yet to be identified, we believe that our carboplatin/paclitaxel treatment schedule is acceptable given its overall tolerability. Several phase II trials have utilized either carboplatin or cisplatin with paclitaxel, but no randomized comparisons of weekly chemoradiotherapy regimens have been reported (Table 5). Due to the vast heterogeneity amongst these trials, it is difficult to make definitive comparisons. Our study, for instance, evaluated only patients with oropharynx primaries, while most others included multiple primary sites with variability in terms of surgical resectability. Furthermore, ours was the only trial to evaluate chemoradiation regimens in the setting of HPV other than Sunteralingam et al (19), which included cetuximab and reported high rates of mucositis. Additionally, there is a wide variability in the chemotherapy regimens administered and the type of radiation delivered amongst these studies. (20–23)

A number of studies utilized a lower dose, weekly cisplatin, either alone or in combination with other agents (17, 18, 24, 30). However, no comparisons with high-dose cisplatin are available. HPV is now an important prognostic biomarker in SCCOP. Current data demonstrates three year survival rates of greater than 80% in patients with HPV positive tumors when treated with combined chemoradiotherapy (5). As long-term survival is more likely achievable in these patients, freedom from long-term and late side effects is an emerging goal. Efforts are currently underway to reduce toxicity without undermining the effect of chemoradiotherapy. RTOG 1016 (NCT01302834) is large randomized trial enrolling HPV positive oropharyngeal cancer patients to treatment with both cetuximab and accelerated-fractionation radiotherapy versus two cycles of high-dose cisplatin with accelerated-fractionation radiotherapy. This study is rapidly accruing patients and plans to enroll close to 800 subjects. The Eastern Oncology Cooperative Group has now completed a dose de-escalation study (ECOG 1308), whereby HPV-associated oropharynx tumors that were complete responders to induction chemotherapy were treated with 54 Gy of IMRT with cetuximab. The toxicity data was presented at the 2012 American Society of Clinical Oncology Annual Meeting (25). The final results of both trials are eagerly awaited with the hope that reduced intensity chemoradiotherapy regimens will provide similar benefits to those of traditional platinum-based therapies.

The retrospective nature of this study explains our inherent limitations, as does the fairly small sample size and short follow-up time. Our results should therefore be interpreted with caution. However, the statistical methodology to create a balanced dataset for comparison, utilizing pairwise matching of the subjects and well-balanced cohorts, strengthens our work. In particular, propensity score matching was employed to produce a matched dataset of patients balanced by age, stage, smoking and tumor HPV status. This resulted in a reduction of sample size but allowed for a more accurate analysis (26).

The results of our pairwise-matched analysis are interesting and hypothesis-generating, and they imply that a better-tolerated, organ-preservation approach with a weekly carboplatin and paclitaxel-based chemoradiation regimen provides clinical efficacy similar to that of a more toxic, bolus cisplatin chemoradiation protocol. They also confirm numerous earlier observations of better outcomes in HPV-related SCCOP. Prospective, randomized studies evaluating weekly chemoradiotherapy regimens with high-dose cisplatin and radiation may be warranted in patients with oropharyngeal cancers, especially if outcomes from RTOG 1016 and ECOG 1308 fail to demonstrate an advantage with cetuximab-radiotherapy or reduced-intensity radiation with cetuximab.

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Figure 1.

Patients whose outcomes are compared were treated according to UMCC 9921 or UMCC 0221 protocol.

Figure 2.
Survival at 3 years: A, overall survival, B, disease specific survival.

Figure 3.

Overall survival by treatment protocol and HPV status of the tumor.

Table 1

Demographics of the matched patients. Thirty-five pairs of subjects (70 subjects) matched for age, clinical stage, smoking status, and tumor HPV status.

	9921 (n=35)	0221 (n=35)	P-value
Age mean (SD)	55.0 (7.6)	55.0 (7.9)	0.99
Stage n(%)			1.00
Stage 3	7 (20%)	7 (20%)	
Stage 4	28 (80%)	28 (80%)	
Gender n(%)			0.03
Female	10 (29%)	3 (9%)	
Male	25 (71%)	32 (91%)	
ECOG n(%)			0.05
0	30 (86%)	22 (63%)	
1	5 (14%)	13 (37%)	
Smoking Status n(%)			1.00
Never	8 (23%)	8 (23%)	
Past	14 (40%)	14 (40%)	
Current	13 (37%)	13 (37%)	
HPV Result			1.00
+ve	27 (77%)	27 (77%)	
-ve	8 (23%)	8 (23%)	

Table 2

Comparison of overall survival in the pairwise-matched datasets.

Predictor	Univariate model p-value	HR in univariate Cox model (95% CI)	Multivariable model p-value	Hazard Ratio in Multivariable model (95% CI)
Protocol (0221 vs. 9921)	0.027	0.35(0.14, 0.89)	NS	
Female vs. Male	0.0003	5.48 (2.16, 13.92)	0.0054	3.83(1.49, 9.86)
Stage (4 vs. 3)	0.62	1.43 (0.35, 5.86)	NS	
ECOG (1 vs. 0)	0.81	0.86 (0.24, 3.07)	NS	
Never vs. Current	0.34	0.47(0.10, 2.25)	NS	
Past vs. Current Smoker	0.013	0.083 (0.012, 0.59)	NS	
HPV status (+ve vs. -ve)	0.001	0.19 (0.068, 0.51)	0.0094	0.26 (0.09, 0.72)

Table 3

Toxicity rates in matched datasets.

	All-grade toxicities			Grade 3–4 toxicities		
	9921	0221	P-value	9921	0221	P-value
Leukopenia	25(71%)	6(17%)	<0.0001	5(14%)	0(0%)	0.03
Neutropenia	19(54%)	3(9%)	<0.0001	12(34%)	0(0%)	<0.0001
Anemia	21(60%)	0(0%)	<0.0001	1(3%)	0(0%)	0.50
Thrombopenia	9(26%)	1(3%)	0.006	1(3%)	1(3%)	0.51
Nausea	23(66%)	10(29%)	0.002	3(9%)	3(9%)	0.33
Vomiting	17(49%)	10(29%)	0.05	3(9%)	3(9%)	0.33
Neutropathy	9(26%)	1(3%)	0.006	0	0	
Diarrhea	5(14%)	0(0%)	0.03	1(3%)	0(0%)	0.06
Fatigue/weakness	14(40%)	19(54%)	0.09	1(3%)	1(3%)	0.51
Mucositis	100%	100%		24(75%)	15(47%)	0.01

--Inestimable in GEE model

Table 4

G-tube dependence at 6 months after completion of treatment.

	9921	0221	P-value
G-tube 6 mos	9(26%)	2 (6%)	0.05
In HPV+ves (n=27 pairs)	7 (26%)	2 (7%)	0.14
In HPV–ves (n=8 pairs)	2 (25%)	0(0%)	0.47

Table 5

Efficacy and Toxicities of Various Chemoradiation Protocols.

Manuscript	N subj/ Median follow -up	Regions included	Chemo regimen	Stage	Radiation	DFS or PFS	Locoregional control	Survival	Grade 3-4 toxicities				Long-term G-tube dependence
									neutropenia	mucositis	fatigue/ lethargy		
Current analysis	70/36mos	OP	Induction x1 with 5-FU 1000mg/m2/d Cix5days and cisplatin 100mg/m2 d1 or carboplatin AUC 6 d, then CRT with cisplatin 100mg/m2 q3weeks; +/- adjuvant paclitaxel 175mg/m2 q3weeks x2. CRT with weekly carboplatin AUC 1 and paclitaxel 30mg/m2	III, 20%, IV, 80%, all resectable	70 Gy, daily	NR	NR	OS 71% at 3 years p=0.027 DSS 81% at 3 years p<0.01	34% p<0.0001	75% p=0.01	3%	26% at 6 months	
								OS 88% at 3 years p=0.027 DSS 97% at 3 years p<0.01	0 p<0.0001	47% p=0.01	3%	6% at 6 months	
Weekly chemo-RT regimens													
Suntharalingam et al. (19)	43/31 mos	OP 67%, larynx 14%, HP 9%, NP 9%	CRT with weekly paclitaxel 40mg/m2, carboplatin AUC 2; cetuximab 400mg/m2 load, then 250mg/m2 weekly.	Stage III -IV, all M0	70.2Gy, daily	DFS 58% at 3 years	CR 84%, LRC, 72% at 3 years	OS 59% at 3 years OP: HPV +100%, HPV- 43% (p=0.032).	21%	79%	NR	NR	NR
Semrau et al (22)	84/36 mos	OP 77.4%, HP 22.6%	CRT with weekly paclitaxel 40mg/m2 and carboplatin AUC 1for up to 6 cycles	IV, all inoperable	Hyperfractionated- accelerated RT to 69.2 Gy or conventional RT to 70-72 Gy	PFS 41% at 2 years, 29.4% at 5 years	NR	OS 46.3% at 2 years, 35.3% at 5 years.	Leukopenia 6%	51.2%	NR	Median retention of G-tube 58 weeks	

Manuscript	N subj/ Median follow -up	Regions included	Chemo regimen	Stage	Radiation	DFS or PFS	Locoregional control	Survival	Grade 3–4 toxicities			Long-term G-tube dependence
									neutropenia	mucositis	fatigue/ lethargy	
Sharma et al. (24)	153/22 mos	OP 92%, NP 8%	None (RT alone)	II 9.2%, III 36.8%, IV 54%, resectability NR	70Gy, daily	Median PFS 22 mos	CR 67.1% (p=0.044)	OS 62% at 3 years (p=0.024)	NR	16% (p=0.002)	NR	NR
		OP 63.2%, NP 37.7%	CRT with weekly cisplatin 40mg/m2	II 3.9%, III 37.7%, IV 55.9%, resectability NR		Median PFS 24 mos	CR 80.5% (p=0.044)	OS 42% at 3 years (p=0.024)		40% (p=0.002)		
Maguire et al. (17)	39/37. 5mos	OP 59%, larynx 20%, HP 13%, OC 7%	CRT with weekly cisplatin 33mg/m2	III 38%, IVa 62%	70 Gy, BID	PFS 82% at 3 years	LRC 87% at 3 years	Actuarial OS 80% at 3 years	Leukopenia 26%	38%	28%	NR
Haddad et al. (27)	58/34 mos	OP 62%, OC 17%, larynx 10%, UP 7%	CRT with weekly x4 carboplatin AUC 1.5 and paclitaxel 45mg/m2; daily amifostine 500mg SQ for the duration of RT	III 14%, IV 86%, all M0, resectability NR	72 Gy (daily x18, then BID)	PFS 90% at 3 years	LRC 96% at 3 years	OS 89% at 3 years	NR	70%	NR	1.7%
		OP 58%, OC 21%, larynx 17%	CRT with weekly x4 carboplatin AUC 1.5 and paclitaxel 45mg/m2							75%		
Lee et al (18)	32/28. 2 mos	OP 28%, OC 25%, HP 13%, larynx 16%, NP 6%	CRT with weekly 5-FU 750mg/m2 and cisplatin 20mg/m2	III 44%, IV 56%, 18% unresectable, all M0	69.2 Gy, daily	PFS 66% at 2 years	CR 41%, ORR 91%	76% at 2 years	8%	16%	NR	0%
Carter et al. (10)	52/61 mos	NR	CRT with weekly paclitaxel 40mg/m2 and carboplatin AUC 1	III 33%, IV 67%, all M0	69.6Gy BID	PFS 50% at 3 years	CR 67%	60% at 3 years	4%	55%	12%	NR

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									neutropenia	mucositis	fatigue/ lethargy	
Chougule et al. (23)	43/49 mos	OP 35%, larynx 25%, HP 16%, OC 14%, NP 10%	CRT with weekly paclitaxel 60mg/m ² and carboplatin AUC 1	III 28%, IV 72%, 67% unresectable, all M0	66-72Gy, daily	NR	CR 65- 83%	median OS 51.5 mos, 40% at 5 years	12%	90%	NR	4.6%
High-dose cisplatin based CRT												
Ang et al (15, RTOG9914)	84/2.2 years	OP 66%, OC 12%, HP 11%, larynx 12%	CRT with cisplatin 100mg/m ² d 1, 22	III 12%, IV 88%, all M0	72 Gy (daily x18, then BID)	DFS 53.5% at 2 years	CR 83%	OS 71.6% at 2 years	NR	53%	9%	11%
Forastiere et al (16, RTOG 91-11)	547/3. 8 years	larynx	A. Induction x2-3 cycles with cisplatin 100mg/m ² d1 and 5-FU 1000mg/m ² /d CIx5days followed by RT	III 64%, IV 36%, all resectable	70 Gy, daily	DFS, 52% at 2 years, 38% at 5 years (p=0.02 vs. XRT alone)	Laryngeal preservation 75% at 2 years	OS 76% at 2 years, 55% at 5 years	NR	24%	NR	NR
			B. CRT with cisplatin 100mg/m ² d1, 22, 43.			DFS, 61% at 2 years, 36% at 5 years (p=0.006 vs. XRT alone)	Laryngeal preservation 88% at 2 years	OS 74% at 2 years, 54% at 5 years		43%		
			C. None			DFS, 44% at 2 years, 27% at 5 years	Laryngeal preservation 70% at 2 years	OS 75% at 2 years, 56% at 5 years		24%		
Adelstein et al (28)	295/4 1 mos	OC 16.8%, OP 54.7%, HP 20%, larynx 8.5%	A. None	III, IV, all M0, all unresectable	70 Gy, daily	NR	CR 27.4% (p=0.002 vs. arm C)	OS 23% at 3 years (p=0.014 vs. arm B), DSS 33% at 3 years (p=0.01 vs. arm B)	Leukopenia, 1% (p<0.001)	6% (p=0.03 vs. arm B)	NR	NR
			B. CRT with cisplatin 100mg/m ² d1, 22, 43				CR 40.2%	OS 37% at 3 years, DSS 51% at 3 years	Leukopenia, 40% (p<0.001)	15%		

Manuscript	N subj/ Median follow -up	Regions included	Chemo regimen	Stage	Radiation	DFS or PFS	Locoregional control	Survival	Grade 3–4 toxicities			Long-term G-tube dependence
									neutropenia	mucositis	fatigue/ lethargy	
			C. CRT with cisplatin 75mg/m2 q4weeks and 5-FU 1000mg/m2/d CIx4days		60–70 Gy, split course		CR 49.4%	OS 27% at 3 years, DSS 41% at 3 years	Leukopenia, 29% (p<0.001)	8%		

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IMRT, intensity-modulated radiation therapy; OP, oropharynx; HP, hypopharynx; NP, nasopharynx; OC, oral cavity; UP, unknown primary; 5-FU, 5-fluorouracil; 3D-CRT, 3-dimensional conformal radiation therapy; DFS, disease-free survival; CR, complete response; PFS, progression-free survival; OS, overall survival; DSS, disease-specific survival; LRC, locoregional control rate; CRT, chemoradiotherapy; ORR, overall response rate calculated as complete plus partial response;