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

Irina Y. Dobrosotskaya, MD, PhD,[1†] Emily Bellile, MS,[2] Matthew E. Spector, MD,[3] Bhavna Kumar, MS,[4] Felix Feng, MD,[5] Avraham Eisbruch, MD,[5] Gregory T. Wolf, MD,[3] Mark E. P. Prince, MD,[3] Jeffrey S. Moyer, MD,[3] Theodoros Teknos, MD,[4] Douglas B. Chepeha, MD,[3] Heather M. Walline, MS,[3] Jonathan B. McHugh, MD,[6] Kitrina G. Cordell, DDS, MS,[7] P. Daniel Ward, MD,[8] Serena Byrd, MD,[9] Jessica H. Maxwell, MD,[10] Susan Urba, MD,[1] Carol R. Bradford, MD,[3] Thomas E. Carey, PhD,[3] Francis P. Worden, MD[1*]

[1]Department of Internal Medicine, University of Michigan, Ann Arbor, MI, [2]Department of Biostatistics, University of Michigan, Ann Arbor, MI, [3]Department of Otolaryngology, University of Michigan, Ann Arbor, MI, [4]The Ohio State University, Department of Otolaryngology/Head Neck Surgery, Columbus, OH, [5]University of Michigan, Department of Radiation Oncology, Ann Arbor, MI, [6]Department of Pathology, University of Michigan, Ann Arbor, MI, [7]Louisiana State University Health Sciences Center, Department of Oral and Maxillofacial Pathology, New Orleans, LA, [8]University of Utah School of Medicine, Department of Facial Plastic and Reconstructive Surgery, Salt Lake City, UT, [9]St. Louis University School of Medicine, Department of Otolaryngology, St. Louis, MO, [10]University of Pittsburgh Medical Center, Department of Otolaryngology, Pittsburgh, PA, [11]Henry Ford Health System, 2799 W. Grand Blvd., Detroit, Michigan.

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ABSTRACT: *Background:* Optimal treatment for locally advanced squamous cell carcinoma of the oropharynx (SCCOP) is not well defined. Here we retrospectively compare survival and toxicities from 2 different organ preservation protocols.

Methods. The matched dataset consisted of 35 patients from each trial matched for age, stage, smoking, and tumor human papillomavirus (HPV) status. Patients in the University of Michigan Cancer Center (UMCC) trial 9921 were treated with induction chemotherapy (IC) followed by high-dose cisplatin and radiation in responders or surgery in nonresponders. Patients in the 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, gastrostomy tube (G-tube) dependence was not statistically different.

Conclusion. These data suggest that survival outcomes in patients with locally advanced SCCOP are not compromised with weekly chemotherapy and radiation therapy, and such treatment is generally more tolerable. © 2013 Wiley Periodicals, Inc. *Head Neck* **36:** 617–623, 2014

KEY WORDS: chemoradiation, oropharynx, HPV, weekly, toxicity

INTRODUCTION

Squamous cell carcinoma of the head and neck accounts for approximately 3% to 4% of all new cancer diagnoses each year.[1] 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 SCC of the oropharynx (SCCOP), especially those with human papillomavirus (HPV)-positive disease.[5] As the number of HPV-related oropharyngeal 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 the 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 oropharyngeal 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 CRT strategies do, however, seem to be more tolerable than their high-dose platinum counterparts.[9–11]

To evaluate for efficacy and tolerability, we compared a weekly carboplatin-radiotherapy and paclitaxel-radiotherapy

***Corresponding author:** F. P. Worden, University of Michigan, Department of Internal Medicine, Division of Hematology/Oncology, 1500 E. Medical Center Dr., SPC 5848, Ann Arbor, MI 48109. E-mail: fworden@med.umich.edu

†Current address: Henry Ford Health System, 2799 W. Grand Blvd., Detroit, Michigan.

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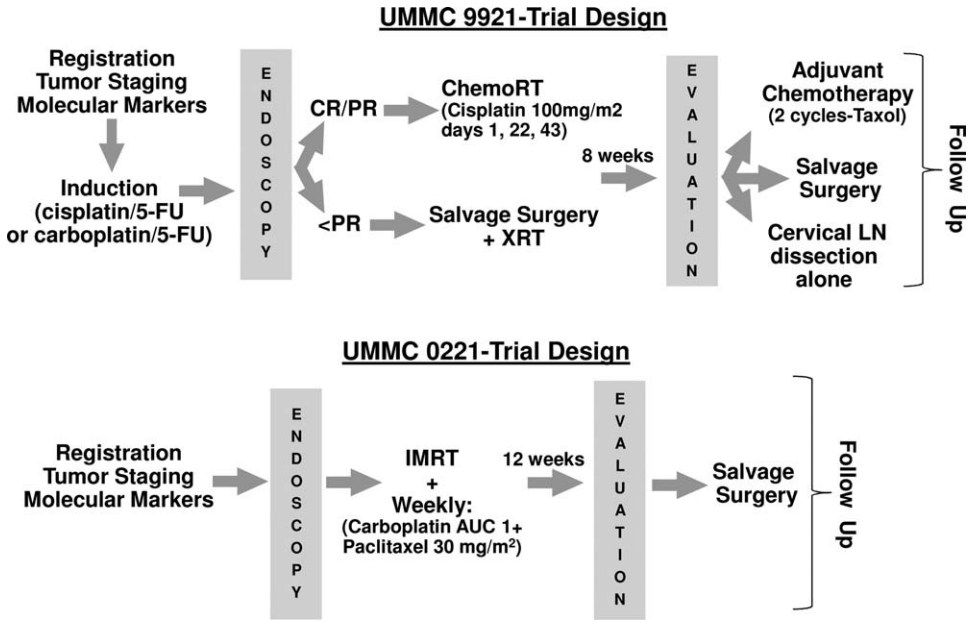

FIGURE 1. Patients whose outcomes are compared were treated according to University of Michigan Cancer Center (UMCC) 9921 trial or the UMCC 0221 trial protocols.

regimen against a chemoselection regimen utilizing high-dose cisplatin and radiotherapy after 1 cycle of induction chemotherapy (IC).

MATERIALS AND METHODS

Patient populations

We retrospectively conducted pairwise matching of patients from 2 prospective, single arm phase II trials that used different treatment strategies for stage III/IV SCCOP (University of Michigan Cancer Center [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, whereas 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 are shown in Figure 1. UMCC 9921 trial[6] enrolled patients from January 1, 2000, through November 30, 2002. It used chemoselection with 1 cycle of IC with 5-fluorouracil at 1000 mg/m^2/day by continuous infusion, days 1 through 5, plus either cisplatin at 100 mg/m^2 ($n = 31$) or carboplatin ($n = 4$) dosed at an area under curve (AUC) of 6 on day 1. Patients were then assessed by direct laryngoscopy 3 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 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 (100 mg/m^2) or carboplatin (AUC 6) on days 1, 22, and 43. Tissue volumes at risk of harboring subclinical disease received 59 to 63 Gy at 1.7 to 1.8/fraction. Nonresponders (patients with 50% or less reduction in bidimensional product of the primary tumor area) underwent definitive surgery followed by adjuvant radiation (66 Gy). Eight weeks after completion of CRT, direct laryngoscopy was performed. Patients without residual disease were offered adjuvant paclitaxel (2 cycles at 175 mg/m^2 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 the time of diagnosis were among the indications for planned neck dissection.[6] Posttherapy evaluations consisted of clinical examinations every 6 to 8 weeks and positron emission tomography (PET)-CT imaging at 3 and 12 months. UMCC 0221 trial[9] used IMRT (70 Gy delivered in 2 Gy fractions over 7 weeks) concurrently with weekly chemotherapy, carboplatin (AUC 1) plus paclitaxel (30 mg/m^2). IMRT planning objectives included sparing of the swallowing structures (ie, pharyngeal constrictor muscles, esophagus, glottic and supraglottic larynx, major salivary glands, and oral cavity). Posttherapy evaluations consisted of clinical examinations every 6 to 8 weeks and PET-CT imaging at 3 and 12 months.

Human papillomavirus testing

HPV testing on pretreatment biopsies was performed using HPV polymerase chain reaction–mass array, which detects and identifies 15 high-risk HPV subtypes using

TABLE 1. Demographics of the matched patients. Thirty-five pairs of patients (70 patients) matched for age, clinical stage, smoking status, and tumor human papillomavirus status.

	UMCC 9921 ($n = 35$)	UMCC 0221 ($n = 35$)	p value
Age mean (SD)	55.0 (7.6)	55.0 (7.9)	.99
Stage no. (%)			1
Stage 3	7 (20)	7 (20)	
Stage 4	28 (80)	28 (80)	
Sex no. (%)			.03
Female	10 (29)	3 (9)	
Male	25 (71)	32 (91)	
ECOG			.05
0	30 (86)	22 (63)	
1	5 (14)	13 (37)	
Smoking status no. (%)			1
Never	8 (23)	8 (23)	
Past	14 (40)	14 (40)	
Current	13 (37)	13 (37)	
HPV			1
Positive	27 (77)	27 (77)	
Negative	8 (23)	8 (23)	

Abbreviations: UMCC, University of Michigan Cancer Center; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus.

type-specific, multiplex, competitive polymerase chain reaction, and single base extension followed by matrix-assisted laser desorption ionization-time of flight mass spectrometry analysis, as previously described.[12]

Statistical analysis

Propensity score matching of patients treated on these 2 protocols yielded 35 pairs of subjects (70 patients) matched for age, clinical stage, smoking status (never smoked, past smoker, or current smoker) and tumor HPV status. Primary endpoints 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 gastrostomy (G)-tube use beyond 6 months. Generalized estimating equation models were used 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 $< .05$ was considered significant. Of the patients treated on the UMCC 9921 protocol, 3 underwent early surgery because of the failure of IC. The analysis shown in this article 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 review board, 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 among the 2 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 Eastern Cooperative Oncology Group (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%; $p = .05$). Both groups enrolled predominantly male patients, although the proportion of women was higher in the 9921 trial (29% vs 9%; $p = .03$). IC was unsuccessful in 3 patients in the 9921 group, and therefore they required early surgery.

Survival outcomes

In the univariate analysis (Figure 2A), survival at 36 months was superior in the UMCC 0221 group compared

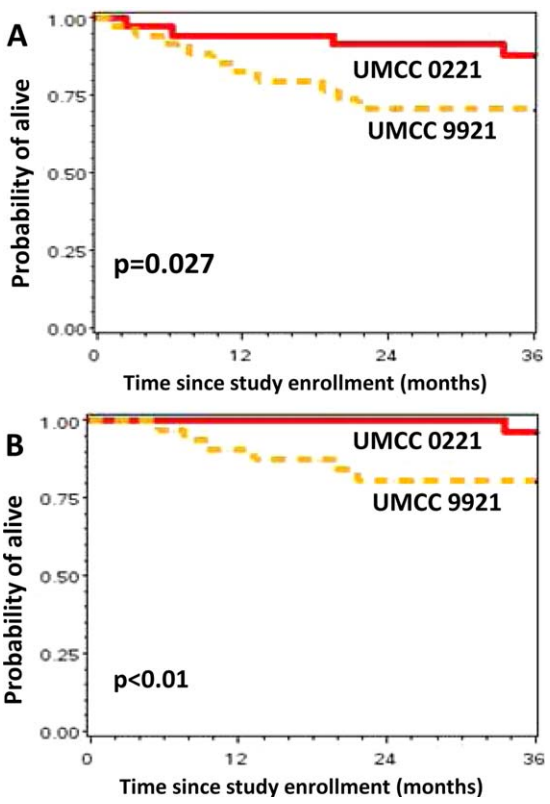

FIGURE 2. Survival at 3 years. (A) Overall survival. (B) Disease-specific survival. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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	HR in multivariable model (95% CI)
Protocol (UMCC 0221 vs UMCC 9921)	.027	0.35 (0.14–0.89)	NS	
Female vs male	.0003	5.48 (2.16–13.92)	.0054	3.83 (1.49–9.86)
Stage (4 vs 3)	.62	1.43 (0.35–5.86)	NS	
ECOG (1 vs 0)	.81	0.86 (0.24–3.07)	NS	
Never vs current smoker	.34	0.47 (0.10–2.25)	NS	
Past vs current smoker	.013	0.083 (0.012–0.59)	NS	
HPV status (positive vs negative)	.001	0.19 (0.068–0.51)	.0094	0.26 (0.09–0.72)

Abbreviations: HR, hazard ratio; CI, confidence interval; UMCC; University of Michigan Cancer Center; NS, not significant; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus.

to the UMCC 9921 group (88% vs 71%; hazard ratio [HR], 0.35; 95% confidence interval [CI], 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 versus 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-positive patients in both protocols, a trend toward an association between improved survival and UMCC 0221 protocol was observed within the HPV-positive group ($p = .06$). The best survival was seen in HPV-positive patients in UMCC 0221, whereas the worst survival was observed in HPV-negative patients treated on UMCC 9921 ($p = .01$). Previously published analyses reported 70.4% OS and 75.8% DSS rates at 4 years in UMCC 9921. 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 UMCC 0221. Exclusion of the 3 patients on the 9921 protocol who underwent early surgery did not affect the OS 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; $p = .09$; 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 trial patients, albeit it was not statistically significant (26% vs 6%; $p = .05$). This did not vary by HPV status (Table 4). When the 3 early surgery patients from the 9921 protocol were excluded from analysis, the difference across protocols became statistically significant ($p = .04$).

DISCUSSION

Weekly administration of platinum-based chemotherapy with radiation, while potentially allowing for lower toxicity,[13] has not been established as the standard of care for patients with locally advanced squamous cell carcinoma of the head and neck. Furthermore, there are no randomized trials demonstrating the benefit of taxane-based CRT 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 patients with oropharyngeal cancer 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 CRT regimens, we elected to compare these 2 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] whereas weekly chemoradiation is better tolerated overall, with lower incidence of side effects, as seen in our study and other trials utilizing weekly CRT.[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

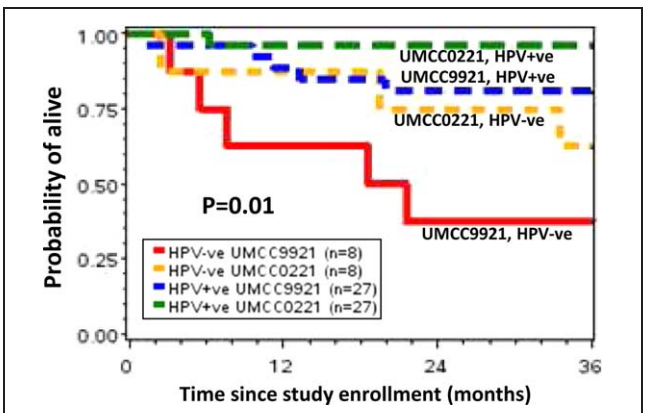

FIGURE 3. Overall survival by treatment protocol and human papillomavirus (HPV) status of the tumor. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 3. Toxicity rates in matched datasets.

	All-grade toxicities			Grade 3–4 toxicities		
	UMCC 9921 (%)	UMCC 0221 (%)	*p* value*	UMCC 9921 (%)	UMCC 0221 (%)	*p* value*
Leukopenia	25 (71)	6 (17)	< .0001	5 (14)	0 (0)	.03
Neutropenia	19 (54)	3 (9)	< .0001	12 (34)	0 (0)	< .0001
Anemia	21 (60)	0 (0)	< .0001	1 (3)	0 (0)	.50
Thrombopenia	9 (26)	1 (3)	.006	1 (3)	1 (3)	.51
Nausea	23 (66)	10 (29)	.002	3 (9)	3 (9)	.33
Vomiting	17 (49)	10 (29)	.05	3 (9)	3 (9)	.33
Neuropathy	9 (26)	1 (3)	.006	0	0	
Diarrhea	5 (14)	0 (0)	.03	1 (3)	0 (0)	.06
Fatigue/weakness	14 (40)	19 (54)	.09	1 (3)	1 (3)	.51
Mucositis	100%	100%		24 (75)	15 (47)	.01

Abbreviation: UMCC, University of Michigan Cancer Center.

*Inestimable in generalized estimating equation model.

cancers. In our experience, there was a decreased long-term G-tube dependence with weekly CRT.

Although our data were 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 CRT regimen for locally advanced SCCOP. Because 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 CRT regimens have been reported (Table 5). Because of the vast heterogeneity among these trials, it is difficult to make definitive comparisons. Our study, for instance, evaluated only patients with oropharyngeal primaries, whereas 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 Suntharalingam 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.[11,20–22]

A number of studies utilized a lower dose, weekly cisplatin, either alone or in combination with other agents.[17,18,23] However, no comparisons with high-dose cisplatin are available.

HPV is now an important prognostic biomarker in SCCOP. Current data demonstrates 3-year survival rates of >80% in patients with HPV-positive tumors when treated with combined CRT.[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 CRT. RTOG 1016 (NCT01302834) is a large randomized trial enrolling patients who are HPV-positive and have oropharyngeal cancer to treatment with both cetuximab and accelerated-fractionation radiotherapy versus 2 cycles of high-dose cisplatin with accelerated-fractionation radiotherapy. This study is rapidly accruing patients and plans to enroll close to 800 subjects. The ECOG has now completed a dose de-escalation study (ECOG 1308), whereby HPV-associated oropharyngeal tumors that were complete responders to IC were treated with 54 Gy of IMRT with cetuximab. Annual Meeting, and the efficacy data will be presented at the 2013 American Society of Clinical Oncology Annual Meeting.[24] The final results of the RTOG are now eagerly awaited with the hope that a reduced intensity CRT regimen will provide similar benefits to 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 used 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.[25]

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 CRT 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

TABLE 4. Gastrostomy tube dependence at 6 months after completion of treatment.

	UMCC 9921 (%)	UMCC 0221 (%)	*p* value
G-tube ≥6 mo	9 (26)	2 (6)	.05
In HPV positive ($n = 27$ pairs)	7 (26)	2 (7)	.14
In HPV negative ($n = 8$ pairs)	2 (25)	0 (0)	.47

Abbreviations: UMCC, University of Michigan Cancer Center; G-tube, gastrostomy tube; HPV, human papillomavirus.

TABLE 5. Efficacy and toxicities of various chemoradiation protocols.

Article	No. of patients/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	70/36 mo	OP	Induction ×1 with 5-FU 1000 mg/m^2/d CI ×5 d and cisplatin 100 mg/m^2 d1 or carboplatin AUC 6 d, then CRT with cisplatin 100 mg/m^2 q3 wk; +/- adjuvant paclitaxel 175 mg/m^2 q3 wk ×2	III, 20%, IV, 80%, all resectable	70 Gy, daily	NR	NR	OS 71% at 3 y $p = .027$ DSS 81% at 3 y $p < .01$	34% $p < .0001$	75% $p = .01$	3%	26% at 6 mo
			CRT with weekly carboplatin AUC 1 and paclitaxel 30 mg/m^2					OS 88% at 3 y $p = .027$ DSS 97% at 3 y $p < .01$	0 $p < .0001$	47% $p = .01$	3%	6% at 6 mo
Weekly chemoradiotherapy regimens												
Suntharalingam et al[19]	43/31 mo	OP 67%, larynx 14%, HP 9%, NP 9%	CRT with weekly paclitaxel 40 mg/m^2, carboplatin AUC 2; cetuximab 400 mg/m^2 load, then 250 mg/m^2 weekly	Stage III–IV, all M0	70.2 Gy, daily	DFS 58% at 3 y	CR 84%, LRC, 72% at 3 y	OS 59% at 3 y OP: HPV+ 100%, HPV- 43% ($p = .032$)	21%	79%	NR	NR
Semrau et al[21]	84/36 mo	OP 77.4%, HP 22.6%	CRT with weekly paclitaxel 40 mg/m^2 and carboplatin AUC 1 for 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 y, 29.4% at 5 y	NR	OS 46.3% at 2 y, 35.3% at 5 y	Leukopenia 6%	51.2%	NR	Median retention of G-tube 58 wk
Sharma et al[23]	153/22 mo	OP 92%, NP 8%	None (RT alone)	II 9.2%, III 36.8%, IV 54%, resectability NR	70 Gy daily	Median PFS 22 mo	CR 67.1% ($p = .044$)	OS 62% at 3 y ($p = .024$)	NR	16% ($p = .002$)	NR	NR
		OP 63.2%, NP 37.7%	CRT with weekly cisplatin 40 mg/m^2	II 3.9%, III 37.7%, IV 55.9%, resectability NR		Median PFS 24 mo	CR 80.5% ($p = .044$)	OS 42% at 3 y ($p = .024$)		40% ($p = .002$)		
Maguire et al[17]	39/37.5mo	OP 59%, larynx 20%, HP 13%, OC 7%	CRT with weekly cisplatin 33 mg/m^2	III 38%, IVa 62%	70 Gy, BID	PFS 82% at 3 y	LRC 87% at 3 y	Actuarial OS 80% at 3 y	Leukopenia 26%	38%	28%	NR
Haddad et al[26]	58/34 mo	OP 62%, OC 17%, larynx 10%, UP 7%	CRT with weekly ×4 carboplatin AUC 1.5 and paclitaxel 45 mg/m^2; daily amifostine 500 mg SQ for the duration of RT	III 14%, IV 86%, all M0, resectability NR	72 Gy (daily ×18, then BID)	PFS 90% at 3 y	LRC 96% at 3 y	OS 89% at 3 y	NR	70%	NR	1.7%
		OP 58%, OC 21%, larynx 17%	CRT with weekly ×4 carboplatin AUC 1.5 and paclitaxel 45 mg/m^2							75%		
Lee et al[18]	32/28.2 mo	OP 28%, OC 25%, HP 13%, larynx 16%, NP 6%	CRT with weekly 5-FU 750 mg/m^2 and cisplatin 20 mg/m^2	III 44%, IV 56%, 18% unresectable, all M0	69.2 Gy, daily	PFS 66% at 2 y	CR 41%, ORR 91%	76% at 2 y	8%	16%	NR	0%
Carter et al[10]	52/61 mo	NR	CRT with weekly paclitaxel 40 mg/m^2 and carboplatin AUC 1	III 33%, IV 67%, all M0	69.6 Gy BID	PFS 50% at 3 y	CR 67%	60% at 3 y	4%	55%	12%	NR
Chougule et al[22]	43/49 mo	OP 35%, larynx 25%, HP 16%, OC 14%, NP 10%	CRT with weekly paclitaxel 60 mg/m^2 and carboplatin AUC 1	III 28%, IV 72%, 67% unresectable, all M0	66–72 Gy, daily	NR	CR 65–83%	median OS 51.5 mo, 40% at 5 y	12%	90%	NR	4.6%
High-dose cisplatin based CRT												
Ang et al[15] (RTOG 9914)	84/2.2 y	OP 66%, OC 12%, HP 11%, larynx 12%	CRT with cisplatin 100 mg/m^2, d1, 22	III 12%, IV 88% all M0	72 Gy (daily ×18, then BID)	DFS 53.5% at 2 y	CR 83%	OS 71.6% at 2 y	NR	53%	9%	11%
Forastiere et al[16] (RTOG 91-11)	547/3.8 y	Larynx	A. Induction ×2–3 cycles with cisplatin 100 mg/m^2 d1 and 5-FU 1000 mg/m^2/d CI ×5d followed by RT	III 64%, IV 36%, all resectable	70 Gy, daily	DFS, 52% at 2 y, 38% at 5 y ($p = .02$ vs XRT alone)	Laryngeal preservation 75% at 2 y	OS 76% at 2 y, 55% at 5 y	NR	24%	NR	NR
			B. CRT with cisplatin 100 mg/m^2 d1, 22, 43			DFS, 61% at 2 y, 36% at 5 y ($p = .006$ vs XRT alone)	Laryngeal preservation 88% at 2 y	OS 74% at 2 y, 54% at 5 y		43%		
			C. None			DFS, 44% at 2 y, 27% at 5 y	Laryngeal preservation 70% at 2 y	OS 75% at 2 y, 56% at 5 y		24%		
Adelstein et al[14]	295/41 mo	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 y ($p = .014$ vs arm B), DSS 33% at 3 y ($p = .01$ vs arm B)	Leukopenia, 1% ($p < .001$)	6% ($p = .03$ vs arm B)	NR	NR
			B. CRT with cisplatin 100 mg/m^2 d1, 22, 43				CR 40.2%	OS 37% at 3 y, DSS 51% at 3 y	Leukopenia, 40% ($p < .001$)	15%		
			C. CRT with cisplatin 75 mg/m^2 q4 wk and 5-FU 1000 mg/m^2/d CI ×4 d		60–70 Gy, split course		CR 49.4%	OS 27% at 3 y, DSS 41% at 3 y	Leukopenia, 29% ($p < .001$)	8%		

Abbreviations: DFS, disease-free survival; PFS, progression-free survival; G-tube, gastrostomy tube; OP, oropharynx; 5-FU, 5-fluorouracil; CI, confidence interval; AUC, area under the curve; CRT, chemoradiotherapy; NR, not reported; OS, overall survival; DSS, disease-specific survival; HP, hypopharynx; NP, nasopharynx; CR, complete response; LRC, locoregional control rate; HPV, human papillomavirus; RT, radiation therapy; OC, oral cavity; BID, twice daily; UP, unknown primary; SQ, subcutaneous; ORR, overall response rate calculated as complete plus partial response; RTOG, Radiation Therapy Oncology Group; XRT, external radiation therapy.

advantage with cetuximab-radiotherapy or reduced-intensity radiation with cetuximab.

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