Matched pair analysis for comparison of survival outcome of alternative regimens to standard three-weekly cisplatin-based concurrent chemoradiation of head and neck cancer

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Background: To compare head and neck cancer (HNC) patients treated with three-weekly versus weekly cisplatin-based or other chemotherapy-based concurrent chemoradiation (CRT) and CRT with versus without induction chemotherapy (ICT) to investigate differences in overall survival (OS) and cancer-specific survival (CSS).

Methods: HNC patients treated with definitive or adjuvant CRT at Roswell Park Comprehensive Cancer Center between 2003 and 2017 were retrospectively reviewed. Propensity score matching was performed to obtain three sets of balanced matched pairs: three-weekly and weekly cisplatin CRT, three weekly and non-cisplatin CRT, CRT with and without ICT. Multivariate Cox regression and Kaplan-Meier analyses were used to estimate and compare survival outcomes.

Results: A total of 623 patients received either definitive (81%) or post-operative (19%) RT. Of these, 283 patients concurrently received three-weekly cisplatin (45%); 189 patients (30%) received weekly cisplatin; 151 patients (24%) received non-cisplatin regimen. Median follow-up was 55.4 months (interquartile range, 38.0–88.7). Patients who received CRT alone and those who received ICT and CRT had no difference in 5-year OS (51.5% and 41.0% respectively, P=0.53) and CSS (64.9% and 49.7% respectively, P=0.21). Compared to patients who received three-weekly cisplatin, patients who received weekly cisplatin had no difference in 5-year OS (59.3% *vs.* 54.1%, P=0.35) and CSS (70.3% *vs.* 62.4%, P=0.09); patients who received non-cisplatin CRT also had no difference in 5-year OS (54.5% *vs.* 58.3%, P=0.51) and CSS (67.5% *vs.* 64.7%, P=0.45).

Conclusions: No significant difference in OS and CSS was observed in any of the three pairs of CRT

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regimens. ICT prior to CRT did not improve survival of CRT alone. Non-cisplatin and weekly cisplatin regimens did not prove to be inferior to the standard three-weekly cisplatin.

Keywords: Head and neck cancer (HNC); concurrent chemoradiation (CRT); cisplatin; induction chemotherapy (ICT); overall survival (OS)

Submitted Jul 02, 2020. Accepted for publication Jan 07, 2021.
doi: 10.21037/atm-20-5032
View this article at: http://dx.doi.org/10.21037/atm-20-5032

Introduction

Concurrent chemoradiation (CRT) with high-dose cisplatin (HDC) (three cycles of 100 mg/m^2 given once every 3 weeks) produces better locoregional control (LRC) and overall survival (OS) compared to radiotherapy (RT) alone in several randomized trials of head and neck cancer (HNC) (1-7). Compared to RT alone, however, CRT with HDC reports roughly 20–40% greater rate of high-grade toxicity that significantly deters up to 40% of patients from completing the aggressive treatment (3-8).

Low-dose cisplatin (LDC) (30–50 mg/m^2 given once weekly) regimens show promising LRC, OS, and cancer-specific survival (CSS) with acceptable rate of severe acute toxicity (9-11). Several retrospective analyses suggest comparable efficacy and improved toxicity profile with LDC (12-15). Three randomized trials, however, report conflicting data that HDC versus LDC (16,17) and LDC versus HDC (18) is superior in the post-operative setting.

Multiple non-cisplatin based regimens have been tested but have not supplanted HDC (19-24). Induction chemotherapy (ICT), despite its efficacy compared to RT alone in larynx preservation (25,26) and reduction of distant metastases (1,4,25,26), does not improve survival compared to CRT alone (27,28).

In this study, we aimed to compare HNC patients treated with (I) ICT and CRT *vs.* CRT alone, (II) HDC- *vs.* LDC-based CRT, (III) HDC- *vs.* other chemotherapy-based CRT to determine whether there is a significant difference in OS and CSS.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5032).

Methods

Patient population

An institutional database of HNC patients treated with definitive or post-operative CRT between 2003 and 2017 at Roswell Park Comprehensive Cancer Center was retrospectively reviewed. Patients who received CRT were included regardless of dosing schedule and chemotherapy agent; those who received RT alone or treatment with non-curative intent were excluded. Patients who received ICT followed by CRT were included; those who received ICT alone or ICT with RT were excluded. Length of follow-up, for those still alive, was defined as length of time between date of diagnosis to last date of follow-up visit.

Statistical analysis

Multivariate (MVA) logistic regression analysis was performed using backward selection ($\alpha<0.20$) of potential confounders to identify patient factors and treatment factors associated with survival. All P values were two-sided and factors with P values ≤ 0.05 were considered statistically significant. MVA Cox regression analysis was performed to identify factors that are associated with OS and CSS. Kaplan-Meier analysis was used to estimate survival of matched cohorts.

Propensity score matching was performed in patients with (I) CRT with and without ICT, (II) HDC-CRT and LDC-CRT, (III) HDC-CRT and non-cisplatin CRT. Survival outcomes were compared. Baseline characteristics, including age, gender, pre-RT weight, smoking status, p16 status, tumor staging, primary tumor site, and treatments received were matched to construct well-balanced pairs.

Propensity score matching was performed using the nearest neighbor matching without replacement method in 1:1 ratio with a caliper width of 0.1 of the standard deviation of the logit (29). SAS (SAS Institute, Cary, NC, USA) and R (version 3.6.1, R Project for Statistical Computing, Vienna, Austria) software were used.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Roswell Park Comprehensive Cancer Center (EDR-103707) and individual consent for this retrospective analysis was waived.

Results

Baseline characteristics

We analyzed a total of 623 patients, of whom 506 were males (81%) and 117 were females (19%) with a median age at time of diagnosis of 61 years [interquartile range (IQR), 50.4–66.6]. About 95% [593] of these HNC patients had squamous cell carcinoma. The most common site of primary tumor was oropharynx (42%). Median follow-up was 55.4 months (IQR, 38.0–88.7 months). All patients received either definitive (81%) or post-operative (19%) RT, median dose 70 Gy (IQR, 70–70 Gy) for all cohorts.

Standard regimen of three-weekly HDC was concomitantly used to treat 283 patients (45%); weekly LDC (30–50 mg/m^2 once weekly) was given to 189 patients (30%); 151 patients (24%) received other chemotherapy regimen which included weekly cetuximab, weekly carboplatin, platinum regimen not otherwise specified, and crossover to carboplatin or cetuximab. Total or mean cumulative dose in each cohort is unknown due to incomplete information in the database. Prior to matching, median OS for HDC cohort was 40.3 months (IQR, 26.2–63.5), LDC was 42.4 months (IQR, 19.8–78.4), and other chemotherapy was 37.9 months (IQR, 13.8–69.2). Taxane-based ICT was given to 70 patients (11%). Median OS before matching for this cohort was 34.6 months (IQR, 16.5–65.3). The baseline patient and treatment characteristics before matching are summarized in *Table 1*.

Survival outcome

MVA showed no significant association between alternative chemotherapy regimen and survival. In comparison to standard HDC dosing, neither non-cisplatin nor weekly LDC was associated with any significant change in OS [hazard ratio (HR) 0.95, 95% confidence interval (CI), 0.70–1.28, P=0.72] or CSS (HR 1.14, 95% CI, 0.79–1.65, P=0.48). ICT was also not associated with any significant change in OS (HR 1.28, 95% CI, 0.89–1.82, P=0.18) or CSS (HR 1.41, 95% CI, 0.93–2.13, P=0.10). The results of MVA on survival outcome are organized in *Table 2*.

Chemoradiation with and without ICT

A total of 51 pairs were matched, with all variables well balanced (*Table 3*). Median overall follow-up was 71.7 months (IQR, 43.4–98.4). Median OS was 35.3 months (IQR, 14.3–74.2) and 36.0 months (IQR, 17.7–60.0) for non-ICT and ICT cohorts, respectively (P=0.53). OS at 5 years was 51.5% (95% CI, 39.1–67.7%) for patients who did not receive ICT and 41.0% (95% CI, 28.8–58.5%) for patients who received ICT (P=0.53, *Figure 1*). CSS at 5 years was 64.9% (95% CI, 52.2–80.7%) for non-ICT cohort and 49.7% (95% CI, 36.2–68.3%) for ICT cohort (P=0.21, *Figure 2*).

HDC and LDC chemoradiation

A total of 183 pairs were matched, with all variables well balanced (*Table 3*). Median overall follow-up was 60.4 months (IQR, 38.0–88.4). Median OS was 38.7 months (IQR, 24.8–61.5) and 44.8 months (IQR, 20.8–78.6) for HDC and LDC cohorts, respectively (P=0.35). OS at 5 years was 59.3% (95% CI, 51.9–67.7%) for patients treated with HDC and 54.1% (95% CI, 46.9–62.2%) for patients treated with LDC (P=0.35, *Figure 3*). CSS at 5 years was 70.3% (95% CI, 63.0–78.4%) for HDC cohort and 62.4% (95% CI, 55.2–70.5%) for LDC cohort (P=0.09, *Figure 4*).

HDC and non-cisplatin chemoradiation

A total of 94 pairs were matched, with all variables well balanced (*Table 3*). Median overall follow-up was 52.3 months (IQR, 39.1–94.5). Median OS was 37.7 months (IQR, 21.4–60.5) and 42.6 months (IQR, 19.9–70.9) for HDC and other chemotherapy cohorts, respectively (P=0.51). OS at 5 years was 54.5% (95% CI, 44.7–66.4%) for patients treated with three-weekly HDC and 58.3% (95% CI, 48.6–69.8%) for patients treated with non-

Table 1 Baseline characteristics before matching

Variable	Cis q3wk		Cis q1wk		Other		P
	N	%	N	%	N	%	
Gender							0.29
Male	234	83	156	83	116	77	
Female	49	17	33	17	35	23	
Total	283	100	189	100	151	100	
Age (yrs)							<0.001
<61	173	61	91	48	60	40	
≥61	110	39	98	52	91	60	
Total	283	100	189	100	151	100	
Smoker							0.008
Never	71	25	37	20	26	17	
Former	147	52	87	46	93	62	
Current	65	23	65	34	32	21	
Total	283	100	189	100	151	100	
HPV							0.007
Negative	47	17	50	26	33	22	
Positive	121	43	59	31	42	28	
NA	115	41	80	42	76	50	
Total	283	100	189	100	151	100	
Comorbidity (no.)							0.05
0	63	22	42	22	17	11	
1	87	31	51	27	41	27	
2	69	24	48	25	44	29	
3+	64	23	48	25	49	32	
Total	283	100	189	100	151	100	
T stage							<0.001
X	1	0	0	0	2	1	
0-2	145	51	79	42	68	45	
3-4	136	48	109	58	71	47	
NA	1	0	1	1	10	7	
Total	283	100	189	100	151	100	
N stage							<0.001
0-1	78	28	61	32	67	44	
2-3	203	72	127	67	74	49	
NA	2	1	1	1	10	7	
Total	283	100	189	100	151	100	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Cis q3wk		Cis q1wk		Other		P
	N	%	N	%	N	%	
M stage							<0.001
0	277	98	182	96	135	89	
1	5	2	4	2	5	3	
NA	1	0	3	2	11	7	
Total	283	100	189	100	151	100	
Primary site							0.03
NA	23	8	27	14	26	17	
Oral cavity	25	9	22	12	9	6	
Nasopharynx	14	5	2	1	2	1	
Oropharynx	130	46	70	37	63	42	
Hypopharynx	15	5	14	7	9	6	
Glottis	33	12	21	11	19	13	
Salivary	5	2	3	2	2	1	
Other	0	0	3	2	5	3	
Unknown	22	8	15	8	9	6	
Multiple	16	6	12	6	7	5	
Total	283	100	189	100	151	100	
Histology							<0.001
Squamous	278	98	182	96	133	88	
Other	5	2	7	4	18	12	
Total	283	100	189	100	151	100	
RT type							0.63
Definitive	230	81	149	79	125	83	
Adjuvant	53	19	40	21	26	17	
Total	283	100	189	100	151	100	
RT total dose (Gy)							0.15
Median	70		70		70		
IQR	70–70		70–70		70–70		
RT start year							0.01
<2011	72	25	50	26	58	38	
≥2011	211	75	139	74	93	62	
Total	283	100	189	100	151	100	
RT complete							0.02
No	3	1	10	5	8	5	
Yes	278	98	178	94	141	93	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Cis q3wk		Cis q1wk		Other		P
	N	%	N	%	N	%	
NA	2	1	1	1	2	1	
Total	283	100	189	100	151	100	
Treatment response							<0.001
No response	6	2	7	4	11	7	
Partial	237	84	142	75	92	61	
Complete	23	8	22	12	30	20	
NA	17	6	18	10	18	12	
Total	283	100	189	100	151	100	
Surgery							0.51
No	225	80	147	78	125	83	
Yes	58	20	42	22	26	17	
Total	283	100	189	100	151	100	
Induction chemo							0
No	264	93	156	83	133	88	
Yes	19	7	33	17	18	12	
Total	283	100	189	100	151	100	
Nutrition support							0.07
No	122	43	62	33	55	36	
Yes	161	57	127	67	96	64	
Total	283	100	189	100	151	100	
Hospitalized							0.97
No	215	76	142	75	112	74	
Yes	67	24	46	24	39	26	
NA	1	0	1	1	0	0	
Total	283	100	189	100	151	100	
WBC count							0.11
Normal	242	86	153	81	113	75	
Low	5	2	5	3	5	3	
High	25	9	20	11	17	11	
NA	11	4	11	6	16	11	
Total	283	100	189	100	151	100	
Hemoglobin (g/dL)							<0.001
≥12	229	81	132	70	86	57	
<12	43	15	46	24	49	32	
NA	11	4	11	6	16	11	
Total	283	100	189	100	151	100	

Cis, cisplatin; q3wk, once every 3 weeks; Q1wk, once every week; HPV, human papilloma virus; NA, not available; RT, radiotherapy; IQR, interquartile range; Chemo, chemotherapy; WBC, white blood cell.

Table 2 Cox regression analysis of survival outcome

Variable	Overall survival						Cancer-specific survival					
	UVA			MVA			UVA			MVA		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Chemo												
Cis q3wk	1	Ref		1	Ref		1	Ref		1	Ref	
Cis q1wk	1.36	1.03–1.79	0.03	0.97	0.72–1.30	0.82	1.69	1.21–2.36	0.002	1.17	0.81–1.70	0.4
Others	1.79	1.36–2.37	<0.001	1.04	0.75–1.42	0.83	2.03	1.44–2.87	<0.001	1.05	0.70–1.57	0.81
ICT												
No	1	Ref		1	Ref		1	Ref		1	Ref	
Yes	1.54	1.12–2.12	0.007	1.29	0.90–1.85	0.17	1.8	1.25–2.59	0.002	1.46	0.96–2.23	0.07
Gender												
Male	1	Ref					1	Ref				
Female	1.13	0.85–1.50	0.41				1.08	0.76–1.53	0.66			
Age (yrs)												
<61	1	Ref		1	Ref		1	Ref		1	Ref	
≥61	1.57	1.24–1.97	<0.001	1.56	1.22–1.99	<0.001	1.57	1.19–2.08	0.001	1.68	1.25–2.26	<0.001
Smoker												
Never	1	Ref		1	Ref		1	Ref		1	Ref	
Former	1.92	1.36–2.72	<0.001	1.51	1.04–2.18	0.03	1.91	1.25–2.91	0.003	1.31	0.84–2.06	0.23
Current	2.53	1.75–3.67	<0.001	2.23	1.51–3.30	<0.001	2.49	1.59–3.90	<0.001	1.98	1.23–3.17	0.005
HPV												
Negative	1	Ref		1	Ref		1	Ref		1	Ref	
Positive	0.51	0.37–0.71	<0.001	0.92	0.65–1.30	0.63	0.58	0.39–0.86	0.006	1.2	0.79–1.82	0.39
NA												
Comorbidity (no.)												
0	1	Ref					1	Ref				
1	0.8	0.56–1.13	0.21				0.74	0.49–1.12	0.15			
2	1.1	0.78–1.55	0.59				0.94	0.63–1.41	0.78			
3+	1.23	0.88–1.73	0.23				0.99	0.66–1.48	0.97			
T stage												
X	2.43	0.34–17.43	0.38				3.75	0.52–27.16	0.19			
0–2	1	Ref		1	Ref		1	Ref		1	Ref	
3–4	2.32	1.81–2.97	<0.001	1.87	1.44–2.41	<0.001	2.95	2.15–4.05	<0.001	2.33	1.69–3.21	<0.001
N stage												
0–1	1	Ref					1	Ref				
2–3	0.95	0.74–1.22	0.69				1.14	0.84–1.55	0.41			

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Overall survival						Cancer-specific survival					
	UVA			MVA			UVA			MVA		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
NA												
M stage												
0	1	Ref		1	Ref		1	Ref		1	Ref	
1	3.89	2.17–6.95	<0.001	1.02	0.49–2.14	0.96	3.87	1.98–7.59	<0.001	0.77	0.35–1.70	0.52
NA												
Histology												
Squamous	1	Ref		1	Ref		1	Ref		1	Ref	
Other	2	1.31–3.06	0.001	0.87	0.46–1.63	0.66	2.3	1.42–3.74	<0.001	0.98	0.43–2.21	0.96
Primary site												
NA	1	Ref		1	Ref		1	Ref		1	Ref	
OC	0.84	0.54–1.31	0.44				0.93	0.56–1.54	0.77			
NP	0.68	0.32–1.44	0.32				0.77	0.34–1.73	0.53			
OP	0.43	0.30–0.61	<0.001	1.13	0.73–1.73	0.59	0.39	0.26–0.59	<0.001	1.08	0.63–1.83	0.78
HP	0.95	0.59–1.54	0.84				0.89	0.50–1.58	0.68			
Glottis	0.8	0.52–1.22	0.3				0.68	0.41–1.15	0.15			
Salivary	0.78	0.35–1.73	0.54				0.96	0.40–2.27	0.92			
Other	0.33	0.08–1.34	0.12				0.46	0.11–1.91	0.29			
Unknown	0.39	0.22–0.69	0.001	1.07	0.54–2.12	0.84	0.29	0.13–0.61	0.001	0.86	0.35–2.12	0.75
Multiple	1.15	0.70–1.87	0.59				0.93	0.51–1.70	0.81			
RT total dose (Gy)												
<70	1	Ref		1	Ref		1	Ref		1	Ref	
≥70	0.66	0.50–0.86	0.002	0.82	0.60–1.11	0.2	0.57	0.42–0.78	<0.001	0.72	0.51–1.03	0.07
RT start year												
<2011	1	Ref					1	Ref				
≥2011	0.91	0.71–1.17	0.49				0.97	0.72–1.31	0.84			
RT complete												
No	1	Ref		1	Ref		1	Ref		1	Ref	
Yes	0.16	0.10–0.25	<0.001	0.53	0.33–0.86	0.01	0.12	0.08–0.20	<0.001	0.44	0.27–0.71	0.001
Response												
None	1	Ref		1	Ref		1	Ref		1	Ref	
Partial	0.08	0.05–0.12	<0.001	0.08	0.05–0.13	<0.001	0.05	0.03–0.08	<0.001	0.05	0.03–0.08	<0.001
Complete	0.5	0.31–0.81	0.005	0.45	0.27–0.75	0.002	0.46	0.28–0.76	0.002	0.46	0.28–0.77	0.003

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Overall survival						Cancer-specific survival					
	UVA			MVA			UVA			MVA		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Surgery												
No	1	Ref					1	Ref				
Yes	0.86	0.64–1.16	0.34				0.92	0.65–1.31	0.66			
Nutrition support												
No	1	Ref		1	Ref		1	Ref				
Yes	1.29	1.01–1.65	0.04	0.95	0.72–1.26	0.74	1.29	0.96–1.74	0.09			
Hospitalized												
No	1	Ref		1	Ref		1	Ref		1	Ref	
Yes	1.65	1.28–2.12	<0.001	1.52	1.17–1.98	0.002	1.49	1.09–2.02	0.01	1.31	0.95–1.81	0.1
WBC count												
Normal	1	Ref		1	Ref		1	Ref		1	Ref	
Low	2.55	1.39–4.68	0.002	1.61	0.85–3.08	0.15	2.94	1.50–5.76	0.002	1.84	0.89–3.80	0.1
High	2.04	1.47–2.82	<0.001	1.27	0.89–1.80	0.18	2.35	1.62–3.41	<0.001	1.36	0.90–2.06	0.14
Hemoglobin (g/dL)												
≥12	1	Ref		1	Ref		1	Ref		1	Ref	
<12	2.38	1.86–3.06	<0.001	1.36	1.05–1.77	0.02	2.5	1.86–3.36	<0.001	1.05	0.75–1.47	0.78

Table 3 Baseline characteristics after matching

Variable	Cis q3wk		Cis q1wk		P	Cis q3wk		Other		P	No ICT		ICT		P
	N	%	N	%		N	%	N	%		N	%	N	%	
Gender					0.89					0.86					0.36
Male	153	84	151	83		74	79	76	81		47	92	43	84	
Female	30	16	32	17		20	21	18	19		4	8	8	16	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Age (yrs)					0.30					0.88					1
<61	101	55	90	49		46	49	44	47		33	65	33	65	
≥61	82	45	93	51		48	51	50	53		18	35	18	35	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Smoker					0.40					0.45					0.42
Never	45	25	35	19		16	17	14	15		14	27	8	16	
Former	83	45	85	46		63	67	58	62		17	33	20	39	
Current	55	30	63	34		15	16	22	23		20	39	23	45	

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Cis q3wk		Cis q1wk		P	Cis q3wk		Other		P	No ICT		ICT		P
	N	%	N	%		N	%	N	%		N	%	N	%	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
HPV					0.20					0.93					0.82
Negative	37	20	49	27		18	19	20	21		12	24	15	29	
Positive	73	40	59	32		30	32	31	33		18	35	17	33	
NA	73	40	75	41		46	49	43	46		21	41	19	37	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Comorbidity (no.)					0.82					0.89					1
0	41	22	41	22		11	12	10	11		12	24	13	25	
1	57	31	49	27		27	29	26	28		17	33	16	31	
2	43	23	47	26		30	32	27	29		11	22	10	20	
3+	42	23	46	25		26	28	31	33		11	22	12	24	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
T stage					0.46					0.61					1
X	0	0	0	0		0	0	1	1		0	0	0	0	
0–2	89	49	77	42		46	49	50	53		17	33	17	33	
3–4	93	51	105	57		47	50	43	46		32	63	33	65	
NA	1	1	1	1		1	1	0	0		2	4	1	2	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
N stage					0.71					0.66					1
0–1	50	27	58	32		42	45	39	41		10	20	11	22	
2–3	132	72	124	68		51	54	55	59		39	76	39	76	
NA	1	1	1	1		1	1	0	0		2	4	1	2	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
M stage					1					1					1
0	178	97	178	97		91	97	91	97		47	92	48	94	
1	4	2	4	2		2	2	3	3		2	4	2	4	
NA	1	1	1	1		1	1	0	0		2	4	1	2	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Primary site					0.97					0.99					1
NA	18	10	26	14		11	12	9	10		6	12	7	14	
Oral cavity	22	12	21	11		9	10	7	7		2	4	2	4	
Nasopharynx	2	1	2	1		3	3	2	2		1	2	2	4	
Oropharynx	77	42	70	38		47	50	46	49		24	47	19	37	
Hypopharynx	12	7	14	8		4	4	4	4		5	10	7	14	

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Cis q3wk		Cis q1wk		P	Cis q3wk		Other		P	No ICT		ICT		P
	N	%	N	%		N	%	N	%		N	%	N	%	
Glottis	20	11	20	11		11	12	13	14		2	4	3	6	
Salivary	2	1	3	2		1	1	2	2		1	2	1	2	
Other	0	0	0	0		0	0	0	0		1	2	1	2	
Unknown	17	9	15	8		5	5	7	7		4	8	4	8	
Multiple	13	7	12	7		3	3	4	4		5	10	5	10	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Histology					1					1					1
Squamous	178	97	177	97		90	96	91	97		49	96	50	98	
Other	5	3	6	3		4	4	3	3		2	4	1	2	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
RT type					0.90					1					NA
Definitive	147	80	145	79		79	84	79	84		51	100	51	100	
Adjuvant	36	20	38	21		15	16	15	16		0	0	0	0	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
RT total dose (Gy)					0.53					0.83					0.69
Median	70		70			70		70			70		70		
IQR	70–70		70–70			70–70		70–70			70–70		70–70		
RT start year					1					0.88					0.84
<2011	48	26	47	26		29	31	31	33		25	49	23	45	
≥2011	135	74	136	74		65	69	63	67		26	51	28	55	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
RT complete					0.08					0.62					1
No	2	1	9	5		2	2	1	1		2	4	2	4	
Yes	179	98	173	95		91	97	93	99		49	96	49	96	
NA	2	1	1	1		1	1	0	0		0	0	0	0	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Treatment response					0.65					0.86					0.97
No response	5	3	6	3		6	6	4	4		4	8	3	6	
Partial	148	81	138	75		69	73	69	73		35	69	37	73	
Complete	17	9	21	11		9	10	12	13		8	16	8	16	
NA	13	7	18	10		10	11	9	10		4	8	3	6	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Surgery					1					0.71					1
No	142	78	142	78		75	80	78	83		50	98	51	100	

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Cis q3wk		Cis q1wk		P	Cis q3wk		Other		P	No ICT		ICT		P
	N	%	N	%		N	%	N	%		N	%	N	%	
Yes	41	22	41	22		19	20	16	17		1	2	0	0	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
ICT					0.16					1					NA
No	164	90	154	84		85	90	84	89		51	100	0	0	
Yes	19	10	29	16		9	10	10	11		0	0	51	100	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Chemotherapy					NA					NA					1
Cis q3wk	183	100	0	0		94	100	0	0		18	35	18	35	
Cis q1wk	0	0	183	100		0	0	0	0		22	43	22	43	
Other	0	0	0	0		0	0	94	100		11	22	11	22	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Nut support					0.38					0.46					1
No	68	37	59	32		40	43	34	36		21	41	21	41	
Yes	115	63	124	68		54	57	60	64		30	59	30	59	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Hospitalized					0.86					0.62					1
No	140	77	136	74		71	76	67	71		45	88	44	86	
Yes	42	23	46	25		23	24	27	29		6	12	7	14	
NA	1	1	1	1		0	0	0	0		0	0	0	0	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
WBC count					0.64					0.32					0.79
Normal	157	86	149	81		81	86	76	81		37	73	40	78	
Low	1	1	3	2		3	3	2	2		1	2	2	4	
High	16	9	20	11		5	5	12	13		8	16	5	10	
NA	9	5	11	6		5	5	4	4		5	10	4	8	
Total	183	100	183	100		94	100	94	100		51	100	51	100	
Hgb (g/dL)					0.37					0.86					0.83
≥12	140	77	128	70		71	76	69	73		28	55	31	61	
<12	34	19	44	24		18	19	21	22		18	35	16	31	
NA	9	5	11	6		5	5	4	4		5	10	4	8	
Total	183	100	183	100		94	100	94	100		51	100	51	100	

Cis, cisplatin; q3wk, once every 3 weeks; Q1wk, once every week; IC, induction chemotherapy; HPV, human papilloma virus; NA, not available; RT, radiotherapy; IQR, interquartile range; ICT, induction chemotherapy; Nut, nutrition; WBC, white blood cell; Hgb, hemoglobin

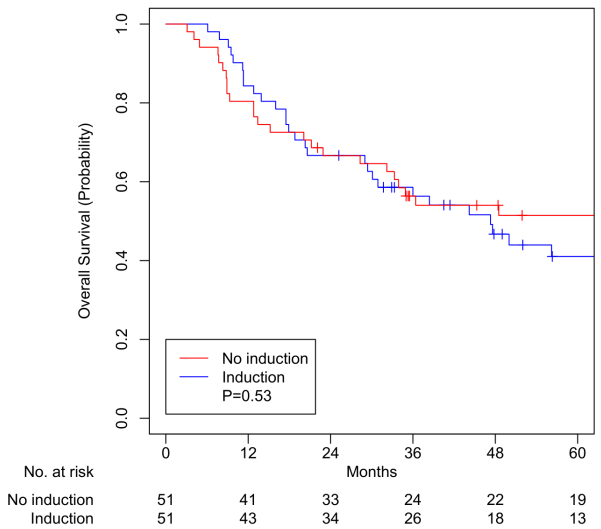

Figure 1 Overall survival for chemoradiation with *vs.* without induction after matching.

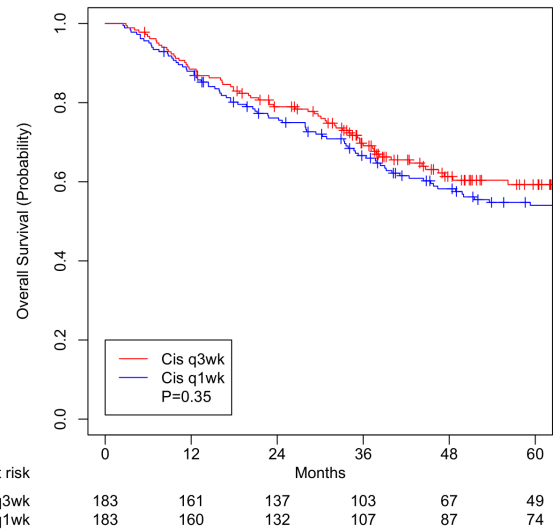

Figure 3 Overall survival for three-weekly cisplatin (cis q3wk) *vs.* weekly cisplatin (cis q1wk) chemoradiation after matching.

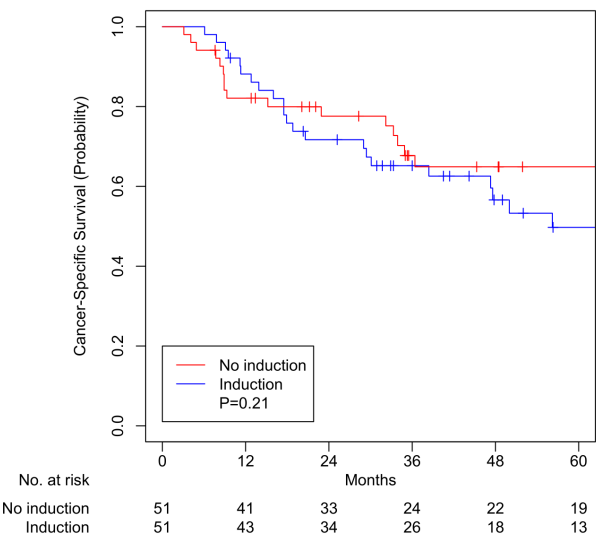

Figure 2 Cancer-specific survival for chemoradiation with *vs.* without induction after matching.

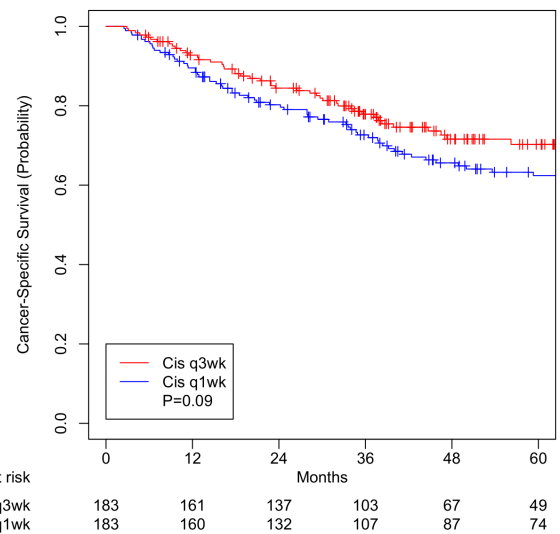

Figure 4 Cancer-specific survival three-weekly cisplatin (cis q3wk) *vs.* weekly cisplatin (cis q1wk) chemoradiation after matching.

cisplatin CRT (P=0.51, *Figure 5*). CSS at 5 years was 67.5% (95% CI, 57.8–78.9%) for HDC cohort and 64.7% (95% CI, 55.0–76.0%) for non-cisplatin cohort (P=0.45, *Figure 6*).

Discussion

Analysis of well-balanced matched pairs of CRT regimens found: (I) ICT does not show to increase survival benefit of CRT alone, (II) HDC may not be the optimal dose as LDC shows insignificant difference in survival, and (III) non-cisplatin regimens fail to improve survival compared to HDC but may be an effective alternative for patients who are unfit to tolerate cisplatin. These findings are consistent with the literature.

We controlled for variables such as current smoking

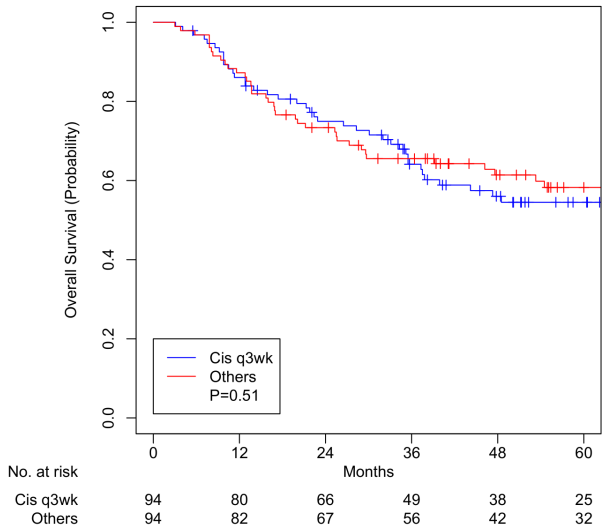

Figure 5 Overall survival for three-weekly cisplatin (cis q3wk) *vs.* non-cisplatin (other) chemoradiation after matching.

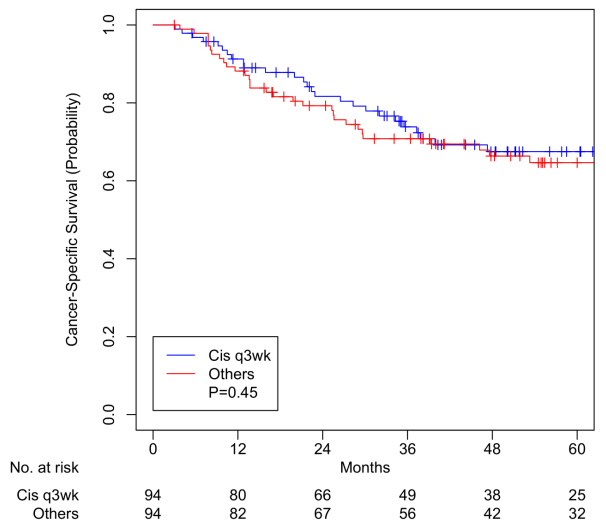

Figure 6 Cancer-specific survival for three-weekly cisplatin (cis q3wk) *vs.* non-cisplatin (other) chemoradiation after matching.

status, older age, advanced tumor stage, unexpected hospitalization, and nutrition support (*Table 2*) that are known to be associated with worse survival in our patients as well as other variables by performing propensity score matching in three groups of patients and created well-balanced matched-pairs (*Table 3*). Compared to patients who received ICT prior to CRT, patients who did not receive ICT had no difference in 5-year OS (51.5% *vs.* 41.0%, P=0.53, *Figure 1*) and CSS (64.9% *vs.* 49.7%, P=0.21, *Figure 2*). Compared to patients who received HDC-CRT, patients who received LDC had no difference in 5-year OS (59.3% *vs.* 54.1%, P=0.35, *Figure 3*) and CSS (70.3% *vs.* 62.4%, p=0.09, *Figure 4*); patients who received non-cisplatin also had no difference in 5-year OS (54.5% *vs.* 58.3%, P=0.51, *Figure 5*) and CSS (67.5% *vs.* 64.7%, P=0.45, *Figure 6*).

ICT compared to chemoradiation alone

Despite its potential to reduce tumor burden and assist in the administration of and patient selection for adjuvant therapy, ICT in treatment of HNC remains debatable with unproven advantage over standard-of-care with CRT alone (*Tables 4-6*).

Pignon *et al.* in a meta-analysis of 87 trials found that CRT had a greater mortality benefit than ICT, though ICT offered a significant reduction of distant metastasis (DM) risk (HR 0.73, 95% CI, 0.61–0.88, P=0.001) (1).

Three recent phase III randomized trials compared docetaxel, cisplatin, and 5-flurouracil (TPF) ICT followed by CRT against CRT alone in patients with locally advanced HNC (28,29,34). Two of these trials fell short of their target accrual (145 of targeted 330 patients in PARADIGM, 285 of targeted 400 patients in DeCIDE trial) and failed to show significant difference in OS between the two arms (HR 1.09, 95% CI, 0.59–2.03, P=0.77 in PARADIGM; HR 0.91, 95% CI 0.59–1.41, P=0.70 in DeCIDE), and both showed 3-year OS rates over 20% higher than the expected 50–55% in the two arms (28,29). Although we reviewed a heterogeneous patient population including those with advanced as well as earlier stage disease and used taxane-based of ICT, analysis of our matched pairs supports the lack of improvement in survival with taxane-based induction before CRT. Similarly, a retrospective analysis of over 8,000 patients in the National Cancer Data Base (NCDB) by Stokes *et al.* reports that ICT does not offer significant survival advantage when compared to CRT alone (HR 0.96, 95% CI, 0.88–1.05, P=0.35) while making it more likely for patients to receive lower (<66 Gy) RT doses (P<0.01); subgroup analysis on advanced disease also did not show difference in survival with ICT (30). Chen *et al.* retrospectively analyzed over 10,000 HNC patients in Taiwan who were treated with either CRT alone or ICT (docetaxel- or platinum-based) preceding locoregional treatment and also showed superior survival rate (P<0.0001) with CRT alone (32).

Table 4 References for studies on induction chemotherapy

ICT	Study							Chemo	RT	OS			DFS		
	Author, year	Design	Incl pd	Tx	Arms	Pts (no.)	Median f/u (mo.)	Regimen	Dose to 1' (Gy)	3-yr OS	5-yr OS	Diff in OS	3-yr DFS	5-yr DFS	Diff in DFS
ICT *vs.* Surg	Wolf *et al.* (VA Larynx), 1991 (25)	Prosp PIII, LC	–	Def	A. ICT then RT	166	33	PF	66–76	60%	–	p=0.98	58%	53%	P=0.12
					B. Surg then RT	166		–	50–50.4 +/– 10	63%	–		70%	65%	
	Lefebvre *et al.* (EORTC 24891), 1996 (26)	Prosp PIII, PSC	1990–1992	Def	A. ICT then RT	100	51	PF	50 +/– 20	57%	30%	None reported	43%	25%	None reported
					B. Surg then RT	94		–	50 +/– 14	43%	35%		32%	27%	
	Forastiere *et al.* (RTOG 91–11), 2003 (3)	Prosp PIII, LC	1992–2000	Def	A. ICT then RT	173	45.6	Cis–5FU	70	76% (2yr)	55%	None reported	52% (2–yr)	38%	A>C, P=0.02;
					B. CRT	172		HDC	70	74% (2-yr)	54%		61% (2-yr)	36%	B>C, P=0.006
					C. RT alone	173		–	70	75% (2-yr)	56%		44% (2-yr)	27%	
ICT *vs.* CRT alone	Haddad *et al.* (PARADIGM), 2013 (27)	Prosp PIII	2004–2008	Def	A. ICT then CRT	70	49	TPF–> Doce/ Carbo	72/70	73%	67%	P=0.77	67% (PFS)	–	P=0.82
					B. CRT alone	75		HDC	72	78%	70%		69% (PFS)	–	
	Cohen *et al.* (DeCIDE), 2014 (28)	Prosp PIII	2004–2009	Def	A. ICT tbe CRT	138	30	TPF–> DFHX	74–75	–	67%	P=0.68	–	–	–
					B. CRT alone	135		DFHX	74–75	–	67%		–	–	–
	Ghi *et al.*, ABSTRACT only (30)	Prosp PIII	2008–2014	Def	A. ICT then CRT	207	41.3	TPF –> Cis–5FU or Cetux	70	58%	–	A>B, P=0.025	47% (PFS)	–	A>B, P=0.015
					B. CRT alone	208		Cis–5FU or Cetux	70	46%	–		37% (PFS)	–	
	Stokes *et al.*, 2017 (31)	Retrosp	2003–2011	Def	A. ICT then CRT	1569	29.7	NA	>66	–	–	p=0.35	–	–	–
					B. CRT alone	6462		NA	>66	–	–		–	–	–

Table 4 (*continued*)

Table 4 (*continued*)

ICT	Study							Chemo	RT	OS			DFS		
	Author, year	Design	Incl pd	Tx	Arms	Pts (no.)	Median f/u (mo.)	Regimen	Dose to 1' (Gy)	3-yr OS	5-yr OS	Diff in OS	3-yr DFS	5-yr DFS	Diff in DFS
	Chen *et al.*, 2016 (32)	Retrosp	2002–2011	Def	A. CRT alone	7986	50	Pt–based	70	50%	44%	A>B/C, P<0.0001	–	46%	A>B/C, P<0.0001
					B. ICT +/– RT/CRT	503		Docetaxel–based	70	38%	30%		–	41%	
					C. ICT +/– RT/CRT	2232		Pt–based	70	38%	30%		–	38%	
	Ock *et al.*, 2016 (33)	Retrosp	2005–2013	Def	A. ICT then CRT	144	52.4	Varied	60	77%	–	A>B, P=0.017 (matched)	65% (PFS)	–	P=0.06
					B. CRT alone	80		Varied	60	57%	–		54% (PFS)	–	
	Merlano *et al.*, Ongoing (34)	Prosp PIII	Ongoing	Def	A. ICT then CRT	–	–	TPF- > Cetux	70	–	–	–	–	–	–
					B. CRT alone	–	–	HDC	70	–	–	–	–	–	–
	Yang *et al.*, 2019 (35)	Prosp PIII, NPC	2008–2015	Def	A. ICT then CRT	238	82.6	PF- > HDC	–	89%	81%	A>B, P=0.04	81%	73%	A>B, P=0.007
					B. CRT alone	238		HDC	–	88%	77%		74%	63%	
	Zhang *et al.*, 2019 (36)	Prosp PIII, NPC	2013–2016	Def	A. ICT then CRT	242	42.7	Gem-Cis –> HDC	70	95%	–	A>B, HR 0.43	85%	–	A>B, P=0.001
					B. CRT alone	238		HDC	70	90%	–		77%	–	

Chemo, chemotherapy; RT, radiotherapy; CRT, chemoradiation; OS, overall survival; DFS, disease–free survival; PFS, progression–free survival; ICT, induction chemotherapy; Incl pd, inclusion period; Tx, treatment; Pts, patients; f/u, follow–up; 1', primary; Diff, difference; Surg, surgery; Pros, prospective; PIII, phase III; Retrosp, retrospective; LC, laryngeal cancer; PSC, pyriform sinus cancer; NPC, nasopharyngeal cancer; TPF, docetaxel-Platinum-5-Fluorouracil (Docetaxel 75 mg/m^2 on day 1, cisplatin 75–100 mg/m^2 on day 1, 5-fluorouracil 750–1,000 mg/m^2 on days 1–4 as continuous infusion; 3–4 cycles on 21–day interval); PF, Platinum-5-Fluorouracil (Cisplatin 80–100 mg/m^2 given as rapid intravenous infusion followed by 5-fluorouracil 800–1,000 mg/m^2/day continuous 24-hour infusion for 5 days; 2–4 cycles on 21-day interval); Def, definitive; Cis-5FU, Cisplatin-5-Fluorouracil (Cisplatin 75–100 mg/m^2 bolus then 5–fluorouracil 1 g continuous infusion for 2–3 cycles); HDC, high dose cisplatin (80–100 mg/m^2 3–weekly ×2–3 cycles); Doce, Docetaxel (20 mg/m^2 weekly for 4 cycles); Carbo, Carboplatin (weekly); DFHX, Docetaxel-fluorouracil-hydroxyurea; Cetux, Cetuximab (initial dose 400 mg/m^2 during the week before radiotherapy followed by maximum of 7 doses of 250 mg/m^2 during radiotherapy; Pt, Platinum; Gem-Cis, Gemcitabine-Cisplatin (Gemcitabine 1 g/m^2 on days 1 and 8, cisplatin 80 mg/m^2 on days 1 ,22, 43).

Table 5 References for studies on induction chemotherapy

ICT	Study		LRC		DC			Response	
	Author	Arms	2-yr LRC	Diff in LRC	3-yr DC	5-yr DC	Diff in DC	Overall Resp	Diff in Resp
ICT *vs.* Surg	Wolf *et al.* (25)	A. ICT –> RT	92%, ns	B>A, P=0.0005	89%, ns	–	A>B, P=0.016	–	None reported
		B. Surg –> RT	95%, ns		83%, ns	–		–	
	Lefebvre *et al.* (26)	A. ICT –> RT		None reported	72%	65%	A>B, P=0.041	–	None reported
		B. Surg –> RT			57%	52%		–	
	Forastiere *et al.* (3)	A. ICT –> RT	61% [54–69]	B>A, P=0.003	91%, 2-yr DC	85%	B>C, P=0.03	–	–
		B. CRT	78% [72–85]	A *vs*. C, P=0.16	92%, 2-yr DC	88%		–	–
		C. RT alone	56% [48–63]	B>C, P<0.001	84%, 2-yr DC	78%		–	–
ICT *vs.* CRT alone	Haddad *et al.* (27)	A. ICT –> CRT	84%, ns	None reported	93%, ns	–	None reported	–	–
		B. CRT alone	85%, ns		89%, ns	–		–	–
	Cohen *et al.* (28)	A. ICT –> CRT	70%	P=0.16	–	62%	P=0.37	74%	P=0.45
		B. CRT alone	60%		–	60%		79%	
	Ghi *et al.*, Abstract (30)	A. ICT –> CRT	–	–	–	–	–	–	–
		B. CRT alone	–	–	–	–	–	–	–
	Stokes *et al.* (31)	A. ICT –> CRT	–	–	–	–	–	–	–
		B. CRT alone	–	–	–	–	–	–	–
	Chen *et al.* (32)	A. CRT alone	–	–	–	–	–		
		B. ICT +/– RT/CRT	–	–	–	–	–		
		C. ICT +/– RT/CRT	–	–	–	–	–		
	Ock *et al.* (33)	A. ICT –> CRT	69% (3-yr)	P=0.11	89%	–	P=0.85	76%	A>B, P=0.005 (matched)
		B. CRT alone	59% (3-yr)		87%	–		53%	
	Merlano *et al.*, ongoing (34)	A. ICT –> CRT	–	–	–	–	–	–	–
		B. CRT alone	–	–	–	–	–	–	–
	Yang *et al.* (35)	A. ICT –> CRT	88% (5-yr)	P=0.21	86%	83%	A>B, P=0.014	–	–
		B. CRT alone	85% (5-yr)		82%	73%		–	–
	Zhang *et al.* (36)	A. ICT –> CRT	92% (3-yr)	None reported	91%	–	None reported	97%	None reported
		B. CRT alone	91% (3-yr)		84%	–		97%	

LRC, locoregional control; DC, distant control; ICT, induction chemotherapy; CRT, chemoradiation; RT, radiotherapy; Diff, difference; Resp, response; Surg, surgery; TPF, docetaxel-platinum-5-fluorouracil (docetaxel 75 mg/m^2 on day 1, cisplatin 75–100 mg/m^2 on day 1, 5-fluorouracil 750–1,000 mg/m^2 on days 1–4 as continuous infusion; 3–4 cycles on 21-day interval); PF, platinum-5-fluorouracil (cisplatin 80–100 mg/m^2 given as rapid intravenous infusion followed by 5-fluorouracil 800–1,000 mg/m^2/day continuous 24-hour infusion for 5 days; 2–4 cycles on 21-day interval).

Table 6 References for studies on induction chemotherapy (continued)

ICT	Study		Severe acute toxicity (grade 3–5)															
	Author	Arms	Pts (no.)	N/V	Mucositis	Dysphagia	Leukopenia	Neutropenia	Tbcp	Anemia	Infection	Renal	Neuro	Skin	Ototoxic	Total toxic deaths	All	Diff in acute toxicity
ICT *vs.* Surg	Wolf *et al.* (25)	A. ICT –> RT	–	–	–	–	–	–	–	–	–	–	–	–	–	5	–	None reported
		B. Surg –> RT	–	–	–	–	–	–	–	–	–	–	–	–	–	3	–	
	Lefebvre *et al.* (26)	A. ICT –> RT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Not assessed
		B. Surg –> RT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
	Forastiere *et al.* (3)	A. ICT –> RT	168	14%	20%	19%		52% (hematologic)			5%	2%	4%	10%	–	5	66%	None reported
		B. CRT	171	20%	43%	35%		47% (hematologic)			4%	4%	5%	7%	–	9	77%	
		C. RT alone	171	0	24%	19%		3% (hematologic)			1%	0	0	9%	–	5	47%	
ICT *vs.* CRT alone	Haddad *et al.* (27)	A. ICT –> CRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Not assessed
		B. CRT alone	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
	Cohen *et al.* (28)	A. ICT –> CRT	124	6%/3%	51%	12%	26%	3%	3%	7%	11%	–	–	18%	–	–	47%	A>B, P=0.002
		B. CRT alone	133	5%/2%	47%	15%	11%	2%	2%	3%	14%	–	–	24%	–	–	24%	
	Ghi *et al.*, Abstract (30)	A. ICT –> CRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Not assessed
		B. CRT alone	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
	Stokes *et al.* (31)	A. ICT –> CRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Not assessed
		B. CRT alone	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	

Table 6 (*continued*)

Table 6 (*continued*)

ICT	Study		Severe acute toxicity (grade 3–5)															
	Author	Arms	Pts (no.)	N/V	Mucositis	Dysphagia	Leukopenia	Neutropenia	Tbcp	Anemia	Infection	Renal	Neuro	Skin	Ototoxic	Total toxic deaths	All	Diff in acute toxicity
	Chen *et al.* (32)	A. CRT alone	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Not assessed
		B. ICT +/– RT/CRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
		C. ICT +/– RT/CRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
	Ock *et al.* (33)	A. ICT –> CRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Not assessed
		B. CRT alone	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
	Merlano *et al.*, Ongoing (34)	A. ICT –> CRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Not assessed
		B. CRT alone	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
	Yang *et al.* (35)	A. ICT –> CRT	No report on acute adverse events. Eye damage significantly higher with CRT alone than ICT–>CRT (16% *vs.* 10%, P=0.03)															
		B. CRT alone																
	Zhang *et al.* (36)	A. ICT –> CRT	239	23%	29%	–	26%	28%	11%	10%	0	3%	–	2%	0	–	76%	None reported
		B. CRT alone	237	14%	32%	–	20%	11%	1%	1%	0	0%	–	4%	0	–	56%	

ICT, induction chemotherapy; Pts, patients; N/V, nausea or vomiting; Tbcp, thrombocytopenia; Neuro, neurological; Diff, difference; Surg, surgery; TPF, docetaxel-platinum-5-fluorouracil (docetaxel 75 mg/m^2 on day 1, cisplatin 75–100 mg/m^2 on day 1, 5–fluorouracil 750–1,000 mg/m^2 on days 1–4 as continuous infusion; 3–4 cycles on 21-day interval); PF, platinum-5-fluorouracil (cisplatin 80–100 mg/m^2 given as rapid intravenous infusion followed by 5-fluorouracil 800–1,000 mg/m^2/day continuous 24-hour infusion for 5 days; 2–4 cycles on 21-day interval); CRT, chemoradiation; RT, radiotherapy.

In contrast, Ghi *et al.* in Italy randomized 420 patients to receive TPF then CRT (with cisplatin or cetuximab) or CRT (with cisplatin or cetuximab) alone and demonstrated 3-year OS (57.6% *vs.* 45.7%, HR 0.72, 95% CI, 0.55–0.96, P=0.025) and PFS (46.8% *vs.* 36.7%, HR 0.73, 95% CI, 0.57–0.94, P=0.015) favoring TPF over CRT alone (30). The 3-year OS rates fall within the expected range but may reflect compromised survival due to use of cetuximab- rather than solely cisplatin-based CRT. A retrospective single-center analysis with propensity score matching by Ock *et al.* was similar to our study but had different results that too showed survival benefit with taxane-based ICT, which improved 3-year OS (77.4% *vs.* 56.7%, HR 0.48, 95% CI, 0.26–0.87, P=0.017) as well as complete response rates (75.7% *vs.* 52.9%, P=0.005) compared to CRT alone (33). Subgroup analysis was also done and showed that male patients with N2-3 oropharyngeal cancer had improved OS with ICT followed by CRT.

The ongoing phase III trial (INTERCEPTOR) by Gruppo Oncologico del Nord-Ovest comparing TPF followed by cetuximab-CRT and HDC-CRT alone (clinicaltrials.gov, NCT00999700) will stratify patients by HPV status (34).

ICT may also play a role in locoregionally advanced nasopharyngeal cancer (LA-NPC.) Yang *et al.* recently reported on 476 patients with LA-NPC that demonstrated long-term OS (81% *vs.* 77%, P=0.04) and disease-free survival (DFS) (73% *vs.* 63%, P=0.007) benefits with ICT preceding standard CRT (35). Zhang *et al.* randomized a similarly sized cohort of LA-NPC patients to receive gemcitabine and cisplatin-based ICT or CRT alone and also reported improved 3-year OS (HR 0.43, 95% CI, 0.24–0.77) and 3-year DFS (85% *vs.* 77%, P=0.001) with ICT (36).

With the possible exception of LA-NPC, routine use of ICT may not be advised given increased toxicity and no clear survival benefit. In our patients, we no longer routinely use ICT except: (I) on a clinical trial or (II) if required to achieve 30 days of smoking cessation in current smokers. Current smokers are known to have significantly reduced survivals that can be effectively ameliorated by 30 days of smoking cessation (37). This OS benefit justifies use of ICT; moreover, ICT allows initiation of treatment without significant delay from the time of diagnosis which can also reduce survival (38).

Optimal cisplatin dose for chemoradiation

In addition to studies showing the OS and LRC benefits of HDC (1-7), as shown in *Tables 7-9*, 2 of 3 studies of LDC with RT showed significant OS benefit over RT alone and the third showed significant improvement in LRC.

Szturz *et al.* in a meta-analysis of 59 prospective studies with over 5,200 locally advanced HNC patients found no significant difference in OS was observed between HDC- and LDC-CRT. In the definitive setting, LDC had greater compliance (88% *vs.* 71%, P=0.0017) and less toxicity such as myelosuppression (leukopenia P=0.0083, neutropenia P=0.0024), severe nephrotoxicity (P=0.01) and severe nausea and/or vomiting (P<0.0001) compared to HDC (15).

Our findings are consistent with those of Szturz *et al.*; LDC appears to be equivalent to HDC in terms of OS. Although in our study we controlled for adverse events such as hospitalizations and risk factors such as comorbidities to create matched pairs, we are aware that in the early years of this analysis many patients were given LDC specifically because they were felt to be unable to tolerate HDC. Thus, we suspect that there remained a bias that favored HDC despite our attempts to correct with match pairing. This may explain the non-significant decrease in CSS with LDC.

As shown in *Tables 7-9*, the majority of publications appear to reveal greater cisplatin-related toxicity with HDC than LDC. This warrants future study.

Non-cisplatin agents for chemoradiation

Non-platinum agents such as cetuximab (IgG1 monoclonal antibody against epidermal growth factor receptor) and other platinum agents such as carboplatin (second generation platinum drug) have been investigated (*Tables 10-12*). Two randomized phase III trials by Gillison *et al.* (RTOG 1016) and Mehanna *et al.* (De-ESCALATE) examined the outcome of cetuximab (400 mg/m^2 loading dose then seven weekly 250 mg/m^2 doses) versus HDC given concomitantly with RT (70 Gy in standard fractions over six weeks) used to treat patients with HPV-positive oropharyngeal cancer; both trials failed to demonstrate non-inferiority of cetuximab over cisplatin (19,20). RTOG 1016 showed that cetuximab neither met the non-inferiority criteria for OS (P=0.51) nor improved acute (P=0.16) or late (P=0.19) severe toxicity profile of cisplatin while exhibiting inferior 5-year progression-free survival (67.3% *vs.* 78.4%, P=0.0002). De-ESCALATE study also showed that cetuximab did not reduce overall severe toxicity (P=0.98) while showing worse 2-year OS (89.4% *vs.* 97.5%, P=0.001) and 2-year recurrence (16.1% *vs.* 6.0%, P=0.001) compared to cisplatin. Our non-cisplatin cohort included patients

Table 7 References for studies on cisplatin–based chemoradiotherapy regimen

CIS-CRT	Study							Chemo	RT	OS			DFS		
	Author, year	Design	Incl pd	Tx	Arms	Pts (no.)	Median f/u (mo.)	Regimen	Dose to 1' (Gy)	3-yr OS	5-yr OS	Diff in OS	3-yr DFS	5-yr DFS	Diff in DFS
HDC *vs.* RT	Pignon *et al.* (MACH–NC), 2009 (1)	Retrosp	1965–2000	Def/Adj	CRT *vs.* LRT	Total 17,346	67.2	Varied	Varied	CRT has 6.5% 5-yr absolute OS benefit, P<0.001			CRT improves DFS, P<0.0001		
					ICT *vs.* LRT			Varied	Varied						
	Adelstein *et al.*, 2003 (2)	Prosp PIII	1992–1999	Def	A. RT alone	95	41	–	70	23%	14%	B>A, P=0.014	33%	24%	B>A, P=0.01
					B. CRT	87		HDC	70	37%	26%		51%	45%	
					C. Split CRT	89		Cis–5FU	60–70	27%	21%		41%	41%	
	Cooper *et al.* (RTOG 9501), 2004 (5)	Prosp PIII	1995–2000	Adj	A. RT alone	210	45.9	–	60–66	45%	40%	P=0.19	38%	25%	B>A, P=0.04
					B. CRT	206		HDC	60–66	55%	45%		48%	35%	
	Bernier *et al.* (EORTC 22931), 2004 (6)	Prosp PIII	1994–2000	Adj	A. RT alone	167	60	–	66	48%	40%	B>A, P=0.02	40% (PFS)	36% (PFS)	B>A, P=0.04
					B. CRT	167	60	HDC	66	60%	53%		55% (PFS)	47% (PFS)	
LDC *vs.* RT	Bachaud *et al.*, 1996 (9)	Prosp PIII	1984–1988	Adj	A. RT alone	44	36	–	65–74	46% (2-yr)	13%	B>A, P<0.01	44% (2-yr)	23%	B>A, P<0.02
					B. CRT	39	36	LDC	65–74	72% (2-yr)	36%		68% (2-yr)	45%	
	Sharma *et al.*, 2010 (10)	Prosp PII, OP/NPC	2003–2005	Def	A. RT alone	76	22	–	70	42%	–	B>A, P=0.024	42% (PFS)	–	P=0.88
					B. CRT	77	22	LDC	70	62%	–		37% (PFS)	–	
	Ghosh-Laskar *et al.*, 2016 (11)	Prosp PIII	2000–2007	Def	A. RT alone	57	48	–	66–70	–	36%	P=0.11		25%	B>A, P=0.03
					B. CRT	65	48	LDC	66–70	–	56%			39%	
HDC *vs.* LDC	Lee *et al.*, 2018 (12)	Retrosp	2007–2012	Def	A. HDC-CRT	65	–	HDC	66.4, mean	81%	–	P=0.34	64% (PFS)	–	P=0.81
					B. LDC-CRT	155	–	LDC	68.4, mean	67%	–		60% (PFS)	–	

Table 7 (*continued*)

Table 7 (*continued*)

CIS-CRT	Study							Chemo	RT	OS			DFS		
	Author, year	Design	Incl pd	Tx	Arms	Pts (no.)	Median f/u (mo.)	Regimen	Dose to 1' (Gy)	3-yr OS	5-yr OS	Diff in OS	3-yr DFS	5-yr DFS	Diff in DFS
	Helfenstein *et al.*, 2019 (13)	Retrosp	2008–2015	Def/Adj	A. HDC-CRT	127	40.6	HDC	69–72/60–66	Cum. cis dose >200 mg/m^2 on OS, P=0.10			Cum cis dose >200 mg/m^2 on PFS, P=0.97		
					B. LDC-CRT	187	40.6	LDC	69–72/60–66						
	Bauml *et al.*, 2019 (14)	Retrosp	2000–2014	Def	A. HDC-CRT	2200	–	HDC	–	–	–	P=0.44	–	–	–
					B. LDC-CRT	701	–	LDC	–	–	–		–	–	–
	Szturz *et al.*, 2017 (15)	Retrosp	–	Def/Adj	A. HDC-CRT	31 studies	–	HDC	66–70/60–66	–	–	No diff in OS in Def/Adj setting	Unable to merge data from studies		
					B. LDC-CRT	17 studies	–	LDC	66–70/60–66	–	–				
	Tsan *et al.*, 2012 (16)	Prosp PIII, OC	2008–2010	Adj	A. HDC-CRT	26	12	HDC	66	79% (1-yr)	–	P=0.98	–	–	–
					B. LDC-CRT	24	12	LDC	66	72% (1-yr)	–		–	–	–
	Noronha *et al.*, 2018 (17)	Prosp PIII	2013–2017	Def/Adj	A. HDC-CRT	150	22	HDC	60 or 70	53%	–	P=0.48	48% (2-yr PFS)	–	P=0.21
					B. LDC-CRT	150	22	LDC	60 or 70	53%	–		55% (2-yr PFS)	–	

Chemo, chemotherapy; RT, radiotherapy; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; Cis, cisplatin; CRT, chemoradiation; Incl pd, inclusion period; Tx, treatment; f/u, follow-up; 1', primary; Diff, difference; Retrosp, retrospective; Prosp, prospective; PII/III, phase II/III; Def, definitive; Adj, adjuvant; LRT, locoregional treatment; ICT, induction chemotherapy; HDC, high dose cisplatin (80–100 mg/m^2 3-weekly, 2–3 cycles); Cis-5FU, cisplatin-5-fluorouracil (Cisplatin 75–100 mg/m^2 bolus then 5-fluorouracil 1 g continuous infusion for 2–3 cycles); LDC, low dose cisplatin (30–50 mg/m^2 weekly, 6–9 cycles); OP, oropharyngeal cancer; NPC, nasopharyngeal cancer; OC, oral cavity squamous cell cancer.

Table 8 References for studies on cisplatin–based chemoradiotherapy regimen (continued)

CIS-CRT	Study		LRC		DC			Response	
	Author	Arms	2-yr LRC	Diff in LRC	3-yr DC	5-yr DC	Diff in DC	Overall resp	Diff in resp
HDC *vs.* RT	Pignon *et al.* (1)	CRT *vs.* LRT	CRT improves LRC, P=0.04		ICT improves DC, P=0.001			–	–
		ICT *vs.* LRT						–	–
	Adelstein *et al.* (2)	A. RT alone	–	–	–	–	–	27.4% (CR)	C>A, P=0.002; A *vs.* B, P=0.07
		B. CRT	–	–	–	–	–	40.2% (CR)	
		C. Split CRT	–	–	–	–	–	49.4% (CR)	
	Cooper *et al.* (5)	A. RT alone	72%	B>C, P=0.01	77%, ns		P=0.46	–	–
		B. CRT	82%		80%, ns			–	–
	Bernier *et al.* (6)	A. RT alone	69%, 5-yr LRC	B>A, P=0.007	–	75%	P=0.61	–	–
		B. CRT	88%, 5-yr LRC		–	79%		–	–
LDC *vs.* RT	Bachaud *et al.* (9)	A. RT alone	59%	B>A, P=0.05	81% (2-yr)	49%	None reported	–	–
		B. CRT	84%		73% (2-yr)	58%		–	–
	Sharma *et al.* (10)	A. RT alone	53%, overall	P=0.26	97%, overall	–	P=0.05	67% (CR)	B>A, P=0.04
		B. CRT	66%, overall		90%, overall	–		81% (CR)	
	Ghosh-Laskar *et al.* (11)	A. RT alone	32%, 5-yr LRC	B>A, P=0.01	–	–	None reported	–	–
		B. CRT	49%, 5-yr LRC		–	–		–	–
HDC *vs.* LDC	Lee *et al.* (12)	A. HDC-CRT	–	–	–	–	–	92%	P=0.81
		B. LDC-CRT	–	–	–	–	–	91%	
	Helfenstein *et al.* (13)	A. HDC-CRT	–	–	–	–	–	–	–
		B. LDC-CRT	–	–	–	–	–	–	–
	Bauml *et al.* (14)	A. HDC-CRT	–	–	–	–	–	–	–
		B. LDC-CRT	–	–	–	–	–	–	–
	Szturz *et al.* (15)	A. HDC-CRT	Unable to merge data		Unable to merge data			80.0%	No diff
		B. LDC-CRT						89.0%	
	Tsan *et al.* (16)	A. HDC-CRT	71% (1-yr)	P=0.81	–	–	–	–	–
		B. LDC-CRT	60% (1-yr)		–	–	–	–	–
	Noronha *et al.* (17)	A. HDC-CRT	73%	A>B, P=0.014	–	–	–	–	–
		B. LDC-CRT	59%		–	–	–	–	–

Cis, cisplatin; CRT, chemoradiation; LRC, locoregional control; DC, distant control; Diff, difference; Resp, response; HDC, high dose cisplatin (80–100 mg/m^2 3-weekly, 2–3 cycles); LDC, low dose cisplatin (30–50 mg/m^2 weekly, 6–9 cycles); RT, radiotherapy; LRT, locoregional treatment; CR, complete response; ns, not specified.

Table 9 References for studies on cisplatin–based chemoradiotherapy regimen (continued)

CIS-CRT	Study		Severe acute toxicity (grade 3–5)															
	Author	Arms	Pts (no.)	N/V	Mucositis	Dysphagia	Leukopenia	Neutropenia	Tbcp	Anemia	Infection	Renal	Neuro	Skin	Oto–toxic	Total toxic deaths	All	Diff in acute toxicity
HDC *vs.* RT	Pignon *et al.* (1)	CRT *vs.* LRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Not assessed
		ICT *vs.* LRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
	Adelstein *et al.* (2)	A. RT alone	98	6%	33%		1%	–	0	0	–	1%	–	13%	–	2	52%	B>A, P<0.0001
		B. CRT	95	16%	45%		42%	–	3%	18%	–	8%	–	7%	–	4	89%	B>C, P=0.02
		C. Split CRT	94	9%	47%		31%	–	3%	19%	–	0	–	2%	–	2	77%	C>A, P<0.001
	Cooper *et al.* (5)	A. RT alone	210	0	18%	15%	0			0	0	0	0	10%	–	0	34%	B>A, P<0.001
		B. CRT	206	19%	30%	24%	38% (hematologic)			3%	6%	2%	5%	7%	–	4	77%	
	Bernier *et al.* (6)	A. RT alone	167	–	21%	12%	–	–	–	–	–	–	–	1%	–	1	–	B>A, P=001
		B. CRT	167	12%	41%	10%	16%	13%	–	–	–	–	–	2%	–	1	–	
LDC *vs.* RT	Bachaud *et al.* (9)	A. RT alone	44	–	–	–	–	–	–	–	–	–	–	–	–	0	18%	None reported
		B. CRT	39	–	–	–	–	–	–	–	–	–	–	–	–	0	41%	
	Sharma *et al.* (10)	A. RT alone	76	–	–	–	–	–	–	–	–	–	–	–	–	0	20%	B>A, P=0.015
		B. CRT	77	–	–	–	–	–	–	–	–	–	–	–	–	0	40%	
	Ghosh-Laskar *et al.* (11)	A. RT alone	57	–	21%	–	–	–	–	–	–	–	–	26%	–	0	–	None reported
		B. CRT	65	–	35%	–	–	–	–	–	–	–	–	23%	–	2	–	
HDC *vs.* LDC	Lee *et al.* (12)	A. HDC-CRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
		B. LDC-CRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 9 (*continued*)

Table 9 (*continued*)

CIS-CRT	Study		Severe acute toxicity (grade 3–5)															
	Author	Arms	Pts (no.)	N/V	Mucositis	Dysphagia	Leukopenia	Neutropenia	Tbcp	Anemia	Infection	Renal	Neuro	Skin	Oto–toxic	Total toxic deaths	All	Diff in acute toxicity
	Helfenstein *et al.* (13)	A. HDC-CRT	127	–	–	–	–	–	–	–	–	33%	–	–	–	–	–	A>B, P=0.02
		B. LDC-CRT	187	–	–	–	–	–	–	–	–	21%	–	–	–	–	–	
	Bauml *et al.* (14)	A. HDC-CRT	2200	HDC: higher rate of AKI (HR 1.72, P<0.001), neutropenia (HR 2.21, P=0.005), dehydration (HR 1.15, P=0.04), hearing loss (HR 1.34, P=0.004)														
		B. LDC-CRT	701															
	Szturz *et al.* (15)	A. HDC-CRT	25,6 studies	16, 10%	42, 37%	26, 20%	19, 19%	18, 14%	4, 2%	8, 6%	5, 11%	5, 3%	2, 5%	11, 6%	3, 2%	3, 2%	–	Bold = sig diff
		B. LDC-CRT	14,3 studies	3, 16%	25, 51%	8, 54%	1, 12%	5, 9%	1, 2%	4, 3%	8, NA%	1, 2%	1, NA%	14, 12%	NA, 2%	2, 1%	–	
	Tsan *et al.* (16)	A. HDC-CRT	26	12%	39%	54%	0	0	0	4%		–	–	8%	–	–	81%	B>A, P=0.02
		B. LDC-CRT	24	21%	75%	54%	13%	4%	0	4%	–	–	–	8%	–	–	92%	
	Noronha *et al.* (17)	A. HDC-CRT	149	7%	18%	39%	16%	13%	2%	5%	34%	0%	0%	8%	13%	10	85%	A>B, P=0.006
		B. LDC-CRT	148	1%	17%	42%	3%	1%	3%	2%	21%	0%	0%	7%	5%	5	72%	

Cis, cisplatin; CRT, chemoradiation; Pts, patients; N/V, nausea or vomiting; Tbcp, thrombocytopenia; Neuro, neurological; Diff, difference; HDC, high dose cisplatin (80–100 mg/m^2 3-weekly, 2–3 cycles); LDC, low dose cisplatin (30–50 mg/m^2 weekly, 6–9 cycles); RT, radiotherapy; LRT, locoregional treatment; AKI, acute kidney injury; HR, hazard ratio.

Table 10 References for studies on non–cisplatin chemoradiotherapy regimen

Study							Chemo	RT	OS			DFS		
Author, year	Design	Incl pd	Tx	Arms	Pts (no.)	Median f/u (mo.)	Regimen	Dose to 1' (Gy)	3-yr OS	5-yr OS	Diff in OS	3-yr DFS	5-yr DFS	Diff in DFS
Bonner *et al.*, 2006 (19)	Prosp PIII	1992–2002	Def	A. RT alone	213	54	–	70–76.8	45%	32%	B>A, P=0.03	31% (PFS)	–	B>A, P=0.04
				B. Cetux-CRT	211	54	Cetux	70–76.8	55%	40%		42% (PFS)	–	
Gillison *et al.* (RTOG 1016), 2019 (20)	Prosp PIII, HPV-OP	2011–2014	Def	A. HDC-CRT	406	54	HDC	70	90%	85%	A>B, P=0.016	82%	78%	A>B, P=0.0002
				B. Cetux-CRT	399	54	Cetux	70	87%	78%		72%	67%	
Mehanna *et al.* (DeESCALATE), 2019 (21)	Prosp PIII, HPV-OP	2012–2016	Def	A. HDC-CRT	166	25.9	HDC	70	98% (2-yr)	–	A>B, P=0.0012	–	–	–
				B. Cetux-CRT	168	25.9	Cetux	70	89% (2-yr)	–		–	–	–
Shapiro *et al.*, 2014 (22)	Retrosp	2002–2008	Def	A. HDC-CRT	259	53.1	HDC	70	–	87% (4-yr)	A>C, P<0.0001	–	–	–
				B. Carbo-CRT	52	53.1	Carbo-5-FU	70	–	70% (4-yr)	B>C, P=0.002	–	–	–
				C. Cetux-CRT	49	53.1	Cetux	70	–	41% (4-yr)	A *vs.* B, P=0.35	–	–	–
Denis *et al.*, 2004 (23)	Prosp PIII, OP	1994–1997	Def	A. RT alone	113	66	–	70	–	16%	B>A, P=0.05	–	15%	B>A, P=0.01
				B. Carbo-CRT	109	66	Carbo-5FU	70	–	22%		–	27%	
Tao *et al.* (REACH), ABSTRACT only (24)	Prosp PIII	Ongoing	Def	A. HDC-CRT	–	–	HDC	70	–	–	–	–	–	–
				B. Cetux/Ave–RT	–	–	Cetux-Ave	70	–	–	–	–	–	–

Chemo, chemotherapy; RT, radiotherapy; OS, overall survival; DFS, disease–free survival; PFS, progression–free survival; CIS, cisplatin; CRT, chemoradiation; Incl pd, inclusion period; Tx, treatment; Pts, patients; f/u, follow-up; 1', primary; Diff, difference; Prosp PIII, prospective phase III; Retrosp, retrospective; Def, definitive; HDC, high-dose cisplatin (80–100 mg/m^2 3-weekly, 2–3 cycles); Carbo-5FU: carboplatin-5-Fluorouracil (carboplatin 70 mg/m^2 and 5-fluorouracil 600 mg/m^2/day continuous infusion for 4 days, 3 cycles on 21-day interval); Cetux: cetuximab (initial dose 400 mg/m^2 during the week before radiotherapy followed by maximum of 7 doses of 250 mg/m^2 during radiotherapy); Ave: avelumab (10 mg/kg intravenous infusion over 1 hour every 2 weeks during RT and for 12 months following radiotherapy); HPV, human papilloma virus; OP, oropharyngeal cancer.

Table 11 References for studies on non–cisplatin chemoradiotherapy regimen (continued)

Study, author	Arms	LRC		DC			Response	
		2-yr LRC	Diff in LRC	3-yr DC	5-yr DC	Diff in DC	Overall Resp	Diff in Resp
Bonner *et al.* (19)	A. RT alone	41%	B>A, P=0.005	83%	–	None reported	64%	B>A, P=0.02
	B. Cetux-CRT	50%		84%	–		74%	
Gillison *et al.* (20)	A. HDC-CRT	90% (5-yr)	A>B, P=0.0005	–	–	P=0.09	–	–
	B. Cetux-CRT	83% (5-yr)		–	–		–	–
Mehanna *et al.* (21)	A. HDC-CRT	94%	A>B, P=0.0007	97%, ns	–	A>B, P=0.01	–	–
	B. Cetux-CRT	84%		91%, ns	–		–	–
Shapiro *et al.* (22)	A. HDC-CRT	94% (4-yr)	C>A, P<0.0001	–	88% (4-yr)	None reported	–	–
	B. Carbo-CRT	90% (4-yr)		–	82% (4-yr)		–	–
	C. Cetux-CRT	60 (4-yr)		–	71% (4-yr)		–	–
Denis *et al.* (23)	A. RT alone	25% (5-yr)	B>A, P=0.002	83%, ns	–	None reported	–	–
	B. Carbo-CRT	48% (5-yr)		82%, ns	–		–	–
Tao *et al.*, Abstract only (24)	A. HDC-CRT	–	–	–	–	–	–	–
	B. Cetux/Ave-RT	–	–	–	–	–	–	–

LRC, locoregional control; DC, distant control; Cis, cisplatin; CRT, chemoradiation; Diff, difference; Resp, response; RT, radiotherapy; Cetux, cetuximab; Carbo, carboplatin; HDC, high dose cisplatin; Cetux/Ave, cetuximab or avelumab.

who received weekly cetuximab and those who received modified regimen of crossover to cetuximab, but we did not directly compare cisplatin- with cetuximab-based CRT in our retrospective review of a heterogeneous patient population. Although we showed that patients who received non-cisplatin regimen had no difference in OS with those who received cisplatin, this may be the result of including other platinum-based regimen in our non-cisplatin cohort. It appears safe to assume that cetuximab is neither less toxic nor equally as effective as cisplatin, which thus cannot be replaced in treating HPV-positive oropharyngeal cancer.

There is an unmet need for an alternative CRT regimen for patients who cannot tolerate or risk the sequelae of severe toxicity with cisplatin. Prospective studies on alternative chemotherapy schedules and agents as well as immune checkpoint inhibitors (23) are warranted.

Conclusions

Survivals in our cohort were similar regardless of use of ICT, LDC, or non-cisplatin regimens. In the absence of a clear survival benefit, we only use ICT on clinical trial or as a temporizing maneuver for a patient trying to quit smoking. Patients unable to tolerate HDC should know

Table 12 References for studies on non-cisplatin chemoradiotherapy regimen (continued)

Study, author	Arms	Severe acute toxicity (grade 3–5)															
		Pts (no.)	N/V	Mucositis	Dysphagia	Leukopenia	Neutropenia	Tbcp	Anemia	Infection	Renal	Neuro	Skin	Ototoxic	Total toxic deaths	All	Diff in acute toxicity
Bonner *et al.* (19)	A. RT alone	212	6%	52%	30%	–	–	–	6%	1%	–	–	1%	–	–	–	No sig diff
	B. Cetux-CRT	208	4%	56%	26%	–	–	–	1%	1%	–	–	17%	–	–	–	
Gillison *et al.* (20)	A. HDC-CRT	398	19%	42%	37%	12%	15%	–	11%	–	3%	–	8%	3%	6	82%	P=0.16
	B. Cetux-CRT	394	8%	46%	32%	0%	1%	–	0%	–	0%	–	12%	0%	6	77%	
Mehanna *et al.* (21)	A. HDC-CRT	162	–	–	–		12% (hematologic)			12%	7%	6%	4%	2%	–	–	P=0.49
	B. Cetux-CRT	165	–	–	–		1% (hematologic)			13%	0%	10%	30%	2%	–	–	
Shapiro *et al.* (22)	A. HDC-CRT	No data on acute toxicity. Late toxicity was highest with 5FU/carboplatin (25%) *vs.* cisplatin (8%) *vs.* cetuximab (7.7%).															B>A, P=0.05; B>C, P=0.02
	B. Carbo-CRT																
	C. Cetux-CRT																
Denis *et al.* (23)	A. RT alone	No data on acute toxicity. Late toxicity no significant difference between arms															
	B. Carbo-CRT																
Tao *et al.*, Abstract only (24)	A. HDC-CRT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	B. Cetux/Ave-RT	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Cis, cisplatin; CRT, chemoradiation; Pts, patients; N/V, nausea or vomiting; Tbcp, thrombocytopenia; Neuro, neurological; Diff, difference; RT, radiotherapy; Cetux, cetuximab; HDC, high dose cisplatin; Carbo, carboplatin; Cetux/Ave, cetuximab or avelumab; 5FU, 5-fluorouracil.

that their survival may not be significantly impacted.

Acknowledgments

The authors thank Adam Oberkircher PA and Kelsey Smith PA for their tireless efforts to provide excellent care of these patients.

Funding: This work was supported by the National Cancer Institute Cancer Center Support Grant (P30CA016056). Funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Dr. Mukund Seshadri) for the series "Head and Neck Cancers – Disease Biology, Diagnostics, Prevention and Management" published in *Annals of Translational Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-5032

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-5032

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-5032). The series "Head and Neck Cancers – Disease Biology, Diagnostics, Prevention and Management" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Roswell Park Comprehensive Cancer Center (EDR-103707) and individual consent for this retrospective analysis was waived.

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Cite this article as: Han HR, Ma SJ, Hermann GM, Iovoli AJ, Wooten KE, Arshad H, Gupta V, McSpadden RP, Kuriakose MA, Markiewicz MR, Chan JM, Platek ME, Ray AD, Gu F, Hicks WL Jr, Singh AK. Matched pair analysis for comparison of survival outcome of alternative regimens to standard three-weekly cisplatin-based concurrent chemoradiation of head and neck cancer. Ann Transl Med 2021;9(10):913. doi: 10.21037/atm-20-5032

