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CLINICAL INVESTIGATION **Head and Neck**

LOCOREGIONALLY ADVANCED HEAD AND NECK CANCER TREATED WITH PRIMARY RADIOTHERAPY: A COMPARISON OF THE ADDITION OF CETUXIMAB OR CHEMOTHERAPY AND THE IMPACT OF PROTOCOL TREATMENT

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Purpose: The addition of platinum-based chemotherapy (ChRT) or cetuximab (ExRT) to concurrent radiotherapy (RT) has resulted in improved survival in Phase III studies for locoregionally advanced head and neck cancer (LAHNC). However the optimal treatment regimen has not been defined. A retrospective study was performed to compare outcomes in patients who were treated definitively with ExRT or ChRT.

Methods: Cetuximab with concurrent RT was used to treat 29 patients with LAHNC, all of whom had tumors of the oral cavity, oropharynx, or larynx. All patients were T2 to T4 and overall American Joint Committee on Cancer Stage III to IVB, with a Karnofsky Performance Status (KPS) score of 60 or greater. ChRT was used to treat 103 patients with similar characteristics. Patients were evaluated for locoregional control (LRC), distant metastasis-free survival (DMFS), disease-specific survival (DSS), and overall survival (OS). Median follow-up for patients alive at last contact was 83 months for those treated with ExRT and 53 months for those treated with ChRT. Cox proportional hazard models were used to assess independent prognostic factors.

Results: The LRC, DMFS, and DSS were not significantly different, with 3-year rates of 70.7%, 92.4%, and 78.6% for ExRT and 74.7%, 86.6%, and 76.5% for ChRT, respectively. The OS was significantly different between the two groups ($p = 0.02$), with 3-year rates of 75.9% for ExRT and 61.3% for ChRT. OS was not significant when patients who were on protocol treatments of ExRT or ChRT were compared. Also, OS was not significant when multivariate analysis was used to control for potential confounding factors.

Conclusion: In our single-institution retrospective review of patients treated with ExRT or ChRT, no significant differences were found in LRC, DMFS, DSS, or OS. © 2008 Elsevier Inc.

Head-and-neck cancer, Cetuximab, Chemoradiotherapy.

INTRODUCTION

Multiple Phase III randomized trials have demonstrated improvements in locoregional control (LRC) and overall survival (OS) in patients with locoregionally advanced squamous cell carcinomas of the head and neck (LAHNC) treated with concurrent chemotherapy and radiotherapy (ChRT) compared with radiotherapy alone (1–7). However, there have been many trials in which the addition of chemotherapy to radiotherapy did not enhance survival. This latter finding led to the MACH-NC Collaborative Group meta-analysis of 63 trials, which demonstrated a 6.5% benefit for concurrent chemotherapy and radiotherapy (8), although the addition of chemotherapy is detrimental with respect to greater acute and possibly late toxicity (2, 3, 6). The authors of the meta-analysis did conclude that the routine addition of chemotherapy to radiotherapy was ''debatable'' (8). Since that time, there have been additional investigations supporting the use of chemotherapy (1, 7).

A recently published, Phase III randomized trial demonstrated improved LRC as well as OS using concurrent cetuximab, an anti–epidermal growth factor receptor antibody, with radiotherapy (ExRT) over radiotherapy alone in LAHNC (9). These improvements in outcome were achieved without an increase in the most debilitating radiation-induced toxicities of dysphagia and mucositis. Cetuximab did produce a characteristic acneiform rash, which did not appear to interfere with the delivery of radiotherapy (10); cetuximab also resulted in infrequent allergic infusion reactions.

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This finding has stimulated significant interest in integrating cetuximab into current treatment regimens. Currently, the Radiation Therapy Oncology Group is performing a Phase III trial randomizing patients with LAHNC to ChRT, with or without cetuximab. Unfortunately, there is not an arm that uses ExRT in this trial. The hypothesis that ExRT may deliver equivalent or improved results over ChRT or the combination of all three treatments will remain untested. Therefore we have undertaken a review of the outcomes of patients treated with either ChRT or ExRT at our institution over the last decade.

METHODS AND MATERIALS

A total of 31 patients with LAHNC who were treated at the University of Alabama–Birmingham were enrolled on a Phase I (n = 16) and a Phase III (n = 15) protocol and treated with ExRT between April 1997 and December 2001 (9, 11). Two patients were excluded from further analyses (both from the Phase I protocol), as 1 patient had recurrent disease at presentation and 1 did not tolerate the loading dose of cetuximab. From May 1997 to November 2005, 103 patients who received ChRT were identified with the same general tumor and patient characteristics as the ExRT cohort (primary squamous cell carcinoma of the oral cavity, oropharynx, or larynx, T2 to T4, overall American Joint Committee on Cancer AJCC stage III to IVB, and Karnofsky Performance Status [KPS] score of 60 or greater), and had no previous surgery or induction chemotherapy. Only patients treated with conventional radiation fields (*i.e.,* not intensity-modulated radiation therapy) were included. It should be noted that this was not an attempt to create matched pairs, but merely to include a similar population of patients who were treated with curative intent.

Of the 103 patients treated with platinum-based ChRT, 43 were treated on a number of different institutional and multi-institutional protocols. In 63 patients, chemotherapy consisted of a platinum doublet (in 42 patients platinum–taxol, and in 21 platinum–5-fluorouracil), and in 40 a platinum alone. In addition all patients had the same group of treating physicians (S.A.S., W.R.C., G.E.P., L.M.N., R.F.M., and J.A.B.).

Primary endpoints included LRC, distant metastasis-free survival (DMFS), disease-specific survival (DSS), and OS. Patient characteristics included gender, KPS, and age at diagnosis. KPS was interpreted based on patient condition at the initial consult if one was not recorded in the chart. Tumor characteristics included primary site, T-stage, N-stage, and overall AJCC stage. Treatment characteristics included use of cetuximab or platinum-based chemotherapy, duration of radiotherapy treatment, radiotherapy dose, and use of altered fractionation. Follow-up was calculated from the start of radiotherapy. The Social Security Death Index was queried for patients lost to follow-up for more than 1 year (12).

Pearson's Chi-square test was used for nonparametric comparisons between groups.

Kaplan-Meier survival analyses were used to assess LRC, DMFS, DSS, and OS. The log-rank test was used to assess significance between groups. Multivariate Cox regression was used to model predictors of outcomes, including patient, tumor, and treatment characteristics. Potential predictors from the univariate analysis were entered in a stepwise fashion using 0.05 for entry and 0.1 for removal.

In addition, to control for bias that may be inherent to treatment assignment, we conducted a propensity analysis. Patient and tumor characteristics (age at diagnosis, gender, KPS, T-stage, N-stage, and overall AJCC stage) were used to construct a binary logistic regression model to assign a probability score to each patient with regard to the likelihood of having received treatment with ExRT. A stepwise approach was used wherein variables were entered into the model with $p < 0.05$ and removed with $p > 0.10$. Predictors for treatment assignment were used to stratify outcome analyses (13). All statistical analyses were performed in Statistical Package for the Social Sciences version 15.0 (SPSS Inc, Chicago, IL) and SAS version 9.0 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics are listed in Table 1. There were no significant differences between the groups for patient, tumor, or treatment characteristics, except for T-stage. Patients in the ChRT regimens had significantly higher T-stage tumors compared with ExRT patients ($p = 0.02$). On propensity analysis, higher T-stage predicted for assignment to ChRT ($p = 0.002$). Median follow-up of patients alive at last contact was 83 months for ExRT and 53 months for ChRT.

In all, 24 of 103 patients failed locoregionally in the ChRT cohort, whereas 8 of 29 patients failed in a similar manner in the ExRT cohort. Actuarial rates of LRC were not significantly different between the groups; 70.7% at 3 years in the ExRT and 74.7% at 3 years for the ChRT (log-rank p = 0.98; Fig. 1a). Because patients in the ChRT cohort had higher T-stage compared with the ExRT cohort (which also predicted for ChRT treatment assignment), controlling for T-stage showed that ChRT produced a slightly higher rate of LRC that was not significant (log-rank $p = 0.36$).

Only 11 of 103 patients experienced distant metastases in the ChRT group, in comparison to 5 of 29 in the ExRT group. Rates of DMFS were similar: 92.4% at 3 years for ExRT and 86.6% at 3 years for ChRT (log-rank $p = 0.88$; when controlling for T-stage $p = 0.38$; Fig. 1b).

In all, 54 of 103 ChRT patients died, compared with 12 of 29 ExRT patients. The cause of death was available for 30 of 66 patients, with the remainder ascertained through the Social Security Death Index. Of these 30 patients with known causes of death, only 5 died of causes other than recurrent disease: 2 with aspiration pneumonia (ChRT), 1 of cisplatin toxicity (ChRT), 1 of esophageal cancer (ExRT) and 1 of pancreatic cancer (ChRT). Therefore, when modeling DSS, there were no significant differences between the groups (Table 2), with 3-year rates of 76.5% for ChRT and 78.6% for ExRT (log-rank $p = 0.71$; when controlling for T-stage, $p = 0.52$).

Differences in OS were significant, with 3-year actuarial rates of 61.3% for ChRT and 75.9% for ExRT (log-rank $p = 0.02$; Fig. 1c). Median survival was 54 months for ChRT and was not reached for ExRT patients. Because T-stage was significantly higher and this predicted for selection of ChRT, when controlling for T-stage this OS advantage decreased to nonsignificance, still slightly favoring ExRT ($p = 0.19$).

We postulated that an additional source of bias may have been protocol inclusion. All patients receiving ExRT were on protocol, as compared with only 43 of 103 of ChRT

Table 1. Patient characteristics

Factor	ExRT (*n*, %)	ChRT (*n*, %)	*p**	ChRT (*n*, %)		*p*†
				Protocol	Nonprotocol	
Gender						
Male	23 (79.3)	80 (77.7)	0.85	33 (76.7)	47 (78.3)	0.96
Female	6 (20.7)	23 (22.3)		10 (23.3)	13 (21.3)	
Primary site						
Larynx	8 (27.6)	24 (23.3)	0.72	8 (18.6)	16 (26.7)	0.05
Oral cavity	2 (6.9)	11 (10.7)		9 (20.9)	2 (3.3)	
Oropharynx	19 (65.5)	68 (66.0)		26 (60.5)	42 (70.0)	
Tumor stage						
T2	12 (41.4)	18 (17.5)	0.02	6 (14.0)	12 (20.0)	0.07
T3	10 (34.5)	40 (38.8)		17 (39.5)	23 (38.3)	
T4	7 (25.1)	45 (43.7)		20 (46.5)	25 (41.7)	
Nodal stage						
N0	5 (17.2)	22 (21.4)	0.65	11 (25.6)	11 (18.3)	0.47
N1	6 (20.7)	14 (13.6)		3 (7.0)	11 (18.3)	
N2	16 (55.2)	53 (51.5)		25 (58.1)	29 (48.4)	
N3	2 (6.9)	13 (12.6)		4 (9.3)	9 (15.0)	
AJCC stage						
III	8 (27.6)	19 (18.4)	0.28	7 (16.2)	12 (20.0)	0.50
IV	21 (72.4)	84 (81.6)		36 (83.7)	48 (80.0)	
Altered fractionation						
No	11 (37.9)	58 (56.3)	0.08	27 (62.8)	31 (51.7)	0.11
Yes	18 (62.1)	45 (43.7)		16 (37.2)	29 (48.3)	
	Median (range)	Median (range)		Median (range)	Median (range)	
KPS score‡	90 (70–90)	80 (60–100)	0.10	80 (70–100)	80 (60–100)	0.19
Radiotherapy dose‡	74.4 Gy (70.0–76.8)	70.2 Gy (45.0–81.6)	0.17	70.2 Gy (45–72.8)	72.0 Gy (68–81.6)	0.08
Age (y)‡	54 (34–80)	55 (23–78)	0.83	53 (23–75)	56 (39–78)	0.78
Length of radiotherapy‡ (days)	46 (43–54)	50 (30–73)	0.12	47 (33–70)	52 (30–73)	0.01

Abbreviations: AJCC = American Joint Committee on Cancer; ChRT = concurrent platinum-based chemotherapy–radiotherapy; ExRT = concurrent cetuximab–radiotherapy, KPS = Karnofsky Performance Status.

* ExRT vs. ChRT.

† ExRT vs. ChRT-protocol vs. ChRT-nonprotocol.

‡ Comparisons between groups based on cutoffs listed in Table 3.

patients. When comparing these three groups, only primary site ($p = 0.05$) and length of radiotherapy ($p = 0.01$) were significantly different (Table 1). For LRC, DMFS, and DSS outcomes, there were no significant differences among the three groups (Table 2). OS was 75.9%, 67.6%, and 61.3% at 3 years for ExRT, ChRT-protocol, and ChRT-nonprotocol patients, respectively (log-rank $p = 0.002$; Fig. 1d). Both ExRT and ChRT-protocol patients exhibited improved OS vs. ChRT-nonprotocol patients ($p = 0.001$ and $p = 0.01$, respectively). There was no OS difference between protocol patients receiving ExRT or ChRT ($p = 0.43$).

Finally, OS was modeled using Cox regression analysis including potential prognostic factors. Both T-stage and KPS predicted for improved OS (Table 3). Treatment assignment was significant for ExRT compared with nonprotocol ChRT (HR 2.32, 95% CI, 1.15–4.68), whereas ExRT was nonsignificant compared with that in ChRT patients on protocol (HR, 1.25; 95% CI, 0.56–2.77; Table 3).

DISCUSSION

The standard of care for LAHNC continues to evolve and varies with the stage of disease, as exemplified by the National Comprehensive Cancer Network (NCCN) 2007 guidelines (14). Surgery or radiotherapy remain cornerstones of treatment for patients with LAHNC. Although the 2007 guidelines stipulate that concurrent cisplatin alone is preferred, it does provide for several other concurrent systemic options, including various chemotherapies and cetuximab. These recommendations regarding systemic chemotherapies are based on the results of a meta-analysis as well as several subsequent individual trials that show that platinum-based chemotherapy added concurrently to locoregional radiotherapy leads to an improvement in OS for many patients with LAHNC in a variety of primary sites (1–8). This large database of Phase III trials of ChRT for LAHNC is contrasted by a single recent, positive (for both LRC and OS), randomized trial of ExRT vs. radiotherapy alone (9). Therefore the NCCN guidelines suggest that there is overlap between the indications for ChRT and ExRT; and as such, further comparisons between the two regimens to better discern their relative efficacy are warranted. A retrospective review of patients with LAHNC was performed to address this issue. In fact ChRT and ExRT produced similar results.

Selection of the most advantageous combination of chemotherapeutic, biologic, and radiotherapy regimens is

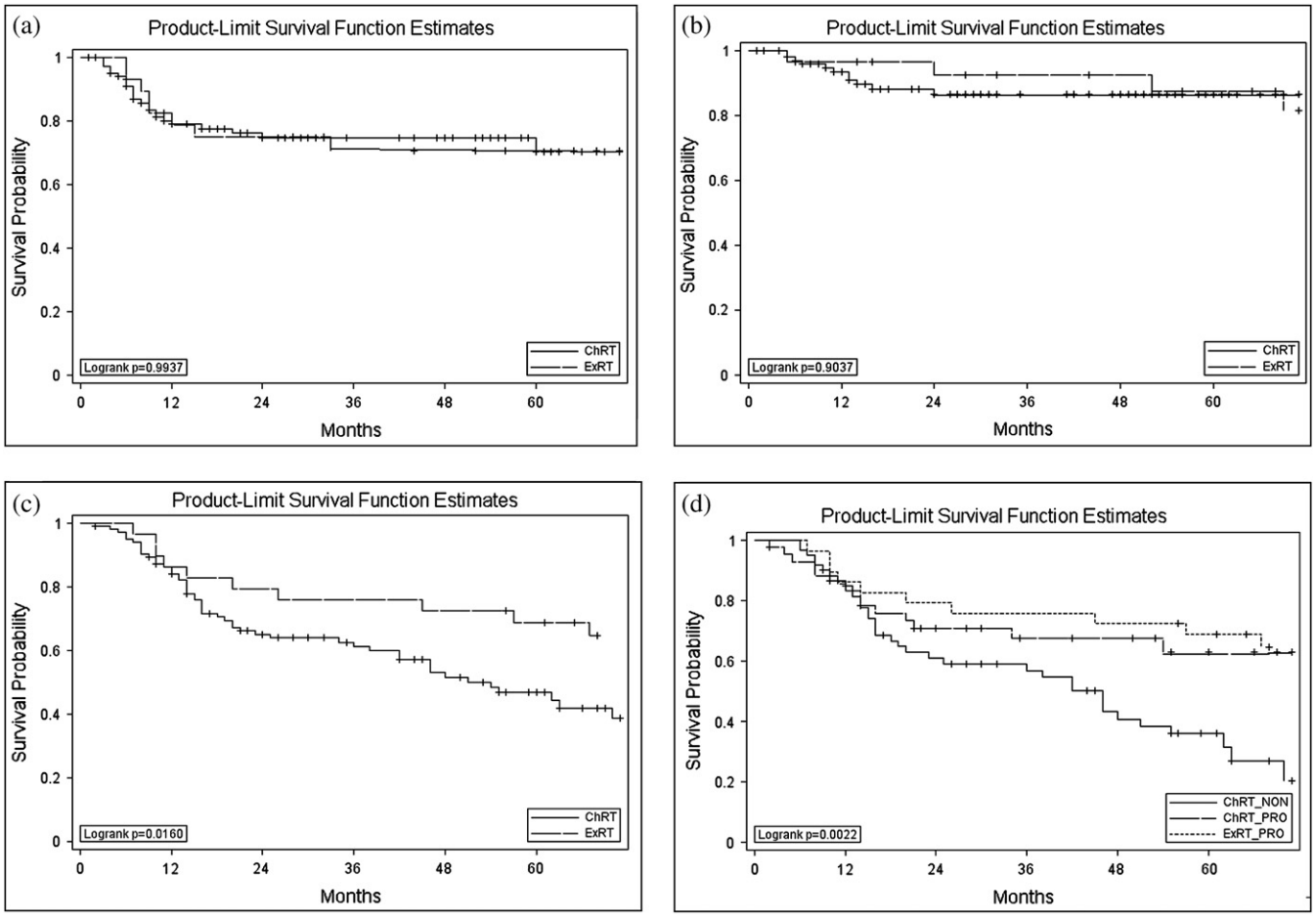

Fig. 1. Outcomes of concurrent cetuximab–radiotherapy (ExRT) treatment vs. ChRT = concurrent platinum-based chemotherapy–radiotherapy (ChRT) for (a) locoregional control, (b) distant metastasis–free survival, (c) overall survival, and (d) overall survival by protocol entry. ChRT-PRO = concurrent platinum-based chemotherapy–radiotherapy on protocol; ChRT-NON = concurrent platinum-based chemotherapy–radiotherapy not on protocol.

complicated by heterogeneous results among Phase III trials, which may be caused by inclusion of dissimilar patients. A selection of recent Phase II and III trials examining ChRT demonstrates an OS at 3 years ranging from 27% to 55% (1–7, 15–17). In comparison, treatment with ExRT in a recent Phase III trial demonstrated a 3-year survival of 55% (9). The OS of patients treated with ExRT at UAB was higher, with a 3-year actuarial rate of 75.9%. Although this may indicate a selection bias, ChRT patients treated on protocol also exhibited a similar improvement compared with patients in published ChRT protocols, with a 3-year OS of 67.6% (Fig. 1d). These results are consistent with the finding that patients with LAHNC who are entered on protocols in the United States (7, 15, 17) tend to have a somewhat higher

Table 2. Tumor control outcomes at 3 years

Outcome	ExRT	ChRT	p*	ChRT		$p^{\dagger}$
				Protocol	Nonprotocol	
Locoregional control (SE)	70.7 (8.8)	74.7 (4.6)	0.98	71.8 (7.3)	76.6 (6.1)	0.85
Distant metastasis–free survival (SE)	92.4 (5.2)	86.6 (3.8)	0.88	94.1 (4.0)	81.3 (5.8)	0.17
Disease-specific survival (SE)	78.6 (7.8)	76.5 (4.6)	0.71	76.0 (7.0)	77.0 (6.2)	0.90
Overall survival (SE)	75.9 (7.9)	61.3 (5.0)	0.02	67.6 (7.5)	56.9 (6.7)	0.002

Abbreviations: ChRT = concurrent platinum-based chemotherapy–radiotherapy; ExRT = concurrent cetuximab–radiotherapy; SE = standard error.

* ExRT vs. ChRT.

† ExRT vs. ChRT-protocol vs. ChRT-nonprotocol.

Table 3. Cox regression analysis results for overall survival

Factor	HR (95% CI)	*p*
Treatment regimen		
ExRT	1.0	
ChRT nonprotocol	2.32 (1.15–4.68)	0.02
ChRT protocol	1.25 (0.56–2.77)	0.58
Patient age (y)		
≤54	1.0	
>55	1.49 (0.88–2.52)	0.14
Tumor stage at diagnosis		
4	1.0	
2	0.51 (0.23–1.13)	0.10
3	0.48 (0.27–0.86)	0.01
KPS score		
≤80	1.0	
>80	0.37 (0.20–0.72)	0.003
Radiation dose (Gy)		
≤70.2	1.0	
>70.2	1.52 (0.78–2.95)	0.22
Primary site		
Oropharynx	1.0	
Larynx	0.59 (0.30–1.16)	0.12
Oral cavity	1.59 (0.73–3.44)	0.24
Length of radiotherapy (days)		
≤49	1.0	
>49	1.05 (0.58–1.89)	0.87

Abbreviations: ChRT = concurrent platinum-based chemotherapy–radiotherapy; CI = confidence interval; ExRT = concurrent cetuximab–radiotherapy, HR = hazard ratio; KPS = Karnofsky Performance Status.

OS compared with those in international trials (2, 5, 8). These trends may represent regional practices for protocol selection.

Interestingly the survival results in the present group of patients treated with ExRT is similar to results obtained in a Phase II trial of trimodality treatment consisting of cetuximab and cisplatin given concurrently with radiotherapy (17). A total of 22 patients were enrolled, and 3-year LRC and OS were excellent at 71% and 76%, respectively. This trimodality treatment is currently being compared with concurrent cisplatin and radiotherapy in a Phase III randomized trial. Unfortunately, however, it was determined that an unrealistic number of patients would have been required to potentially include a third arm of ExRT without cisplatin. Therefore future comparisons of ExRT and ChRT will most likely be retrospective in nature, as is the case with the present communication.

In our experience, ExRT and ChRT produced comparable outcomes for patients with LAHNC. The only significant difference between the groups at baseline was in the T-stage. T-stage did predict for LRC ($p = 0.01$), DMFS ($p = 0.02$), and OS ($p < 0.001$) on univariate (data not shown) as well as OS on multivariate analyses (Table 3). Although a survival benefit was seen for ExRT compared with ChRT in the univariate analysis, this benefit was not significant when controlling for T-stage, inclusion on protocol (Fig. 1d and Table 2), or on multivariate analysis (Table 3). In the ChRT group OS, may have been impacted by the use of heterogenous regimens (*i.e.,* different doses, combination of agents, and schedules). For example, consideration must be given to the possibility that intensification of ChRT may have resulted in severe late morbidity or exacerbation of pre-existing comorbid conditions, leading to shorter OS.

The ChRT group also fared more poorly by the inclusion of nonprotocol patients. Protocol eligibility has been shown to be a good prognostic factor for OS (18, 19). Often this may not be measured by such factors as age or KPS. For example, quantification of frailty in the elderly population is a difficult task (20, 21). When ExRT and ChRT-protocol patients were compared, there were no differences in LRC ($p = 0.83$), DMFS ($p = 0.26$), DSS ($p = 0.89$), or OS ($p = 0.43$) endpoints (data not shown). It is possible that ExRT outcomes may have been impaired by the inclusion of 8 patients from the Phase I trial who received less than full-dose cetuximab (11).

When considering treatment options, it is important to assess not only the efficacy but the toxicity of a treatment regimen. For example, some patient populations express a preference for reduced late toxicity, even with the understanding that there may be a survival decrement in that choice (22). Cisplatin increases rates of acute radiotherapy-induced toxicities including mucositis and dysphagia, in addition to its potential inherent hematologic toxicities, which may adversely impact the delivery of radiotherapy or may predispose patients to infectious processes (2, 3, 6). In contrast, cetuximab does not increase these acute toxicities (9); however it is associated with a characteristic acneiform rash, electrolyte abnormalities, and rare anaphylactic reactions (9). Reports of late toxicities are quite variable, but a selection of recent trials demonstrates a 3% to 51% rate of serious late toxicity with platinum-based based chemoradiotherapy, which in most trials is higher than with radiotherapy alone (2–7, 15, 16). In contrast, reported serious late toxicity using ExRT was not significantly different from radiotherapy alone (9, 23).

CONCLUSION

In our retrospective review of patients treated at a single institution with concurrent cetuximab or platinum-based chemotherapy in combination with radiotherapy, there did not appear to be differences in LRC, DMFS, DSS, or OS. The finding that ExRT may be comparable to ChRT gives further support to its inclusion as an important option for LAHNC patients in the 2007 NCCN guidelines (14). This suggestion of equivalence of the ExRT regimen may prompt oncologists to consider this less toxic regimen for many patients with LAHNC, especially those who are considered to be at a lower risk for distant metastases or who are borderline or unsuitable for concurrent platinum-based ChRT. It should be noted that bias is inherent in this retrospective review, and that we may not have accounted for all confounding factors. Ultimately, a randomized clinical trial will be required to definitively address this question.

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