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Cisplatin versus Cetuximab Given Concurrently with Definitive Radiation Therapy for Locally Advanced Head and Neck Squamous Cell Carcinoma

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Key Words
Radiation · Cetuximab · Cisplatin · Head and neck · Neoplasms

Abstract
Objective: Whether or not cisplatin and cetuximab are similarly effective in improving outcomes when added to radiation therapy (RT) in squamous cell carcinoma of the head and neck is unknown. ***Methods:*** Retrospective analysis was performed of patients treated with definitive RT and cisplatin (n = 18) or cetuximab (n = 29). ***Results:*** T and N classifications, stage, human papillomavirus status and smoking history were balanced in the two groups; however, patients in the cisplatin group were younger and had a better performance status. Delivery of RT was similar between the two groups. Median follow-up was 23 (4–64) months. Disease-specific survival (DSS) at 3 years was 83% in the cisplatin group and 31% in the cetuximab group. Recurrent disease was more common in the cetuximab group compared with the cisplatin group (17 vs. 4 patients). Propensity score analysis to adjust for differences in patient characteristics which influenced treatment selection showed that DSS was indeed longer with cisplatin than with cetuximab (DSS hazard ratio 0.15, confidence interval 0.033, 0.66; p = 0.012). ***Conclusions:*** DSS was superior in the patients given cisplatin with definitive RT compared to cetuximab with definitive RT due to a lower risk of recurrent disease in the cisplatin group. These observations could not be explained by differences between the two groups in the patient and tumor characteristics or in treatment delivery.

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is a common malignancy, with more than 500,000 newly diagnosed cases worldwide in 2002 [1]. A meta-analysis of 93 randomized trials showed that chemotherapy given concurrently with radiation therapy (RT) improved overall survival (OS) over RT alone in patients with locally advanced HNSCC [2]. The meta-analysis demonstrated that platinum-based therapy and monotherapy were the most efficacious treatment options

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when combined concurrently with radiation. Cisplatin is commonly considered to be the gold standard that other regimens are compared to; however, the acute toxicity of cisplatin and RT is significant and limits its application to younger patients with minimal comorbidities.

More recently, cetuximab given concurrently with RT was also shown to improve OS over RT alone in patients with locally advanced HNSCC [3, 4]. Whether or not cisplatin and cetuximab are similarly effective in improving outcomes when added to RT is unknown as there are no published controlled randomized trials to guide decision making. Herein, we report a single institution retrospective analysis of 47 patients with locally advanced HNSCC treated with definitive RT and either concurrent cisplatin or cetuximab.

Materials and Methods

Study Design and Patient Selection

This was an Institutional Review Board-approved retrospective analysis of all patients with locally advanced HNSCC treated with definitive RT concurrently with either cisplatin or cetuximab at a single institution between 2005 and 2010. Patients were identified from the Institutional Review Board-approved HNSCC registry protocol initiated in 2005. Eligibility criteria for this retrospective analysis included: stage III, IVa or IVb HNSCC that was treated with definitive RT concurrently with either scheduled cisplatin (100 mg/m^2 on days 1, 22 and 43 of RT) or cetuximab (400 mg/m^2 loading dose before RT, then 250 mg/m^2 per week during RT for 7 doses). HNSCC subsites included oral cavity, oropharynx, larynx, hypopharynx, and unknown primary with a level II and/or III neck mass. Intensity-modulated radiation therapy was administered once daily, 5 days weekly, using either a Varian Linear Accelerator (Varian Medical Systems Inc.) or a Tomotherapy Hi-ART System® (Tomotherapy Inc.). The total dose of RT to gross disease was 6,600–7,000 cGy in 33–35 fractions of 200 cGy each over 7 weeks in all but 1 patient (unknown primary site received 30 fractions). Additional areas of intermediate risk received 6,300 cGy and regions in the ipsilateral and contralateral neck at risk for microscopic disease received 5,600 cGy.

Exclusion criteria included primary surgical resection, induction chemotherapy or alternative chemotherapy given with RT. Forty-seven patients met the entry criteria for the retrospective analysis and are the subject of this report: 18 received cisplatin and 29 received cetuximab concurrently with RT.

Standard Assessments

The institution employed a standardized initial evaluation, treatment, supportive care and long-term surveillance approach for these patients. The initial evaluation included a multi-disciplinary team and tumor board assessment involving otolaryngology, radiation oncology, medical oncology and pathology. The primary tumor site was identified and biopsied and the cancer was staged by experienced oncologic otolaryngologists using clinical (fiber optic endoscopy and/or laryngoscopy) and radiographic (CT, MRI and/or FDG-PET/CT) methods.

In general, cisplatin was given concurrent with definitive RT in those patients with a favorable ECOG performance status (0–1), age <70 years and low comorbidity burden, and cetuximab was given with definitive RT in patients with an unfavorable ECOG performance status (2–3), age ≥70 years and/or with high comorbidity burden. Due to the presence of the latter patient characteristics in the cetuximab group, once daily fractionation of radiation was chosen because of concerns about excessive toxicity with altered fractionation of radiation.

During definitive RT with concurrent cisplatin or cetuximab, adverse events (AEs) were monitored. Following completion of definitive therapy, patients underwent an office-based fiber optic endoscopy and neck examination and CT of the neck at 6–8 weeks, followed by a clinical exam and FDG-PET/CT at 10–16 weeks. Subsequently, patients underwent office examinations every 1–3 months for 3 years along with CT of the neck and chest every 6 months for 3 years. After 3 years, examinations occurred 1–2 times per year for at least 2 additional years.

Data Captured

Baseline clinical and pathologic data collected included age, gender, race, smoking history, ECOG performance status, ACE-27 comorbidity index [5], insurance (Medicare, Medicaid, private, other/none), primary site, TNM classification [6] and human papillomavirus (HPV) relationship (based on p16 by immunohistochemistry and/or nonkeratinizing squamous cell carcinoma on histology, both surrogate markers for HPV) [7]. Treatment data collected included variables related to radiation (total dose, number of fractions, dose per fraction, elapsed days), cisplatin (total dose, number of doses, milligrams per dose), and cetuximab (total dose, number of doses, milligrams per dose). Selected AEs captured included incidence and grade of mucositis, incidence and grade of acneiform rash, weight change from start to end of RT, and requirement for and duration of PEG tube. AEs were graded using NCI-CTC version 3.0.

Other data collected included OS (interval from diagnosis to either death or last follow-up alive) and disease-specific survival (DSS; time from initiation of CRT to death due to disease). Causes of death were determined, including primary cancer, secondary cancer, treatment-related mortality (TRM), intercurrent illness and other/unknown.

Statistical Plan

Patients were stratified by chemotherapy regimen (cisplatin or cetuximab) given with definitive RT. Survival outcomes were estimated using the Cox proportional hazards methods, adjusted using a propensity score for sex, race, age, ECOG performance score, primary site, overall stage, HPV status, type of insurance, smoking status and comorbidity score. Baseline clinical and pathologic data were tabulated for each chemotherapy group and compared using Fisher's exact test, a nonparametric test for trend over an ordinal covariate (Jonckeheere-Terpstra test), nonparametric Wilcoxon rank-sum and t tests. Treatment delivery (RT; cisplatin or cetuximab) was analyzed using descriptive statistics, and a comparison of RT delivery by chemotherapy regimen was performed by Wilcoxon rank-sum test. Selected AEs were analyzed by descriptive statistics and were compared between chemotherapy groups by Wilcoxon rank-sum test, Fisher's exact test or a test for the difference of proportions over an ordinal scale (Jonckheere-Terpstra test). Causes of death were tabulated and stratified by chemotherapy group.

Results

Patient Characteristics

Of the 47 patients identified, 18 received cisplatin and 29 received cetuximab concurrently with definitive RT (table 1). Tumor T and N classifications, stage, gender, race, smoking history and HPV status were balanced in the two treatment groups. Patients in the cisplatin group were younger (median 55 vs. 62 years, respectively; p = 0.015) and had better performance status (median 0 vs. 1, respectively; p = 0.042) compared to those in the cetuximab group.

Treatment Delivery

Delivery of RT as measured by median total dose, proportion of patients who received 33–35 fractions, elapsed days and daily dose was similar between the two treatment groups (table 2). The planned RT dose was delivered in 94.4% of the cisplatin group and 93.1% of the cetuximab group (p = 0.90). Three patients (1 cisplatin group and 2 cetuximab group) received an abbreviated course of RT due to social/transportation issues, respiratory failure and hospitalization for opiate withdrawal. The median (range) number of doses of cisplatin or cetuximab given were 2 (1–3) and 8 (1–15), respectively.

Survival

At last follow-up, 20 patients were alive without primary cancer, 2 patients were alive with primary cancer and 25 patients had expired (due to primary cancer in 19, second cancer in 1, intercurrent illness in 2 and other causes in 3; table 3). The sites of recurrent disease are shown in table 3. Recurrent disease was more common in the cetuximab group compared to the cisplatin group (p = 0.018). The most common site of recurrent disease was local-regional only, and most (8 of 10) of the local-regional only recurrences occurred in the cetuximab group. The median (range) follow-up of all patients was 23 (4–64) months: 35 (7–64) months in the cisplatin group and 18 (4–54) months in the cetuximab group.

DSS at 3 years was 83% in the cisplatin group and 31% in the cetuximab group. OS at 3 years was 75% in the cisplatin group and 27% in the cetuximab group (fig. 2). Propensity score analysis to adjust for differences in patient characteristics which influenced treatment selection showed that DSS was indeed longer with cisplatin than with cetuximab (DSS hazard ratio 0.15, confidence interval 0.033, 0.66; p = 0.012). A similarly adjusted analysis also showed that OS was longer with cisplatin than with cetuximab (OS hazard ratio 0.24, confidence interval 0.067, 0.89; p = 0.033).

Table 1. Patient and tumor characteristics

Characteristic	Radiation with cisplatin (n = 18)	Radiation with cetuximab (n = 29)	p value
Median age, years	55	62	0.015
Range	35–78	46–86	
Sex			0.32
Male	15 (83.3%)	19 (65.5%)	
Female	3 (16.7%)	10 (34.5%)	
Race			0.99
Caucasian	14 (77.8%)	21 (72.4%)	
African American	3 (16.7%)	6 (20.7%)	
Native American	1 (5.6%)	2 (6.9%)	
Smoking history			0.94
Yes	14 (77.8%)	26 (89.7%)	
No	4 (22.2%)	3 (10.3%)	
Insurance			0.076
Private	5 (27.8%)	4 (13.8%)	
Medicare	3 (16.7%)	15 (51.7%)	
Medicaid	9 (50.0%)	9 (31.0%)	
None	1 (5.6%)	1 (3.4%)	
ECOG performance status			0.042
0	11 (61.1%)	8 (27.6%)	
1	4 (22.2%)	13 (44.8%)	
2	3 (16.7%)	6 (20.7%)	
3	0 (0.0%)	2 (6.9%)	
ACE comorbidity index			0.083
0 (none)	5 (27.8%)	5 (17.2%)	
1 (mild)	7 (38.9%)	8 (27.6%)	
2 (moderate)	4 (22.2%)	5 (17.2%)	
3 (severe)	2 (11.1%)	11 (37.9%)	
Primary Site			0.29
Oropharynx	10 (55.6%)	13 (44.8%)	
Oral cavity	0 (0.0%)	3 (10.3%)	
Larynx	7 (38.9%)	7 (24.1%)	
Level II/III neck mass (unknown primary)	1 (5.6%)	2 (6.9%)	
Hypopharynx	0 (0.0%)	4 (13.8%)	
T classification			0.58
T1	0 (0.0%)	1 (3.4%)	
T2	0 (0.0%)	3 (10.3%)	
T3	8 (44.4%)	10 (34.5%)	
T4	9 (50.0%)	13 (44.8%)	
Tx	1 (5.6%)	2 (6.9%)	
N classification			0.66
N0 and N1	6 (33.3%)	12 (41.4%)	
N2a–c	11 (61.1%)	15 (51.7%)	
N3	1 (5.6%)	2 (6.9%)	
Overall stage			0.55
III	3 (16.7%)	7 (24.1%)	
IVa/IVb	15 (83.3%)	22 (75.9%)	
HPV related			0.99
Oropharynx	7	7	
Level II/III neck mass (unknown primary)	1	1	
Hypopharynx	0	1	

Table 2. Treatment delivery of radiation

Treatment variable	Radiation with cisplatin (n = 18)	Radiation with cetuximab (n = 29)	p value
Elapsed days	49 (25–62)	49 (29–72)	0.77
Number of fractions	35 (17–35)	35 (17–35)	–
Patients who received 33–35 fractions	16 (89%)	27 (93%)	0.63
Daily dose	2.0 (2.0–2.10)	2.0 (2.0–2.22)	0.86
Total dose	70 (34–71)	70 (34–73)	0.96
Completed planned dose	94.4%	93.1%	0.90

Values are median (range), unless otherwise indicated.

Table 3. Status at last follow-up and site of recurrent disease

Variable	Radiation with cisplatin (n = 18)	Radiation with cetuximab (n = 29)
Status		
Alive without disease	13 (72.2%)	7 (24.1%)
Alive with disease	1 (5.6%)	1 (3.4%)
Deceased	4 (22.2%)	21 (72.4%)
Primary cancer	3	16
Secondary cancer	0	1
Intercurrent illness	0	2
Other/unknown	1	2
Site of recurrence		
Total (p = 0.018)	4 (22.2%)	17 (58.6%)
Local-regional only	2	8
Distant only	0	2
Both	2	7

Table 4. Selected AEs

Toxicity/event	Radiation with cisplatin (n = 18)	Radiation with cetuximab (n = 29)	p value
Mucositis grade	2 (0–3)	2 (0–3)	0.82
Weight loss, kg	9.4 (0–21)	6 (0–22)	0.24
PEG tube placement, n	12 (66.7%)	15 (51.7%)	0.37
Duration of PEG, days	218.5 (49–1,073)	239 (16–1,088)	0.83

Values are median (range), unless otherwise indicated.

DSS for HPV-related (n = 17) and HPV-unrelated (n = 30) HNSCC were stratified by treatment group (fig. 1). In the HPV-related and HPV-unrelated cohorts, a trend to better DSS was observed in the cisplatin group compared to the cetuximab group (p = 0.058 and 0.036, respectively).

Selected AEs

The median grade of mucositis and the proportion of patients requiring PEG tube placement were similar between the cisplatin and the cetuximab groups (table 4). Acneiform rash developed in 22 (76%) patients in the cetuximab group (grade 1 in 8 patients and grade 2–3 in 14 patients).

Discussion

In this retrospective analysis, DSS was superior in patients treated with cisplatin and definitive RT compared to cetuximab and definitive RT. This DSS difference was due to a greater proportion of patients in the cetuximab group who developed recurrence of their primary cancer and died compared to the cisplatin group. The key predictors of cancer recurrence including tumor T and N classifications, stage, gender, smoking history and HPV status were balanced between the two treatment groups. However, differences in patient characteristics between the two treatment groups were present. Older age and reduced performance status in the cetuximab group could impact primary cancer recurrence and DSS by adversely affecting delivery of RT and chemotherapy, or could impact survival by affecting TRM or deaths from intercurrent illness; however, the data in this analysis do not support this conclusion. Delivery of RT was similar between the two treatment groups and the delivery of cisplatin and of cetuximab was comparable to that observed in other studies [3, 8]. Deaths from intercurrent illness and TRM were proportionately similar between the two treatment groups.

The propensity score analysis showed that DSS differed between the two groups even after adjustment for differences in patient characteristics which influenced treatment selection. The choice to treat a patient with cisplatin versus cetuximab was guided, in part, by characteristics of the patient. Some of these characteristics were related to the patient's prognosis, so a direct, unadjusted comparison of the two groups would be likely to produce biased and misleading estimates. Any differences in DSS could be due to the nature of the patients undergoing each

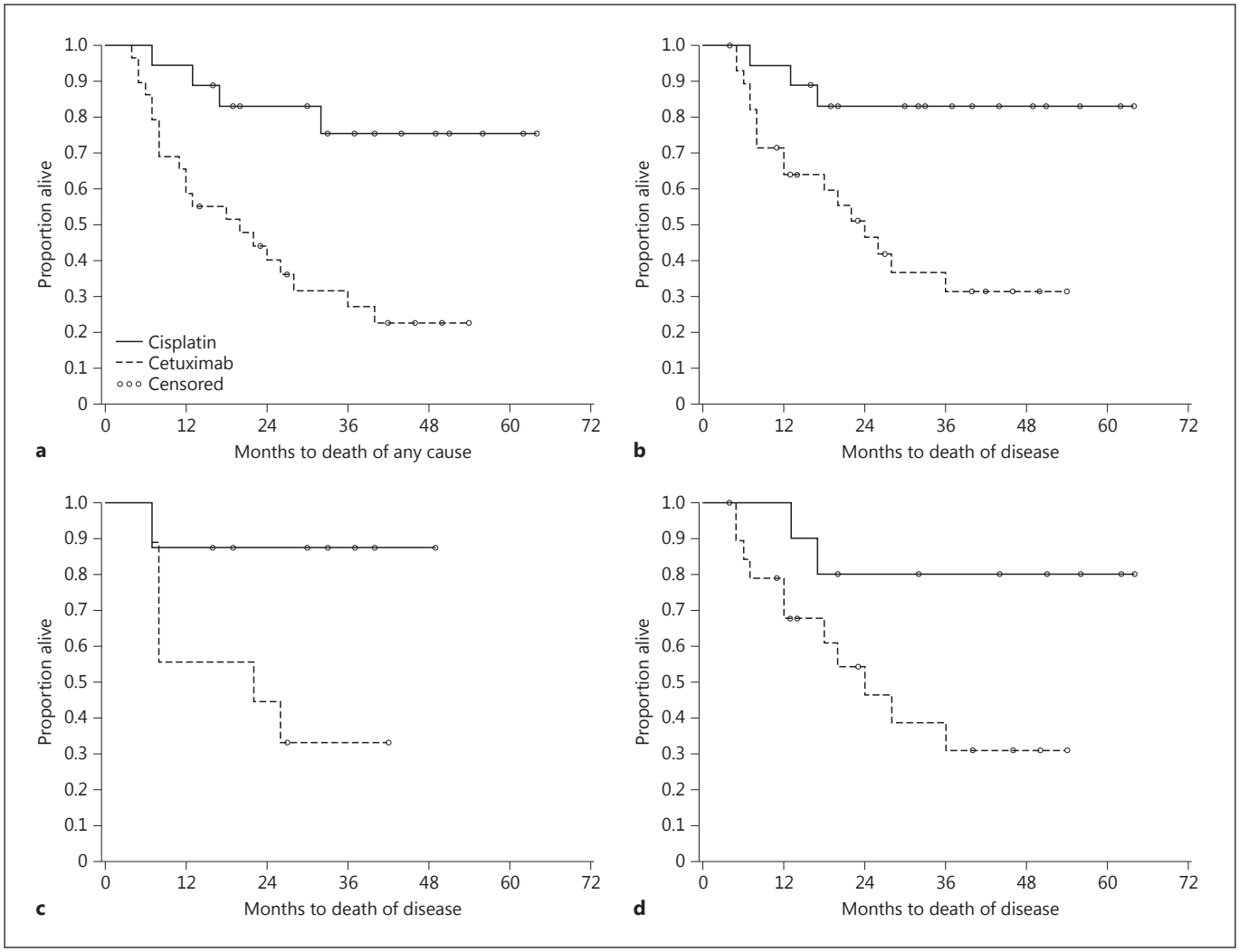

Fig. 1. Survival curves stratified by chemotherapy regimen: DSS for all patients (**a**), OS for all patients (**b**), DSS for the HPV-related patients (**c**) and DSS for the HPV-unrelated patients (**d**).

therapy and only spuriously correlated with the therapy itself. In the present patient sample, there are measurable differences in age and performance status, and possibly in ACE-27 comorbidity index. These biases can be reduced by simultaneous adjusting for several patient characteristics using a propensity score. A propensity score is the patient's probability of receiving one drug or the other based on the patient's age, performance status and any other characteristics thought to be a source of bias. That probability is included as a covariate in the subsequent Cox proportional hazards model of DSS, so the hazard ratio for cisplatin-cetuximab describes the difference in hazard of death (that is, the instantaneous death rate) conditional upon the characteristics included in the propensity score. In effect, it allows comparison of DSS in patients of the same age, performance status and any other characteristic thought to be a source of bias, and summarizes those comparisons in a single, adjusted estimate of hazard. The adjustment, while not resulting in a perfect match, does reduce the major biases resulting from observable characteristics related to the patient's outcome.

Two other retrospective comparisons of definitive RT and either cetuximab or chemotherapy to treat patients with locally advanced HNSCC yielded conflicting conclusions. In contrast to our study, a comparison of patients treated with definitive RT and cetuximab (n = 29) or chemotherapy (n = 103) showed no significant differences in locoregional control, distant metastasis-free sur-

vival, DSS or OS [9]. However, differences in patient characteristics between the two treatment groups (higher T classification and inclusion of nonprotocol patients in the chemotherapy group) and the use of heterogeneous regimens in the chemotherapy group confounds the data interpretation. A strength of our study was that all patients in the chemotherapy group were treated with high-dose bolus cisplatin. A comparison of patients treated at Memorial Sloan-Kettering Cancer Center with definitive RT and cetuximab (n = 49) or high-dose bolus cisplatin (n = 125) showed significant differences in the 2-year locoregional failure rate (39.9 vs. 5.7%, respectively; $p < 0.0001$), 2-year failure-free survival (44.5 vs. 87.4%, respectively; $p < 0.0001$) and 2-year OS (66.6 vs. 92.8%, respectively; $p = 0.0003$) [10]. On multivariate analysis, treatment with definitive RT and cisplatin was associated with better locoregional control and OS. The observation of better locoregional control and OS in the group treated with definitive RT and cisplatin compared to RT and cetuximab is similar to our report.

A previous analysis of the Bonner et al. [4] trial found that the patients who benefited most from the addition of cetuximab to RT had the phenotypic features of HPV-related HNSCC: oropharynx primary, smaller T classification, younger, male and good performance status. In our study, DSS in the HPV-related cohort may be better in the cisplatin group compared to the cetuximab group ($p = 0.058$). Our data should be interpreted cautiously given the small sample and the retrospective nature of the analysis. The comparative effectiveness of these two agents is being addressed by the ongoing Radiation Therapy Oncology Group (RTOG) 1,016 trial which is comparing outcomes of HPV-related oropharyngeal HNSCC treated with definitive RT and either concurrent cisplatin or cetuximab.

Preliminary emerging literature suggests a potential difference in the expression of the epidermal growth factor receptor (EGFR) and in the role of EGFR inhibitors in HPV-related versus HPV-unrelated HNSCC. Several, but not all, studies documented lower EGFR expression in HPV-related HNSCC in comparison to HPV-unrelated HNSCC [11–16]. However, the level of expression of EGFR by immunohistochemistry has not been demonstrated to consistently correlate with tumor response to EGFR inhibitors in HNSCC [17]. A randomized trial demonstrated that the addition of the EGFR monoclonal antibody panitumumab to chemotherapy improved the OS of patients with HPV-negative recurrent or metastatic HNSCC whereas no survival benefit was found in the HPV-positive cohort [18]. Also, RTOG 0522 showed a nonsignificant trend toward poorer progression-free survival in HPV-related HNSCC treated with cetuximab and concurrent accelerated RT plus cisplatin in comparison with RT plus cisplatin alone [19]. More data are required to clarify the role of EGFR inhibitors in HPV-related HNSCC.

The median weight loss was lower in the cetuximab group compared to the cisplatin group even though the median grades of mucositis were similar. A prospective controlled study observed similar rates of grade 3 or greater mucositis between patients randomized to receive definitive RT alone or with cetuximab [3]. Differences in the expected acute toxicity profiles between definitive RT given with cetuximab or cisplatin must be considered in the context of the patient's characteristics when deciding which treatment approach to recommend.

In this retrospective study, we observed that DSS was superior in the patients given cisplatin with definitive RT compared to cetuximab with definitive RT due to a lower risk of recurrent disease in the cisplatin group. These observations could not be explained by differences between the two groups in the patient and tumor characteristics or in treatment delivery. Prospective validation of the findings is indicated.

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