Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2016 August 01; 95(5): 1346–1354. doi:10.1016/j.ijrobp.2016.03.011.

Correlation between the severity of cetuximab-induced skin rash and clinical outcome for head and neck cancer patients: The XXXX experience

Voichita Bar-Ad, MD¹, Qiang (Ed) Zhang, PhD², Paul M. Harari, MD³, Rita Axelrod, MD¹, David I. Rosenthal, MD⁴, Andy Trotti, MD⁵, Christopher U. Jones, MD⁶, Adam S. Garden, MD⁴, Guobin Song, MD⁷, Robert L. Foote, MD⁸, David Raben, MD⁹, George Shenouda, MD¹⁰, Sharon A. Spencer, MD¹¹, Jonathan Harris, MS², and Quynh-Thu Le, MD¹²

¹Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA

²NRG Oncology Statistics and Data Management Center, Philadelphia, PA

³University of Wisconsin School of Medicine and Public Health, Madison, WI

⁴University of Texas-MD Anderson Cancer Center, Houston, TX

⁵H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

⁶Radiological Associates of Sacramento, Sacramento, CA

⁷Virginia Mason Medical Center, Seattle, WA

⁸Mayo Clinic, Rochester, MN

⁹University of Colorado Comprehensive Cancer Center, Denver, CO

¹⁰McGill University, Montreal, Quebec, Canada

¹¹University of Alabama at Birmingham, Birmingham, AL

¹²Stanford University Medical Center, Stanford, CA

Abstract

Corresponding author: Voichita Bar-Ad, MD, Kimmel Cancer Center of Jefferson Medical College, Thomas Jefferson University Hospital, Department of Radiation Oncology, 111 South 11th Street, Philadelphia, PA 19107, Phone: 215-955-5936, Fax: 215-955-0412, voichita.bar-ad@jefferson.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Previous presentation: The results were presented at the American Society of Clinical Oncology Annual Meeting, Chicago, June 2014.

Author disclosures: Dr. Bar-Ad reports research funding from Bristol-Myers Squibb and RTOG. Dr. Foote reports a patent or intellectual property interest from the Mayo Clinic. Dr. Jones reports a consulting or advisory position with Lilly and a speakers' bureau with Bristol-Myers Squibb. Dr. Le reports research funding from Amgen. Dr. Raben reports a consulting or advisory position with Astra Zeneca, Ferring and Merck. Dr. Rosenthal reports stock or other ownership interest in Concordia; a consulting or advisory position with Merck Serono and research funding from Merck Serono. Dr. Zhang reports that an immediate family member is employed by and owns stock in Pfizer.

Purpose—The purpose of the present study was to evaluate severity of cetuximab-induced skin rash and its correlation with clinical outcome and late skin toxicity in patients with head and neck squamous cell carcinoma treated with chemoradiotherapy and cetuximab.

Materials & Methods—Analysis included patients who received loading dose and 1 cetuximab dose concurrent with definitive chemoradiotherapy (70Gy + cisplatin) or postoperative chemoradiotherapy (60–66Gy + docetaxel or cisplatin).

Results—Six hundred two patients were analyzed; 383 (63.6%) developed Grade 2–4 cetuximab rash. Patients manifesting Grade 2–4 rash had younger age ($p<0.001$), fewer pack-years smoking history ($p<0.001$), were more likely to be males ($p=0.04$), and had p16-negative ($p=0.04$) oropharyngeal tumors ($p=0.003$).

In univariate analysis, Grade 2–4 rash was associated with better overall survival (OS) (hazard ratio [HR] 0.58, $p<0.001$) and progression-free survival (PFS) (HR 0.75, $p=0.02$), and reduced distant metastasis (DM) rate (HR 0.61, $p=0.03$), but not local-regional failure (LRF) (HR 0.79, $p=0.16$) relative to Grade 0–1 rash. In multivariable analysis, HRs for OS, PFS, DM, and LRF were 0.68 ($p=0.008$), 0.85 ($p=0.21$), 0.64 ($p=0.06$), and 0.89 ($p=0.48$). Grade 2 rash was associated with improved survival in p16 negative patients (HR 0.28 (0.11–0.74)) but not in p16 positive patients (HR 1.10 (0.42–2.89)) ($p=0.05$ for interaction). Twenty-five percent of patients with Grade 2–4 acute in-field radiation dermatitis experienced Grade 2–4 late skin fibrosis vs. 14% of patients with Grade 0–1 acute in-field radiation dermatitis ($p=0.002$).

Conclusion—Grade 2–4 cetuximab rash was associated with better survival possibly due to reduction of distant metastasis. This observation was noted mainly in p16 negative patients. Grade 2–4 acute in-field radiation dermatitis was associated with higher rate of late Grade 2–4 skin fibrosis.

INTRODUCTION

Several preclinical and correlative biomarker studies from various laboratories had detected epidermal growth factor receptor (EGFR) as a predictor of radiation response of head and neck squamous-cell cancers (HNSCC) and had identified EGFR and its down-stream signaling molecules as appealing targets for therapeutic intervention (1–3). The efficacy and safety of cetuximab (a chimeric monoclonal antibody that binds to the extracellular ligand-binding domain of EGFR, preventing activation and dimerization of the receptor) have been studied in combination with radiotherapy (RT) in several clinical trials (4–7). A large international trial testing the efficacy of RT with cetuximab versus RT alone showed that the combination of cetuximab and RT yielded improved locoregional control and reduced the mortality without added hematologic and mucosal toxicities (4). Thus, the international trial provided the proof-of-principle for selective tumor targeting in the treatment of locally advanced HNSCC and phase II and III prospective randomized trials were designed to assess whether adding cetuximab to a chemoradiation regimen will further improve the outcome in patients with stage III–IV disease (1).

Occurrence of more severe cetuximab-induced skin toxicity has been shown to correlate with better treatment response and longer survival in studies across multiple malignancies (19–28). Patient- and tumor-related markers predicting cetuximab-induced skin toxicity are

still not well defined. This investigation analyzes the prognostic value of cetuximab-induced skin toxicity for treatment efficacy in patients with locoregionally advanced HNSCC enrolled in two randomized trials: Studies XXXX and YYYY.

MATERIALS & METHODS

Study XXXX, a phase II prospective randomized trial, tested whether RT with concurrent cetuximab and cisplatin or cetuximab and docetaxel improve disease-free survival over a historical patient cohort treated with RT and concurrent cisplatin (RTOG 9501) in patients with high risk pathologic features following surgical resection of advanced HNSCC. NRG Oncology Study YYYY, a phase III prospective randomized trial, tested the addition of cetuximab to definitive RT with concurrent cisplatin in patients with advanced HNSCC.

The analyzed population was limited to patients eligible for their respective trial, received RT, chemotherapy (cisplatin or docetaxel), and loading dose plus at least one concurrent dose of cetuximab (Figure 1 CONSORT diagram). The study population was divided into 3 treatment groups: Study YYYY definitive RT + cisplatin + cetuximab (Arm A); Study XXXX postoperative RT + cisplatin + cetuximab (Arm B); and Study XXXX postoperative RT + docetaxel + cetuximab (Arm C). Skin toxicity was reported using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. For statistical analysis, the grade for cetuximab rash was primarily dichotomized into two groups: 0–1 vs. 2–4 based on findings from past publications (8,9) and the analysis included patients who received loading dose and 1 cetuximab dose concurrent with chemoradiotherapy, as previously used by other groups. We also analyzed the data with the skin rash grade as a continuous variable, and comparing any skin rash vs. no skin rash, or Grade 0–2 skin rash vs. Grade 3–4 rash, respectively.

In-field skin reaction grade was defined as the maximum of *Dermatitis radiation NOS* and *Radiation recall syndrome* within 90 days from the start of RT. Late skin fibrosis grade was defined as the maximum of *Skin fibrosis* > 90 days after the start of RT.

Statistical Analysis

A patient was considered to have a complete response (CR) if there is no measurable or palpable tumor either on clinical or radiographic (CT scan or MRI) examination. This endpoint only applies to Study YYYY since patients in Study XXXX received postoperative treatment. Failure for overall survival (OS) was death due to any cause. Failure for progression-free survival (PFS) was defined as distant metastases (DM), local-regional failure (LRF), or death due to any cause. LRF was defined as local-regional recurrence or progression (including salvage surgery for the primary site with tumor present or unknown, neck dissection > 15 weeks after the end of radiation therapy with tumor present or unknown), or death due to study cancer or unknown causes as first event. DM and death due to other causes were considered competing risks. Similarly, LRF was a competing risk for DM.

All failure times were measured from the date of random assignment to the date of failure, competing risk, or last follow up. CR rates were compared by Fisher's exact test and odds

ratios were estimated by logistic regression modeling for the probability of Grade 2–4 cetuximab-induced rash. Rates for PFS and OS were estimated by Kaplan-Meier method. Rates of LRF and DM rates were estimated by cumulative incidence method. Groups were compared by 2-sided stratified (by treatment group) log-rank test. Hazard ratios (HRs) were estimated by Cox models stratified by treatment group. Exploratory analyses were conducted to all primary sites and oropharyngeal site with smoking and p16 status.

Late fibrosis rates were compared by Fisher's exact test and odds ratios were estimated by logistic regression modeling the probability of Grade 2–4 late skin fibrosis.

Patient characteristics were compared by Fisher's exact test (categorical variables) or Wilcoxon rank-sum test (ordinal or continuous variables).

RESULTS

Incidence and associated risk factors for the cetuximab-related skin rash

Six-hundred two patients were analyzed. Five-hundred eight (84.3%) experienced cetuximab rash; patient characteristics by grade of cetuximab rash are shown in Table 1 and Table 1a. Patients with Grade 2–4 rash had younger age ($p<0.001$), fewer pack-years smoking history ($p<0.001$), were more likely to be males ($p=0.04$), and had p16-negative ($p=0.04$) oropharyngeal primary site ($p=0.003$).

Prognostic value of the Cetuximab-related skin rash for tumor response

When all 406 patients exposed to cetuximab in Study YYYY were analyzed, 88.6% (234 of 264) of patients experiencing Grade 2–4 rash had CR compared to 81.0% (115 of 142) of patients with Grade 0–1 rash ($p=0.04$). In univariate and multivariate analysis (adjusted for T and N classifications), the odds ratios were 1.83 ([95%CI 1.04–3.23], $p=0.04$) and 1.77 ([95%CI 1.00–3.15], $p=0.05$), respectively, indicating increase in CR rate for patients with Grade 2–4 rash. Similar CR rates were seen in the subset of patients (Group I) with known pack-years smoking history and p16 status in any primary site (91.2% vs. 83.9%) and when limited to oropharyngeal cancer (Group II) (90.7% vs. 84.8%).

Prognostic value of the Cetuximab-related skin rash for OS, PFS, DM, and LRF

At median follow-up of 4.5 years (range 0.1–7.0) for surviving patients, 200 of 602 patients have died. In univariate analysis, Grade 2–4 rash was associated with better OS relative to Grade 0–1 rash with HR 0.58 ([95%CI 0.44–0.76], $p<0.001$, Figure 2A), with HRs of 0.50 (Arm A), 0.76 (Arm B), and 0.70 (Arm C), respectively (Figure 3). The results are similar when limited to Group I (HR 0.58[95%CI 0.39–0.86], $p=0.007$) and to Group II (HR 0.53[95%CI 0.28–1.00], $p=0.05$). After adjusting for standard prognostic factors, the HRs were 0.68 ([95%CI 0.51–0.91], $p=0.008$) in all patients, 0.63 ([95%CI 0.42–0.94], $p=0.02$) for patients in Group I, and 0.58 ([95%CI 0.30–1.12], $p=0.11$) for patients in Group II (Table 2). Within the oropharyngeal cancer group, there is a differential effect of rash by p16 status ($p=0.05$) where Grade 2–4 rash is associated with a significantly reduced risk of death in the p16 negative group (HR 0.28 [95%CI 0.11–0.74]), but not in the p16 positive group (HR

1.10, [95%CI 0.42–2.89]). The test of interaction among all patients in Group I was not significant ($p=0.17$).

In univariate analysis, Grade 2–4 rash was associated with increased PFS rate relative to Grade 0–1 rash with HR 0.75 ([95%CI 0.59–0.96], $p=0.02$, Figure 2B and Table 3), with HRs of 0.76 (Arm A), 0.70 (Arm B), and 0.76 (Arm C), respectively. Results are not significant when limited to patients in Group I with a HR 0.82 ([95%CI 0.58–1.16], $p=0.27$) or to Group II ([HR 0.87[95%CI 0.50–1.51], $p=0.62$). After adjustment for standard prognostic factors, the HRs were 0.85 ([95%CI 0.66–1.10], $p=0.21$) in all patients, 0.87 ([95%CI 0.61–1.23], $p=0.42$) for patients in Group I, and 0.93 ([95%CI 0.53–1.63], $p=0.79$) for Group II. Within the oropharyngeal cancer group, there was a differential effect of rash by p16 status ($p=0.02$) where Grade 2–4 rash was associated with significantly reduced risk of progression/death for the p16 negative group (HR 0.39 ([95%CI 0.16–0.95]), but not for the p16 positive group (HR 1.60, [95%CI 0.72–3.53]). The test of interaction among patients in Group I was not significant ($p=0.16$).

In univariate analysis, Grade 2–4 rash was associated with a lower rate of DM relative to Grade 0–1 rash with HR 0.61 ([95%CI 0.39–0.96], $p=0.03$, Figure 2C and Table 4), with HRs of 0.51 (Arm A), 0.74 (Arm B), and 0.93 (Arm C), respectively (Figure 4). Results are also significant when limited to patients in Group I with HR 0.50 ([95%CI 0.28–0.89], $p=0.02$) and to Group II (HR 0.30[95%CI 0.13–0.70], $p=0.006$) in this exploratory analysis. After adjustment for standard prognostic factors, the HRs were 0.64 ([95%CI 0.41–1.01], $p=0.06$) in all patients, 0.51 ([95%CI 0.29–0.92], $p=0.03$) for Group I and 0.32 ([95%CI 0.14–0.77], $p=0.01$) limited to Group II. Exploratory analysis did not detect significant interaction between p16 status and Grade 2–4 rash in all primary sites ($p=0.68$) or limited to oropharyngeal cancer ($p=0.27$). There were very few DM events in the two subgroups. However, grade 2–4 rash was associated with significantly reduced risk of DM for the p16 negative patients in both groups.

There was no statistically significant difference in LRF between patients with Grade 2–4 and Grade 0–1 rash in univariate (HR 0.79 [95%CI 0.58–1.10], $p=0.16$) and multivariable analysis (HR 0.89 [95%CI 0.64–1.23], $p=0.48$, Figure 2D and Table 5). In univariate analysis, HRs are 0.91 (Arm A), 0.56 (Arm B), and 0.65 (Arm C), respectively (Figure 5). HRs are 1.07 [95%CI 0.66–1.75] and 1.14 [95%CI 0.70–1.87] for patients in Group I and 1.57 [95%CI 0.65–3.76] and 1.61 [95%CI 0.67–3.89] for Group II. In the oropharyngeal group, the test of interaction between p16 status and Grade 2–4 rash was $p=0.06$. The hazard ratio indicated a reduced risk for LRF in the p16 negative group (HR 0.55 [95%CI 0.15–1.98]) for patients with Grade 2–4 rash when compared to those with Grade 0–1 rash, but not for p16 positive group (HR 3.64 [95%CI 0.86–15.47]). However, the number of events was small and the confidence intervals crossed unity.

In univariate analysis, Grade 1–4 rash relative to Grade 0 rash was associated with better OS (HR 0.62 [95%CI 0.44–0.88], $p=0.006$), but not better PFS (HR 0.86 [95%CI 0.62–1.19], $p=0.35$), or lower DM rate (HR 0.84 [95%CI 0.46–1.54], $p=0.58$) or lower LRF rate (HR 0.84 [95%CI 0.55–1.29], $p=0.43$). Grade 3–4 rash relative to Grade 0–2 rash was associated with better OS and PFS (HR 0.65 [95%CI 0.44–0.97], $p=0.03$ and HR 0.59 [95%CI 0.42–

0.83], $p=0.003$, respectively), and a lower DM rate (HR 0.31 [95%CI 0.13–0.70], $p=0.005$) but not a lower LRF rate (HR 0.72 [95%CI 0.48–1.10], $p=0.13$). Rash grade as a continuous variable was associated with better OS with increasing grade with HR 0.76 ([95%CI 0.66–0.88], $p<0.001$), a better PFS with increasing grade with HR 0.85 ([95%CI 0.75–0.95], $p=0.006$), a lower DM rate with increasing grade with HR 0.75 ([95%CI 0.60–0.93], $p=0.01$), but not a lower LRF rate with increasing grade with HR 0.88 ([95%CI 0.75–1.03], $p=0.12$).

Prognostic value of other high-grade acute toxicities for clinical outcomes

Higher rates of CR were seen in patients developing Grade 3–4 acute dysphagia (in Study YYYY) when compared with patients developing Grade 0–2 acute dysphagia ($p=0.01$), and a better PFS was seen in patients developing Grade 3–4 acute mucositis when compared with patients developing Grade 0–2 acute mucositis ($p=0.02$). See Table 6 (Supplement).

Prognostic value of the acute in-field radiation dermatitis for late skin fibrosis

For 359 patients with Grade 2–4 acute in-field radiation dermatitis, 88 of 359 (24.5%) patients subsequently experienced Grade 2–4 late skin fibrosis compared to 32 of 227 (14.1%) patients with Grade 0–1 acute in-field radiation dermatitis ($p=0.002$). The estimated odds ratio was 1.92 [95%CI 1.23–3.00].

DISCUSSION

The patients in our study had been exposed to RT, cisplatin or docetaxel and cetuximab; the severity of the cetuximab-induced skin toxicity has been correlated with clinical outcomes. Within the present analysis, frequency and grading of cetuximab-induced skin rash were within the range of previously published data (9–17). Patients developing Grade 2–4 rash did experience better outcome compared to patients developing Grade 0–2 rash with a HR of 0.68 ($p=0.008$) for OS, most probably due to the reduced DM rate (HR 0.64, $p=0.06$). Although most of the events were driven by Study YYYY patients, who comprised the largest group, similar trends were seen with the Study XXXX patients (Figure 3).

In multivariate analysis, there was no statistically significant difference between patients with Grade 2–4 and Grade 0–1 rash in PFS (HR 0.85 ($p=0.21$) or LRF (HR 0.89, $p=0.48$), although PFS and LRF are more disease-specific parameters for HNSCC. Also interestingly, a bigger effect of the severe skin rash on DM failure rate was seen in the Study YYYY group (HR=0.51) than in the Study XXXX groups (HRs=0.74 cisplatin, 0.93 docetaxel) (Figure 4), but the findings were reversed for LRF with less effect for LRF in Study YYYY (HR=0.91) than in Study XXXX (HRs=0.56 cisplatin, 0.65 docetaxel) (Figure 5). Overall, there was no difference in LRF between the two groups (with Grade 2–4 rash vs Grade 0–1 skin rash) since the Study YYYY drove the results. Additional research is needed to identify other factors that can help explain the observed survival difference between the two groups, and confirm the actual differences in disease outcomes.

Clinical and tumor-related factors have been investigated and associated with cetuximab-induced skin toxicity within the study population. Our study suggested that HNSCC patients with Grade 2–4 rash had younger age, less cigarette use, were male, and had an

oropharyngeal primary site. Looking at dermatitis as a class effect of all EGFR-targeting agents, male gender and younger age have been identified as predictors of skin toxicity when erlotinib was added to gemcitabine in pancreatic cancer (18). Younger patients (<70 years) and males receiving cetuximab for colorectal cancer have also been shown to experience a higher rate of grade 3 skin rash (12).

There was a significant interaction between p16 status and rash grade ($p=0.05$ for OS; $p=0.02$ for PFS) in the oropharyngeal cancer group in our study. Within the p16 negative group, Grade 2–4 rash was associated with a decrease in risk of death and progression. Exploratory analysis did not detect a significant interaction between p16 status and rash grade for DM ($p=0.27$). These results suggest that severe skin rash is a predictor of good outcome for patients with p16 negative oropharyngeal tumors, but not for those with p16 positive cancers. The underlying basis for these intriguing results remains unexplained but could be related to the fact that EGFR expression is much lower in p16 positive oropharyngeal cancer than p16 negative tumors (19). However, these results should be interpreted with caution as the number of events within the oropharyngeal cancer group with known p16 status was small, especially for the p16 positive group. Further investigations are needed to determine the molecular basis for the difference in the impact of cetuximab rash in p16 positive and negative oropharyngeal carcinoma and for different clinical endpoints.

Furthermore, there may be an interaction of cytotoxics and cetuximab in relationship to rash development. A recent meta-analysis showed that the addition of cytotoxic chemotherapy to cetuximab significantly increases the risk of high-grade acneiform rash compared with cetuximab monotherapy (20). The reasons for this finding remain unclear. Studies failed to demonstrate pharmacokinetic interactions between cetuximab and irinotecan (21), gemcitabine–carboplatin (22), irinotecan–5-FU–folinic acid (23), 5-FU–folinic acid oxaliplatin (24) and cisplatin–vinorelbine (25), suggesting that this is not a likely explanation. Alternatively, chemotherapy may alter epidermal homeostasis; whether chemotherapeutic agents modify the risk by enhancing an inflammatory response remains to be investigated. Intriguingly, in our study, more severe skin rash seemed to be associated with less DM when cetuximab was added to cisplatin-radiation, but not to docetaxel-radiation (Figure 4). Mucositis and skin toxicity were the major acute toxic effects for patients with HNSCC treated with weekly Docetaxel and RT in GORTEC 98-02 phase II trial (26).

Constitutive activation of EGFR as a result of gene amplification, mutation, or overexpression of its ligands has been associated with response to EGFR targeting strategies. Although expression levels of EGFR had no impact on PFS or OS for patients with recurrent and metastatic HNSCC treated with cetuximab and docetaxel, high levels of its variant III (EGFRvIII) and its ligand amphiregulin identified patients who are less likely to benefit from this combination (27).

Studies in colorectal cancers have also provided new insights in the prognostic significance of the cetuximab rash (28). Based on the current knowledge, KRAS-mutated colorectal cancer doesn't respond well to anti-EGFR directed antibodies (29,30). Intriguingly, the largest correlation between cetuximab-induced skin toxicity and PFS or OS was noted in

patients bearing a KRAS codon-12-mutated tumor, a subgroup which was expected to have the lowest probability to respond to cetuximab. It was concluded that cetuximab-induced skin toxicity is of prognostic rather than that of predictive value and may reflect a more responsive immune system (21).

We observed a significant correlation between other high-grade toxicities (Grade 3–4 acute dysphagia, Grade 3–4 acute mucositis) and certain outcomes besides skin rash, in our cohort. These findings corroborate with the previously reported data in other solid tumors. Grade 2 acute enteritis, proctitis and cystitis were correlated with a higher rate of CR for patients treated with preoperative chemoradiotherapy for locally advanced rectal cancer (31). Grade of 3 for skin reaction, cystitis, proctitis, or enteritis were found to be significantly correlated with OS, LRF, and stoma-free survival for patients treated with definitive radiochemotherapy for anal cancer (32). Similar data was reported for patients with locally advanced HNSCC treated with RT and concurrent cisplatin-based chemotherapy who developed Grade of 3 radiation dermatitis, mucositis, or dysphagia (33). Normal tissues and tumor tissue may behave similarly with respect to treatment response ((31).

It is also important to recognize that both cetuximab and RT may cause skin toxicity. Although they induce a distinct phenotype (acneiform rash vs. radiation dermatitis), there is certainly a possibility of overlap in skin toxicity. It is also worthy to note that patients manifesting Grade 2–4 acute in-field radiation dermatitis in our study were associated with higher risk of late Grade 2–4 skin fibrosis.

Our study has several limitations. The assessment of acneiform rash and its treatment may vary significantly among investigators and institutions that conducted these trial and such discrepancies may limit accurate reporting.

There is non-uniformity in the management of rash among oncologists, particularly with regard to the use and timing of administration of antibiotics, skin creams and anti-inflammatory medications. Moreover, the severity of in-field radiation dermatitis may be influenced by the use of skin bolus resulting in more superficial dose. Grading systems specific for EGFR inhibitors skin toxicity such as the Multinational Association for Supportive Care in Cancer EGFR Inhibitor Skin Toxicity Tool may be integrated into the future versions of CTCAE in order to improve accuracy of reporting (34,35).

CONCLUSIONS

The present analysis demonstrates that Grade 2–4cetuximab-induced skin toxicity is associated with better survival in the HNSCC populations studied. Grade 2–4 acute in-field radiation dermatitis in our study was associated with a higher risk of late Grade 2–4 skin fibrosis. These results need to be validated in other trials.

Acknowledgments

This project was supported by grants U10CA21661, U10CA180868, U10CA180822 and U10CA37422 from the National Cancer Institute (NCI) and Bristol-Myers Squibb.

References

1. Ang KK, Berkey BA, Tu V, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res.* 2002; 62:7350–7356. [PubMed: 12499279]
2. Bonner JA, Raisch KP, Trummell HQ, et al. Enhanced apoptosis with combination C225/radiation treatment serves as the impetus for clinical investigation in head and neck cancers. *J Clin Oncol.* 2000; 18(suppl):47S–53S. [PubMed: 11060327]
3. Huang SM, Bock JM, Harari PM. Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. *Cancer Res.* 1999; 59:1935–1940. [PubMed: 10213503]
4. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006; 354:567–578. [PubMed: 16467544]
5. Vermoken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol.* 2007; 25(16):2171–2177. [PubMed: 17538161]
6. Lefebvre JL, Pointreau Y, Rolland F, et al. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPIN randomized phase II study. *J Clin Oncol.* 2013; 31(7):853–859. [PubMed: 23341517]
7. Ang K, Zhang Q, Rosenthal D, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol.* 2014; 32(27):2940–2950. [PubMed: 25154822]
8. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomized trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol.* 2010; 11:21–28. [PubMed: 19897418]
9. Saltz LB, Kies MS, Abbruzzese JL, et al. The presence and intensity of the cetuximab-induced acne-like rash predicts increased survival in studies across multiple malignancies. *Proc Am Soc Clin Oncol.* 2003; 21 suppl; abstract 817.
10. Orditura M, De Vita F, Galizia G, et al. Correlation between efficacy and skin rash occurrence following treatment with the epidermal growth factor inhibitor cetuximab: a single institution retrospective analysis. *Oncol Rep.* 2009; 21(4):1023–1028. [PubMed: 19288004]
11. Gatzemeier U, von Pawel J, Vynnychenko I, et al. First-cycle rash and survival in patients with advanced non-small-cell lung cancer receiving cetuximab in combination with first-line chemotherapy: a subgroup analysis of data from the FLEX phase 3 study. *Lancet Oncol.* 2011; 12(1):30–37. [PubMed: 21169060]
12. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med.* 2009; 360:1408–1417. [PubMed: 19339720]
13. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004; 351:337–345. [PubMed: 15269313]
14. Lenz HJ, Van Cutsem E, Khambata-Ford S, et al. Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. *J Clin Oncol.* 2006; 24:4914–4921. [PubMed: 17050875]
15. Pessino A, Artale S, Sciallero S, et al. First-line single-agent cetuximab in patients with advanced colorectal cancer. *Ann Oncol.* 2008; 19:711–716. [PubMed: 18073221]
16. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med.* 2007; 357:2040–2048. [PubMed: 18003960]
17. Jatoi A, Green EM, Rowland KM Jr, et al. Clinical predictors of severe cetuximab induced rash: observations from 933 patients enrolled in north central cancer treatment group study N0147. *Oncology.* 2009; 77:120–123. [PubMed: 19622902]
18. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007; 25:1960–1966. [PubMed: 17452677]

19. Hong A, Dobbins T, Lee CS, et al. Relationships between epidermal growth factor receptor expression and human papillomavirus status as markers of prognosis in oropharyngeal cancer. *Eur J Cancer*. 2010; 46(11):2088–2096. [PubMed: 20537890]
20. Balagula Y, Wu S, Su X, Lacouture ME. The effect of cytotoxic chemotherapy on the risk of high-grade acneiform rash to cetuximab in cancer patients meta-analysis. *Ann Oncol*. 2011; 22:2366–2371. [PubMed: 21402620]
21. Delbaldo C, Pierga JY, Dieras V, et al. Pharmacokinetic profile of cetuximab(Erbitux) alone and in combination with irinotecan in patients with advancedEGFR-positive adenocarcinoma. *Eur J Cancer*. 2005; 41:1739–1745. [PubMed: 16051481]
22. Robert F, Blumenschein G, Herbst RS, et al. Phase I/IIa study of cetuximab withgemcitabine plus carboplatin in patients with chemotherapy-naïve advanced non-small-cell lung cancer. *J Clin Oncol*. 2005; 23:9089–9096. [PubMed: 16301597]
23. Folprecht G, Lutz MP, Schoffski P, et al. Cetuximab and irinotecan/5-fluorouracil/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma. *Ann Oncol*. 2006; 17:450–456. [PubMed: 16303861]
24. Arnold D, Hohler T, Ditttrich C, et al. Cetuximab in combination with weekly 5-fluorouracil/folinic acid and oxaliplatin (FUFOX) in untreated patients with advanced colorectal cancer: a phase Ib/II study of the AIO GI Group. *Ann Oncol*. 2008; 19:1442–1449. [PubMed: 18441330]
25. Rosell R, Robinet G, Szczesna A, et al. Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer. *Ann Oncol*. 2008; 19:362–369. [PubMed: 17947225]
26. Callais G, Bardet E, Sire C, et al. Radiotherapy with concomitant weekly docetaxel for Stages III/IV oropharynx carcinoma. Results of the 98-92 GORTEC Phase II trial. *Int J Radiat Oncol Biol Phys*. 2004; 58(1):161–166. [PubMed: 14697434]
27. Tinhofer I, Klinghammer K, Weichert W, et al. Expression of amphiregulin and EGFRvIII affect outcome of patients with squamous cell carcinoma of the head and neck receiving cetuximab-docetaxel treatment. *Clin Cancer Res*. 2011; 17(15):5197–5204. [PubMed: 21653686]
28. Stintzing S, Kapaun C, Laubender RP, et al. Prognostic value of cetuximab-related skin toxicity in metastatic colorectal cancer patients and its correlation with parameters of the epidermal growth factor receptor signal transduction pathway: Results from a randomized trial of the GERMAN AIO CRC Study Group. *Int J Cancer*. 2013; 132:236–245. [PubMed: 22644776]
29. Lievre A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol*. 2008; 26:374–379. [PubMed: 18202412]
30. Di Fiore F, Blanchard F, Charbonnier F, et al. Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by Cetuximab plus chemotherapy. *Br J Cancer*. 2007; 96:1166–1169. [PubMed: 17375050]
31. Wolff HA, Gaedcke J, Junk K, et al. High-grade acute organ toxicity during preoperative radiochemotherapy as positive predictor for complete histopathologic tumor regression in multimodal treatment of locally advanced rectal cancer. *Strahlenther Onkol*. 2010; 186(1):30–35. [PubMed: 20082185]
32. Wolff HA, Raus I, Jung K, et al. High-grade acute organ toxicity as positive prognostic factor in primary radiochemotherapy for anal cancer. *Int J Radiat Oncol Biol Phys*. 2011; 79(5):1467–1478. [PubMed: 20605354]
33. Wolff HA, Daldrop B, Jung K, et al. High-grade organ toxicity as positive prognostic factor in adjuvant radiation and chemotherapy for locally advanced head and neck cancer. *Radiology*. 2011; 258(3):864–871. [PubMed: 21339350]
34. Lacouture ME, Maitland ML, Segaert S, et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. *Support Care Cancer*. 2010; 18:509–522. [PubMed: 20145956]
35. Chan A, Tan EH. How well does the MESTT correlate with CTCAE scale for the grading of dermatological toxicities associated with oral tyrosine kinase inhibitors? *Support Care Cancer*. 2010 in press.

SUMMARY

Present study evaluated the severity of cetuximab-induced skin rash and its correlation with clinical outcome and late skin toxicity in patients HNSCC treated with chemoradiotherapy and cetuximab in two prospective randomized trials. Grade 2–4 cetuximab rash was associated with better survival possibly due to reduction of distant metastasis. This observation was noted mainly in p16 negative patients. Grade 2–4 acute in-field radiation dermatitis was associated with higher rate of late Grade 2–4 skin fibrosis.

Figure 1.
CONSORT diagram. XXXX

Figure 2.
Kaplan-Meier estimates of OS, PFS, DM, and LRF by grade of cetuximab rash experienced.

Figure 3. Kaplan-Meier estimates of overall survival by grade of cetuximab rash experienced and study arm.

Figure 4.
Distant metastasis by grade of cetuximab rash and study arms.

Figure 5.
Local-regional failure bygrade of cetuximab rash and study arms.

Table 1

Pretreatment Characteristics and Treatment Delivery by Grade of Cetuximab Rash

Treatment group	Grade 0 (n=94)	Grade 1 (n=125)	Grade 2 (n=263)	Grade 3-4/1 (n=120)	Total (n=602)
Study XXXX RT+cisplatin+cetuximab	58 (61.7%)	84 (67.2%)	182 (69.2%)	82 (68.3%)	406 (67.4%)
Study XXXX RT+ cisplatin+cetuximab	17 (18.1%)	25 (20.0%)	35 (13.3%)	17 (14.2%)	94 (15.6%)
Study XXXX RT+docetaxel+cetuximab	19 (20.2%)	16 (12.8%)	46 (17.5%)	21 (17.5%)	102 (16.9%)
Age (years)					
Mean (standard deviation)	59.0 (8.00)	59.1 (9.22)	55.6 (8.66)	54.6 (8.68)	56.7 (8.86)
Median (min-max)	58.5 (39-80)	59 (21-79)	56 (25-77)	55 (30-76)	57 (21-80)
Gender					
Male	74 (78.7%)	102 (81.6%)	224 (85.2%)	109 (90.8%)	509 (84.6%)
Female	20 (21.3%)	23 (18.4%)	39 (14.8%)	11 (9.2%)	93 (15.4%)
Zubrod performance status					
0	53 (56.4%)	74 (59.2%)	173 (65.8%)	74 (61.7%)	374 (62.1%)
1	41 (43.6%)	51 (40.8%)	90 (34.2%)	46 (38.3%)	228 (37.9%)
Smoking history: pack-years[2]	(n=79)	(n=107)	(n=231)	(n=96)	(n=513)
Mean (standard deviation)	31.0 (28.50)	34.9 (29.05)	23.8 (27.84)	22.3 (28.14)	26.9 (28.60)
Median (min-max)	28 (0-110)	30 (0-135)	15 (0-162)	15 (0-120)	20 (0-162)
Primary site					
Oral cavity	16 (17.0%)	19 (15.2%)	36 (13.7%)	21 (17.5%)	92 (15.3%)
Oropharynx	49 (52.1%)	66 (52.8%)	163 (62.0%)	85 (70.8%)	363 (60.3%)
Hypopharynx	7 (7.4%)	12 (9.6%)	15 (5.7%)	1 (0.8%)	35 (5.8%)
Larynx	22 (23.4%)	28 (22.4%)	49 (18.6%)	13 (10.8%)	112 (18.6%)
p16 status (oropharynx only)	(n=25)	(n=32)	(n=100)	(n=50)	(n=207)
p16-negative	6 (24.0%)	11 (34.4%)	22 (22.0%)	7 (14.0%)	46 (22.2%)
p16-positive	19 (76.0%)	21 (65.6%)	78 (78.0%)	43 (86.0%)	161 (77.8%)
p16 status (all primary sites)	(n=53)	(n=71)	(n=167)	(n=73)	(n=364)
p16-negative	27 (50.9%)	40 (56.3%)	79 (47.3%)	24 (32.9%)	170 (46.7%)
p16-positive	26 (49.1%)	31 (43.7%)	88 (52.7%)	49 (67.1%)	194 (53.3%)
T stage, clinical					

	Grade 0 (n=94)	Grade 1 (n=125)	Grade 2 (n=263)	Grade 3-4 ^[1] (n=120)	Total (n=602)
T0	0 (0.0%)	0 (0.0%)	3 (1.1%)	2 (1.7%)	5 (0.8%)
T1	6 (6.4%)	6 (4.8%)	12 (4.6%)	6 (5.0%)	30 (5.0%)
T2	31 (33.0%)	54 (43.2%)	100 (38.0%)	49 (40.8%)	234 (38.9%)
T3	26 (27.7%)	32 (25.6%)	79 (30.0%)	36 (30.0%)	173 (28.7%)
T4	30 (31.9%)	31 (24.8%)	64 (24.3%)	23 (19.2%)	148 (24.6%)
Tx	1 (1.1%)	0 (0.0%)	2 (0.8%)	3 (2.5%)	6 (1.0%)
Unknown	0 (0.0%)	2 (1.6%)	3 (1.1%)	1 (0.8%)	6 (1.0%)
N stage, clinical					
N0	9 (9.6%)	23 (18.4%)	25 (9.5%)	14 (11.7%)	71 (11.8%)
N1	22 (23.4%)	9 (7.2%)	29 (11.0%)	18 (15.0%)	78 (13.0%)
N2a	7 (7.4%)	13 (10.4%)	25 (9.5%)	17 (14.2%)	62 (10.3%)
N2b	30 (31.9%)	39 (31.2%)	95 (36.1%)	34 (28.3%)	198 (32.9%)
N2c	20 (21.3%)	34 (27.2%)	76 (28.9%)	30 (25.0%)	160 (26.6%)
N3	6 (6.4%)	2 (1.6%)	9 (3.4%)	5 (4.2%)	22 (3.7%)
Nx	0 (0.0%)	0 (0.0%)	2 (0.8%)	1 (0.8%)	3 (0.5%)
Unknown	0 (0.0%)	5 (4.0%)	2 (0.8%)	1 (0.8%)	8 (1.3%)
Treatment duration (days)					
Mean (standard deviation)	50.0 (8.33)	51.6 (6.72)	51.1 (7.79)	52.4 (8.32)	51.3 (7.79)
Median (min-max)	50 (15-81)	50 (30-76)	49 (7-114)	50 (43-89)	49 (7-114)
Number of cetuximab doses delivered					
Mean (standard deviation)	6.8 (1.37)	7.1 (1.05)	7.2 (1.08)	6.0 (1.84)	6.9 (1.38)
Median (min-max)	7 (2-8)	7 (2-8)	7 (2-9)	7 (2-9)	7 (2-9)

^[1] Grade 3 and 4 skin rash were combined since only 6 patients had grade 4.

^[2] A pack-year is defined as the equivalent of smoking one pack of cigarettes a day for 1 year.

Table 1a
Pretreatment Characteristics and Treatment Delivery by Treatment Group and Grade of Cetuximab Rash

	RTOG 0522 RT+cisplatin+cetuximab			RTOG 0234 RT+cisplatin+cetuximab			RTOG 0234 RT+docetaxel+cetuximab		
	Grade 0-1 (n=142)	Grade 2-4 (n=264)		Grade 0-1 (n=42)	Grade 2-4 (n=52)		Grade 0-1 (n=35)	Grade 2-4 (n=67)	
Age (years)									
Mean (standard deviation)	59.8 (7.53)	55.9 (7.97)		59.0 (9.34)	55.0 (10.47)		56.1 (11.57)	53.0 (9.48)	
Median (min-max)	59 (41-76)	55.5 (34-76)		58 (40-80)	57 (27-73)		58 (21-79)	55 (25-77)	
Gender									
Male	121 (85.2%)	244 (92.4%)		35 (83.3%)	39 (75.0%)		20 (57.1%)	50 (74.6%)	
Female	21 (14.8%)	20 (7.6%)		7 (16.7%)	13 (25.0%)		15 (42.9%)	17 (25.4%)	
Zubrod performance status									
0	95 (66.9%)	182 (68.9%)		15 (35.7%)	31 (59.6%)		17 (48.6%)	34 (50.7%)	
1	47 (33.1%)	82 (31.1%)		27 (64.3%)	21 (40.4%)		18 (51.4%)	33 (49.3%)	
	(n=123)	(n=233)		(n=30)	(n=41)		(n=33)	(n=53)	
Smoking history: pack-years ^[1]									
Mean(standard deviation)	36.2 (30.31)	22.4 (27.14)		25.1 (27.22)	28.5 (34.14)		29.7 (22.68)	23.4 (25.87)	
Median (min-max)	30 (0-135)	15 (0-162)		20 (0-110)	20 (0-120)		35.7 (0-80)	16.5 (0-86)	
Primary site									
Oral cavity	0 (0.0%)	0 (0.0%)		19 (45.2%)	25 (48.1%)		16 (45.7%)	32 (47.8%)	
Oropharynx	89 (62.7%)	203 (76.9%)		16 (38.1%)	20 (38.5%)		10 (28.6%)	25 (37.3%)	
Hypopharynx	13 (9.2%)	10 (3.8%)		3 (7.1%)	2 (3.8%)		3 (8.6%)	4 (6.0%)	
Larynx	40 (28.2%)	51 (19.3%)		4 (9.5%)	5 (9.6%)		6 (17.1%)	6 (9.0%)	
	(n=37)	(n=118)		(n=12)	(n=14)		(n=8)	(n=18)	
p16 status (oropharynx only)									
p16-negative	12 (32.4%)	24 (20.3%)		2 (16.7%)	2 (14.3%)		3 (37.5%)	3 (16.7%)	
p16-positive	25 (67.6%)	94 (79.7%)		10 (83.3%)	12 (85.7%)		5 (62.5%)	15 (83.3%)	
	(n=69)	(n=151)		(n=31)	(n=40)		(n=24)	(n=49)	
p16 status (all primary sites)									
p16-negative	38 (55.1%)	51 (33.8%)		14 (45.2%)	23 (57.5%)		15 (62.5%)	29 (59.2%)	
p16-positive	31 (44.9%)	100 (66.2%)		17 (54.8%)	17 (42.5%)		9 (37.5%)	20 (40.8%)	
T stage, clinical									
T0	0 (0.0%)	0 (0.0%)		0 (0.0%)	3 (5.8%)		0 (0.0%)	2 (3.0%)	
T1	0 (0.0%)	0 (0.0%)		8 (19.0%)	5 (9.6%)		4 (11.4%)	13 (19.4%)	

	RTOG 0522 RT+cisplatin+cetuximab		RTOG 0234 RT+cisplatin+cetuximab		RTOG 0234 RT+docetaxel+cetuximab	
	Grade 0-1 (n=142)	Grade 2-4 (n=264)	Grade 0-1 (n=42)	Grade 2-4 (n=52)	Grade 0-1 (n=35)	Grade 2-4 (n=67)
T2	56 (39.4%)	112 (42.4%)	17 (40.5%)	19 (36.5%)	12 (34.3%)	18 (26.9%)
T3	47 (33.1%)	93 (35.2%)	4 (9.5%)	10 (19.2%)	7 (20.0%)	12 (17.9%)
T4	39 (27.5%)	59 (22.3%)	12 (28.6%)	13 (25.0%)	10 (28.6%)	15 (22.4%)
Tx	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	5 (7.5%)
Unknown	0 (0.0%)	0 (0.0%)	1 (2.4%)	2 (3.8%)	1 (2.9%)	2 (3.0%)
N stage, clinical						
N0	23 (16.2%)	25 (9.5%)	4 (9.5%)	8 (15.4%)	5 (14.3%)	6 (9.0%)
N1	13 (9.2%)	23 (8.7%)	8 (19.0%)	10 (19.2%)	10 (28.6%)	14 (20.9%)
N2a	11 (7.7%)	28 (10.6%)	4 (9.5%)	6 (11.5%)	5 (14.3%)	8 (11.9%)
N2b	46 (32.4%)	94 (35.6%)	18 (42.9%)	16 (30.8%)	5 (14.3%)	19 (28.4%)
N2c	43 (30.3%)	85 (32.2%)	5 (11.9%)	8 (15.4%)	6 (17.1%)	13 (19.4%)
N3	6 (4.2%)	9 (3.4%)	1 (2.4%)	1 (1.9%)	1 (2.9%)	4 (6.0%)
Nx	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.8%)	0 (0.0%)	1 (1.5%)
Unknown	0 (0.0%)	0 (0.0%)	2 (4.8%)	1 (1.9%)	3 (8.6%)	2 (3.0%)
AJCC stage, clinical						
I	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (2.9%)	0 (0.0%)
II	0 (0.0%)	0 (0.0%)	2 (4.8%)	2 (3.8%)	0 (0.0%)	2 (3.0%)
III	25 (17.6%)	33 (12.5%)	5 (11.9%)	9 (17.3%)	9 (25.7%)	13 (19.4%)
IV	117 (82.4%)	231 (87.5%)	33 (78.6%)	37 (71.2%)	22 (62.9%)	49 (73.1%)
Unknown	0 (0.0%)	0 (0.0%)	2 (4.8%)	3 (5.8%)	3 (8.6%)	3 (4.5%)
RT type						
3DCRT	16 (11.3%)	23 (8.7%)	28 (66.7%)	30 (57.7%)	28 (80.0%)	32 (48.8%)
IMRT	126 (88.7%)	241 (91.3%)	14 (33.3%)	22 (42.3%)	7 (20.0%)	35 (52.2%)
Treatment duration (days)						
Mean (standard deviation)	49.4 (7.26)	51.0 (8.21)	53.6 (8.01)	52.5 (7.76)	54.0 (5.88)	52.5 (7.09)
Median (min-max)	49 (15-70)	49 (7-114)	52 (44-81)	50 (44-89)	53 (44-70)	51 (44-78)
Number of cetuximab doses delivered						
Mean (standard deviation)	7.2 (1.31)	7.1 (1.48)	6.7 (0.93)	6.2 (1.25)	6.6 (0.85)	6.2 (1.26)
Median (min-max)	8 (2-8)	8 (2-9)	7 (2-7)	7 (2-7)	7 (4-7)	7 (3-7)

/// A pack-year is defined as the equivalent of smoking one pack of cigarettes a day for 1 year.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2**Overall Survival by Grade of Cetuximab Rash**

	Cetuximab Rash		
	Grade 0–1	Grade 2–4	p-value
All patients			
Deaths/total	94/219	106/383	
Univariate hazard ratio (95% CI)	Reference	0.58 (0.44–0.76)	<0.001
Multivariate hazard ratio (95% CI) ^[1]	Reference	0.68 (0.51–0.91)	0.008
Known p16 status (any primary site) and known pack-years			
Deaths/total	45/106	56/202	
Univariate hazard ratio (95% CI)	Reference	0.58 (0.39–0.86)	0.007
Multivariate hazard ratio (95% CI) ^[2]	Reference	0.63 (0.42–0.94)	0.02
With p16 × rash interaction term ^[3]			
p16-positive	Reference	0.96 (0.46–2.01)	
p16-negative	Reference	0.51 (0.31–0.84)	0.17 (interaction)
Known p16 status (oropharynx only) and known pack-years			
Deaths/total	16/49	27/130	
Univariate hazard ratio (95% CI)	Reference	0.53 (0.28–1.00)	0.05
Multivariate hazard ratio (95% CI) ^[2]	Reference	0.58 (0.30–1.12)	0.11
With p16 × rash interaction term ^[3]			
p16-positive	Reference	1.10 (0.42–2.89)	
p16-negative	Reference	0.28 (0.11–0.74)	0.05 (interaction)

CI: confidence interval.

Hazard ratios estimated from Cox models stratified by treatment group.

^[1] Adjusted for age (>50 vs. ≤50), Zubrod performance status (1 vs. 0), primary site (non-oropharynx vs. oropharynx), T stage (T4 vs. T1–3), and N stage (N2b–N3 vs. N0–N2a).

^[2] Adjusted for age (>50 vs. ≤50), Zubrod performance status (1 vs. 0), p16 status (p16-negative vs. p16-positive), T stage (T4 vs. T1–3), N stage (N2b–N3 vs. N0–N2a), and pack-years (> 10 vs. ≤10).

^[3] Model ^[2] plus cetuximab rash × p16 status interaction.

Table 3**Progression-Free Survival by Grade of Cetuximab Rash**

	Cetuximab Rash		
	Grade 0–1	Grade 2–4	p-value
All patients			
Events/total	110/219	160/383	
Univariate hazard ratio (95% CI)	Reference	0.75 (0.59–0.96)	0.02
Multivariate hazard ratio (95% CI) ^[1]	Reference	0.85 (0.66–1.10)	0.21
Known p16 status (any primary site) and known pack-years			
Events/total	52/106	88/202	
Univariate hazard ratio (95% CI)	Reference	0.82 (0.58–1.16)	0.27
Multivariate hazard ratio (95% CI) ^[2]	Reference	0.87 (0.61–1.23)	0.42
With p16 × rash interaction term ^[3]			
p16-positive	Reference	1.21 (0.66–2.20)	
p16-negative	Reference	0.71 (0.45–1.11)	0.16 (interaction)
Known p16 status (oropharynx only) and known pack-years			
Events/total	18/49	47/130	
Univariate hazard ratio (95% CI)	Reference	0.87 (0.50–1.51)	0.62
Multivariate hazard ratio (95% CI) ^[2]	Reference	0.93 (0.53–1.63)	0.79
With p16 × rash interaction term ^[3]			
p16-positive	Reference	1.60 (0.72–3.53)	
p16-negative	Reference	0.39 (0.16–0.95)	0.02 (interaction)

CI: confidence interval.

Hazard ratios estimated from Cox models stratified by treatment group.

^[1] Adjusted for age (>50 vs. ≤50), Zubrod performance status (1 vs. 0), primary site (non-oropharynx vs. oropharynx), T stage (T4 vs. T1–3), and N stage (N2b–N3 vs. N0–N2a).

^[2] Adjusted for age (>50 vs. ≤50), Zubrod performance status (1 vs. 0), p16 status (p16-negative vs. p16-positive), T stage (T4 vs. T1–3), N stage (N2b–N3 vs. N0–N2a), and pack-years (> 10 vs. ≤10).

^[3] Model ^[2] plus cetuximab rash × p16 status interaction.

Table 4

Distant Metastasis by Grade of Cetuximab Rash

	Cetuximab Rash		
	Grade 0–1	Grade 2–4	p-value
All patients			
Events/total	36/219	41/383	
Univariate hazard ratio (95% CI)	Reference	0.61 (0.39–0.96)	0.03
Multivariate hazard ratio (95% CI) ^[1]	Reference	0.64 (0.41–1.01)	0.06
Known p16 status (any primary site) and known pack-years			
Events/total	23/106	23/202	
Univariate hazard ratio (95% CI)	Reference	0.50 (0.28–0.89)	0.02
Multivariate hazard ratio (95% CI) ^[2]	Reference	0.51 (0.29–0.92)	0.03
With p16 × rash interaction term ^[3]			
p16-positive	Reference	0.61 (0.23–1.63)	
p16-negative	Reference	0.46 (0.22–0.98)	0.68 (interaction)
Known p16 status (oropharynx only) and known pack-years			
Events/total	12/49	10/130	
Univariate hazard ratio (95% CI)	Reference	0.30 (0.13–0.70)	0.006
Multivariate hazard ratio (95% CI) ^[2]	Reference	0.32 (0.14–0.77)	0.01
With p16 × rash interaction term ^[3]			
p16-positive	Reference	0.50 (0.16–1.57)	
p16-negative	Reference	0.17 (0.04–0.73)	0.27 (interaction)

CI: confidence interval.

Hazard ratios estimated from Cox models stratified by treatment group.

^[1] Adjusted for for primary site (non-oropharynx vs. oropharynx), T stage (T4 vs. T1–3), and N stage (N2b–N3 vs. N0–N2a).

^[2] Adjusted for p16 status (p16-negative vs. p16-positive), T stage (T4 vs. T1–3), N stage (N2b–N3 vs. N0–N2a), and pack-years (> 10 vs. ≤ 10).

^[3] Model ^[2] plus cetuximab rash × p16 status interaction.

Table 5**Local-Regional Failure by Grade of Cetuximab Rash**

	Cetuximab Rash		
	Grade 0–1	Grade 2–4	p-value
All patients			
Events/total	62/219	95/383	
Univariate hazard ratio (95% CI)	Reference	0.79 (0.58–1.10)	0.16
Multivariate hazard ratio (95% CI) ^[1]	Reference	0.89 (0.64–1.23)	0.48
Known p16 status (any primary site) and known pack-years			
Events/total	24/106	52/202	
Univariate hazard ratio (95% CI)	Reference	1.07 (0.66–1.75)	0.80
Multivariate hazard ratio (95% CI) ^[2]	Reference	1.14 (0.70–1.87)	0.60
With p16 × rash interaction term ^[3]			
p16-positive	Reference	1.83 (0.78–4.30)	
p16-negative	Reference	0.85 (0.45–1.59)	0.16 (interaction)
Known p16 status (oropharynx only) and known pack-years			
Events/total	6/49	31/130	
Univariate hazard ratio (95% CI)	Reference	1.57 (0.65–3.76)	0.32
Multivariate hazard ratio (95% CI) ^[2]	Reference	1.61 (0.67–3.89)	0.32
With p16 × rash interaction term ^[3]			
p16-positive	Reference	3.64 (0.86–15.47)	
p16-negative	Reference	0.55 (0.15–1.98)	0.06 (interaction)

CI: confidence interval.

Hazard ratios estimated from Cox models stratified by treatment group.

^[1] Adjusted for for Zubrod performance status (1 vs. 0), primary site (non-oropharynx vs. oropharynx), T stage (T4 vs. T1–3), and N stage (N2b–N3 vs. N0–N2a).

^[2] Adjusted for Zubrod performance status (1 vs. 0), p16 status (p16-negative vs. p16-positive), T stage (T4 vs. T1–3), N stage (N2b–N3 vs. N0–N2a), and pack-years (> 10 vs. ≤ 10).

^[3] Model ^[2] plus cetuximab rash × p16 status interaction.

Table 6**Clinical Outcome by Grade of Acute Mucositis and Dysphagia**

	Grade 0–2	Grade 3–4	p-value
Univariate odds ratio (95%CI) for acute mucositis grade			
Complete response (RTOG 0522 only)	Reference	1.60 (0.89–2.88)	0.12
Univariate hazard ratios (95%CI) for acute mucositis grade			
Overall survival	Reference	0.89 (0.66–1.18)	0.41
Progression-free survival	Reference	0.74 (0.58–0.96)	0.02
Local-regional failure	Reference	0.80 (0.58–1.11)	0.19
Distant metastasis	Reference	0.73 (0.45–1.17)	0.19
Univariate odds ratio (95%CI) for acute dysphagia grade			
Complete response (RTOG 0522 only)	Reference	2.03 (1.15–3.59)	0.01
Univariate hazard ratios (95%CI) for acute dysphagia grade			
Overall survival	Reference	1.01 (0.76–1.34)	0.95
Progression-free survival	Reference	0.86 (0.67–1.09)	0.21
Local-regional failure	Reference	0.80 (0.58–1.10)	0.18
Distant metastasis	Reference	0.79 (0.50–1.25)	0.31

CI: confidence interval.

Odds ratios estimated from logistic regression model.

Hazard ratios estimated from Cox model stratified by treatment group.