Consistent administration of cetuximab is associated with favorable outcomes in recurrent/ metastatic head and neck squamous cell carcinoma at endemic carcinogen exposure area: a retrospective observational study

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Background. This study aimed to analyze the clinical outcomes associated with patients with recurrent / metastatic head and neck squamous cell carcinoma (RM HNSCC) who received cetuximab-based chemotherapy in a real-world clinical setting. **Methods.** The clinical data were extracted from RM HNSCC patients diagnosed between 2016 and 2019. Kaplan-Meier survival estimates and Cox proportional hazards model were used for survival analyses. **Results.** Out of 106 RM HNSCC patients (mean age = 55.1 years), 38.7% exhibited recurrent disease and 61.3% had metastatic disease. The majority of patients showed a habit of addictive substance use, including alcohol (67.0%), betel nuts (71.7%), or tobacco (74.5%). The primary tumor sites included oral cavity (64.1%), hypopharynx (19.8%), and oropharynx (16.0%). The median cetuximab cycle of 106 patients was 11(2–24). The disease control rate (DCR) was 48.1%, and the overall response rate (ORR) was 28.3%. The median progression-free survival (PFS) and overall survival (OS) were 5.0 and 9.23 months, respectively. Patients treated with more than 11 cycles of cetuximab exhibited longer median PFS and median OS than patients treated with less than 11 cycles (median PFS: 7.0 vs. 3.0 months, $p < 0.001$; OS: 12.43 vs. 4.46 months, $p = 0.001$). Patients without previous concurrent chemoradiotherapy (CRT) may be associated with better median PFS than with previous CRT (6.0 vs. 4.0 months, $p = 0.046$). Multi-variate analysis revealed perineural invasion and less cycles of cetuximab (<11 cycles) were two independent risk factors associated with disease progression. In

addition, reduction in treatment cycles of cetuximab and the advanced lymph node metastasis were independent prognostic factors predicting poorer overall survival. In summary, our study provides important real-world data of cetuximab-containing treatment in RM HNSCC. Consistent administration of cetuximab could be associated with more favorable outcomes in RM HNSCC at the endemic carcinogen exposure area.

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Abstract

Background. This study aimed to analyze the clinical outcomes associated with patients with recurrent/metastatic head and neck squamous cell carcinoma (RM HNSCC) who received cetuximab-based chemotherapy in a real-world clinical setting.

Methods. The clinical data were extracted from RM HNSCC patients diagnosed between 2016 and 2019. Kaplan-Meier survival estimates and Cox proportional hazards model were used for survival analyses.

Results. Out of 106 RM HNSCC patients (mean age = 55.1 years), 38.7% exhibited recurrent disease and 61.3% had metastatic disease. The majority of patients showed a habit of addictive substance use, including alcohol (67.0%), betel nuts (71.7%), or tobacco (74.5%). The primary tumor sites included oral cavity (64.1%), hypopharynx (19.8%), and oropharynx (16.0%). The median cetuximab cycle of 106 patients was 11(2–24). The disease control rate (DCR) was 48.1%, and the overall response rate (ORR) was 28.3%. The median progression-free survival (PFS) and overall survival (OS) were 5.0 and 9.23 months, respectively.

Patients treated with more than 11 cycles of cetuximab exhibited longer median PFS and median OS than patients treated with less than 11 cycles (median PFS: 7.0 vs. 3.0 months, $p < 0.001$; OS: 12.43 vs. 4.46 months, $p = 0.001$). Patients without previous concurrent chemoradiotherapy (CRT) may be associated with better median PFS than with previous CRT (6.0 vs. 4.0 months, $p = 0.046$).

Multi-variate analysis revealed perineural invasion and less cycles of cetuximab (<11 cycles) were two independent risk factors associated with disease progression. In addition, reduction in treatment cycles of cetuximab and the advanced lymph node metastasis were independent prognostic factors predicting poorer overall survival.

In summary, our study provides important real-world data of cetuximab-containing treatment in RM HNSCC. Consistent administration of cetuximab could be associated with more favorable outcomes in RM HNSCC at the endemic carcinogen exposure area.

Keywords: recurrent and/or metastatic head and neck cancer, cetuximab, prognosis, survival

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy in the world, and recurrent and/or metastatic head and neck squamous cell carcinoma (RM-HNSCC) harbors lethal clinical features and dismal medical outcomes (Parkin et al. 2005). Over 90% of head and neck cancers are squamous cell carcinomas, which develop from the mucosa of the oral cavity, oropharynx, larynx, or hypopharynx (Warnakulasuriya 2009). In western countries, oropharyngeal SCC accounts for the largest group of HNSCC, with a minority of the patients related to human papillomavirus (HPV) infection (Gatta et al. 2015, Gillison et al. 2000) HNSCC, with a minority of the patients related to human papillomavirus (HPV) infection (Gatta et al. 2015, Gillison et al. 2000). However, oral cavity SCC is the most predominant site of head and neck cancer in Taiwan due to high oral betel nut consumption (Belcher et al. 2014; Chang et al. 2017). Virus-induced HNSCC in western countries is different from its Taiwanese counterpart in that the mechanism of tumorigenesis of HNSCC in Taiwan is mainly related to carcinogens and addictive substances, including alcohol, betel nuts, or tobacco (Cancer 2012). These carcinogen-related HNSCCs harbor higher *Ras* oncogene mutations and increased chromosome instability, which implies that the genetic background and clinical features may be unique in these patients (Chang et al. 1991; Kuo et al. 1994; Riaz et al. 2014).

Epidermal growth factor receptor (EGFR) is usually upregulated with increased levels of its ligand transforming growth factor alpha (TGF-α) noted in most HNSCCs, with both proteins contributing to the carcinogenesis of HNSCC (Grandis 2007). Upregulation of EGFR is an independent poor prognostic factor in HNSCCs (Ang et al. 2004; Dassonville et al. 1993). Cetuximab, an IgG1 chimeric monoclonal antibody targeting EGFR, has been the one of the first-line treatments for RM HNSCC patients with low programmed death ligand 1 (PD-L1) expression (Burtness et al. 2019; Vermorken et al. 2008).The addition of cetuximab to platinum-based chemotherapy with fluorouracil (platinum-fluorouracil) improved the overall response rates, median progression-free survival (PFS), and overall survival (OS) compared with chemotherapy alone. Another combination of cetuximab with chemotherapy agents like taxane also demonstrated substantial benefits (Adkins et al. 2018; Friesland et al. 2018; Guigay et al. 2019). However, most of these clinical trials are conducted in western countries with less patients of primary oral cavity cancer and the data regarding the effect of carcinogens like betel nuts on outcome is very limited. In addition, the percentage of HPV infection status is quite different between Asian and western countries, indicating distinct tumor microenvironments (Wang et al. 2019).

In Taiwan, cetuximab combined with systemic chemotherapy has been proved as the first line treatment in patients with RM HNSCC by the National Health Insurance since 2016. After

approval of application, the patients can receive cetuximab-containing treatment without copayment. Due to limited financial resource, cetuximab can only be administered to a total of eighteen cycles if no progression was noted. Different from clinical trials which can achieve therapeutic efficacy with cetuximab maintenance, patients in real life were not affordable continuous maintenance with high-cost cetuximab to control their diseases. Therefore, making modification of treatment protocol a possible strategy (Hsu & Lu 2016; Shih et al. 2015). However, the impact of above modification like limited cetuximab treatment cycle on patient outcome is still an open-ended question. Moreover, the real-world data of cetuximab in RM HNSCC patients with a high percentage of exposure to different carcinogen remains is also very limited. To answer above questions, we conducted this retrospective and single-arm study to analyze clinical data, hoping to elucidate the clinical outcome and prognostic factors in this subset of RM HNSCC patients.

Materials and methods

Patient Characteristics

Clinicopathological data of patients with HNSCC were confirmed by pathological examination of the specimens from biopsy or surgery, and the positive samples were collected and analyzed. A total of 106 cases of RM HNSCC were identified with metastasis or recurrence and were deemed unsuitable for locoregional curative treatment in the Kaohsiung Medical University Hospital. The inclusion criteria included: age at diagnosis (20 years or older), tumor histology of squamous cell carcinoma (grade 1 to grade 3), ICD-9 site code-specific for the oral cavity (OC), hypopharynx (HPC), oropharynx (OPC), and larynx, and patients treated with cetuximab during January 2016–April 2019. The exclusion criteria included patients with secondary malignancy; tumor histology of carcinoma *in situ*, and SCC from the nasopharynx and salivary glands.

Study design

This was an observational, retrospective, single-center, single-arm study and the treatment schema was showed in *Fig.* 1. The collected medical and demographic data included age, gender, alcohol, betel nut usage, tobacco habits, and other clinical parameters from the medical records or interviews with patients. The clinicopathological factors included types and grade of histology, size of tumor, lymph node status, surgical margin, perineural invasion, lymphovascular invasion, and extranodal extension. We defined CRT (chemoradiation)-refractory patients as patients with disease progression during CRT or within three months after the end of CRT. We evaluated the results of a retrospective and single-arm study with the primary endpoint of assessing outcomes in a southern Taiwan comprehensive cancer institution.

We analyzed the median OS and PFS (defined as the time from registration to objective disease progression or death from any cause) after the addition of cetuximab to chemotherapy. The secondary endpoints of this study included the assessment of treatment response and disease control. This study was approved by the Institutional Review Board and Ethics Committee of Kaohsiung Medical University Hospital (KMUHIRB-E(II)-20190357). The data were analyzed anonymously, and therefore, no additional informed consent was required. All the methods were performed in accordance with the approved guidelines and regulations.

Treatment

All the patients received cetuximab (250 mg/m^2) weekly with a loading dose of 400 mg/m^2 till disease progression existed. The regimen of chemotherapy included PF 75/1000 (cisplatin at 75 mg/m^2 or carboplatin at AUC=5 every 3 weeks plus fluorouracil at 1,000 mg/m^2/d for 4 days every 3 weeks), PF 60/800 (cisplatin at 60 mg/m^2 or carboplatin at AUC5 every 3 weeks plus fluorouracil at 800 mg/m^2/d for 4 days every 3 weeks), taxane-based chemotherapy (docetaxel and cisplatin 75 mg/m^2 both at day 1 and every 3 weeks for four courses of paclitaxel 80 mg/m^2 weekly), and MTX (methotrexate 40 mg/m^2 weekly). Patients could receive chemotherapy or concurrent chemoradiotherapy with weekly cisplatin administration previously before recruitment.

Treatment Response and Safety Assessment

All our patients followed regularly at outpatient department of medical oncology and department (OPD) of otorhinolaryngology. During cetuximab treatment period, the patients visited OPD of medical oncology weekly and otorhinolaryngology monthly. The evaluation of disease status included tumor site inspection, laboratory text, and imagine studies. Treatment response was assessed and determined by computed tomography (CT) or magnetic resonance imaging (MRI) at baseline (before cetuximab) and at 3-month intervals after treatment was started. Imaging study within 4 weeks before cetuximab was acceptable, and imaging study could be performed whenever clinical physicians suspected disease progression. RECIST version 1.1were used to determine disease progression and tumor response.

The treatment response of patients was classified into four categories: complete response (CR, disappearance of all target lesions), partial response (PR, decrease in target lesion diameter sum > 30%), progression disease (PD, increase in target lesion diameter sum > 20%), and stable disease (SD, does not meet other criteria). The calculation of overall response rate (ORR) was based on the best objective response achieved during cetuximab treatment. After disease progression, further treatments and survival status were documented every 3 months. Regarding safety assessment, treatment-related adverse events were monitored weekly throughout the study

and evaluated using Common Terminology Criteria for Adverse Events version 4.0.

Statistical Analysis

The primary goal of the study was to analyze the outcome of cetuximab-based chemotherapy in recurrent or metastatic settings, including a comparison between median PFS and OS among patients receiving different cycles of cetuximab and different regimens of chemotherapy. The location of primary sites (OC, OPC, or HPC), histological grade (Grade 1, 2, 3), tumor size and status (T1, T2, T3, T4), lymph node status (N0, N1, N2, N3), stage at initial diagnosis (I, II, III, or IV), surgery status (with or without previous surgery), CRT (with or without previous CRT), and chemotherapy before cetuximab therapy (with or without prior chemotherapy) were all included for analysis. Between-group comparisons were analyzed by using Fisher's exact test and Pearson's chi-square test for different categorical variables. We estimated median PFS and OS with Kaplan−Meier analysis, and we analyzed differences between the curves by using the log-rank test. We defined the median PFS as the time between the start of disease progression and treatment, including disease progression or death. Patients alive and without disease progression by the last follow-up visit were considered as potential right censoring subjects, and the follow-up interval were truncated at the end of study. Univariate and multivariable analyses by using the Cox proportional hazard model was preformed to analyze prognostic factors in cetuximab treatment. The factors for above analysis included age at initial diagnosis, location of primary sites, histological grade, pathological feature (margin, LVI, PNI, and ENE), tumor size, lymph node status, stage at initial diagnosis, previous treatment before cetuximab (surgery, chemotherapy, or CRT), combined regimen and dosage of chemotherapy. All p-values were considered significant if $p < 0.05$ and were two-sided. Statistical analyses were performed using STATA version 11 (STATA Corp., TX, USA).

Results

Baseline characteristics of patients

The clinical data of 106 patients (including 99 males and 7 females) with a median age of 55.1 years were collected for this study. Among these patients, 65 patients (61.3%) had metastatic disease and 41 patients (38.4%) had recurrent disease while initiation of cetuximab. Almost all patients had addiction of alcohol or betel nuts, or history smoking, including 61 patients (57.5%) with all carcinogen exposure. Only 5 patients (4.7%) have no previous exposure to above risk factors. Regarding the tumor site, most of the primary sites had origins in the oral cavity (64.1%), sequentially hypopharynx (19.8%), and oropharynx (16.0%). The majority of patients were in advanced disease, such as T3-4, N2-3, or clinical stage 4. The detail basic information of study population was listed in Table 1.

Treatment modality

With respect to prior treatment before cetuximab treatment, most patients experience various HNSCC treatment including surgery (78.3%), chemotherapy (81.1%) and CRT (80.2%). In addition, there were 34 CRT-refractory patients who suffered from disease progression during CRT or within three months after the end of CRT.

The major reason for cetuximab treatment is recurrent disease with metastatic tumors. The median cycles of cetuximab were 11 cycles (2–24), with 60 patients receiving >11 cycles of cetuximab, and 46 patients receiving ≤11 cycles of cetuximab. Among these patients, 76 patients received chemotherapy with EXTREME regimen (cisplatin and fluorouracil) and 17 patients received taxane-based chemotherapy. The median cetuximab administration cycles in these 76 patients with a PF regimen was 11 (range: 2-24) while the median cetuximab cycles in 17 patients using taxane-based regimen was 12 (range: 4–23). There was no significant difference in the number of cetuximab cycles between these two groups ($p = 0.427$). The details of the treatment modalities are shown in Table 2. The demographic data of different cetuximab cycles (≥11 and <11) were shown in Supplementary Table S1 and Table S2.

Treatment outcomes

After cetuximab treatment, clinical response was observed in 20 patients including 1 complete response and 29 partial response, with ORR of 28.3%. When the patients with stable disease (n=21, 19.8%) were included into analysis, the disease control rate was 48.1%. The median PFS and OS were 5 months and 9.23 months, respectively. As of data cut-off, only one patient did not progress, and 38 patients survived eventually. The median PFS was 5 months (95% CI 3.0–6.0 months) and the median OS was 9.23 months (95% CI 7.03–13.84 months). The treatment responses according to different stages were shown in Supplementary Table S3.

The median PFS in different sub-groups stratified by treatment modalities was shown in *Fig.* 2. Notably, the patients who received more cetuximab treatment (≥ 11 cycles) had better median PFS than patients received less cetuximab (7 months vs 3 months, $p< 0.001$). Additionally, the median PFS was longer in patients without prior CRT (6 months vs 4 months, $p = 0.046$). Other factors including chemotherapy regimen (PF or taxane-based), chemotherapy dose (PF dose), or CRT refraction status didn't lead to significant effect on PFS. When it comes to analysis of OS, the patients who received more cetuximab treatment (≥ 11 cycles) had better median OS than patients received less cetuximab (12.43 months vs 4.46 months, $p< 0.001$). Other factors including chemotherapy regimen, chemotherapy dose, or didn't lead to significant effect on PFS. The OS curves were shown in *Fig.* 3.

Next, we applied landmark method for further validation. Since the response could observes

within the first 3 months following cetuximab exposure, a 3-months landmark was used. After excluding the patients who progressed or died within the three months, the patients with more cycles of cetuximab (≥ 11 cycles) still showed better median PFS (8 months vs 2 months, p = 0.057) and OS (13.9 months vs 5.07 months, p=0.0002) than the patients treated with less cycles of cetuximab.

To clarify the effects of CRT-refraction on the survival, we evaluated median PFS and OS in patients with or without C RT-refraction. In non-CRT-refractory cohort (n=72), the median PFS and OS were 5.00 months (95% CI = 3.00–7.00) and 10.43 months (95% CI = 7.03–14.64), respectively. The 3-year OS was 28.72% (95% CI = 17.25–41.24). Further evaluation of these 72 subjects, 27 patients with < 11 cetuximab cycles obtained a 3-year PFS rate of 3.70% (95% CI =0.27–15.90), and a 3-year OS rate of 2.22% (95% CI = 0.18–10.15). Additionally, 45 patients with ≥ 11 cetuximab cycles obtained a 3-year PFS rate of 11.57% (95% CI =1.04–36.08), and a 3-year OS rate of 37.07% (95% CI = 21.60–52.59). The patients treated with more cetuximab cycle also showed better median PFS and OS then the patients treated with less cetuximab cycles, shown in *Fig.* 4.

In the CRT-refractory patients, the median PFS and OS were 3.00 months (95% CI =3.00–6.00) and 7.8 months, respectively. The 3-year OS rate was 25.30% (95% CI = 10.32–43.53). Six CRT-refractory patients who used taxane-based regimen obtained a median PFS and OS of 3.00 months (95% CI = 2.00–8.00) and 5.62 months (95% CI = 2.03–NA), respectively. The 3-year OS was 16.67% (95% CI = 0.77–51.68).

Risk factor investigation for disease progression

Risks of disease progression were analyzed by univariate regression consisting of parameters as age, alcohol, betel nuts, tobacco consumption, tumor site, margin positivity, histologic features (including LVI, PNI, and ENE), tumor size, lymph node status, stage, previous treatment modality (including surgery, chemotherapy, and CRT), treatment status, cetuximab cycles, dose, and regimens of chemotherapy. In addition, a subsequent multivariate regression analysis was performed to evaluate the significant progression factors in univariate analysis.

As shown in Table 3, positive PNI was the independent factor related with shorter median PFS. Besides, N3 disease showed a trend toward poorer PFS (p = 0.055, univariate analysis). After adjustment for other different variables in the multivariate analysis, this difference became significant (HR = 2.57; $p = 0.043$). Significantly, treatment with more cetuximab cycles (≥ 11 cycles) was the favorite factor associated with a better median PFS (HR = 0.19; $p < 0.001$, and HR = 0.18; $p < 0.001$ during both, univariate and multivariate analysis, respectively).

Determining the risk factor for poorer overall survival

Similar clinicopathological factors were analyzed for overall survival. N2 disease showed a significantly negative impact on OS (HR = 2.09; $p = 0.022$ and HR = 4.79; $p = 0.006$ in univariate and multivariate analyses, respectively). Treatment with more cetuximab cycles showed a significant, positive effect on OS (HR = 0.46; $p = 0.002$ and HR = 0.48; $p = 0.010$ in both univariate and multivariate analyses, respectively). Other factors with a trend toward shorter OS include N3 disease ($p = 0.170$). After adjustment for other variables, this difference became significant in the multivariate analysis (HR = 7.34; $p = 0.005$). These results are shown in Table 4.

Safety and tolerability

All grade and the worst grade 3 and grade 4 treatment related adverse events (AEs) in patients received cetuximab therapy are listed in Table 5. Among the patients treated with the platinum/5FU and cetuximab regimen, the most commonly AEs were skin rash (2.6%), anemia (2.6%), neutropenia (1.3%), vomiting (1.3%) and febrile (1.3%). Among patients treated with the taxane-based regimen, only one patient suffered from grade 3 febrile (5.9%). There was no grade 3 or grade 4 AE in others groups. In general, skin rash was the most frequent cetuximab-related AE, but most of patients were tolerable. There was no interstitial lung disease observed in our patients.

Discussion

The treatment options for HNSCC are sophisticated and take multidisciplinary specialists to tailor personalized treatment for individual patients. Since 2008, the addition of cetuximab to chemotherapy has become the first-line treatment of RM HNSCC regarding the advancement in response and survival (Vermorken et al. 2008). However, HNSCC is a heterogenous disease and considerable effects of carcinogens have been reported especially in the Asian population (Network 2015). Besides, drug accessibility of expensive drugs and the restrictions of the reimbursement policy also has an impact on the responses and outcomes of treatment in many countries, including Taiwan (Davidoff et al. 2018; Hsu et al. 2019; Morgan & Kennedy 2010). This retrospective study points out the important role of cetuximab cycles in RM HNSCC, especially in an endemic carcinogen exposure area, such as Taiwan.

In this study, 106 patients treated with cetuximab-based regimens were assessed; most patients had the habit of using an addictive substance and over half the patients had concurrent exposure to all the three addictive substances. However, our outcomes were not inferior when indirectly compared to the other clinical trials, such as the EXTREME regimen conducted by European cancer institutes (De Mello et al. 2014) and EXTREME trial (Vermorken et al. 2008).

The possible reasons may contribute to regular and frequent follow-up, laboratory and imagine study to detect disease progression and guide subsequent treatment plan when progression was noted. As compared to the aforementioned Asian trial, including Japanese (Tahara et al. 2016) and Chinese trial (Guo Y et al. 2014), the ORR of our study is slightly lower, which may relate to usage of cetuximab maintenance, different regimens of chemotherapy, and patient population with distinct endemic carcinogen exposure. The patients of Japanese trial received cetuximab maintenance and chemotherapy with carboplatin and paclitaxel. However, there was nearly no effect of betel nuts in the Japanese population. The effects of carcinogen were also not mentioned in the Chinese and Korean population. The results of above studies were summarized in Table 6 (Adkins et al. 2018; Bossi et al. 2017; De Mello et al. 2014; Friesland et al. 2018; Guigay et al. 2016; Guigay et al.2012; Guigay et al. 2019; Guo Y et al. 2014; Tahara et al. 2016; Vermorken et al. 2008).

Importantly, the median PFS and OS of our study are compatible with another retrospective study (De Mello et al. 2014). Moreover, our real-world results were also comparable with other clinical trials. As we just mentioned, these may contribute to every diagnosed patient receiving frequent physical and imaging examinations, taking care form multidisciplinary team (including nurse case management, integrating expertise of medical oncologist, surgeon, radiologists, case managers, nurses, nutritionists, and pharmacists), and meeting periodically to discuss treatment direction, evaluate therapeutic effects, and provide further recommendations. As noted in breast cancer care, earlier detection from more aggressive monitoring could lead to improved treatment strategies and possibly improved survival (Graham et al. 2014).

Although our study was conducted retrospectively in a single medical center, our study reflects the observation of the real-world setting in an endemic carcinogen exposure area. However, our study still had limitations in terms of relatively smaller sample size and immortal time bias. To address the immortal time bias and reverse causality, we applied landmark analysis, which suggested more cycles of cetuximab may bring survival benefit in HNSCC patients. The heterogeneous study population is also an issue. Unlike the EXTREME or TPEX studies which excluded CRT-refractory patients, we included CRT-refractory patients for analysis. Besides, patients who received non-platinum chemotherapy regimens, including taxane and MTX, were also included. Heterogeneity of study population may confound the analysis. However, our findings revealed the real-world condition in term of financial burden of novel treatment, which lead to absence of cetuximab maintenance. In addition, our study included and evaluated the Taiwanese population with high incidence of oral cavity cancer which may be related to strong carcinogen exposure, including alcohol, betel nuts, and tobacco. Previous studies had revealed lower expression of tumor suppressor gene p53 alterations, higher percentage of MDM2 protein expression, as well as higher rate of Ras oncogene mutation after

long-term exposure to betel nuts (Huang et al. 2001; Kuo et al. 1994; Kuo et al. 1999). Besides, the upregulation of *EGFR* has been confirmed in betel-nuts-associated cancer of the oral cavity associated with poor prognosis (Sheu et al. 2009). Three top amplicons, including KRAS, MAPK1, and CCND1, have been observed in cancer of oral cavity from Taiwanese patients, and hence, all could possibly contribute to activation of the EGFR signaling (Sheu et al. 2009). EGFR protein upregulation, excluding the effect of *EGFR* gene copy number on protein overexpression, was related to poor differentiation of the tumor cells and lymph node metastasis, especially ENE (Huang et al. 2017). Taking together, cetuximab targeting EGFR on HNSCC cells can induce potent antibody dependent cell-mediated cytotoxicity, which can further augment anti-tumor effect when combined with chemotherapy (Specenier & Vermorken 2013).

The restrictions in targeted therapy-related reimbursement policies defer patients' benefits in RM HNSCC. The limitation of the total 18 cycles of cetuximab without maintenance has been executed since 2016 in Taiwan. In other countries, cetuximab maintenance plays an important role in improving survival and outcomes with tolerable adverse events (Wakasugi et al. 2015). The median duration of maintenance was 11 weeks in the EXTREME trial, 16 weeks in the real-world study in France, and 17 weeks in the real-world study of Portugal. Broadening the duration of the eligible patient population to the targeted therapies may be an effective way to improve the clinical outcomes of treatments.

Conclusions

Consistent administration of cetuximab provides potential clinical benefits in HNSCC patients at endemic carcinogen exposure area in the Asian population and hence, longer cetuximab maintenance is urgent and warranted in these patients with poor prognostics.

Acknowledgments

We acknowledge the support from the following grants: KMUH107-7M12, KMUH108-8R23, KMUH108-8M12, and KMHK-DK109004 from the Kaohsiung Medical University Hospital.

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Table 1(on next page)

Table 1. Baseline characteristics in the entire cohort (N=106).

HPC: hypophyngeal cancer; OC: oral cavity cancer; OPC: oropharyngeal cancer; LVI: lymphovascular invasion; PNI: perineural invasion; ENE: extranodal extension.

1

Variables	n (%)
Age, years (mean ± SD)	55.1 ± 9.9
Alcohol	71 (67.0%)
Betel nuts	76 (71.7%)
Smoking	79 (74.5%)
Primary sites	
HPC	21 (19.8%)
OC	68 (64.1%)
OPC	17 (16.0%)
Grade	
1	28 (26.4%)
2	57 (53.8%)
3	16 (15.1%)
Unknown	5 (4.7%)
Margin positivity	11 (10.4%)
LVI, positive	4 (3.8%)
PNI, positive	9 (8.5%)
ENE, positive	5 (4.7%)
Tumor size	
T0	2 (1.9%)
T1	14 (13.2%)
T2	24 (22.6%)
T3	16 (15.1%)
T4	50 (47.2%)
Lymph node status	
N0	27 (25.5%)
N1	12 (11.3%)
N2	56 (52.8%)
N3	11 (10.4%)
Stage at initial diagnosis	
I	9 (8.5%)
II	6 (5.7%)
III	11 (10.4%)
IV	80 (75.5%)

2 Table 1. Baseline characteristics in the entire cohort (N=106).

HPC: hypophyngeal cancer; OC: oral cavity cancer; OPC: oropharyngeal cancer; LVI: lymphovascular invasion; PNI: perineural invasion; ENE: extranodal extension.

Table 2(on next page)

Table 2. Treatment modality.

CRT: concurrent chemoradiotherapy; PF: cisplatin and fluorouracil; ORR: overall response rate; DCR: disease control rate; PFS: progression-free survival; OS: overall survival; 95% CI: 95% confidence intervals.

1

Variables	n (%)
Previous treatment	
Surgery	83 (78.3%)
Chemotherapy	86 (81.1%)
CRT	85 (80.2%)
CRT-refractory	34 (32.1%)
Erbitux applied reason	
Metastasis	65 (61.3%)
Recurrence	41 (38.7%)
Erbitux cycle, median (range)	11 (2-24)
< 11	46 (43.4%)
≥ 11	60 (56.6%)
Regimen of chemotherapy	
PF	76 (71.7%)
Taxane-based	17 (16.0%)
Others	13 (12.3%)
Platinum	
Cisplatin	85 (80.2%)
Carboplatin	5 (4.7%)
Chemotherapy dose	
60/800	36 (34.0%)
75/1000	57 (53.8%)
Disease progressed	105 (99.1%)
ORR	30 (28.3%)
DCR	51 (48.1%)
Median PFS (months, 95% CI)	5.00 (3.00-6.00)
All-cause mortality	68 (64.2%)
Median OS (months, 95% CI)	9.23 (7.03-13.84)

2 Table 2. Treatment modality.

3 CRT: concurrent chemoradiotherapy; PF: cisplatin and fluorouracil; ORR: overall response rate;

4 DCR: disease control rate; PFS: progression-free survival; OS: overall survival; 95% CI: 95%

5 confidence intervals.

Table 3(on next page)

Table 3. Cox regression for disease progression.

HPC: hypophyngeal cancer; OC: oral cavity cancer; OPC: oropharyngeal cancer; LVI: lymphovascular invasion; PNI: perineural invasion; ENE: extranodal extension; CRT: concurrent chemoradiotherapy; PF: cisplatin and fluorouracil; HR: hazard ratio; 95% CI: 95% confidence intervals. *Variables with p-value less than 0.2 in univariate analysis were included in multivariate model.

1

Variables	Comparison	Univariate		Multivariate*	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age	Years	0.99 (0.97-1.01)	0.502	-	
Alcohol	Yes vs. no	1.47 (0.88-2.44)	0.141	1.47 (0.81-2.64)	0.202
Betel nuts	Yes vs. no	1.17 (0.67-2.05)	0.578	-	
Smoking	Yes vs. no	0.92 (0.50-1.69)	0.783	-	
Histology	OC vs. HPC	1.32 (0.81-2.17)	0.270	-	
	OPC vs. HPC	0.95 (0.49-1.83)	0.871	-	
Margin	With vs. without residual tumor	1.30 (0.67-2.51)	0.442	-	
Grade	2 vs. 1	0.87 (0.55-1.38)	0.563	-	
	3 vs. 1	1.03 (0.56-1.91)	0.920	-	
LVI	Positive vs. negative	2.04 (0.69-6.02)	0.195	0.43 (0.11-1.72)	0.231
PNI	Positive vs. negative	**2.89 (1.26-6.65)**	**0.012**	**3.19 (1.08-9.46)**	**0.036**
ENE	Positive vs. negative	1.18 (0.38-3.61)	0.776	-	
Tumor size	T1 vs. T0	0.19 (0.04-0.85)	0.029	0.75 (0.14-3.96)	0.739
	T2 vs. T0	0.29 (0.07-1.28)	0.102	0.78 (0.16-3.75)	0.751
	T3 vs. T0	0.41 (0.09-1.83)	0.244	-	
	T4 vs. T0	0.27 (0.06-1.13)	0.073	0.82 (0.17-3.89)	0.805
Lymph node status	N1 vs. N0	1.19 (0.60-2.37)	0.620	-	
	N2 vs. N0	1.73 (1.06-2.81)	0.027	1.85 (0.98-3.51)	0.059
	N3 vs. N0	2.04 (0.98-4.24)	0.055	**2.57 (1.03-6.43)**	**0.043**
Stage	II vs. I	1.66 (0.59-4.69)	0.339	-	
	III vs. I	1.76 (0.72-4.28)	0.214	-	
	IV vs. I	1.50 (0.75-3.02)	0.252	-	
Surgery	With vs. without	0.80 (0.50-1.28)	0.354	-	
Chemotherapy before target therapy	With vs. without	0.87 (0.53-1.42)	0.585	-	
CRT-refractory	Yes vs. no	1.32 (0.87-1.99)	0.191	1.18 (0.72-1.91)	0.511
Erbitux applied reason	Metastasis vs. recurrence	1.002 (0.68-1.49)	0.992	-	
Erbitux cycle, median (range)	≥ 11 vs. <11	**0.19 (0.11-0.30)**	**<0.001**	**0.18 (0.09-0.33)**	**<0.001**
Regimen of chemotherapy	Taxane-based vs. PF	0.75 (0.44-1.29)	0.297	-	
	Others vs. PF	0.85 (0.47-1.54)	0.591	-	
Platinum	Carboplatin vs. Cisplatin	0.55 (0.22-1.39)	0.206	-	

Chemotherapy dose	75/1000 vs. 60/800	0.90 (0.56-1.43)	0.644	-

Table 3. Cox regression for disease progression. HPC: hypophyngeal cancer; OC: oral cavity cancer; OPC: oropharyngeal cancer; LVI: lymphovascular invasion; PNI: perineural invasion; ENE: extranodal extension; CRT: concurrent chemoradiotherapy; PF: cisplatin and fluorouracil; HR: hazard ratio; 95% CI: 95% confidence intervals.

*Variables with p-value less than 0.2 in univariate analysis were included in multivariate model.

Table 4(on next page)

Table 4. Cox regression for overall mortality.

HPC: hypophyngeal cancer; OC: oral cavity cancer; OPC: oropharyngeal cancer; LVI: lymphovascular invasion; PNI: perineural invasion; ENE: extranodal extension; CRT: concurrent chemoradiotherapy; PF: cisplatin and fluorouracil; HR: hazard ratio; 95% CI: 95% confidence intervals. *Variables with p-value less than 0.2 in univariate analysis were included in multivariate model.

1

Variables	Comparison	Univariate		Multivariate*	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age	Years	1.004 (0.98-1.03)	0.738	-	
Alcohol	Yes vs. no	1.87 (0.95-3.67)	0.070	2.00 (0.94-4.26)	0.073
Betel nuts	Yes vs. no	1.50 (0.74-3.04)	0.260	-	
Smoking	Yes vs. no	0.72 (0.37-1.42)	0.341	-	
Histology	OC vs. HPC	1.41 (0.76-2.64)	0.278	-	
	OPC vs. HPC	1.44 (0.67-3.12)	0.350	-	
Margin	With vs. without residual tumor	0.86 (0.40-1.86)	0.703	-	
Grade	2 vs. 1	0.91 (0.52-1.60)	0.737	-	
	3 vs. 1	1.16 (0.57-2.36)	0.672	-	
LVI	Positive vs. negative	1.89 (0.62-5.78)	0.266	-	
PNI	Positive vs. negative	1.92 (0.76-4.88)	0.169	0.54 (0.16-1.80)	0.318
ENE	Positive vs. negative	0.92 (0.27-3.14)	0.890	-	
Tumor size	T1 vs. T0	0.05 (0.01-0.27)	<0.001	0.10 (0.01-1.13)	0.063
	T2 vs. T0	0.07 (0.02-0.36)	0.001	0.14 (0.02-1.02)	0.052
	T3 vs. T0	0.06 (0.01-0.33)	0.001	0.21 (0.02-1.73)	0.145
	T4 vs. T0	0.08 (0.02-0.35)	0.001	0.26 (0.03-2.01)	0.198
Lymph node status	N1 vs. N0	1.59 (0.63-4.00)	0.322	3.09 (0.72-13.16)	0.128
	N2 vs. N0	**2.09 (1.11-3.92)**	**0.022**	**4.79 (1.55-14.77)**	**0.006**
	N3 vs. N0	1.92 (0.76-4.88)	0.170	**7.34 (1.85-29.16)**	**0.005**
Stage	II vs. I	2.75 (0.79-9.51)	0.110	1.69 (0.19-15.31)	0.640
	III vs. I	0.85 (0.23-3.18)	0.812	0.15 (0.02-1.42)	0.098
	IV vs. I	1.56 (0.62-3.91)	0.341	0.14 (0.02-1.08)	0.060
Surgery	With vs. without	0.66 (0.38-1.13)	0.127	0.83 (0.46-1.51)	0.541
Chemotherapy before target therapy	With vs. without	1.25 (0.64-2.46)	0.517	-	
CRT-refractory	Yes vs. no	1.20 (0.73-1.98)	0.479	-	
Erbitux applied reason	Metastasis vs. recurrence	1.16 (0.70-1.91)	0.561	-	
Erbitux cycle, median (range)	≥ 11 vs. <11	**0.46 (0.28-0.75)**	**0.002**	**0.48 (0.27-0.84)**	**0.010**
Regimen of chemotherapy	Taxane-based vs. PF	0.75 (0.38-1.49)	0.417	-	
	Others vs. PF	0.90 (0.43-1.89)	0.777	-	
Platinum	Carboplatin vs. Cisplatin	0.51 (0.16-1.64)	0.260	-	

Chemotherapy dose	75/1000 vs. 60/800	1.19 (0. 66-2.17)	0.564	-

Table 4. Cox regression for overall mortality. HPC: hypophyngeal cancer; OC: oral cavity cancer; OPC: oropharyngeal cancer; LVI: lymphovascular invasion; PNI: perineural invasion; ENE: extranodal extension; CRT: concurrent chemoradiotherapy; PF: cisplatin and fluorouracil; HR: hazard ratio; 95% CI: 95% confidence intervals.

*Variables with p-value less than 0.2 in univariate analysis were included in multivariate model.

Table 5(on next page)

Table 5. adverse effects observed according to CTCAE version 4.0.

1 Table 5. adverse effects observed according to CTCAE version 4.0.

	PF				Taxane-based				Others			
	All grades		Grade 3-4		All grades		Grade 3-4		All grades		Grade 3-4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Febrile	7	9.2	1	1.3	4	23.5	1	5.9	2	15.4	0	-
Neutropenia	24	31.6	1	1.3	6	35.3	0	-	2	15.4	0	-
Skin rash	46	60.5	2	2.6	9	52.9	0	-	5	38.5	0	-
Anemia	51	67.1	2	2.6	14	82.4	0	-	4	30.8	0	-
Hypomagnesemia	31	40.8	0	-	11	64.7	0	-	4	30.8	0	-
Pneumonia	7	9.2	0	-	2	11.8	0	-	1	7.7	0	-
Infusion reaction	5	6.6	0	-	0	-	0	-	0	-	0	-
Vomiting	28	36.8	1	1.3	5	29.4	0	-	8	61.5	0	-

2

Table 6(on next page)

Table 6. Comparisons between different trials of cetuximab-based chemotherapy.

ORR: overall response rate; OS: overall survival; Q3W: every three weeks; AUC: area under the curve.

1

Study	Country	Year	Author	Chemotherapy	Cetuximab maintenance	Numbers	ORR (%)	OS (m)
Extreme	Belgium	2008	Vermorken JB	Cisplatin 100 mg/m2 D1 Fluorouracil 1000mg/m2 D1-4 Q3W	Weekly	222	36	10.1
GORTEC 2008-03	France and Belgium	2012	Guigay J	Cisplatin 75 mg/m2 D1 Docetaxel 75mg/m2 D1 Q3W	Biweekly	54	44	14
NCT01177956	China and South Korea	2014	Guo Y	Cisplatin 75 mg/m2 D1 Fluorouracil 750mg/m2 D1-5 Q3W	Weekly	68	55.9	12.6
CET-INT	Italy	2017	Bossi P	Cisplatin 75 mg/m2 D1 Paclitaxel 175 mg/m2 D1 Q3W	Weekly	191	51.7	11
CSPRO-HN02	Japan	2016	Tahara M	Carboplatin AUC 2.5 D1, D8 Paclitaxel 100 mg/m2 D1, D8 Q3W	Weekly	47	40	14.7
CACTUX	USA	2018	Adkins D	*nab*-paclitaxel 100 mg/m2 weekly Carboplatin AUC 5 D1 or Cisplatin 75 mg/m2 D1 Q3W	Weekly	32	63	18.8
CETMET	Demark	2018	Friesland S	Cisplatin 75 mg/m2 D1 Paclitaxel 175 mg/m2 D1 Q3W	Biweekly	85	63	10.2
TPEx	France and Belgium	2019	Guigay J	Cisplatin 75 mg/m2 D1 Docetaxel 75mg/m2 D1 Q3W	Biweekly	269	46	14.5

Real world practice	European	2014	De Mello RA	Cisplatin 100 mg/m2 D1 Fluorouracil 1000mg/m2 D1-4 Q3W	Weekly	121	23.91	11
Real world practice	Taiwan	2020	Wang	Cisplatin 75 mg/m2 D1 Fluorouracil 1000mg/m2 D1-4 Q3W	No	106	28.3	9.23

Table 6. Comparisons between different trials of cetuximab-based chemotherapy. ORR: overall response rate; OS: overall survival; Q3W: every three weeks; AUC: area under the curve.

Figure 1

Figure 1. Treatment Schema.

Tx: treatment; PF: cisplatin and fluorouracil; CT: computed tomography; MRI: magnetic resonance imaging; SD: stable disease; PR: partial response.

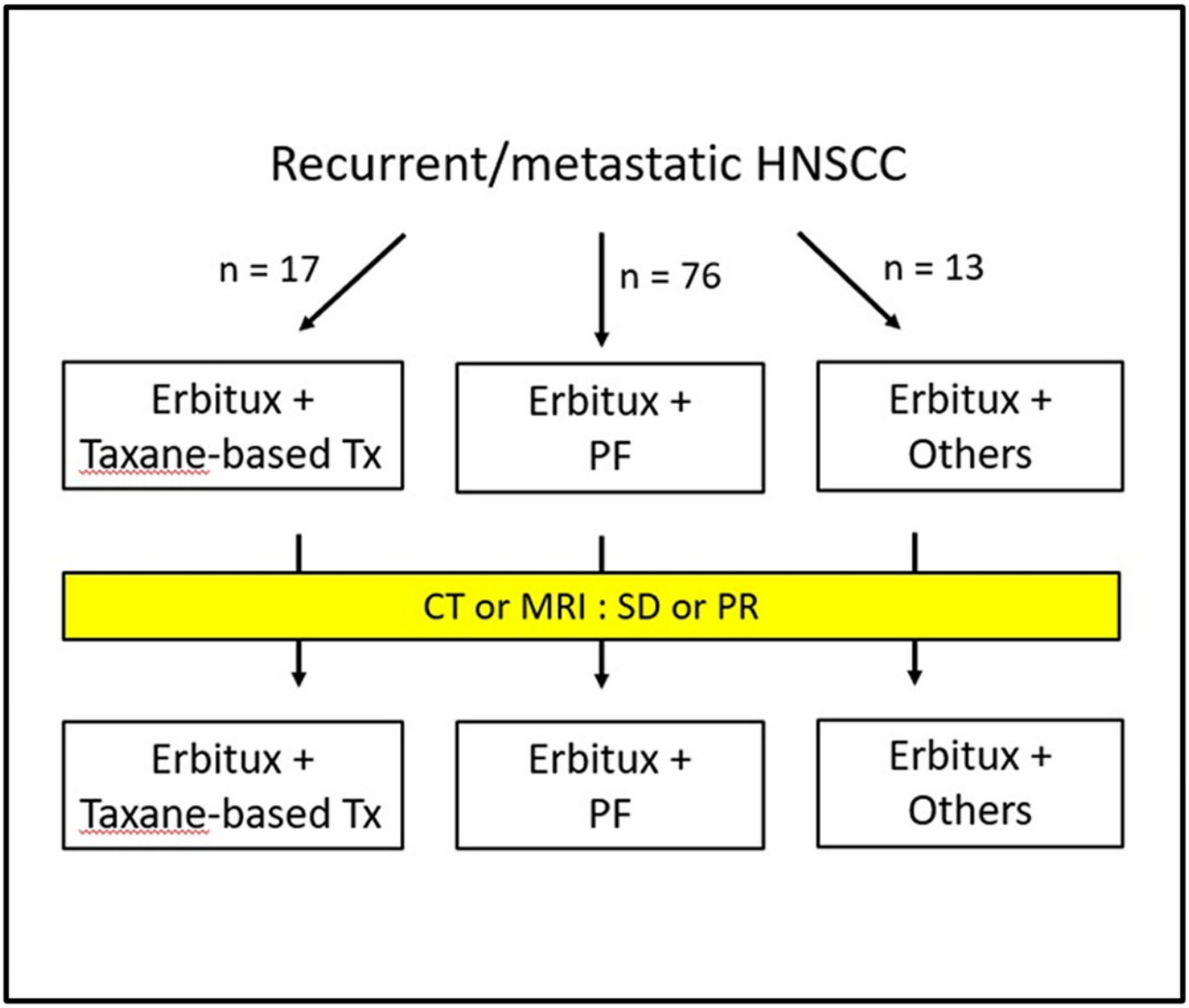

Figure 2

Figure 2. Progression-free survival curve.

Progression-free survival curve according to (A)Erbitux cycle, (B) previous CRT, (C) different chemotherapy regimens, (D) different doses of PF, and (E) CRT-refractory patents or not.

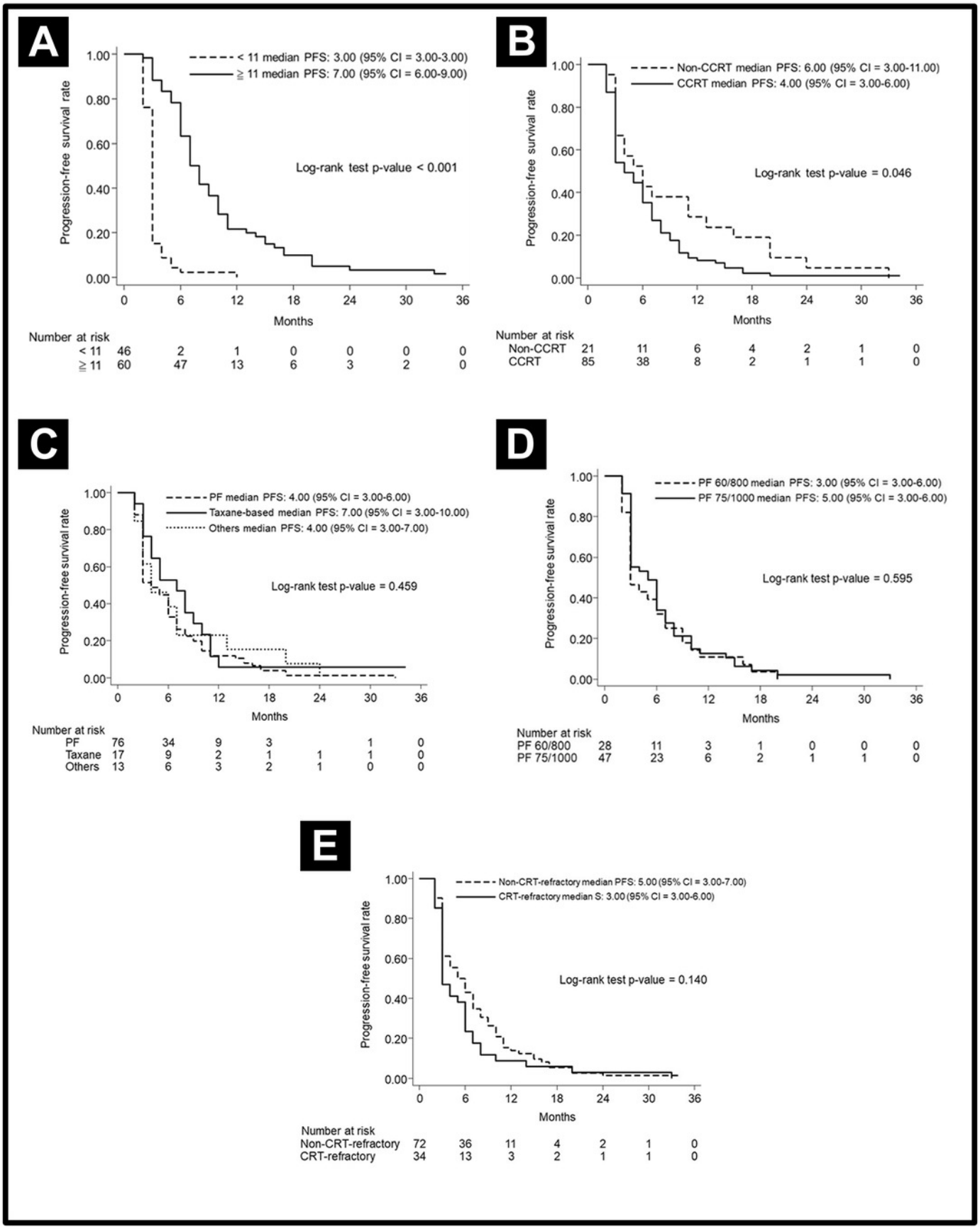
A
< 11 median PFS: 3.00 (95% CI = 3.00-3.00)
≧ 11 median PFS: 7.00 (95% CI = 6.00-9.00)
Log-rank test p-value < 0.001
Progression-free survival rate
Months
Number at risk
< 11 46 2 1 0 0 0 0
≧ 11 60 47 13 6 3 2 0
B
Non-CCRT median PFS: 6.00 (95% CI = 3.00-11.00)
CCRT median PFS: 4.00 (95% CI = 3.00-6.00)
Log-rank test p-value = 0.046
Progression-free survival rate
Months
Number at risk
Non-CCRT 21 11 6 4 2 1 0
CCRT 85 38 8 2 1 1 0
C
PF median PFS: 4.00 (95% CI = 3.00-6.00)
Taxane-based median PFS: 7.00 (95% CI = 3.00-10.00)
Others median PFS: 4.00 (95% CI = 3.00-7.00)
Log-rank test p-value = 0.459
Progression-free survival rate
Months
Number at risk
PF 76 34 9 3 1 0
Taxane 17 9 2 1 1 1 0
Others 13 6 3 2 1 0 0
D
PF 60/800 median PFS: 3.00 (95% CI = 3.00-6.00)
PF 75/1000 median PFS: 5.00 (95% CI = 3.00-6.00)
Log-rank test p-value = 0.595
Progression-free survival rate
Months
Number at risk
PF 60/800 28 11 3 1 0 0 0
PF 75/1000 47 23 6 2 1 1 0
E
Non-CRT-refractory median PFS: 5.00 (95% CI = 3.00-7.00)
CRT-refractory median S: 3.00 (95% CI = 3.00-6.00)
Log-rank test p-value = 0.140
Progression-free survival rate
Months
Number at risk
Non-CRT-refractory 72 36 11 4 2 1 0
CRT-refractory 34 13 3 2 1 1 0

Figure 3

Figure 3. Overall survival curve.

Overall survival curve according to (A)Erbitux cycle,.(B) different chemotherapy regimens, and (C) different doses of PF.

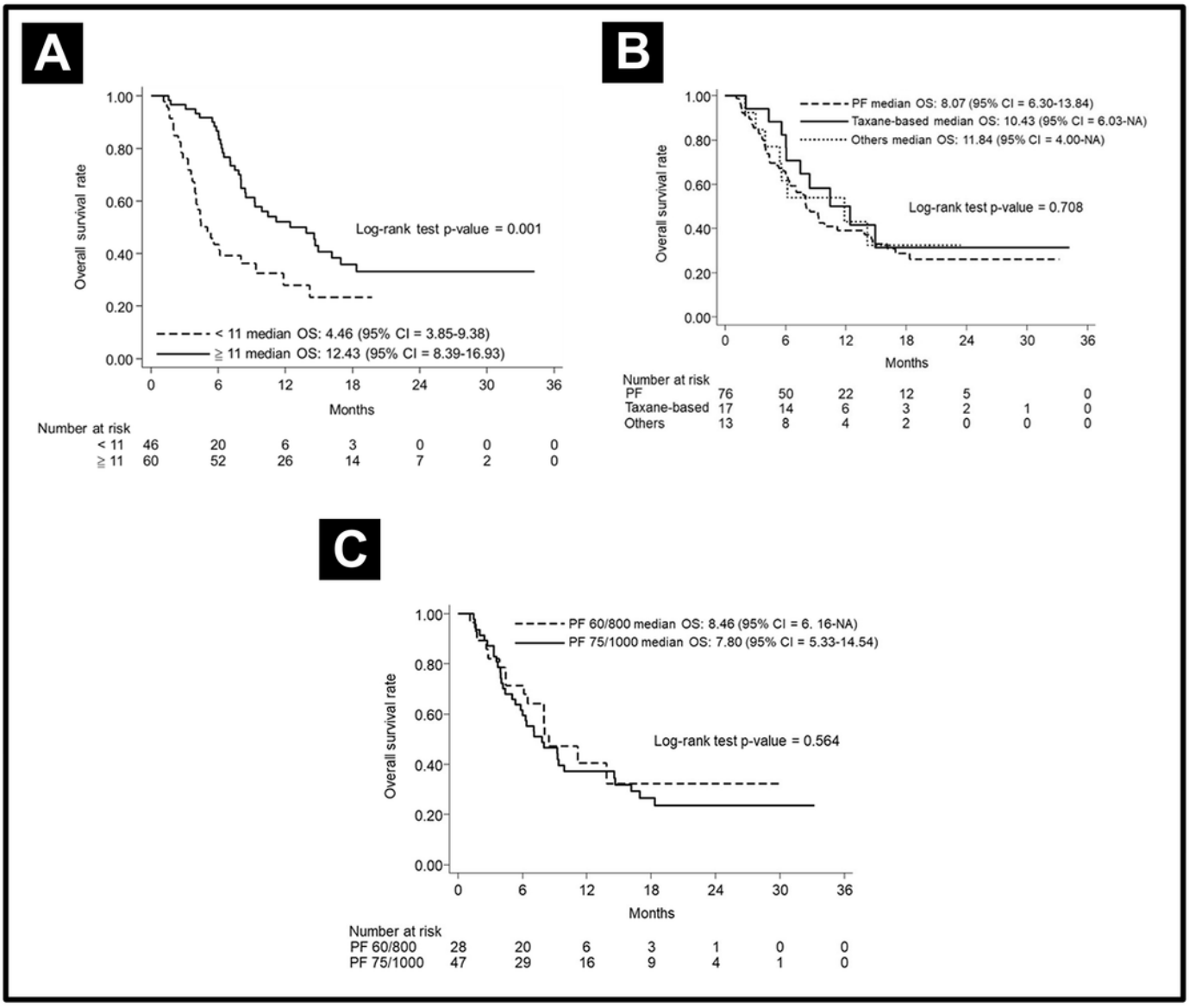

Figure 4

Figure 4. Subgroups analysis in CRT-refractory patients.

(A)Progression-free survival curve and (B) Overall curve according to the cetuximab cycle in CRT- refractory patients.