Cancer and Clinical Oncology; Vol. 7, No. 1; 2018
ISSN 1927-4858 E-ISSN 1927-4866
Published by Canadian Center of Science and Education

Overall Survival in Stage III and IV High-Risk Head and Neck Squamous Cell Carcinoma Patients who received Adjuvant Chemotherapy and Radiation without Cisplatin

Muhammad F Iqbal[1], Edem S Agamah[2] & Krishna Rao[2]

[1]Department of Internal Medicine, Southern Illinois University, Springfield, IL, USA

[2]Division of Hematology/Oncology, Simmons Cancer Institute at SIU, 315 W. Carpenter Street, Springfield, IL., USA

Correspondence: Muhammad F Iqbal, Department of Internal Medicine, Southern Illinois University, Springfield, IL, USA. Tel: 217-545-8000. E-mail: fahairiq@hotmail.com

Received: September 14, 2017 Accepted: October 10, 2017 Online Published: November 23, 2017

doi:10.5539/cco.v7n1p1 URL: https://doi.org/10.5539/cco.v7n1p1

Abstract

Objectives: Microscopically involved resection margins and/or extracapsular spread represent the most significant prognostic factors for poor outcome in head and neck cancer. Purpose of this study was to estimate overall survival, and assess impact of demographic and clinicopathologic variables on survival in stage III and IV high-risk patients who received chemoradiation other than Cisplatin

Methods: Retrospective review

Results: The final cohort of 18 eligible patients had a median age of 66 years and males were 66.66%. Median survival was 20.5 months. Patients were trichotomized into three age groups for comparison; ≤60 years, 61-70 years, ≥71 years. A superior overall survival was observed with advanced age (HR, 4.02; 95%CI, 1.33-12.17, p=0.016). Overall survival was significantly lower in patients with high Charlson comorbidity scores of 3-8 when compared to those with low scores of 0-2 (HR, 25.6; 95%CI, 2.78-236.7, p=0.0009). Young patients had high comorbidity scores (CCI > 2) based on the age-groups; ≤60 years (60%), 61-70 years (28.57%), ≥71 years (none). Tumor stage, positive resection margins, extracapsular spread, perineural involvement, lymphovascular invasion, tumor grade, high-risk human papillomavirus, body mass index, smoking and alcohol did not affect overall survival significantly.

Conclusions: Young age and severe comorbidity should be considered when treating high-risk head and neck cancer squamous cell carcinoma patients with adjuvant chemoradiation therapy other than Cisplatin due to inferior overall survival.

Keywords: head and neck cancer, high risk head and neck squamous cell carcinoma, overall survival in head and neck cancer, cetuximab

1. Introduction

Standard therapeutic management options for head and neck squamous cell carcinomas (HNSCC), which depend on the tumor site, stage, and patient's age and performance status, include surgery, chemotherapy, radiation or a combination of treatments. Historically surgery and/or radiation therapy (RT) were the mainstay of loco-regional treatment in patients with locally advanced resectable disease but rates of local-regional recurrence and distant metastasis were high and long-term prognosis remained poor (Bernier, Vermorken & Koch, 2006). In contrast, adjuvant chemoradiation therapy (CRT) following the surgical resection has been shown to improve overall survival (OS) in operable HNSCC (Bernier et al., 2006, Harari et al., 2014, Bernier & Cooper, 2005, Bernier et al., 2004, Bonner et al., 2006). Multiple pathologic high-risk prognostic factors have been proposed in the literature, mainly on the basis of retrospective analyses, that can affect recurrence and OS in HNSCC. These include microscopically involved surgical margins of resection, extracapsular extension of disease from a lymph node, perineural extension, vascular embolisms, and/or involvement of two or more lymph nodes. It has been substantiated that microscopically involved resection margins and/or extracapsular spread (ECS) of tumor from neck nodes represent the most significant prognostic clinical factors for poor outcome (Bernier & Cooper, 2005).

Supporting data for combined CRT as adjuvant treatment emerged from two independent, large-scale, prospective randomized trials conducted by the European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG). The EORTC 22931 and RTOG 9501 studies were similar in design. They compared addition of concomitant high-dose Cisplatin to RT with RT alone in patients with resected, poor-risk HNSCC (Bernier & Cooper, 2005). Bernier et al. (2005) combined the EORTC and RTOG data to demonstrate that ECS and/or microscopically involved surgical margins were the risk factors for which impact of CRT was most significant. Based on the compelling evidence, concurrent CRT with high-dose Cisplatin is believed to be more effective than adjuvant RT alone in postoperative setting for patients at high-risk of developing a recurrence. This validated combined approach is currently considered as standard therapeutic approach for the high-risk category of HNSCC patients (Bernier et al., 2006, Bernier & Cooper, 2005).

Despite demonstrated benefit of high-dose Cisplatin, its use is nonetheless of concern for many physicians. Combination regimens are associated with higher rates of severe reactions especially involving the mucosa and skin. Late toxic effects, notably dysphagia, are also common. Intravenous rehydration, narcotics for pain management, increased need for nutritional support and invasive procedures for that purpose must be implemented. These imply the need for a considerable intensified supportive care which makes its administration difficult in some settings. A considerable proportion of high-risk HNSCC patients are not considered good candidates for high-dose Cisplatin because of advanced age, renal insufficiency, auditory dysfunction, coexisting conditions, or poor performance status making it an unfavorable option as these patients may be prone to such adverse events (Bernier et al., 2006, Harari et al., 2014, Bernier & Cooper, 2005, Bernier et al., 2004, Bonner et al., 2006).

Alternatively a promising strategy involves incorporation of other targeting agents like cetuximb (Harari et al., 2014). Cetuximab is a monoclonal antibody (mAb) against the epidermal growth factor receptor (EGFR). Bonner et al. (2006, 2010) demonstrated that weekly cetuximab plus high dose RT increases both the duration of locoregional disease control and survival in locally advanced head and neck cancer without increasing the common toxic effects associated with radiotherapy to head and neck.

There is lack of data regarding survival in patients with poor-risk HNSCC who received adjuvant chemoradiation therapy other than Cisplatin. The objectives of present study were to estimate the OS in patients with stage III and IV high-risk HNSCC who received chemotherapy other than Cisplatin and RT after surgery and assess the impact of demographic and clinicopathologic variables on OS.

2. Methods

We collected data by retrospective medical record review in patients diagnosed with poor-risk HNSCC between January 1, 2008 and January 31, 2015, who received treatments at Southern Illinois University School of Medicine (SIU-SOM) and affiliated hospitals. Study approval was obtained from the Institutional Review Board (IRB) i.e. the Springfield Committee for Research Involving Human Subjects (SCRIHS).

Patients diagnosed with HNSCC and treated at SIU-SOM were identified using a database based on the ICD - 9 codes. Inclusion criteria were (1) Patients with stage III and IV HNSCC (Oral cavity, oropharynx, larynx and hypopharyngeal) (2) Presence of pathologic high-risk features including either ECS of the disease and/or microscopically involved mucosal margins of resection (3) Adjuvant chemotherapy regimen other than Cisplatin and RT (4) Availability of electronic pathology reports and therapy records. Exclusion criteria consisted of (1) Histology other than SCC (2) Carcinoma in situ only (3) Tumors not amenable to a surgical resection (4) CRT or RT given prior to surgery (5) History of recurrent HNSCC (6) Treatment with a palliative intent and (7) Unavailable electronic medical records.

In eligible cases, the reasons not to use Cisplatin were; clinical judgment that patient would not be able to tolerate Cisplatin or patients refusing Cisplatin. Data collection included the demographic variables, clinicopathological features and treatments. Age at the time of diagnosis, sex, ethnicity, tumor staging, histologic grade, adverse pathologic features (extracapsular extension, microscopically involved surgical margins, perineural infiltration, lymphovascular invasion), clinically enlarged lymph nodes, smoking status, high-risk Human Papillomavirus (HPV) status, alcohol consumption, co-morbid conditions, body mass index (BMI), details of surgery, chemotherapy, RT and OS were recorded.

Common Terminology Criteria for Adverse Events (CTCEA version 4.0, 2010) was used to document grade 3-4 toxicities related to chemoradiotherapy or RT. Chemotherapy toxicity including hypomagnesemia (Magnesium level < 1.2 mg/dL), skin rash (involving >10% of body surface area), anemia, thrombocytopenia and infections were recorded. Radiation toxicity due to mucositis, pigmentation, erythema, esophagitis, thrush and osteomyelitis was documented.

Patients were trichotomized into three age groups for comparison (≤60 years, 61-70 years, ≥71 years). Ethnicity was classified into Caucasians and others. American Joint Committee on Cancer's sixth (American Joint Committee on Cancer, [AJCC], 2002) and seventh (AJCC, 2010) editions, corresponding to the year of diagnosis, of the AJCC Cancer Staging Manual was used for tumor staging. Pathology reports were used to determine the T and N class. Patients were categorized into current, never, or former based on smoking and alcohol consumption status at the time of diagnosis. The high-risk HPV status was recorded from pathology reports. WHO classification of BMI (WHO, 2000) was used for categorization of patients into underweight, normal weight, overweight, class I obesity and class II obesity. Charlson Comorbidity Index (Hall, Ramachandran, Narayan, Jani & Vijayakumar, 2004, Singh et al., 1997) was used to calculate the comorbidity score and stratify patients based on CCI score. All patients underwent surgery of the primary site including tumor excision, total/partial pharyngectomy, or laryngopharyngectomy ± neck dissection for nodal metastasis. Adjuvant chemotherapy regimens included Cetuximab, Carboplatin, Carboplatin+5-Fluorouracil+Cetuximab, and Paclitaxel+5-Fluorouracil+Hydroxyurea.

Overall survival was the primary outcome measure, defined as survival calculated (in months) from the date of diagnosis to death from any cause, and patients were censored at the last date known to be alive or June 30, 2016 whichever came first.

All statistical analysis was performed using the SPSS software program (version 16.0; SPSS Inc**.).** Study endpoint was OS. Survival analysis was conducted by Kaplan-Meier estimation and Cox proportional hazards regression methods. All baseline characteristics were analyzed as univariable prognostic factors, and impact of these variables on survival was evaluated using the log-rank test. Hazard ratios and 95%CI were calculated for the strength of association. The p-value was considered to be statistically significant at <0.05

3. Results

From January 1, 2008 and January 31, 2015, we identified 740 patients with head and neck cancer. Of these, a total of eighteen (n = 18) stage III and IV high-risk HNSCC patients were eligible for our study. Death was recorded in 11 out of the 18 patients. Median dose of radiation was 60 Gy (range 42-70 Gy). Adjuvant chemotherapy regimens included in our cohort were; Cetuximab (n=13), Carboplatin (n=2), Carboplatin+5-Fluorouracil+Cetuximab (n=2), and Paclitaxel+5-Fluorouracil+Hydroxyurea (n=1). Clinical details of the study population are summarized in Table 1.

Table 1. Clinical Details of the entire cohort comprising of 18 HNSCC patients who received adjuvant CRT other than Cisplatin

Baseline Characteristics		
Variables	HNSCC patients (n=18)	P-Value
Age in years, No. (%)		
• ≤60	5 (27.77)	
• 61-70	7 (38.88)	0.016
• ≥71	6 (33.33)	
Sex, No. (%)		
• Male	12 (66.66)	0.184
• Female	6 (33.33)	
Stage, No. (%)		
• III	7 (38.88)	0.57
• IV	11 (61.11)	
Resection Margins, No. (%)		
• Positive	13 (72.22)	0.54
• Negative	5 (27.77)	
ECS, No. (%)		
• Present	8 (44.44)	0.641
• Absent	10 (55.55)	
Grade of differentiation, No. (%)		
• Moderate	9 (50)	
• Poor	9 (50)	0.926
Perineural involvement, No. (%)		
• Present	10 (55.55)	0.084
• Absent	8 (44.44)	
Lymphovascular invasion, No. (%)		
• Present	4 (22.22)	0.592
• Absent	14 (77.77)	
High-risk HPV status, No. (%)		
• Positive	4 (22.22)	0.333
• Negative	5 (27.77)	
• Unknown	9 (50)	
Enlarged and palpable lymph nodes, No. (%)		
• Present	6 (33.33)	0.325
• Absent	12 (66.66)	
BMI, No. (%)		
• Underweight	4 (22.22)	
• Normal weight	5 (27.77)	
• Overweight	5 (27.77)	0.145
• Class I obesity	2 (11.11)	
• Class II obesity	1 (5.55)	
• Class III obesity	0	
• Unknown	1 (5.55)	
Smoking, No. (%)		
• Current	7 (38.88)	0.113
• Former	5 (27.77)	
• Never	6 (33.33)	
Alcohol consumption, No. (%)		
• Current	4 (22.22)	0.868
• Former	1 (5.55)	
• Never	13 (72.22)	
Charlson comorbidity score, No. (%)		
• 0-2	13 (72.22)	0.0009
• 3-8	5 (27.77)	
RT side effects, No. (%)		
• Yes	7 (38.88)	0.062
• No	11 (61.11)	
Chemotherapy side effects, No. (%)		
• Yes	5 (27.77)	0.342
• No	13 (72.22)	

Abbreviations: ECS, Extracapsular spread; HPV, Human papillomavirus; BMI, Body mass index; CRT, Chemoradiation; RT, Radiation therapy

Median OS was 20.5 months in all patients. Median OS in patients who received Cetuximab was 19 months. Mean survival was 29 months in those who got carboplatin, 25.5 months in Carboplatin+5-Fluorouracil+Cetuximab and 8 months in patients who received Paclitaxel+5-Fluorouracil+Hydroxyurea.

Median age at diagnosis was 66 years (age-range = 49-80 years). OS was inferior in young patients (HR, 0.91; 95%CI 0.85-0.98, p = 0.013). In addition, we conducted an age-group (≤60 years, 61-70 years, ≥71 years) based analysis to assess whether OS was influenced by increased age and observed a statistically significant superior OS in older patients (HR, 4.02; 95%CI, 1.33-12.17, p=0.016). Median OS was 20 months in patients aged ≤60 years, 19 months in patients 61-70 years of age, and 31 months in patients who were ≥71 years.

Majority of patients were Caucasians (n=17, 94.44%). As ethnicity was not widely distributed in our study cohort, the OS was not assessed based on it. Males represented two-thirds of our study cohort. We observed no statistical difference in OS between male or female patients (HR, 2.49; 95%CI, 0.61-10.06). Median OS was 21.5 months in males vs 17 months in females (p = 0.184).

Patients with stage III HNSCC (n=7, 38.88%) and stage IV HNSCC (n=11, 61.11%) showed no significant difference in OS (HR, 1.5; 95%CI, 0.36-6.2). Stage III patients had a median survival of 21 months vs 19 months in stage IV disease (p=0.57). There was no statistical difference in OS between patients with microscopically positive resection margins (n=13, 72.22%) versus those with negative margins of resection (HR, 1.92; 95%CI, 0.22-16.39). Median survival was 23 months in patients with positive margins and 19 months in patients with clear margins of resection (p=0.54). Patients with ECS (n=8, 44.44%) had no difference in the outcome as compared to those with no ECS (n=10, 55.55%) (HR, 1.44; 95%CI, 0.3-6.78). Median survival was 18.5 months in patients with ECS and 27 months in patients without ECS (p=0.641).

Survival of patients with low or moderate grade HNSCC (n=9, 50%) was not different in contrast to high grade tumors (n=9, 50%) (HR, 1.06; 95%CI, 0.29-3.88). Perineural involvement (n=10, 55.5%) (HR, 0.29; 95%CI, 0.07-1.27) and lymphovascular invasion (n=4, 22.22%) (HR, 0.567; 95%CI, 0.06-4.65) had no prognostic value. Median survival was 23.5 months in patients with perinerual infiltration and 16 months in patients without it (p=0.084). However, patients with lymphovascular invasion had a median survival of 19.5 months vs 21.5 months without invasion (p=0.592).

High-risk HPV status didn't impact OS (HR, 0.31; 95%CI, 0.02-3.7). There was no statistical difference in OS between patients with clinically palpable lymph nodes at presentation (n=6, 33.33%) as compared to those without lymphadenopathy (n=12, 66.66%) (HR, 2.11; 95%CI, 0.46-9.68).

According to the WHO BMI classification, patients were categorized into underweight (n = 4, 22.22%), normal weight (n = 5, 27.77%), overweight (n = 5, 27.77%), class I obesity (n = 2, 11.11%) and class II obesity (n = 1, 5.55%). BMI had no significant effect on OS (HR, 0.58; 95%CI, 0.26-1.29). There was no difference in OS among never (n=6, 33.33%), former (n=5, 27.77%) or current smokers (n=7, 38.88%) (HR, 0.41; 95%CI, 0.1-1.62). Similar results were observed with regards to alcohol consumption; never (n = 13, 72.22%), former (n = 1, 5.55%) and current (n = 4, 22.22%) (HR, 1.13; 95%CI, 0.26-4.79).

Patients received a comorbidity score based on the CCI, and OS was assessed based on the scores; 0 (n = 3), 1 (n = 5), 2 (n = 5), 3 (n = 3), 4 (n = 0), 5 (n = 2), 6 (n = 0) and 8 (n = 0). OS was significantly different when all patients were compared based on individual scores (HR, 2.11; 95%CI, 1.14-3.9, p=0.011). Patients with a score of 2 had the highest median survival at 36 months and the lowest median survival of 7 months was observed in those with a score of 3. Patients were categorized into two groups; group 1 with low scores of 0-2 (n=13, 72.22%) and group 2 with high scores of 3-8 (n=5, 27.77%). OS was significantly lower in patient group with high scores (HR, 25.6; 95%CI, 2.78-236.7, p=0.0009).

Young patients had high comorbidity scores based on the age-groups. In age-group ≤60 years, 3 out of 5 patients (60%) had a CCI score greater than 2. In 61-70 years age-group, 2 out of 7 patients (28.57%) had a CCI score of above 2 while in patients ≥71 years, none had a CCI score of above 2.

Patients who experienced a grade 3-4 RT side effect (n=7, 38.88%) and those who did not (n=11, 61.11%) had similar outcome (HR, 0.25; 95%CI, 0.05-1.2). Likewise, patients who experienced chemotherapy side effects (n=5, 27.77%) versus those with no reactions (n=13, 72.22%), had similar OS (HR, 0.47; 95%CI, 0.09-2.3).

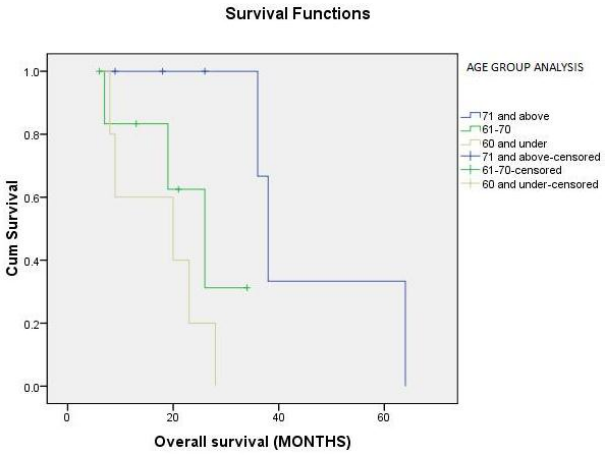

Figure 1. Kaplan-Meier Survival Curves based on age-groups. Patients with age-group ≤60 years, 61-70 years, ≥71 years were compared to each other and a statistically significant superior OS in older patients was observed (p=0.016).

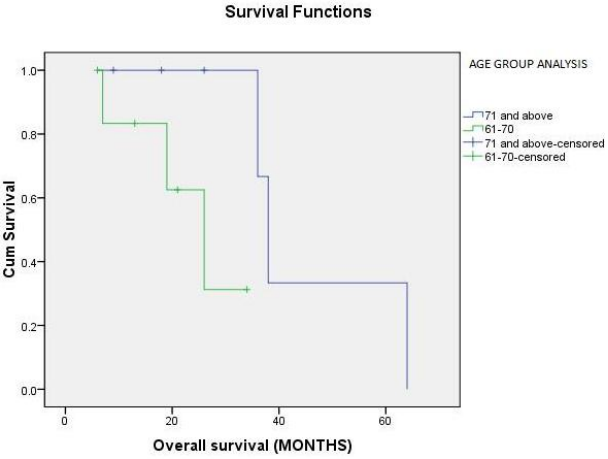

Figure 2. Kaplan-Meier Survival Curves based on age-groups. Patients with age range of 61-70 years are compared to those with ≥71 years at the time of diagnosis. The OS was significantly lower in 61-70 years age group (p=0.049).

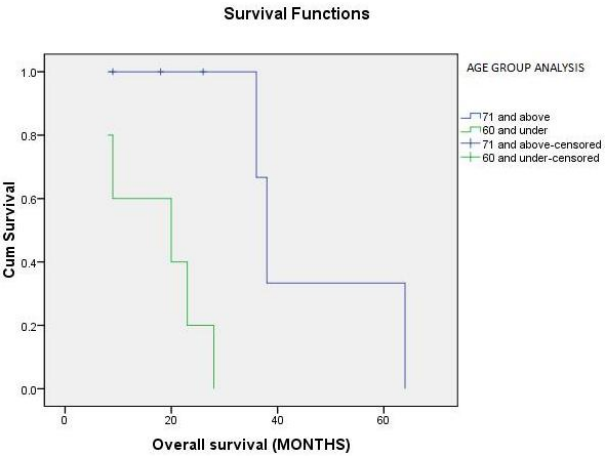

Figure 3. Kaplan-Meier Survival Curves based on age-groups. Patients with age range of ≤60 years are compared to those with ≥71 years at the time of diagnosis. The OS was significantly lower in the group with age range of ≤60 years (p=0.003).

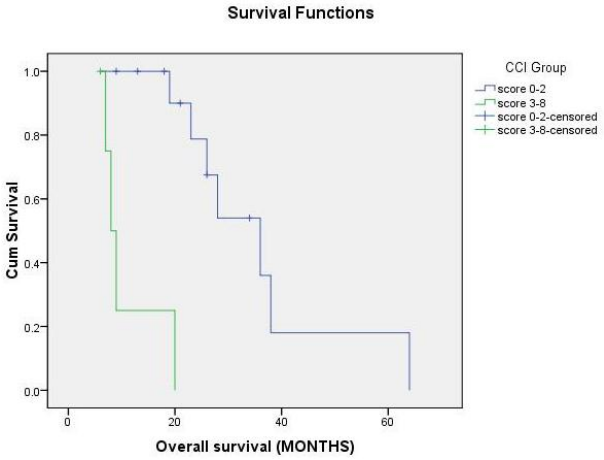

Figure 4. Kaplan-Meier Survival Curves based on the Charlson Comorbidity Index Score. Patients with low scores of 0-2 are compared to those with high scores, 3-8. The OS was significantly higher in the group with scores of 0-2 (p=0.0009).

4. Discussion

This study is a retrospective review of high-risk stage III and IV HNSCC patients who were treated at a single tertiary care institute and OS was evaluated. The salient observations are as follows: (1) High-risk stage III and IV HNSCC patients who received adjuvant chemoradiation therapy other than Cisplatin had a median OS of 20.5 months (2) Patients ≤60 years of age had worse OS (3) Patients with higher CCI scores had distinctively inferior OS. Majority of patients ≤60 years of age had high CCI scores (4) Our analysis did not show a statistically significant difference in OS for the variables including sex, tumor stage, microscopically involved surgical margins, perineural infiltration, ECS, lymphovascular invasion, clinically enlarged lymph nodes, smoking, high-risk HPV, alcohol consumption, BMI, and therapy toxicities.

The present study is important because HNSCC patients who have the high-risk disease are at increased risk for recurrence and poor survival. Literature is scarce regarding the impact of stratified variables on outcomes in high-risk HNSCC. Bonner et al. (2010) showed a higher OS with Cetuximab plus high dose RT compared with RT alone as a primary treatment in locally advanced head and neck cancer. In the postoperative setting, Amini et al. (2016) showed no added benefit of CRT on survival after resection of salivary gland carcinomas. Retrospective comparisons between Cisplatin and Cetuximab have shown mixed results. Strom et al. (2015) found no difference in OS and locoregional control between Cisplatin every 3 weeks or weekly Cetuximab with RT. However, several other retrospective studies have reported better survival with use of Cisplatin concurrently with radiation for definitive therapy of locally advanced head and neck cancer (Riaz et al., 2016, Ley et al., 2013, Levy et al., 2014). A meta-analysis demonstrated that concomitant Cisplatin-based CRT is associated with better OS than Cetuximab+RT in locally advanced HNSCC, probably attributable to better loco-regional disease control (Petrelli et al., 2014). However, no prospective study has yet been published comparing Cisplatin/RT to Cetuximab/RT, and no retrospective or prospective data has been reported on the use of Cetuximab in high risk head and neck cancer patients post-operatively. Bonner et al. (2010) has demonstrated the superiority of cetuximab plus RT over RT alone in the primary treatment setting, while CONCERT-2 (Giralt et al., 2015) and HN.6 (Siu et al., 2017) have shown mixed results with regards to panitumumab (another mAb against EGFR) versus cisplatin in the primary treatment setting. Bernier et al. (2004) observed a median time to death of 72 months in patients treated with postoperative irradiation and Cisplatin vs 32 months after RT alone in locally advanced head and neck cancer. Median OS in our study was 20.5 months. The difference in OS is likely related to study design, setting and highly selected patient population.

Advanced age has generally been associated with worse OS in multiple studies (Chen, Harris, Hara, Sirjani & Divi, 2016, Choi et al., 2016) although in our study advanced age correlated with a superior OS. The higher OS was observed in an individual as well as a stratified approach based on the age-groups. Young patients had high comorbidity scores, which may be the contributing factor to poor survival in those patients. Further studies are warranted given the limited sample size and inclusion of Carboplatin-based regimens in addition to Cetuximab in our study. It would be intriguing if our findings are confirmed on a large-scale because adjuvant CRT other than Cisplatin may be an alternate option for geriatric patients with stage III or IV high-risk HNSCC who do not

tolerate and/or are poor candidates for Cisplatin.

Comorbidity strongly influences the outcomes of cancer patients through direct consequences of comorbid conditions and affecting the tolerability for chemotherapy (Skillington, Kallogjeri, Lewis Jr. & Piccirillo, 2016). Multiple studies have shown adverse relationship of comorbidity with OS (Paleri, Wight & Davies, 2003, Datema, Ferrier, van der Schroeff & Baatenburg de Jong, 2010). Our analysis inherently focused on the high-risk HNSCC population and we used an individual as well as a stratified approach to study the outcome. Our findings corroborate with those of Skillington et al. (2016) that OS is negatively affected by severe comorbidity. We suggest judicious use of adjuvant CRT in patients with severe comorbidities. Continued research for agents that are better tolerated should be pursued for patients with high-risk HNSCC and severe coexisting illnesses.

Mell et al. (2010) reported an inferior OS in women. Median OS was higher in males in our study but not statistically significant. Mixed results exist as to whether positive resection margins impact survival (Haque, Contreras, McNicoll, Eckberg & Petitti, 2006, Binahmed, Nason & Abdoh, 2007, Brandwein-Gensler et al., 2005). Majority of the studies associate positive resection margins with poor survival. ECS has long been recognized as a pertinent adverse prognostic factor in HNSCC at all sites (Kharytaniuk et al., 2016). Pathologic features including ECS, perineural infiltration, and lymphovascular invasion have been associated with poor locoregional control (Langendijk, Slotman, van der Waal, Doornaert, Berkof & Leemans, 2005). In our study, the median survival was lower in patients with ECS or lymphovascular invasion and higher in patients who had clear margins of resection or perinerual infiltration, but these differences did not reach statistical significance.

Patients with HPV-associated HNSCC show better survivals as compared to HPV-negative tumors (Fakhry et al., 2008, Ang et al., 2010). High-risk HPV didn't impact OS in our study, and the disparity is likely due to fewer cases with documented HPV-status. A review of literature showed that patients with higher BMI had increased OS as compared to underweight and normal weight patients (Hollander, Kampman & van Herpen, 2015). Our study cohort did not show any correlation between BMI and OS. There was unequal distribution of patients in the categories based on WHO BMI classification. Increased alcohol consumption and smoking have been associated with unfavorable outcomes in HNSCC (Chen et al., 2011, Miller, Day & Ravenel, 2006, Mayne, Cartmel, Kirsh & Goodwin Jr., 2009, Deleyiannis, Thomas, Vaughan & Davis, 1996). We did not observe any correlation between smoking or alcohol intake and OS. Interestingly, patients who experienced grade ≥ 2 Cetuximab-induced skin rash had better OS than those with grade 1 or no rash (Bonner et al., 2010). Grade 3-4 chemotherapy or irradiation-induced toxicity had no impact on survival in our study.

Our study is limited by its retrospective design and the external validity of our results may be limited to patients treated in similar tertiary care settings. Sample size was small and the long study period may have included outdated supportive care practices. Nonetheless, our observations are important and should contribute to current literature on outcomes after adjuvant treatments for stage III and IV high-risk HNSCC patients.

5. Conclusions

Adjuvant chemoradiation therapy other than Cisplatin in high-risk stage III or IV HNSCC patients is associated with a median OS of 20.5 months. Young age and severe comorbidity are prognostic of poor OS. Our results suggest that adjuvant CRT other than Cisplatin should be used with caution in high-risk HNSCC patients although patients with severe co-illnesses may benefit from the addition of Cetuximab. More research in the form of a Phase II multicenter study would be needed to confirm our findings.

Acknowledgements

Drs Iqbal and Rao had full access to all the data in the study and take responsibility for the integrity of data and the accuracy of data analysis.

Study concept and design: Iqbal, Rao

Acquisition, analysis, or interpretation of data: Agamah, Iqbal

Drafting of the manuscript: Iqbal

Critical revision of the manuscript for important intellectual content: Iqbal, Rao

Statistical analysis: Iqbal, Rao

Study supervision: Rao

Funding: Authors declare that they received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of conflicting interests: The authors declare that there is no conflict of interest

References

Amini, A., Waxweiler, T. V., Brower, J. V., Jones, B. L., McDermott, J. D., Raben, D., … Karam, S. D. (2016). Association of Adjuvant Chemoradiotherapy vs Radiotherapy Alone With Survival in Patients With Resected Major Salivary Gland Carcinoma: Data From the National Cancer Data Base. *JAMA Otolaryngol Head Neck Surg., 142*(11), 1100-1110. https://doi.org/10.1001/jamaoto.2016.2168

Ang, K. K., Harris, J., Wheeler, R., Weber, R., Rosenthal, D. I., Nguyen-Tân, P. F., … Gillison, M. L. (2010). Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med., 363*(1), 24-35. https://doi.org/10.1056/NEJMoa0912217

Bernier, J., & Cooper, J. S. (2005). Chemoradiation after surgery for high-risk head and neck cancer patients: how strong is the evidence? *Oncologist, 10*(3), 215-224. https://doi.org/10.1634/theoncologist.10-3-215

Bernier, J., Cooper, J. S., Pajak, T. F., van Glabbeke, M., Bourhis, J., Forastiere, A., … Lefèbvre, J. L. (2005). Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck, 27*(10), 843-850. https://doi.org/10.1002/hed.20279

Bernier, J., Domenge, C., Ozsahin, M., Matuszewska, K., Lefèbvre, J. L., Greiner, R. H., … van Glabbeke, M. (2004). Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med., 350*(19), 1945-1952. https://doi.org/10.1056/NEJMoa032641

Bernier, J., Vermorken, J. B., & Koch, W. M. (2006). Adjuvant therapy in patients with resected poor-risk head and neck cancer. *J Clin Oncol., 24*(17), 2629-2635. https://doi.org/10.1200/JCO.2005.05.0906

Binahmed, A., Nason, R. W., & Abdoh, A. A. (2007). The clinical significance of the positive surgical margin in oral cancer. *Oral Oncol., 43*(8), 780-784. https://doi.org/10.1016/j.oraloncology.2006.10.001

Bonner, J. A., Harari, P. M., Giralt, J., Azarnia, N., Shin, D. M., Cohen, R. B., …, Ang, K. K. (2006). Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med., 354*(6), 567-578. https://doi.org/10.1056/NEJMoa053422

Bonner, J. A., Harari, P. M., Giralt, J., Cohen, R. B., Jones, C. U., Sur, R. K., … Ang, K. K. (2010). Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol., 11*(1), 21-28. https://doi.org/10.1016/S1470-2045(09)70311-0

Brandwein-Gensler, M., Teixeira, M. S., Lewis, C. M., Lee, B., Rolnitzky, L., Hille, J. J., … Wang, B. Y. (2005). Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. *Am J Surg Pathol., 29*(2), 167-178.

Chen, A. M., Chen, L. M., Vaughan, A., Sreeraman, R., Farwell, D. G., Luu, Q., … Vijayakumar, S. (2011). Tobacco smoking during radiation therapy for head-and-neck cancer is associated with unfavorable outcome. *Int J Radiat Oncol Biol Phys., 79*(2), 414-419. https://doi.org/10.1016/j.ijrobp.2009.10.050

Chen, M. M., Harris, J. P., Hara, W., Sirjani, D., & Divi, V. (2016). Association of Postoperative Radiotherapy With Survival in Patients With N1 Oral Cavity and Oropharyngeal Squamous Cell Carcinoma. *JAMA Otolaryngol Head Neck Surg., 142*(12), 1224-1230. https://doi.org/10.1001/jamaoto.2016.3519

Choi, S. H., Terrell, J. E., Fowler, K. E., McLean, S. A., Ghanem, T., Wolf, G. T., … Duffy, S. A. (2016). Socioeconomic and Other Demographic Disparities Predicting Survival among Head and Neck Cancer Patients. *PLoS One., 11*(3), e0149886. https://doi.org/10.1371/journal.pone.0149886

Datema, F. R., Ferrier, M. B., van der Schroeff, M. P., & Baatenburg, de Jong, R.J. (2010). Impact of comorbidity on short-term mortality and overall survival of head and neck cancer patients. *Head Neck., 32*(6), 728-736. https://doi.org/10.1002/hed.21245

Deleyiannis, F. W., Thomas, D. B., Vaughan, T. L., & Davis, S. (1996). Alcoholism: independent predictor of survival in patients with head and neck cancer. *J Natl Cancer Inst., 88*(8), 542-549. https://doi.org/10.1093/jnci/88.8.542

Edge, S. B. (2010). American Joint Committee on Cancer. *AJCC cancer staging manual.* 7th ed. New York: Springer.

Fakhry, C., Westra, W. H., Li, S., Cmelak, A., Ridge, J. A., Pinto, H., …, Gillison, M. L. (2008). Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst., 100*(4), 261-269. https://doi.org/10.1093/jnci/djn011

Giralt, J., Trigo, J., Nuyts, S., Ozsahin, M., Skladowski, K., Hatoum, G., … Vander Walde, A. (2015). Panitumumab plus radiotherapy versus chemoradiotherapy in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-2): a randomized, controlled, open-label phase 2 trial. *Lancet Oncol., 16*(2), 221-32. https://doi.org/10.1016/S1470-2045(14)71200-8

Greene, F. L. (2002). American Joint Committee on Cancer., American Cancer Society. *AJCC cancer staging manual*. 6th ed. New York: Springer-Verlag.

Hall, W. H., Ramachandran, R., Narayan, S., Jani, A. B., & Vijayakumar, S. (2004). An electronic application for rapidly calculating Charlson comorbidity score. *BMC Cancer, 4*, 94. https://doi.org/10.1186/1471-2407-4-94

Haque, R., Contreras, R., McNicoll, M. P., Eckberg, E. C., & Petitti, D. B. (2006). Surgical margins and survival after head and neck cancer surgery. *BMC Ear Nose Throat Disord, 6*, 2. https://doi.org/10.1186/1472-6815-6-2

Harari, P. M., Harris, J., Kies, M. S., Myers, J. N., Jordan, R. C., Gillison, M. L., … Ang, K. (2014). Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol., 32*(23), 2486-2495. https://doi.org/10.1200/JCO.2013.53.9163

Hollander, D., Kampman, E., van Herpen, C. M. (2015). Pretreatment body mass index and head and neck cancer outcome: A review of the literature. *Crit Rev Oncol Hematol., 96*(2), 328-338. https://doi.org/10.1016/j.critrevonc.2015.06.002

Institute NC. Common Terminology Criteria for Adverse Events v4.0, NIH Publication No. 09-5410. 2009, revised June 2010; https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed Oct 20, 2016.

Kharytaniuk, N., Molony, P., Boyle, S., O'Leary, G., Werner, R., Heffron, C., … Sheahan, P. (2016). Association of Extracapsular Spread With Survival According to Human Papillomavirus Status in Oropharynx Squamous Cell Carcinoma and Carcinoma of Unknown Primary Site. *JAMA Otolaryngol Head Neck Surg., 142*(7), 683-690. https://doi.org/10.1001/jamaoto.2016.0882

Langendijk, J. A., Slotman, B. J., van der Waal, I., Doornaert, P., Berkof, J., & Leemans, C. R. (2005). Risk-group definition by recursive partitioning analysis of patients with squamous cell head and neck carcinoma treated with surgery and postoperative radiotherapy. *Cancer., 104*(7), 1408-1417. https://doi.org/10.1002/cncr.21340

Levy, A., Blanchard, P., Bellefqih, S., Brahimi, N., Guigay, J., Janot, F., … Tao, Y. (2014). Concurrent use of cisplatin or cetuximab with definitive radiotherapy for locally advanced head and neck squamous cell carcinomas. *Strahlenther Onkol., 190*(9), 823-831. https://doi.org/10.1007/s00066-014-0626-0

Ley, J., Mehan, P., Wildes, T. M., Thorstad, W., Gay, H. A., Michel, L., … Adkins, D. (2013). Cisplatin versus cetuximab given concurrently with definitive radiation therapy for locally advanced head and neck squamous cell carcinoma. *Oncology, 85*(5), 290-296. https://doi.org/10.1159/000355194

Mayne, S. T., Cartmel, B., Kirsh, V., & Goodwin, W. J., Jr. (2009). Alcohol and tobacco use prediagnosis and postdiagnosis, and survival in a cohort of patients with early stage cancers of the oral cavity, pharynx, and larynx. *Cancer Epidemiol Biomarkers Prev., 18*(12), 3368-3374. https://doi.org/10.1158/1055-9965.EPI-09-0944

Mell, L. K., Dignam, J. J., Salama, J. K., Cohen, E. E., Polite, B. N., Dandekar, V., … Weichselbaum, R. R. (2010). Predictors of competing mortality in advanced head and neck cancer. *J Clin Oncol, 28*(1), 15-20. https://doi.org/10.1200/JCO.2008.20.9288

Miller, P. M., Day, T. A., & Ravenel, M. C. (2006). Clinical implications of continued alcohol consumption after diagnosis of upper aerodigestive tract cancer. *Alcohol Alcohol., 41*(2), 140-142. https://doi.org/10.1093/alcalc/agh245

Paleri, V., Wight, R. G., & Davies, G. R. (2003). Impact of comorbidity on the outcome of laryngeal squamous cancer. *Head Neck., 25*(12), 1019-1026. https://doi.org/10.1002/hed.10333

Petrelli, F., Coinu, A., Riboldi, V., Borgonovo, K., Ghilardi, M., Cabiddu, M., … Barni, S. (2014). Concomitant platinum-based chemotherapy or cetuximab with radiotherapy for locally advanced head and neck cancer: a

systematic review and meta-analysis of published studies. *Oral Oncol., 50*(11), 1041-1048. https://doi.org/10.1016/j.oraloncology.2014.08.005

Riaz, N., Sherman, E., Koutcher, L., Shapiro, L., Katabi, N., Zhang, Z., … Lee, N. (2016). Concurrent Chemoradiotherapy With Cisplatin Versus Cetuximab for Squamous Cell Carcinoma of the Head and Neck. *Am J Clin Oncol., 39*(1), 27-31. https://doi.org/10.1097/COC.0000000000000006

Singh, B., Bhaya, M., Stern, J., Roland, J. T., Zimbler, M., Rosenfeld, R. M., … Lucente, F. E. (1997). Validation of the Charlson comorbidity index in patients with head and neck cancer: a multi-institutional study. *Laryngoscope, 107*(11 Pt 1), 1469-1475. https://doi.org/10.1097/00005537-199711000-00009

Siu, L. L., Waldron, J. N., Chen, B. E., Winquist, E., Wright, J. R., Nabid, A., … Parulekar, W. R. (2017). Effect of Standard Radiotherapy With Cisplatin vs Accelerated Radiotherapy With Panitumumab in Locoregionally Advanced Squamous Cell Head and Neck Carcinoma: A Randomized Clinical Trial. *JAMA Oncol., 3*(2), 220-226. https://doi.org/10.1001/jamaoncol.2016.4510

Skillington, S. A., Kallogjeri, D., Lewis, J. S., Jr., & Piccirillo, J. F. (2016). Prognostic Importance of Comorbidity and the Association Between Comorbidity and p16 in Oropharyngeal Squamous Cell Carcinoma. *JAMA Otolaryngol Head Neck Surg., 142*(6), 568-575. https://doi.org/10.1001/jamaoto.2016.0347

Strom, T. J., Trotti, A. M., Kish, J., Russell, J. S., Rao, N. G., McCaffrey, J., … Caudell, J. J. (2015). Comparison of every 3 week cisplatin or weekly cetuximab with concurrent radiotherapy for locally advanced head and neck cancer. *Oral Oncol., 51*(7), 704-708. https://doi.org/10.1016/j.oraloncology.2015.04.012

WHO. (2016). The International Classification of adult underweight, overweight and obesity according to BMI; 2000. http://apps.who.int/bmi. Accessed Oct 20, 2016.