Impact of Comorbidity on Initial Treatment and Overall Survival in Elderly Head and Neck Cancer Patients

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Abstract. *Background: Comorbidity is a determinant of treatment selection and survival in various cancers including head and neck cancer (HNC) and is often associated with a higher utilization of non-curative intent treatment. Patients and Methods: In this retrospective study we analyzed 182 consecutively treated HNC patients >65 years old at the Dallas Veterans Affairs Medical Center from January 2000-June 2007. Comorbidity was assessed with the Charlson Comorbidity Index (CCI). Treatment was classified as curative vs. non-curative intent. Results: Median overall survival was 883 days. Patients with a CCI score 0-2 had non-significant higher rate of curative intent treatment than patients with CCI score >2 (83.8% vs. 74.6%, p=0.13). In multivariate analysis, only stage had significant prognostic importance (hazard ratio (HR) 1.66; 95% confidence interval (CI) 1.29-2.14; p<0.0005). In separate multivariate analyses of patients treated with surgery or chemoradiation, CCI was not a significant predictor of survival with HR of 0.88 (95% CI 0.69-1.11; p=0.29) and 1.13 (95% CI 0.83-1.53; p=0.44), respectively. Conclusion: In our elderly HNC population, CCI was not an independent predictor of selection of curative intent treatment or overall survival.*

Cancers of the head and neck (HNC) occur at a rate of approximately 40,000 cases per year in the United States (1). Out of these, about half occur in individuals older than 65 years of age (2). The initial treatment for HNC typically includes surgery and/or radiation, often with chemotherapy. In the elderly population, it often becomes difficult to decide among these treatment options. What further complicates the matter is the prevalence of other comorbidities. The most prevalent risk factors for development of HNC are the use of tobacco (smoke and smokeless) and alcohol. Their uses subsequently increase one's risk of other cardiovascular, pulmonary and gastrointestinal diseases. Moreover, studies have shown that increasing age correlates with an increasing number of comorbidities (3). Comorbidities have also been shown to impact the disease course, treatment selection and overall survival (4). With the increasing age of patients with HNC, concurrent comorbid conditions need to be considered in the overall treatment plan. Some have even suggested supplementing the traditional tumor-node-metastasis (TNM) staging model with patient comorbidity to assist in treatment selection (5). There are several indices to assess comorbidity in cancer patients – Charlson comorbidity index, cumulative index rating scale, Kaplan-Feinstein index, index of coexistent disease, adult comorbidity evaluation-27, among others – and they have been tested across a variety of malignancies (6-10). We chose the Charlson comorbidity index (CCI) in our study given its wide use and known validation in HNC patients (6). The CCI was developed in 1987 based on a cohort of 559 internal medicine service patients and was validated further on a sample of 685 breast cancer patients (7). This weighted index is composed of 19 comorbid conditions and takes into account the number and seriousness of comorbid disease. The goal of our study was two-fold: i) to determine the burden of comorbidity using CCI in this elderly HNC population and ii) to demonstrate the predictive effects of CCI on selection of initial treatment and overall survival in this cohort.

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Patients and Methods

Patients. Our study was an Institutional review board (IRB) approved retrospective analysis of 182 patients over 65 years of age with HNC treated at the Dallas Veterans Affairs Medical Center (DVAMC) between January 2000 and June 2007. Data was extracted from the Computerized Patient Record System (CPRS)

and included gender, age, cancer stage (the American Joint Committee on Cancer/Union of International Cancer Control tumor-note-metastasis (AJCC/UICC TNM) classification and stage groupings were used), cancer site, treatment and other comorbidities. CCI was used to assess comorbidity with scores of 0-2 for low comorbidity and >2 for high comorbidity. Treatment was classified as curative intent versus non-curative intent with curative intent treatment defined as definitive surgery or concurrent chemotherapy and radiation.

Statistical considerations. The primary end point of the study was to evaluate the impact of CCI on overall survival of patients with HNC. The secondary end point was to evaluate the influence of CCI on overall survival in a subgroup of patients who received surgery or chemotherapy and radiation. Descriptive analyses were performed for demographic data. The Kaplan-Meier method was utilized for the analysis of survival. The log rank test was performed to identify significance between the survival curves. Following univariate analysis, a multivariate regression model was used to test the relationship between CCI and potential confounding factors. All data were analyzed through the Minitab 15 Statistical Software® (http://www.minitab.com/en-us/) and statistical significance was defined at $p<0.05$.

Results

A total of 182 consecutive HNC patients treated from January 2000 to June 2007 at DVAMC were evaluated in the present study. The demographics of the patients including age, race, stage, site, treatment, and CCI score are shown in Table I. The patient population was comprised entirely of males with a median age of 72 years (range=65-87 years); 80% were white, 19.5% were black and 0.5% were Hispanic. Twenty-six percent of the cancers were stage I, 20% stage II, 18% stage III and 30% stage IV. The primary cancer site was the oral cavity in 30%, hypopharynx in 4%, oropharynx in 22% and larynx in 38%. Radiation therapy alone was pursued in 26%, surgery alone in 44% and chemoradiation in 21%. The median CCI score was 2 (range, 0-11) with 61% of patients with a score of 0-2 (low comorbidity) and 39% with a score of >2 (high comorbidity). Patients with CCI score 0-2 had a non-significant higher rate of curative intent treatment than patients with CCI score >2 (83.8% *vs*. 74.6%; $p=0.13$).

The median overall survival of the entire cohort was 883 days. In univariate analysis of the entire cohort, the CCI was predictive of overall survival: the median survival of patients with low comorbidity was 1,163 days *vs*. 665 days for high comorbidity ($p=0.06$) (Figure 1). In multivariate analysis including CCI, age, race, alcohol use, primary site, cancer stage and treatment, only clinical stage had a significant prognostic importance (hazard ratio (HR)=1.66; 95% confidence interval (CI)=1.29-2.14; $p<0.0005$). CCI >2 was not independently predictive of outcome (HR=1.11; 95% CI=0.99-1.24; $p=0.76$). Similarly, in separate multivariate analyses of patients treated with curative intent – either with surgery or chemoradiation – CCI was not a significant predictor of survival with HR 0.88 (95% CI=0.69-1.12; $p=0.29$) and 1.13 (95% CI=0.83-1.53; $p=0.44$), respectively.

Discussion

Concurrent comorbid conditions in patients with cancer have been shown to affect disease course, treatment selection, and overall survival (4). Moreover, numerous comorbidity indices have been developed to measure and evaluate the presence of comorbidity in patients with various malignancies and its effects on patient survival. Hall *et al*. demonstrated that patients with HNC were at an increased risk of dying from comorbid diseases associated with HNC compared to the general population and that after 7.5 years this risk of death from comorbid diseases surpassed the same risk from HNC itself (11). Singh *et al*. revealed comorbidity to be a prognostic factor in a small study (n=88) of HNC patients (6). Similarly, Reid *et al*. conducted a larger study of 9,386 elderly (>65 years of age) patients with HNC and found comorbidity to be an "independent, clinically relevant determinant of survival" (12). More recently, a Danish study of 12,623 HNC patients with a median age of 62 years offered further evidence that comorbidity had a significant independent effect on overall survival but not on cancer specific death (suggesting patients died from comorbidity rather than their cancer) (13). All three of these latter studies utilized the CCI as a marker of comorbidity.

Several studies have also been conducted to examine the relationship between comorbidities and treatment selection in HNC patients. The standard treatment of HNC involves a combination of surgery, radiotherapy and/or chemotherapy. However, the feasibility of these options is often questioned in the elderly cancer patient population. The apparent disparities of treatment selection for and clinical trial involvement of elderly patients are demonstrated throughout almost every malignancy (14-16). The fears among trial investigators and clinicians are that elderly patients will not tolerate aggressive measures, suffer increased toxicities and complications, and have resultant poor qualities of life – consequences not solely due to patient age but comorbidity as well. Derks *et al*. wrote that severe comorbidity, more so than age alone, impacted on treatment selection and post-operative complication rates in elderly HNC patients (17). Similarly Bernardi *et al*. found that underlying severe comorbidities, age-related frailty and psychosocial impairments were hindrances to intensive treatment plans (18). Ferrier *et al*. concluded that underlying comorbidity was a major predictor of complications in head and neck surgeries (19). Finally, Hathaway *et al*. demonstrated in a re-evaluation of a prior study on adjuvant chemoradiation in squamous HNC that concurrent comorbidity was one of the reasons patients declined adjuvant therapy (the study (20)

Table I. *Patients' demographics*.

Gender	100% M
Median age (range), years	72 (65-87)
Race (%)	
Caucasian	80
Black	19.5
Hispanic	0.5
Cancer Stage (%)	
0	3
I	26
II	20
III	18
IV	30
Unknown	2
Cancer site (%)	
Oral cavity	30
Hypopharynx	4
Oropharynx	22
Larynx	38
Nasopharynx/oral cavity	4
Unknown primary	1
Treatment (%)	
Radiation-only	26
Surgery	44
Chemoradiation	21
No treatment	9
CCI score (%)	
0-2	61
>2	39

CCI, Charlson comorbidity index.

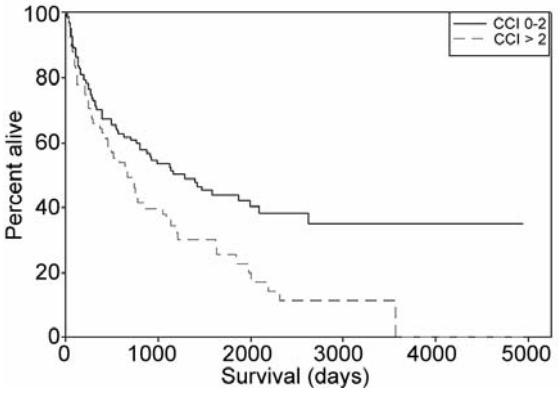

Figure 1. *Kaplan-Meier analysis of patients with CCI 0-2 and CCI >2.*

went on to conclude that adjuvant chemoradiation conferred a survival advantage when offered in conjunction with surgery) – reiterating the prognostic importance of comorbidity (21). Despite these studies assessing the overall impact of comorbidity on treatment selection and outcome, there has yet to be a study that assesses the predictive value of a specific index on selecting patients for initial treatment. Our study chose to test the distinct hypothesis that the CCI could be predictive of initial treatment selection and outcomes in elderly patients with HNC.

Our study, in congruence with prior similar studies, confirmed that comorbidity in itself is a predictor of overall survival. We demonstrated that patients with low comorbidity status (CCI score 0-2) had longer survival than patients with high comorbidity status (CCI >2). However, in multivariate analysis, only clinical stage was found to be a significant independent predictor of overall survival. In that analysis, CCI score >2 was not a significant predictor for a worse overall survival in the entire cohort or in the subgroups that received curative intent surgery or chemoradiation.

The strengths of this study include having one centralized electronic medical record, which allowed for the tracking of every patient over the 7-year time period. This aided in acquiring survival data on virtually every patient (even if a patient left DVAMC and was treated at a different VAMC). In addition, the fact that patients with a CCI >2 did have a worse survival in the univariate analysis suggests that the CCI score was being applied accurately, albeit retrospectively, in this population. Moreover, as HNC is increasing in prevalence in patients >65 years of age, our study's target population was appropriate for clinical practice application.

Our study had certain limitations as well. The population included was entirely male. The retrospective nature of the study limited us to the patient profile, as documented in the CPRS, as well as to the treatment plan selected for reasons deemed appropriate at the time of assessment. Our study also did not take into consideration the performance statuses of the patients. Such a qualifier might have had an effect on the patients' treatment selections and overall outcomes. Lastly, the number of participants included in the study is modest in comparison to some of the other comorbidity trials.

Conclusion

Our study of 182 patients is the first of its kind to assess the predictive ability and impact of a comorbidity index on treatment selection and overall survival in elderly patients with HNC. More specifically, it is the first study to assess the CCI in this predictive manner in this patient population. The presented study demonstrated that in our patient cohort the CCI – as a measure of comorbidity – was a significant predictor of overall survival of the entire cohort in the univariate analysis. However, it was not an independent predictor of selection of curative intent treatment or overall survival. As this study did confirm that the prevalence of comorbidity in this population is significant, the authors agree – as others have suggested (5, 13) – that comorbidity should become part of the overall prognostic assessment of elderly HNC patients. It is evident that the characteristics of

the disease alone do not dictate a patient's overall course; just as important are the individual patient's characteristics including comorbidity profile, performance status and other health habits. Additional studies, preferably prospective, need to be pursued not only to better-analyze the predictive potential of comorbidity indices beyond simply providing a quantitative measure of comorbidity but also to examine the relationship between comorbidity and treatment outcomes so that therapy can be tailored to the individual patient.

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