The prognostic significance of age in oropharyngeal squamous cell carcinoma

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SUMMARY

Objectives: Though the effect of age has been studied in some cancer types, its prognostic significance in oropharyngeal squamous cell carcinoma (OPSCC) remains controversial. Our purpose is to determine the impact of age at diagnosis on *overall survival* (*OS*) and *disease-specific* survival (*DSS*) in patients with OPSCC. If the effect is significant, we aim to clarify the age at which prognosis worsens.

Materials and methods: 15,978 Patients with OPSCC were identified from the Surveillance, Epidemiology, and End Results (SEER) database and separated into 10 year age groups. We obtained data on age at diagnosis, primary location, race, stage, sex, radiological treatment status, and surgical treatment status. Kaplan–Meier methods were used to calculate the *OS* and *DSS* for each age group. *DSS* analysis was supported by a Simple Multivariable Cox Proportional Hazard Regression of all significant variables studied.

Results: Significant disadvantage in *OS* and *DSS* was found with increasing age. A three-group stratification was depicted with the best survival in patients aged 1–44, mildly inferior survival in patients aged 45–64, and increasingly worse survival in patients 65 and older. Multivariable analysis demonstrated statistically significant increases in hazard ratio (HR) after age 65 when compared to ages 1-64.

Conclusion: Increasing age after 65 is associated with worsening *OS* and *DSS* in OPSCC. Poorer prognosis is due to multiple factors, possibly including the effects of aging, which make elderly patients more susceptible to the pathogenesis of OPSCC.

Introduction

In the United States, approximately 5000 new cases of oropharyngeal cancer are diagnosed each year, with 85–90% being squamous cell carcinoma (SCC) [1]. Oropharyngeal squamous cell carcinoma (OPSCC) is diagnosed most frequently in patients older than 45 years of age, though the incidence in patients younger than 45 has increased over the last 20–30 years [2]. While alcohol and tobacco abuse are the strongest risk factors for OPSCC, human papillomavirus (HPV) infection also confers a significant risk, partially accounting for the increased incidence of disease in younger populations.

While age plays a significant role in some cancers, such as thyroid cancer, the notion that age is a significant prognostic factor in head and neck SCC has been controversial. Some studies advocate poorer *overall* or *disease-specific survival* in older patients while others do not [3–6]. Ildstad and colleagues were the first to suggest that age negatively influenced survival in patients with head and neck SCC [7]. Soon after, Chin, et al. disputed the impact of age in a sample of patients specifically with oropharyngeal cancer [8]. Both studies focused on other endpoints and looked at age secondarily. To date, no studies have focused primarily on elucidating the true relationship between age and survival in OPSCC. Our aim is to determine the impact of age on *overall survival* (*OS*) and *disease-specific survival* (*DSS*) in patients with OPSCC, and if significant, try to elucidate the age cutoff when prognosis worsens.

Materials and methods

Data source

The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute is a collection of population-based cancer registries across the United States that publishes

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cancer incidence and survival data covering approximately 28% of the population [9]. Patient demographics, prevalence, primary tumor site, tumor morphology and stage, course of treatment, and other statistics are routinely collected. Data is subject to rigorous quality control and various assessments. This study was exempt from review by our institutional review board.

Patient selection

Our study included patients in the SEER database with OPSCC diagnosed from 2004 to 2009. Any cases with a history of previous malignancy or with multiple primaries were excluded from analysis. Primary location and histological status were established from the SEER variables *ICD-O-3 Site recode* and *Histologyrecodebroadgroupings,* respectively.

Patient stratification

Age at diagnosis, primary location, radiological treatment status, surgical treatment status, grade, race, and stage were obtained from SEER database variables *Agerecodewith1yearolds*, *ICD-O-3 Site recode*, *Radiation*, *RXSummSurgPrimSite1998*, *ICD-O-3 Grade recode*, *RacerecodeWBAIAPI, and AJCC stage (2004+),* respectively. Our use of the term "age" refers to "age at diagnosis" when not otherwise specified. Aside from ages 1–44 which were grouped together, older patients were stratified into 10 year age groups based on an extension of the National Institute of Aging's guidelines, which categorizes the elderly into "young old" (65–74), "older old" (75–48), and "oldest old" (85 and older) [10]. Rather than dichotomizing patients as younger versus older, use of ten-year age groups allows a more detailed analysis of treatment per age.

Demographics

Patients were separated into categories by age, and then stratified according to the individual variables mentioned in Table 1. Overall significance of difference between age groups per categorical variable was obtained using Chi Square (comparing all the values in one row). Statistically significant differences between one age group versus another group per categorical variable were determined by independent *t*-test (comparing one value to another within a row).

Survival analysis

Survival time was obtained through the *survivaltimerecode#ofmonths* function of the SEER database, while *overall survival* (defined as death from any cause) and *disease-specific survival* (death from cancer) was obtained from the *vitalstatusrecodestudycutoffused* and *SEERcausespecificdeathclassification* functions respectively. Kaplan–Meier methods were used to calculate mean *overall survival* by month, mean *disease-specific survival* by month, and their respective graphs. Pairwise *t*-tests of the Kaplan–Meier curves were performed to determine statistical significance. A Simple Multivariable Cox Proportional Hazard Regression analysis was performed on age with covariates that had a significant correlation with *DSS*: race, stage, grade, treatment status, and tumor location. The hazard endpoint was defined as death due to cancer. This multivariate regression provided the hazard ratio of each age group independent of the effect of the covariates included in the analysis.

Statistical analysis

All data analyses were performed with SPSS 21.0 (SPSS, Inc., an IBM Company, Chicago, Illinois). A *P* value of less than 0.05 was considered indicative of a statistically significant difference for all tests.

Results

Demographics: 15,978 patients with OPSCC who were diagnosed between 2004 and 2009 were identified. In the age group 1–44, there were 1069 patients; 4666 in 45–54; 5837 in 55–64; 2975 in 65–74; 1185 in 75–84; and 246 in 85+. Our 65–74 and 75–84 age groups have a significantly larger proportion of grade I tumors ($p < 0.05$) and stage I tumors at presentation ($p < 0.05$), as well as a significantly different overall distribution in primary location ($p < .001$), treatment with radiation (yes/no) ($p < .001$), treatment with surgery (yes/no) ($p < .001$), race ($p < .001$), and sex ($p < .001$) when compared to the 45–54 age group (Table 1).

For age groups 1–44, 45–54, and 55–64 the proportions of patients who received radiation were statistically similar. The proportions of patients receiving radiation were significantly greater for age groups 1–44 and 45–54 compared to elderly groups 65–74, 75–84, and 85+ ($p < 0.05$). Amongst these three elderly groups, 65–74 had the most patients who received radiation, followed by 75–84, while 85+ had the least ($p < 0.05$ for each assessment of difference). Significantly more patients in age groups 1–44, 45–54, and 55–64 received surgery than those aged 65–74, 75–84, and 85+ ($p < 0.05$). The three elderly groups (65–74, 75–84, 85+) did not have a significant difference in the amount of patients who received surgery.

Survival analysis: We observed two significant findings. First, patients aged 1–44 had the best prognosis with a mean *OS* of 57.54 months and mean *DSS* of 59.29 months. Second, we found a significant disadvantage in *OS* and *DSS* at age 65 with continued worsening through 85 years and older. Mean *OS* was 52.14 months for the 55–64 age group; 43.97 months for 65–74; 32.45 months for 75–84; and 20.63 months for the 85+ groups (Table 2a, Fig. 1a). All mean *OS* values were calculated with 95% confidence intervals (CI) and no overlap was observed. Mean *DSS* was 56.31 months for the 55–64 age group; 50.44 months for 65–74; 41.47 months for 75–84; and 30.50 months for 85+ (Table 2b, Fig. 1b). All mean *DSS* values were calculated with 95% CI. Overlap was seen between the confidence intervals of groups 1–44 and 45–54, as well as between groups 45–54 and 55–64. *DSS* Kaplan–Meier curves showed a statistically significant stepwise decrease for age groups after the age of 65 at $p < 0.05$.

The results of the Multivariable Cox Proportional Hazard Regression of age and various covariates with respect to *DSS* are shown in Table 3. Multivariable analysis demonstrated statistically significant increases in hazard ratio (HR) after age 65. Patients 65–74 are 1.5 times more likely to die due to cancer than patients 45–54. The risk is significantly higher in the 75–84 age group who are 2.4 times more likely to die due to cancer than 45–54 patients. Finally, the risk is higher still for patients 85+ who are 3.5 times more likely to die due to cancer than 45–54 year old patients. The HR of each group (65–74, 75–84, and 85+) is significantly different from that of group 45–54 at the 0.05 level. These three age groups did not exhibit any overlap between their 95% confidence intervals. The age specific hazard ratios are independent from the effect of variations in site of the primary tumor, the presence of surgical or radiation treatments, cancer grade, patient race, cancer stage, and patient sex since these variables were included in the analysis.

Discussion

Conflicting results have been reported regarding whether age affects the prognosis of head and neck squamous cell carcinoma.