Matched Analysis of Survival in Patients With Squamous Cell Carcinoma of the Head and Neck Diagnosed Before and After 40 Years of Age

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Objectives: To compare the survival rates of patients 40 years or younger and diagnosed with squamous cell carcinoma of the head and neck (SCCHN) with those of patients older than 40 years who underwent the same treatment. In 2 previous matched-pair analyses, the patients had been matched for tumor stage, site, sex, and date of presentation but not type of treatment.

Methods: Between 1995 and 2001, 46 patients 40 years or younger participated in a prospective epidemiologic study that included more than 500 patients newly diagnosed with SCCHN. We matched each of these patients by sex, race, tumor site, overall stage, and treatment modality with 2 patients older than 40 years. Ultimately, 31 of the younger patients were matched with 62 of the older patients. Survival analysis was performed using Cox proportional hazard models and accounting for the matched trios.

Results: There was no difference in overall, disease-specific, or recurrence-free survival rates between the patients who were 40 years or younger and those older than 40 years. Furthermore, matched survival analysis did not demonstrate a difference in overall survival rate (risk ratio [RR], 0.71; 95% confidence interval [CI], 0.22-2.29; \(P = .56\)), disease-free survival rate (RR, 0.83; 95% CI, 0.20-3.33; \(P = .79\)), or time to recurrence (RR, 1.46; 95% CI, 0.50-4.23; \(P = .49\)), and was not affected by adjustment for medical comorbidities or the severity of cancer-associated symptoms.

Conclusions: We found no evidence of a difference in the survival rates of patients with SCCHN who were 40 years or younger or older than 40 years and underwent similar treatment at our institution.


MOST PATIENTS WHO DEVELOP SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN) ARE OLDER THAN 40 YEARS. ONLY 3% OF THE PATIENTS WHO ARE DIAGNOSED WITH SCCHN ARE YOUNGER THAN 40 YEARS, \(P = .26\), BUT IT HAS BEEN SUGGESTED THAT THEY DEVELOP A MORE AGGRESSIVE TYPE OF THE DISEASE AND THAT THEY MAY HAVE A GENETIC PREPOSITION THAT INCREASES THEIR RISK FOR CANCER. \(P = .56\). HOWEVER, STUDIES ABOUT WHETHER AGE AT DIAGNOSIS AFFECTS PROGNOSIS HAVE HAD CONFlicting RESULTS. \(P = .79\). THE MAJOR LIMITATION OF THESE STUDIES HAS BEEN THE SMALL NUMBER OF PATIENTS YOUNGER THAN 40 YEARS WHO DEVELOP SCCHN AND THE INFLUENCE OF CONFOUNDING FACTORS SUCH AS RACE, SEX, SMOKING STATUS, ALCOHOL CONSUMPTION, TREATMENT BIAS, AND THE PRESENCE OF COMORBIDITIES.

Matched-pair survival analysis allows control for principal prognostic factors, and to adjust for confounding factors known to influence prognosis before a more precise comparison of survival rates between 2 groups is made. Two matched-pair analyses have analyzed age as a prognostic factor for SCCHN. \(P = .56\). Both studies matched patients on the basis of sex, disease site, and date of presentation, and one study also matched them for overall disease stage. Neither study demonstrated a difference in overall or disease-free survival between younger and older patients. We present the first analysis of survival of patients younger than 40 years and diagnosed with SCCHN that matched patients for major prognostic indicators as well as the type of treatment received. We examined long-term survival to determine if age at time of diagnosis has any effect on disease-specific survival and overall survival in patients with SCCHN.

METHODS

PATIENT POPULATION

More than 500 patients with newly diagnosed, previously untreated SCCHN were enrolled in an epidemiologic study at The Uni-
The characteristics of the matched groups are listed in Table 1 to demonstrate appropriate matching. The patients were matched exactly by sex, race, disease site, overall stage (I/II vs III/IV), and treatment. As expected, no significant difference existed between the 2 groups with respect to the matching variables.

The age of the younger patients ranged from 24.2 to 40.9 years (mean, 34.5 years; median, 35.7 years). The age of the younger patients ranged from 24.2 to 40.9 years (mean, 34.5 years; median, 35.7 years).

Table 1. Characteristics of Cases and Controls: Matching Variables

<table>
<thead>
<tr>
<th>Matching Variable</th>
<th>Cases (n = 31)</th>
<th>Matched Controls (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (32.3)</td>
<td>20 (32.3)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (67.7)</td>
<td>42 (67.7)</td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>13 (41.9)</td>
<td>26 (41.9)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>14 (45.2)</td>
<td>28 (45.2)</td>
</tr>
<tr>
<td>Larynx</td>
<td>3 (9.7)</td>
<td>6 (9.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (3.2)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Overall disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>10 (32.3)</td>
<td>20 (32.3)</td>
</tr>
<tr>
<td>III or IV</td>
<td>21 (67.7)</td>
<td>42 (67.7)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>29 (93.5)</td>
<td>58 (93.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (6.5)</td>
<td>4 (6.5)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery only</td>
<td>7 (22.6)</td>
<td>14 (22.6)</td>
</tr>
<tr>
<td>Radiation only</td>
<td>10 (32.3)</td>
<td>20 (32.3)</td>
</tr>
<tr>
<td>Chemotherapy and radiation</td>
<td>7 (22.6)</td>
<td>14 (22.6)</td>
</tr>
<tr>
<td>Surgery and radiation</td>
<td>4 (12.8)</td>
<td>8 (12.8)</td>
</tr>
<tr>
<td>Chemotherapy, radiation, and surgery</td>
<td>3 (9.7)</td>
<td>6 (9.7)</td>
</tr>
</tbody>
</table>

*Case patients were 40 years or younger, matched controls were older than 40 years, and there were 2 controls for each case; values are given as number (percentage).

STATISTICAL METHODS

Survival rates of the younger and older groups were compared using Kaplan-Meier estimates and the log-rank test for equality of survival curves. Matched survival analysis was completed using Cox proportional hazard models. Survival was measured from the time of the first appointment by using overall death, death from disease, and recurrence as censoring variables. Matching was accounted for in the Cox proportional hazard models by including a matching variable that accounted for the matching based on sex, disease site, overall stage, and treatment. The covariates smoking status, alcohol consumption status, Kaplan Feinstein Comorbidity Factor, and Cancer Associated Symptom Index score were also included in the survival model. We evaluated factors that were not matched (smoking status, alcohol consumption status, Kaplan Feinstein Comorbidity Factor, and Cancer Associated Symptom Index score, as well as T stage and N stage) by using the Pearson χ² test and the 2-tailed Fisher exact test to determine whether there was a significant difference between the groups of younger and older patients. This study was powered at 80% to detect a 2-fold difference in survival risk ratio between the younger and the older patients. The power of the study to detect the relative risk obtained was based on the Dupont model.

RESULTS

DEMOGRAPHICS

The characteristics of the matched groups are listed in Table 1 to demonstrate appropriate matching. The patients were matched exactly by sex, race, disease site, overall stage (I/II vs III/IV), and treatment. As expected, no significant difference existed between the 2 groups with respect to the matching variables.

The age of the younger patients ranged from 24.2 to 40.9 years (mean, 34.5 years; median, 35.7 years). The age of matched older patients ranged from 41.0 to 83.0 years (mean, 64.1 years; median, 64.9 years). The specific staging and comorbidity characteristics of the 2
groups are listed in Table 2. The 2 groups were similar except for 2 variables: there were significantly more non-smokers among the younger group \( (P<.001) \), and the Kaplan Feinstein Comorbidity score was lower in the younger group \( (P<.001) \).

**SURVIVAL ANALYSIS**

Follow-up time ranged from 4.8 to 55.7 months (mean±SD, 24.6±12.0 months; median, 26.5 months) in the younger group and 1.5 to 65.2 months (mean±SD, 23.5±16.0 months; median, 19.0 months) in the older group. There were 13 events: 8 deaths due to disease and 5 deaths due to other causes. Mean survival duration until death from any cause (overall death) was 50.2±3.6 months in the younger group and 53.8±3.4 months in the older group \( (P=.73) \). **Figure 1** shows the Kaplan-Meier overall survival curve for the younger and older patients. Mean survival until death from disease was 50.2±3.0 months in the younger group and 58.4±3.0 months in the older group \( (P=.88) \). **Figure 2** compares the Kaplan-Meier disease-specific survival curve for the younger and older patients. Six (19.4%) of the younger patients and 10 (16.1%) of the older patients experienced disease recurrence. Mean survival until recurrence was 32.6±2.6 months in the younger group and 51.8±3.0 months in the older group \( (P=.40) \). **Figure 3** compares the Kaplan-Meier recurrence-free survival curve for the younger and older patients.

**MATCHED SURVIVAL ANALYSIS**

There were no significant differences in risk of overall death, death due to disease, or time to recurrence be-
been a selection bias against postoperative adjuvant ra-
were not matched for treatment type, and there may have
recurrence in the younger patients. However, the groups
There was a statistically higher rate of locoregional re-
mous cell carcinoma of the oral tongue, matching for sex,
matched-pair analysis of younger patients with squa-

Two previous matched-pair analyses examined the
effect of age at time of diagnosis on survival in patients
with SCCHN at all sites. Neither study found any differ-
ece in survival rates based on age at diagnosis. Ver-
schuur et al8 examined 185 patients who developed
SCCHN before 41 years of age. Matching was based on
site, sex, and date of presentation. Race, disease stage,
and treatment were not matching variables; however, most
(86%) of the patients were treated with radiation therapy
alone. The authors did not find any difference in rates
of death due to disease within 5 years between the younger
and older patients (72% vs 68%). Excluding disease stage
tumor stage as matching variables raises concern that
the groups could have been dissimilar with respect to
stage. Schantz et al3 compared 83 younger patients with
SCCHN with patients older than 40 years who were
matched for sex, site, disease stage, and year of presen-
tation, and found no difference in survival rates, but again
the groups were not matched for type of treatment.

Our study confirms previous reports that found no
detectable difference in survival rates between younger
and older SCCHN patients matched for tumor stage and
site. Furthermore, we extended the matching criteria of
the previous studies to include race and treatment type,
and included comorbid conditions and symptoms in our
multivariate analysis. The inclusion of treatment type as
a matching variable controls for potential variability caused
by selection bias, as certain patients may receive more
aggressive treatment. Furthermore, medical and symp-
tom comorbidities have been demonstrated to be inde-
pendent prognosticators in SCCHN.15 Because such co-
morbidities may be more common in some age groups
than in others, we included these potential confounders
in our multivariate adjustment, unlike previous studies
assessing survival of the younger patient with SCCHN.
Finally, every patient in this study participated in a pro-
spective epidemiologic study in which clear documenta-
tion of tobacco and alcohol consumption were ob-
tained, which allowed assessment of their impact. Tobacco
and alcohol consumption did not appear to influence out-
come risk estimates.

The major limitation of this study is the small num-
ber of patients; however, we tried to limit the effect of
potential confounders by matching and included a larger
tween the young and older patients (Table 3). The risk
was unchanged after adjusting for medical and symp-
ton comorbidities in the survival model (Table 3). Fur-
thermore, there was no difference in overall death, death
due to disease, or time to recurrence after adjustment for
T stage, N stage, or tobacco/alcohol consumption (data
not shown).

### Table 3. Risks of Overall Death and Death From Disease Associated With an Age of 40 Years or Younger at the Time of Diagnosis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Overall Death RR (95% CI)</th>
<th>P Value</th>
<th>Death From Disease RR (95% CI)</th>
<th>P Value</th>
<th>Recurrence of Disease RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox regresional analysis on matching variables</td>
<td>0.71 (0.22-2.29)</td>
<td>.56</td>
<td>0.83 (0.20-3.33)</td>
<td>.79</td>
<td>1.46 (0.50-4.230)</td>
<td>.49</td>
</tr>
<tr>
<td>Adjusted for Kaplan-Feinstein Comorbidity Factor, Cancer Symptom Index score, alcohol use, and smoking status</td>
<td>0.65 (0.19-2.21)</td>
<td>.49</td>
<td>0.95 (0.21-4.33)</td>
<td>.49</td>
<td>2.18 (0.69-6.89)</td>
<td>.69</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, risk ratio.

The presence of SCCHN in younger patients was first re-
ported by Byers in 1975, when he described 11 patients
with squamous cell carcinoma of the oral tongue, all of
whom were younger than 30 years; their 2-year survival
rate was 45%, whereas it was 65% in a historical cohort
of older patients. While Byers suggested that squamous
cell carcinoma of the oral tongue seemed to be more ag-
gressive in patients younger than 30 years, the number
of patients was too small to draw a valid statistical con-
clusion. Since this landmark article, conflicting results
have been reported regarding whether age at diagnosis
influences prognosis.2-8 Age at diagnosis as a prognostic factor in squa-
mous cell carcinoma has been most extensively studied in
patients with squamous cell carcinoma of the oral
tongue. Myers et al13 reviewed 37 patients with squa-
mous cell carcinoma of the oral tongue treated at our
institution between 1973 and 1995, and found that the
5-year survival rate of younger patients was similar to pub-
ished findings for more typical, older patients. The
authors also noted that the incidence of squamous cell car-
cinoma of the oral tongue in young adults appears to have
increased since 1973. Friedlander et al14 performed a
matched-pair analysis of younger patients with squa-
mous cell carcinoma of the oral tongue, matching for sex,
year of diagnosis, site of disease (oral tongue) and stage of
disease, and did not find any difference in the 5-year survival rate of younger and older patients (62% vs 69%).
There was a statistically higher rate of locoregional re-
currence in the younger patients. However, the groups
were not matched for treatment type, and there may have
been a selection bias against postoperative adjuvant rad-
iation therapy in the younger group. Pitman et al15 con-
ducted a meta-analysis of patients diagnosed with squa-
mous cell carcinoma of the tongue before the age of 40
years. They matched a group of 128 younger patients by
site (all oral tongue), and disease stage to patients
diagnosed with squamous cell carcinoma of the tongue
after the age of 40 years. The disease-free survival rate
was similar for the 2 groups. Again, no attempt was made
to match for type of treatment or race. Lacy et al4 found
that patients younger than 41 years who had squamous
cell carcinoma at any site appeared to have an overall survival advantage, but the authors did not examine
disease-specific survival or attempt to match for prog-
nostic factors.
control group of older individuals. This study was powered to detect a 2-fold relative risk between the younger and older patients, but this power calculation did not include the additional power afforded by the extensive matching process. The matching for 5 variables known to affect prognosis (sex, race, site, tumor stage, and treatment) make it more likely that any detectable difference was due to age. It is likely that the actual minimal detectable relative risk is smaller than calculated. The number of potential matches was limited by the ability to tightly match for several variables. A large study with strict matching criteria and the ability to detect a very small survival difference is not feasible because of the low incidence of disease among individuals younger than 40 years. Histologic factors such as extracapsular spread and perineural invasion could not be analyzed: because few patients underwent surgical procedures, few pathological specimens were available.

In conclusion, we found no evidence of a difference between the survival rates of patients diagnosed with SCCHN at or before the age of 40 years and those diagnosed at a later age who underwent the same treatment—even after controlling for major prognostic, demographic, and comorbidity indicators.

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REFERENCES