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WILEY
Assessment of Laryngeal Cancer in Patients Younger Than 40 Years

Yuval Nachalon, MD; Uri Alkan, MD; Jacob Shvero, MD; Dan Yaniv, MD; Yotam Shkedy, MD; Dror Limon, MD; Aron Popovtzer, MD

<table>
<thead>
<tr>
<th>Objectives/Hypothesis:</th>
<th>To assess the differences between patients with laryngeal squamous cell carcinoma under 40 years old and those 40 years old or older. A secondary objective was to compare survival outcome between these cohorts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design:</td>
<td>Retrospective chart review.</td>
</tr>
<tr>
<td>Methods:</td>
<td>We reviewed the medical charts of all patients treated in our tertiary referral center for laryngeal squamous cell carcinoma from 2005 to 2014. Patients aged &lt; 40 years at diagnosis were compared to older patients.</td>
</tr>
<tr>
<td>Results:</td>
<td>The study group comprised 160 patients. Of them, 13 were aged &lt; 40 years at diagnosis. Mean age was 35 ± 3.9 years and 64.4 ± 11 years for the two groups. Among the younger patients, 38% were smokers (mean pack/day, 2.2) versus 71% in the older group (mean pack/day, 3). The younger group typically had a more advanced stage than the older group at presentation; eight young patients (62%) had stage III or IV versus 49 (33%) in the older group (P = .042). Mean overall survival was 6.7 ± 1 years for those under 40 years old and 7.7 ± 0.2 years for the older patients (P = .2). The 5-year survival rate was 69% for young patients and 90% for the older group (P = .04). However, there was no significant between-group difference in overall survival or 5-year survival rate when stratified for early- and late-stage disease.</td>
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<td>Conclusions:</td>
<td>There is a lower prevalence of classic risk factors in younger patient with laryngeal carcinoma in this study, suggesting a different etiology compared to our older cohort. The under-40 cohort presented with more advanced disease and had a worse 5-year survival; however, when stratified for early versus late-stage disease, there was no significant difference in overall or 5-year survival between the groups. This may suggest that, despite a different etiology, laryngeal cancer behaves similarly in older and younger patients.</td>
</tr>
<tr>
<td>Key Words:</td>
<td>Larynx, chemotherapy, early glottic cancer.</td>
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<td>Level of Evidence:</td>
<td>4.</td>
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</tbody>
</table>

**INTRODUCTION**

Laryngeal carcinoma is the second most common malignancy of the upper aerodigestive tract, accounting for over 3,500 deaths per year. The estimated incidence in 2015 was 13,560 new cases.\(^1\) It usually develops in males in the 6th to 7th decade of life. Less than 10% of the patients are younger than 40 years of age.\(^2\) Tobacco use and alcohol ingestion are the classic risk factors with a synergistic effect.\(^3\) However, their association in squamous cell carcinoma (SCC) of the larynx in young patients is less prominent.\(^4\),\(^5\) Furthermore, reduced length of exposure to these risk factors may suggest a different disease etiology and behavior. Other risk factors such as human papilloma virus and laryngopharyngeal reflux are still under investigation, and their link to laryngeal cancer is controversial.\(^6\)–\(^8\)

The aim of the present study was to assess the differences between patients with laryngeal squamous cell carcinoma under 40 years old and those 40 years old or older; a secondary objective was to compare survival outcome between these cohorts.

**MATERIALS AND METHODS**

A retrospective chart review was performed of all patients who were treated in a tertiary university-affiliated center for SCC of the larynx from 2005 to 2014. The study was approved by the local institutional review board. Parameters included patient age and sex, presenting symptoms, staging, treatment modalities, recurrence, and survival. Age 40 years was selected as a cutoff point to allow continuity with a prior study.\(^9\) We compared these parameters between patients under 40 years of age and the rest of the cohort. Early-stage disease was defined as stage I or II; stage III or IV were defined as late stage.

Whenever possible, organ preservation was the preferred treatment modality recommended to the patient. In applicable cases, endoscopic resection was performed in early-stage disease. In late-stage disease or early-stage disease that was not amenable to endoscopic surgical resection, chemoradiation was performed. When in doubt, younger patients were treated more aggressively (e.g., chemoradiation). Patients with stage I disease were treated with radiation alone to 63 Gy in 28 fractions; those with stage II were treated to 65.25 Gy in 29 fractions. Patients with stage III were treated with weekly cisplatin (35 mg/m\(^2\)) concomitant to radiation. The radiation protocol in
these patients was 70 Gy in 35 fractions. Treatment was planned in three-dimensional techniques up to 2008; from 2008 all patients were planned using intensity modulated radiation therapy (IMRT).

The patients who underwent upfront total laryngectomy had T4 disease with extensive involvement of the thyroid cartilage and received adjuvant radiation of 60 Gy. Persistent disease was defined as disease that occurred during the first 6 months after treatment ended. Recurrence was defined as evidence of disease within 5 years after treatment ended.

Data were analyzed with IBM SPSS version 22.0 (publication date August 26, 2013; IBM, Armonk, NY). Survival was calculated with the Kaplan-Meier product limit estimate method. Variables were compared between groups by $t$ score and $\chi^2$ tests. A $P$ value of < .05 was considered statistically significant.

**RESULTS**

One hundred sixty patients were identified. Thirteen patients were younger than 40 years at the time of diagnosis. Patient demographic and clinical data are presented in Table I.

**Clinical Presentation**

The most common presenting symptom in both groups was voice change (46% in younger cohort and 90% in older cohort); the next most common presenting symptoms were globus sensation, stridor, and chronic cough, respectively. Thirty-eight percent of the younger patients and 64% of the older cohort presented with early stage disease ($P = .1$). Among the younger patients, 38% were smokers (mean pack/day, 2.2), whereas 71% of the older cohort were smokers (mean pack/day, 3) ($P < .01$). None of the patients in our cohort had alcohol exposure.

Glottic involvement was noted in 54% of younger patients and 61% of older patients, supraglottic involvement was noted in 46% and 39%, respectively ($P = .769$). The majority of both groups were N0: 69% in young patients and 83% in the general cohort.

**Treatment**

Most patients were treated with radiotherapy in both groups. Chemotherapy was given to 46% of the younger patients and to 37% of the older patients. Four young patients (31%) underwent laryngectomy compared to 38 (26%) of older patients. Two young patients had upfront laryngectomy and two had salvage total laryngectomy. One patient had a T3 verrucous carcinoma and underwent frontolateral partial laryngectomy. The other patient had a T1 glottic SCC of the anterior commissure and was supposed to undergo radiotherapy; however, he was restaged as T4aN0 due to thyroid cartilage involvement and had upfront total laryngectomy with adjuvant radiotherapy.

Regarding salvage laryngectomy, one young patient had a supraglottic T3N0, and the second patient had supraglottic T4aN2c. Both patients failed chemoradiation therapy (CRT) and recurred within 2 years of initial therapy.

**Survival**

Mean overall survival (OS) for the young patients was $6.7 \pm 1$ years versus $7.7 \pm 0.2$ years for the rest of the cohort ($P = .2$) (Fig. 1). The 5-year survival rate was 69% for young patients and 90% for the rest of the cohort ($P = .04$). However, no significant between-group difference in OS or 5-year survival rate was noted when stratifying for early- and late-stage disease.

**Response to Treatment**

Recurrence was reported in four (30.8%) young patients and 26 (18%) of the older patients ($P = .1$). Among

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Cohort, N = 160</th>
<th>Young Adults, N = 13</th>
<th>Older Adults, N = 147</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>62 ± 13</td>
<td>35 ± 3.9</td>
<td>64.4 ± 11</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>108 (67)</td>
<td>4 (38)</td>
<td>104 (71)</td>
</tr>
<tr>
<td>Tumor site, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glottis</td>
<td>96 (60)</td>
<td>7 (54)</td>
<td>89 (61)</td>
</tr>
<tr>
<td>Supraglottis</td>
<td>64 (40)</td>
<td>6 (46)</td>
<td>58 (39)</td>
</tr>
<tr>
<td>Stage, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>65 (41)</td>
<td>3 (23)</td>
<td>62 (42.2)</td>
</tr>
<tr>
<td>II</td>
<td>34 (21)</td>
<td>2 (15.3)</td>
<td>32 (21.8)</td>
</tr>
<tr>
<td>III</td>
<td>23 (14)</td>
<td>3 (23.1)</td>
<td>20 (13.6)</td>
</tr>
<tr>
<td>IV</td>
<td>38 (24)</td>
<td>5 (38.5)</td>
<td>33 (22.4)</td>
</tr>
<tr>
<td>Initial treatment, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>41 (26)</td>
<td>3 (30.8)</td>
<td>38 (26)</td>
</tr>
<tr>
<td>Radiation</td>
<td>114 (71)</td>
<td>10 (77)</td>
<td>104 (70.7)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>60 (38)</td>
<td>6 (46)</td>
<td>54 (37.4)</td>
</tr>
<tr>
<td>Recurrence, no. (%)</td>
<td>30 (19)</td>
<td>4 (30.8)</td>
<td>26 (17.6)</td>
</tr>
<tr>
<td>5-year survival rate, %</td>
<td>89</td>
<td>69</td>
<td>90</td>
</tr>
</tbody>
</table>

SD = standard deviation.
patients with advanced disease, four (50%) young and 12 (23%) older patients had recurrence ($P = .189$). Five young patients had recurrent disease, three with supraglottic and two with glottic disease. Recurrence occurred after a mean of 15 months in glottic patients. One was treated with CRT and the other with a second surgical procedure (cordectomy). Regarding patients with a supraglottic recurrence, one acquired the disease after 6 years of follow-up and was defined as a second primary and was treated with CRT, the other two recurred after less than 2 years and underwent salvage total laryngectomy.

**DISCUSSION**

Head and neck (H&N) cancer usually affects patients in their 6th to 7th decade. Long exposure to smoking and alcohol ingestion are well-established risk factors in aerodigestive cancer. Young adults with H&N cancer account for less than 10% of all patients.$^3$ An earlier report from our center spanning over 35 years stated that 2.5% of patients with laryngeal SCC were younger than 40 years of age.$^4$ In the present study, 8% of the patients in our cohort were younger than 40 years of age. When compared to the rest of the cohort, young adults had higher rates of late-stage disease at presentation ($P = .042$). It is unclear why younger patients tend to present in a more advanced stage in our study. Young patients may ignore earlier symptoms of the disease and therefore have later detection. This difference could also be attributed to different disease characteristics and etiology in cohorts. Young patients in our study had significantly lower rates of smoking and none had a history of alcohol ingestion. This is different from what is known in the literature. In general, the society in Israel is conservative and there are lower rates of alcohol ingestion due to religious and social reasons, as reflected in exposure rates in both cohorts. However, lower rates of smoking among young patients compared to older patients may suggest a different disease etiology.

When survival was stratified for early- and late-stage disease, no significant difference in OS or 5-year survival rate was found between the two groups. Our results are similar to large prior database studies. Rutt et al. reviewed the Surveillance, Epidemiology, and End Results (SEER) database and reported 99 cases of laryngeal SCC in patients younger than 30 years of age in 40 years of follow-up, starting in 1973.$^9$ There were no data reported regarding staging, but most patients had glottic SCC. Survival was good and was reported as nearly 90% in patients over 20 years of age. In a population-based study in Zaragoza, Spain, a better survival rate was reported in patients with laryngeal SCC who were younger than 40 years compared to older patients.$^{10}$ Among patients with late-stage disease in our cohort, all were treated according to the same protocol as recommended by the National Comprehensive Cancer Network guidelines. Nevertheless, younger patients had a higher recurrence rate, and all recurred within 2 years. This may suggest that young patients with late-stage disease have a different entity. However, there was no change in overall survival or different treatment modality between the cohorts that could explain this difference. Hence, we assume that disease course is similar regardless of age, leading to a similar treatment algorithm.

The differences in some of the characteristics of the disease between the two groups might be attributed to a different etiology in young patients such as genetic predisposition,$^{11–15}$ diet,$^{16,17}$ human papillomavirus (HPV),$^{18,19}$ and occupational exposures.$^{20,21}$ Toporcov et al.$^{16}$ in the International Head and Neck Cancer Epidemiology Consortium analysis reviewed 25 case-control studies assessing the risk of H&N cancer in young adults. They reported lower attributable fraction for smoking and drinking in young adults compared to older adults. In contrast, a family history of early-onset cancer was associated with a higher risk for H&N cancer in young adults.$^{11}$ This might suggest a genetic predisposition to cancer in general and not a specific mutation affecting the larynx. Jaworowska
et al. noted a common molecular genotype between early-onset breast cancer and larynx cancer.\textsuperscript{11} Several other studies tried to discover specific mutations whose carriers have a higher propensity for larynx cancer, such as lysosomal exoglycosidases,\textsuperscript{10} the NBS1 gene, which repairs DNA breaks,\textsuperscript{14} and genes that control apoptosis.\textsuperscript{15,16}

HPV is responsible for the new epidemic of oropharyngeal SCC. Its role in laryngeal cancer is less certain. Approximately 25% of laryngeal SCC harbor HPV infections, but its clinical relevance is still unclear.\textsuperscript{17} Only two young patients (15%) in our cohort were p16 positive, and we could not identify any different clinical behavior in these patients.

This study has several limitation due to its small sample size and it being a retrospective study, which limits the parameters that could be collected and evaluated and the disproportion between the two groups. Further investigation with larger cohort study would help clarify differences in young patients.

CONCLUSION

The etiology of laryngeal cancer in adults younger than 40 years of age remains unclear. Young adults tend to present at an advanced disease stage. However, when stratified for early- and late-stage disease, there is no difference in survival compared to older adults. This suggests that, regardless of its etiology, the disease behaves the same, and treatment recommendations should therefore be similar.

BIBLIOGRAPHY