A 25-Year Analysis of Veterans Treated for Tonsillar Squamous Cell Carcinoma

James J. Jaber, MD, PhD; Jonathan Moreira, MD; W. Jeffrey Canar, PhD; Carol M. Bier-Laning, MD

Objective: To determine the recurrence and survival outcome based on treatment date, type of treatment, stage of disease, and comorbidity and the recurrence and survival differences based on smoking status as a surrogate for human papillomavirus status in veterans treated for tonsillar squamous cell carcinoma (SCC).

Design: Outcome cohort study.

Setting: Tertiary care Department of Veterans Affairs hospital.

Patients: A consecutive sample from 1981 through 2006 of 683 patients treated for oropharyngeal SCC was screened, and 141 patients with tonsillar SCC without distant metastatic spread and a minimum of 2 years of follow-up were included.

Main Outcome Measures: Disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS).

Results: Disease-free survival was significantly better in cohort II (treated during or after 1997) compared with cohort I (treated before 1997) (2- and 5-year DFS, 82% vs 64% and 67% vs 48%; \( P = .02 \)). Disease-specific survival was better in the surgical vs nonsurgical group (2- and 5-year DSS, 77% vs 46% and 67% vs 30%; \( P < .001 \)), as was the OS (2- and 5-year OS, 66% vs 41% and 45% vs 23%; \( P = .005 \)). In subjects with early-stage disease, OS and DSS were not different regardless of treatment type. In subjects with late-stage disease treated most recently (time cohort II), there was significantly better DSS in those receiving surgical vs nonsurgical treatment (2-year DSS, 70% vs 43%; \( P = .045 \)). Nonsmokers had better OS (94 months vs 41 months; \( P = .001 \)) and lower incidence of recurrence (8% vs 44%; \( P = .02 \)).

Conclusion: In veterans treated for tonsillar SCC, we advocate the consideration of a treatment plan that includes surgery for patients presenting with advanced-stage SCC of the tonsil, even in patients with notable comorbidities.

to CRT.\textsuperscript{14} If all patients with tonsillar SCC are included in a trial, the results for the cohorts with HPV-associated and tobacco-associated tumors should be examined separately to avoid generalizing outcomes to the entire cohort treated with nonoperative management and thus overestimating the results.

Because of the varying interpretations of the studies to date, the optimal treatment for oropharyngeal SCC remains controversial. The changing treatment paradigms and associated controversy led to our interest in studying the outcomes after treatment of oropharyngeal SCC in a population of veterans treated at a tertiary care Department of Veterans Affairs (VA) hospital over the last 25 years. This patient group is a relatively homogeneous and somewhat unique population who are often older with notable comorbidities and fewer social supports. The argument is sometimes made that these characteristics make members of this group unsuitable for certain treatments. The aims of the present study were to examine if changes in outcome were apparent over time and to examine if there were differences in outcome based on treatment type. In addition, we were interested in whether nonsmoking veterans enjoyed better outcomes than smokers, similar to outcomes noted in the general population for nonsmokers with oropharyngeal SCC.\textsuperscript{7,14,15}

Our goal was to examine long-term outcomes in this specific population and use this information to tailor treatment in this group to achieve optimal outcomes.

### METHODS

After receiving approval by the Hines VA institutional review board, including approved waiver of consent, we queried the Hines VA hospital medical records for patients treated for oropharyngeal carcinoma between 1981 and 2006. A total of 683 patients were identified. To limit the study to a more homogeneous group, only patients with a diagnosis of tonsillar carcinoma were included. One hundred forty-one patients who had proven primary tonsillar SCC with complete data were identified, and a retrospective medical record review was performed. All patients had histologically proven tonsillar SCC, no prior head and neck cancer, and no radiographic evidence of distant metastasis at initial presentation with a minimum of 2 years of follow-up. Patients who were followed up at our institution but were originally treated at an outside facility were excluded. The following patient characteristics were collected: age, follow-up time, TNM category and overall stage, according to the American Joint Committee on Cancer staging system, type of treatment, and Adult Comorbidity Evaluation–27 (ACE-27) score. The ACE-27 score was especially designed for patients with cancer and was developed by Piccirillo and Vlahiotis\textsuperscript{16} based on the modified Kaplan-Feinstein Comorbidity Index.

Outcomes analyses were performed by creating Kaplan-Meier life tables and constructing survival curves for disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS). Outcome percentages were extracted directly from these life tables. The log-rank test was used to determine any statistical differences between survival curves. Binary logistic regression analysis was used to determine the association between surgery and outcomes after adjusting for other variables. To compare outcomes between smokers and non-smokers, \(\chi^2\) analysis or the unpaired \(t\) test was used. \(P < .05\) was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc, Chicago, Illinois).

### RESULTS

The study population comprised 141 patients. The distribution of patient and tumor characteristics as well as initial treatment modalities used for the entire group and according to the time cohort are given in Table 1. All patients were male, with a mean age at diagnosis of 64 years (range, 44-87 years). All subjects were followed up

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### Table 1. Patient and Tumor Characteristics for Entire Group and by Time Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort I (&lt;1997) (n=80)</th>
<th>Cohort II (≥1997) (n=61)</th>
<th>Total Cohort (n=141)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>65 (45-87)</td>
<td>63 (44-86)</td>
<td>64 (44-87)</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up, mean (range), mo</td>
<td>57 (1-284)</td>
<td>32 (1-124)</td>
<td>46 (1-284)</td>
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</tr>
<tr>
<td>T category</td>
<td></td>
<td></td>
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<tr>
<td>1-2</td>
<td>35 (34)</td>
<td>40 (66)</td>
<td>75 (54)</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
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<tr>
<td>0-1</td>
<td>42 (52)</td>
<td>18 (29)</td>
<td>60 (42)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>23 (29)</td>
<td>39 (64)</td>
<td>62 (44)</td>
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<td>3</td>
<td>15 (19)</td>
<td>4 (7)</td>
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<tr>
<td>Disease stage</td>
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<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Early (I–II)</td>
<td>19 (24)</td>
<td>10 (16)</td>
<td>29 (21)</td>
<td></td>
</tr>
<tr>
<td>Late (III–IV)</td>
<td>71 (76)</td>
<td>41 (84)</td>
<td>112 (79)</td>
<td></td>
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<tr>
<td>ACE-27 score, No. (%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>7 (9)</td>
<td>6 (10)</td>
<td>13 (9)</td>
<td></td>
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<td>17 (28)</td>
<td>42 (20)</td>
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</tr>
<tr>
<td>3</td>
<td>28 (35)</td>
<td>12 (20)</td>
<td>40 (28)</td>
<td></td>
</tr>
<tr>
<td>With smoking history, No. (%)</td>
<td>74 (93)</td>
<td>53 (88)</td>
<td>128 (91)</td>
<td>NS</td>
</tr>
<tr>
<td>Treated with surgery, No. (%)</td>
<td>48 (60)</td>
<td>34 (56)</td>
<td>82 (58)</td>
<td>NS</td>
</tr>
<tr>
<td>Treated with radiation therapy, No. (%)</td>
<td>71 (89)</td>
<td>59 (97)</td>
<td>130 (92)</td>
<td>NS</td>
</tr>
<tr>
<td>Treated with chemotherapy, No. (%)</td>
<td>22 (28)</td>
<td>27 (44)</td>
<td>49 (35)</td>
<td>.005</td>
</tr>
</tbody>
</table>
for a minimum of 24 months, excluding those who died prior to this time point. The overall distribution of co-morbidities as measured by the ACE-27 score revealed that 28% were severe (grade 3), 30% were moderate (grade 2), and 33% were mild (grade 1), whereas 9% of the study population were grade 0. Not surprisingly, most patients were smokers (91%) and most presented with late-stage (III-IV) disease (79%). The initial treatment plan included surgery in 58% of patients, RT in 92%, and chemotherapy in 35%. The results of Kaplan-Meier analysis showed 2- and 5-year overall survival rates of 56% and 37%, respectively, for the entire cohort of patients (Figure 1). Our analysis of ACE-27 scores and its association with patient survival failed to show any significant difference between groups. However, as the comorbidity score increased in severity it tended to parallel a worse overall outcome (Figure 2).

TIME ANALYSIS

The data were evaluated for changes in outcome based on the date of treatment. The subjects were divided into 2 cohorts based on treatment date: cohort I (n=80) included subjects treated before 1997, cohort II (n=61) included subjects treated in 1997 or later. This cutoff was chosen because 3-dimensional (3-D) conformal treatment planning for RT was initiated at our institution in 1997. Although this study was a retrospective analysis, we were interested in evaluating if differences were apparent in outcome after this significant treatment planning change, recognizing that many other factors also changed over time, including surgical techniques, use of free tissue transfer reconstruction, transoral resection, anesthesia techniques, and chemotherapy regimens. An analysis of the 2 time cohorts did not reveal any significant differences in age, T category, overall stage, ACE-27 scores, smoking habits, or the number of patients undergoing surgical treatment. However, there were 3 significant differences identified among the time cohorts: (1) mean follow-up period in cohort I was significantly longer (57 months vs 32 months; P = .005), (2) the number of patients receiving chemotherapy was significantly greater in cohort II (P = .005), and (3) advanced regional disease (N2 or N3) was greater in cohort II (P < .001).

There were no significant differences in DSS (log rank test, P = .55) and OS (log rank test, P = .84) among the 2 time cohorts. However, there was significantly better 2- and 5-year DFS in cohort II compared with cohort I (2-year DFS, 82% vs 64%, and 5-year DFS, 67% vs 48%, respectively; P = .02) (Figure 3). A further subgroup analysis of the time cohorts based on surgical vs nonsurgical treatment is discussed in the following subsection.

TREATMENT METHODS: SURGERY VS NONSURGERY

To examine the effect of treatment type on outcome, the study population was divided into surgical (n=82) and
nonsurgical (n=59) cohorts and subjected to a similar analysis. Analysis did not reveal any significant differences between the 2 groups in age, ACE-27 score, T category, advanced N category (N2 or N3), overall stage, or smoking history (Table 2). However, 2 significant differences were identified among the treatment groups: (1) follow-up time in the surgical group was significantly longer (56 months vs 32 months; P=.008), and (2) the number of patients undergoing chemotherapy as part of their treatment plan was significantly greater in the nonsurgical arm (P=.001), most likely reflecting the use of combination CRT treatment for advanced-stage disease in the nonsurgical arm.

In our outcome analysis there was a significantly better DSS in the group whose treatment included surgery compared with the nonsurgical group (2- and 5-year DSS for surgery vs nonsurgery, 77% vs 46% and 67% vs 30%, respectively; P<.001) (Figure 4). Similarly, OS was significantly better in the surgical group compared with the nonsurgical group (2- and 5-year OS for surgery vs nonsurgery, 66% vs 41% and 45% vs 23%, respectively; P=.005) (Figure 5). There was no significant difference in DFS (P=.20) between the 2 treatment groups.

We were interested to see if the survival advantage with surgery held up based on the time frame of treatment. Subgroup analysis of time cohorts revealed that patients in cohort I who underwent surgical treatment had better outcomes compared with those in cohort I who had strictly nonsurgical treatment (2- and 5-year DFS, 72% vs 47% and 56% vs 29% [P=.01]; 2- and 5-year DSS, 80% vs 38% and 65% vs 20% [P<.001]; and 2- and 5-year OS, 69% vs 37% and 48% vs 17% [P=.007], respectively). In time cohort II, patients who underwent surgery had no difference in all outcomes measured compared with those who underwent nonsurgical treatment.

**DISEASE STAGE AND COMORBIDITY ANALYSES**

As in most studies, the majority of our patients presented with late-stage disease (79%). We were interested in further studying the survival of this subgroup. Results from a subgroup analysis of the entire cohort showed that patients with advanced disease whose treatment plan included surgery fared better than those with advanced disease who received strictly nonsurgical therapy (2- and 5-year DFS for surgery vs nonsurgery, 63% vs 26% and 45% vs 11% [P<.001]; and 2- and 5-year DSS, 72% vs 33% and 65% vs 13% [P<.001], respectively). Those

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**Table 2. Patient and Tumor Characteristics According to Treatment Modality**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Surgery (n=82)</th>
<th>Nonsurgery (n=59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>65 (44-87)</td>
<td>64 (45-86)</td>
<td>NS</td>
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<tr>
<td>Follow-up, mean (range), mo</td>
<td>56 (2-284)</td>
<td>32 (1-169)</td>
<td>.008</td>
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<td>T category</td>
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<td>1-2</td>
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<td>N category</td>
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<td>8 (13)</td>
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<td>Disease stage</td>
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</tr>
<tr>
<td>Early (I-II)</td>
<td>15 (18)</td>
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</tr>
<tr>
<td>Late (III-IV)</td>
<td>70 (82)</td>
<td>45 (76)</td>
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<tr>
<td>ACE-27 score, No. (%)</td>
<td></td>
<td></td>
<td>NS</td>
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<td>2 (3)</td>
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<td>21 (26)</td>
<td>19 (32)</td>
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<tr>
<td>With smoking history, No. (%)</td>
<td>72 (88)</td>
<td>56 (94)</td>
<td>NS</td>
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<tr>
<td>Treated with radiation therapy, No. (%)</td>
<td>70 (85)</td>
<td>59 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>Treated with chemotherapy, No. (%)</td>
<td>19 (23)</td>
<td>30 (50)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE-27, Adult Comorbidity Evaluation–27; NS, not significant.
with early-stage disease had comparable OS and DSS regardless of their treatment type.

We were interested in the outcome of patients treated most recently with advanced-stage disease because we believed that this group most closely represents the patient population we see currently. We therefore examined outcome in subjects with late-stage disease in time cohort II and compared outcomes based on treatment type. There was a significantly better DSS in cohort II subjects with advanced-stage disease whose treatment plan included surgery vs those with advanced-stage disease who had only nonsurgical treatment (2-year DSS, 70% vs 43%; P = .045) and a nonsignificant trend toward better OS in subjects with advanced-stage disease treated with surgery compared with those with advanced-stage disease treated nonsurgically (2-year OS, 59% vs 32%; P = .06).

Many patients with head and neck cancer have notable comorbidities, and we were interested in whether outcome was different in these groups based on treatment type. There was no significant difference in the outcome for subjects with ACE-27 scores of 0, 1, and 2 based on whether their treatment included surgery. Notably, however, in the group of subjects with the most severe comorbidity score (ACE-27 score of 3), there was significantly better outcome when their treatment plan included surgery compared with nonsurgical treatment (DFS, P = .02; DSS, P < .001; and OS, P = .007).

**LOGISTIC REGRESSION ANALYSIS**

To assess the impact of surgery on 2- and 5-year OS, DSS, and DFS, binary logistic regression analysis controlling for time cohort, disease stage, and ACE-27 score was performed. Table 3 gives the results of this analysis. For all outcomes measured, except 5-year DFS (P = .07), surgical treatment significantly reduced likelihood of death, death from disease, and tumor recurrence.

**SMOKING OUTCOME ANALYSIS**

There were 13 nonsmokers among the entire cohort, representing 9% of the patient population with mean age of 56 years. Although HPV status was not tested directly, we used nonsmoking status as a surrogate for HPV-positive status. Despite this small group, significant differences were observed (Table 4). Nonsmokers had significantly better mean OS (94 months vs 41 months; P = .001 [t test]) and DFS (92 months vs 36 months; P < .001 [t test]) compared with nonsmokers Recurrence at any site was significantly greater in smokers compared with nonsmokers (8% vs 44%; P = .02 [χ² test]).

Prior to 1990, most tonsillar cancer was treated with surgery regardless of stage. Studies demonstrated that for early-stage disease single modality treatment, either surgery or RT, was similar and did not affect outcomes. For late-stage disease, a combined approach with surgery and RT was noted to be superior to single modality treatment, but studies to confirm this finding were limited in reaching significance owing to the overall poor prognosis of patients with late-stage disease. The prevailing consensus at that time was, therefore, single modality for early-stage disease and surgery combined with RT for late-stage disease. Radiation therapy with or without chemotherapy was reserved for patients with unresectable disease, those who were medically inoperable because of existing comorbidities, or those who refused surgery.

More recently, nonsurgical therapies have been re-evaluated. Parsons et al reviewed treatment results from 51 retrospective studies and described 6400 patients with tonsillar cancer who underwent (1) surgery with or without RT or (2) RT with or without neck dissection. An analysis from this study revealed that overall outcomes were the same, but because the rate of severe complications was high at 23% in the surgical subjects, the authors concluded that primary nonsurgical treatment should be advocated. Encouraging results from recent phase 2 and 3 trials have led to the use of definitive CRT in an increasing number of patients with locally advanced tonsil SCC and good performance status.

Surgical treatment of oropharyngeal carcinoma has undergone an evolution of techniques during the last 10 to 15 years. At one time, surgical resection of oropharyngeal carcinoma was limited to a transcervical approach for partial pharyngectomy with or without partial mandibulectomy. Current techniques include transoral resection for appropriate tumors, without the need for mandible resection or splitting. Poulsen et al advocated surgery and postoperative RT, noting less treatment morbidity and a superior outcome for locally advanced tonsil SCC in patients with surgically resectable disease and good perfor-
mance status vs a nonsurgical option. The authors point out that this difference may be attributed to the fact that in their study population the RT patients had poorer performance status, were generally older, and were selected for RT only if they were medically or surgically inoperable. Most recently, Moore et al\textsuperscript{19} evaluated transoral resection of advanced-stage tonsillar SCC with neck dissection with or without adjuvant RT and reported excellent locoregional control, DSS, and OS. In addition, their surgical approach minimized treatment-related morbidity.

Despite the many studies reviewing oncologic outcomes and functional results of patients undergoing various treatments for tonsillar carcinoma, no definite consensus exists about the best treatment options. As a result of this ongoing controversy we were interested in assessing our treatment strategies and their impact on outcomes in a relatively homogeneous veteran population treated for tonsil SCC over the past 25 years. In the present study, patients were separated into treatment date cohorts, cohort I patients were treated before 1997 and cohort II patients were treated during or after 1997. The year 1997 was not arbitrarily chosen as the cutoff, but rather because in 1997, 3-D conformal RT was started at our institution, allowing more precision in delivering external beam RT. On the basis of treatment periods, subjects treated during or after 1997 had an improvement in DFS compared with those treated before 1997 ($P = .02$). Although the disease stage of patients between the 2 time cohorts was not different, there was a difference in the number of subjects receiving chemotherapy. More patients received chemotherapy in the later time cohort. This difference, in addition to the institution of 3-D conformal treatment planning starting in 1997 may have affected this outcome.

In discussing outcome analysis in the different treatments of tonsil SCC, it is easiest to divide strategies into surgical and nonsurgical. In conducting this analysis, patients whose treatment included surgery had significantly better DSS and OS. Furthermore, it was observed that those with late-stage disease and the “sickest” patients (ACE-27 score of 3) had better outcomes when surgery was part of their initial treatment. In addition, subjects with late-stage disease treated during or after 1997 benefited from surgery, as demonstrated by an improved DSS and a nonsignificant trend toward improved OS. The combination of surgery for late-stage disease and modern-day RT treatment planning may be responsible for the improved overall outcomes noted in these subjects. This finding corroborates reports by Poulsen et al\textsuperscript{18} and Moore et al\textsuperscript{19} who advocate that surgery and postoperative RT continues to provide superior outcomes in advanced tonsil SCC. In contrast to Poulsen et al\textsuperscript{18} who advocates surgery only for those with good performance status, our analysis shows that even in patients with notable comorbidities, surgery is associated with better survival.

In recent decades there has been a reported increase in the incidence of tonsillar SCC, and epidemiological and molecular data have indicated the involvement of high-risk HPV in these tumors.\textsuperscript{3} Furthermore, patients with HPV-positive cancer have been shown to have a lower risk of relapse and longer survival compared with patients with HPV-negative tonsillar cancer.\textsuperscript{7,14,15} We believe that it was important in our study to examine the outcome of patients based on tumor HPV status. Because of the large number of subjects in our report, however, it was not feasible for us to analyze all original tumor samples for HPV status. We decided to use smoking status as a surrogate for HPV status. We understand the limits of this analysis and realize that the only true validated method to confirm HPV-positive cancer is to perform polymerase chain reaction analysis on samples to confirm the presence of the HPV genome.\textsuperscript{20} There have been indications in the literature to link smoking status with HPV status and outcome. Although Fakhry et al\textsuperscript{15} found that subjects with HPV-positive tumors had better survival regardless of smoking status, subjects in that study who had HPV-positive tumors were more likely to report less than 20 pack-years of tobacco use. Smoking has been associated with higher epidermal growth factor receptor expression and lower HPV copy number, a combination that has shown poor outcomes in oropharyngeal cancer.\textsuperscript{21,22} In addition, Kumar and colleagues\textsuperscript{21} found that all of the never smokers in their study were HPV positive. Our study demonstrated dramatically better outcomes measured in nonsmokers, which is in agreement with the current literature about a favorable prognosis in the subset of patients with HPV-negative tumors, though we realize that without a more direct measure of HPV status, these results must be interpreted with caution.

This retrospective study provides evidence that veteran patients treated at our institution during or after 1997 enjoyed improved disease control, potentially due to advances in RT planning and the use of chemotherapy. This may represent the improved ability to control locoregional disease with the use of 3-D treatment planning in addition to distant control with chemotherapy. In addition, this study provides evidence that those treated with surgery had improved survival compared with those treated with a strictly nonsurgical treatment plan. One might assume this was because patients with more comorbidities were treated with nonoperative means. However, an analysis of the surgical vs nonsurgical groups revealed that there were almost equal numbers of patients with ACE-27 scores of 2 and 3 in the 2 groups. Furthermore, despite the advances in RT and chemotherapy after 1997, patients presenting with advanced-stage disease benefited from a treatment plan that included surgical intervention, as did those with multiple comorbidities as measured by the ACE-27 score. We advocate the consideration of a treatment plan that includes surgery for patients presenting with advanced-stage SCC of the tonsil, even in patients with notable comorbidities.

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Author Contributions: Dr Bier-Laning had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Canar and Bier-Laning. Acquisition of data: Jaber and Moreira. Analysis and interpretation of data: Jaber, Moreira, Canar, and Bier-Laning. Drafting of the manuscript: Jaber and Bier-Laning. Critical revision of the manuscript for important intellectual content: Canar. Statistical analysis: Canar. Study supervision: Bier-Laning.

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REFERENCES