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Impact of Treating Facilities’ Type and Volume in Patients With Major Salivary Gland Cancer

Craig A. Bollig, MD; Robert P. Zitsch III MD

**Objectives/Hypothesis:** Investigate the relationship between facility volume and type on overall survival (OS) in patients with major salivary gland cancer undergoing surgical treatment.

**Study Design:** Retrospective review of the National Cancer Database (NCDB) 2004–2015.

**Methods:** The NCDB was queried for patients with surgically treated major salivary gland cancer. The mean number of cases treated at each institution was calculated. High-volume facilities (HVFs) were defined as the top 10% of centers. Univariate and multivariate propensity score-matched analyses were performed to evaluate the impact of facility volume and type on OS.

**Results:** A total of 8,658 patients were analyzed. Distribution among facilities was highly skewed, with a median value of 1.38 cases/year (range, 0.11–23.25). On univariate analysis, treatment at HVFs was not associated with improved OS. However, there were significantly more patients with adverse clinical features treated at HVFs. Treatment at HVFs was associated with increased rates of concomitant neck dissections and lower rates of positive margins. In propensity-score matched cohorts, OS was not significantly improved in patients treated at HVFs (hazard ratio [HR]: 0.979; 95% confidence interval [CI]: 0.879–1.091) or academic/research institutions (HR: 0.914; 95% CI: 0.821–1.018).

**Conclusions:** Regionalization of care is occurring in patients with major salivary gland malignancies. Patients treated at HVFs had greater rates of adverse clinical features and more commonly underwent neck dissections, although adjuvant radiotherapy rates were similar between facility types. There was no apparent survival benefit to patients treated at HVFs or academic/research institutions, although there were lower rates of positive margins at HVF.

**Key Words:** Salivary gland cancer, hospital volume.

**Level of Evidence:** NA

**INTRODUCTION**

Salivary gland malignancies are rare tumors that comprise about 5% of all head and neck cancers1 and have a reported incidence of approximately 1.2 cases per 100,000 person-years in the United States.2 With >20 different histologic types as well as the challenges associated with grading malignancies, establishing the diagnosis and formulating the proper treatment plan requires physician expertise and multidisciplinary care.1,3 Surgery remains the mainstay of treatment, although factors such as tumor grade, histologic type, and tumor stage influence treatment decisions such as performance of a neck dissection and administration of adjuvant therapy.1 Due to the relative rarity of salivary gland cancer, facility characteristics, such as clinical volume and academic status, may influence outcomes in patients with these malignancies.

Hospital volume has been shown to impact patient mortality in several studies within head and neck oncology,4–9 whereas others have found no significant relationship.10–12 In an effort to establish a consensus, Eskander et al. conducted a systemic review and meta-analysis in 2014 and concluded that volume-outcome relationships exist within head and neck cancer, although they highlighted a lack available information in the literature regarding patients with salivary gland cancer.13 The aim of this study was to further investigate the relationship between facility volume and facility type on overall survival (OS) in patients with major salivary gland cancer undergoing surgical treatment. Our hypothesis was that patients treated at high volume facilities (HVFs) and academic institutions would have improved OS.

**MATERIALS AND METHODS**

**Database Information and Patient Selection**

To further investigate this objective, we performed a retrospective review of patients undergoing surgical treatment for a major salivary gland malignancy using the National Cancer Database (NCDB) after the study was deemed to be exempt from full institutional review board review. The NCDB is a registry maintained by the Commission on Cancer of the American College of Surgeons and the American Cancer Society, which collects cases from >1,500 facilities and encompasses approximately 70% of newly diagnosed cancers in the United States. There are established criteria to certify the quality of the submitted data, as well as an application process to obtain the data. After
distribution of the data, the Commission on Cancer of the American College of Surgeons and the American Cancer Society are not responsible for the analysis and conclusions presented.

We initially queried the NCDB for all patients ≥18 years old with a primary malignancy of a major salivary gland, using topographic and morphologic codes from the International Classification of Disease for Oncology, Third Revision. Major salivary gland sites included: parotid, submandibular, sublingual, major gland not otherwise specified (NOS), and overlapping lesion of the major salivary glands. The analysis was limited to the most common histologic subtypes, which included patients with mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, adenocarcinoma NOS, salivary duct carcinoma, and malignant mixed tumor. Patients with squamous cell carcinoma were excluded to avoid the possibility of including patients with metastatic cutaneous squamous cell carcinoma. Only patients who received surgical treatment were included. Patients <40 years old were excluded because treating facility type was suppressed in the database, and not available for analysis in these individuals. Patients with unknown clinical T or N staging were also excluded.

Patient Variables and Statistical Analysis

Potentially relevant patient, tumor, and treatment characteristics that were obtained from the NCDB and analyzed are detailed in Tables I and II. Facility volume was computed as the number of patients with a primary salivary gland malignancy treated by each facility annually and was classified as facilities with the top 10% of annual treatment volume. Baseline patient characteristics between the two different facility volume groups included a comparison of age, gender, race, insurance status, residence, Charlson-Deyo comorbidity score, year of diagnosis, and facility type (Table I). The tumor and treatment variables included a comparison of primary tumor site, histologic type, tumor grade, clinical T and N stage, performance of a neck dissection, margin status, and administration of adjuvant radiation therapy (RT) and/or chemotherapy (Table II). Continuous variables were compared using the Student t test, and categorical variables were analyzed using the χ² test. Survival functions were estimated using the Kaplan-Meier method. Univariate and multivariate survival analyses were conducted using Cox proportional hazards models.

Propensity score adjustment was then used to account for differences in characteristics of patients treated at high- and low-volume institutions. The propensity score was calculated using logistic regression to estimate the probability of being treated at a high- and low-volume institution. Propensity scores were divided into quintiles and used in a stratified analysis. The proportional hazards assumption was checked using a Kolmogorov-type supremum test.

Finally, patients were divided into two clinical groups based on risk factors. The low-risk group contained patients with a low or intermediate grade, stage 1 or 2 tumor. The high-risk group contained patients with either a low/intermediate grade, stage 3 or 4 malignancy, or a high-grade tumor of any stage. Patient survival was then compared between high- and low-volume institutions in both the low-risk and high-risk groups using the Kaplan-Meier method and Cox proportional hazard models. For all tests, the threshold for statistical significance was set at P < .05. SAS/STAT version 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

After exclusions were performed as detailed in the methods section, there were 8,658 subjects available for analysis. The case distribution among facilities was highly skewed, with a median value of 1.38 cases/year (range, 0.11–23.25 cases/year). The 75th and 90th percentiles were 2.25 and 4.08 cases/year, respectively. Baseline patient characteristics for patients treated at HVFs/low-volume facilities (LVFs) are compared in Table I. Table II describes the tumor and treatment characteristics for patients treated at HVFs/LVFs. There were statistically significant differences between the two populations in most clinical variables of interest. Overall, the patient cohort treated at HVFs was associated with greater rates of most adverse clinical variables. Lower rates of low and intermediate grade tumors were present at HVFs compared to LVFs, respectively (19.9% and 18.8% vs. 22.5% and 21.3%, P < .0001). Similarly, more patients with locally advanced tumors (31.5% vs. 23.6%, P < .0001) and clinically positive nodal disease (19.3% vs. 15.9%, P < .0001) were treated at HVFs compared to LVFs, respectively. These differences in

<table>
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<tr>
<th>Characteristic</th>
<th>Low Volume (&lt;90th Percentile, n = 5,041)</th>
<th>High Volume (&gt;90th Percentile, n = 3,617)</th>
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<td>Age</td>
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<tr>
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<td>2,376 (47.1)</td>
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<td>1,790 (49.5)</td>
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<td>2,895 (81.5)</td>
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<td>2,303 (46.4)</td>
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<td>Medicare</td>
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<tr>
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<tr>
<td>Urban</td>
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<td>401 (11.3)</td>
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<tr>
<td>Rural</td>
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<td></td>
<td>1+</td>
<td>2,940 (81.3)</td>
<td></td>
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<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
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<td>2004–2009</td>
<td>2,058 (40.8)</td>
<td>1,230 (34.0)</td>
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<tr>
<td>2010–2015</td>
<td>2,983 (59.2)</td>
<td>2,387 (66.0)</td>
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<tr>
<td>Comprehensive community cancer program</td>
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<td>409 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Academic/research</td>
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<td>3,208 (88.7)</td>
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</table>
The results of the univariate survival analyses are detailed in Tables III and IV. The Kaplan-Meier survival curves for HVFs/LVF s and different facility types are demonstrated in Figures 1 and 2, respectively. Treatment at HVFs was not associated with improved survival (hazard ratio [HR]: 0.995; 95% confidence interval [CI]: 0.913-1.085). Similarly, there was no survival advantage seen in patients treated at academic/research institutions (HR: 0.995; 95% CI: 0.852-1.163). As expected, patients with low-grade (HR: 0.172; 95% CI: 0.148-0.199) or intermediate-grade (HR: 0.290; 95% CI: 0.255-0.329) tumors had improved survival compared to those with high-grade lesions. Likewise, patients with locally advanced (HR: 2.762; 95% CI: 2.538-3.003) and clinically positive nodal disease (HR: 3.788; 95% CI: 3.472-4.149) had worse survival than patients with early T stage or cN0 patients, respectively.
To adjust for the differences in clinical risk factors between patients treated in HVFs versus LVFs, propensity scores were used. In this model, neither facility volume ($P = .71$) nor facility type ($P = .24$) were significantly associated with differences in survival. The proportional hazards assumption was checked using a Kolmogorov-type supremum test. The assumption was reasonable for facility type ($P = .3700$) but questionable for facility volume ($P = .0190$). Consequently, the effect of facility volume was examined further using Kaplan-Meier methods and the log-rank test. Stratification was done using propensity scores and facility type. The results were consistent with the previous analysis showing no significant effect of facility volume ($P = .62$).

Finally, a secondary analysis was performed in which patients were divided into two clinical groups based on tumor stage and grade. The low-risk group contained 2,727 patients with a low or intermediate grade, stage 1 or 2 tumor. The high-risk group contained 3,441 patients with either a low/intermediate-grade, stage 3 or 4 malignancy, or a high-grade tumor of any stage. The remaining 2,490 patients with an unknown grade were excluded. As in the primary analysis, there were no statistically significant differences in survival between patients treated at HVFs in the high-risk group ($P = .32$) or the low-risk group ($P = .12$).
DISCUSSION

In a landmark study published in 1979, Luft et al. were the first to report an improvement in patient survival following certain operations in higher-volume institutions. More recently, this has been investigated in several studies within the field of head and neck oncology with mixed results. In a 2009 NCDB study of patients with early-stage laryngeal cancer, Chen et al. demonstrated improved OS in those who were treated at HVFs compared to LVFs, but not medium-volume institutions. Additionally, they did not find any significant difference in OS with regard to facility type. In 2010, the same group reported improved survival in advanced-stage laryngeal cancer patients who received nonsurgical treatment at HVFs; however, this survival advantage was not present in patients who underwent a laryngectomy. They also found greater OS in patients who were treated at an academic research institution. Most recently, David et al. elegantly described a continuous improvement in survival at facilities with increasing patient volume among patients with locally advanced head and neck squamous cell carcinoma undergoing definitive RT treatment. In the only systematic review and meta-analysis on this topic in head and neck oncology, Eskander et al. concluded that volume-outcome relationships exist, although they highlighted a lack of available information in the literature regarding patients with salivary gland cancer. The authors are not aware of any currently published studies devoted to patients with salivary gland malignancies that investigate the impact of hospital volume.

In the current study, we found evidence that regionalization of care in patients with a major salivary gland malignancy has occurred, with most patients seeking treatment at a relatively small number of facilities. Even the top 10% of facilities in terms of annual case volume only treated four or more cases/year. Patient migration to HVFs also seemed to occur over the duration of the study period, in which there was a significant increase in the percentage of cases treated at HVFs from 2004 to 2009 to 2010 to 2015 (59.2% to 66.0%, P < .0001). Patients that were treated at high-volume institutions represented a cohort with more adverse clinical features including greater rates of high-grade and locally advanced malignancies as well as higher rates of positive nodal disease. As to be expected with an overall higher-risk patient population, neck dissections were performed more frequently at HVFs compared to LVFs (78.5% vs. 63.6%, respectively, P < .0001). Positive surgical margins occurred less commonly at HVFs (31.6% vs. 35.6%, P < .0001). Interestingly, despite the overall lower rate of adverse clinical features at LVF, there were virtually identical rates of adjuvant RT administration between HVF and LVF (57.5% vs. 57.8%, respectively, P = .7862).

After a thorough analysis, no survival advantage was seen in patients who were treated at HVFs or academic research facilities on univariate or propensity-score matched multivariate analyses. Additionally, we performed a subgroup analysis of patients with low-risk and high-risk clinical disease factors, and again did not identify a survival advantage among patients treated at HVF or academic research centers. Although intuitively, treatment at a more experienced center would be associated with better patient outcomes, but not all studies within head and neck oncology have demonstrated this relationship, particularly with long-term survival outcomes in surgically treated patients. Chen et al. did not find a survival advantage in patients with locally advanced laryngeal cancer patients undergoing a total laryngectomy at HVF, although improved survival was seen in patients treated nonsurgically. Similarly, in a database review of >6,000 patients undergoing oral cavity resections in Taiwan, Lin and Lin reported equivalent survival outcomes in patients treated at HVFs, although they found improved OS in patients treated by a high-volume surgeon. Within the surgical literature, the most dramatic differences in outcomes at HVFs are seen in complex, unique procedures with high complication rates such as pancreatic resections and esophagectomies. Other mechanisms at HVFs that may translate to improved outcomes in head and neck cancer patients remain to be fully elucidated, but are likely multifactorial. There are several contributing factors proposed in the literature including a greater presence of multidisciplinary tumor boards at HVFs, which was shown to alter treatment plans in 27% of patients with head and neck cancer, usually with an escalation of management. Additionally, differences in the response to and management of complications at HVFs, rather than reductions in overall complication rates, may lead to survival benefits following treatment. Furthermore, HVFs are more likely to have increased adherence to National Comprehensive Cancer Network (NCCN) guidelines, which has been linked to an improvement in survival outcomes. Finally, facility volume may be a surrogate for improved access to a variety of ancillary services, such as nutrition, speech language pathology, palliative care, and oncologic psychiatry, which may minimize treatment interruptions and increase the likelihood of completion of treatment.

Looking at these proposed factors in the literature may offer insight into why a significant difference in OS was not seen in our cohort. With squamous cell carcinomas of the oropharynx, larynx, and hypopharynx, both surgical and nonsurgical treatment are generally regarded as reasonable options with comparable outcomes. In these patients, a multidisciplinary discussion by experienced head and neck surgical, medical, and radiation oncologists of the nuances associated with each option to optimize treatment plans may translate to improved outcomes seen at HVFs in these patients. Conversely, with salivary gland malignancies, the initial treatment recommendation is much more straightforward—surgical resection with possible adjuvant therapy. Although technically challenging in their own right, the surgical procedures performed in our patient cohort (parotidectomy, submandibular gland excision, neck dissection) do not typically have a complication or mortality rate remotely close to that seen in an esophagectomy or pancreatic resection, for example. Additionally, the rates of adjuvant RT administration between groups were equivalent, which is surprising when considering that greater rates of high-risk patients were treated at HVF. This suggests that LVF are at least administering adjuvant RT when indicated by the NCCN guidelines, although...
perhaps more frequently than needed. Furthermore, studies in head and neck cancer patients have typically demonstrated larger volume-outcome survival relationships in patients receiving nonsurgical treatment compared to those treated surgically. This may be a reflection of greater ancillary services at HVFs to help reduce interruptions in RT and improve completion rates. Finally, compared to the typical patient with a head and neck cancer of the aerodigestive tract, patients with salivary gland malignancies typically have lower rates of comorbid substance abuse and medical comorbidities as well as fewer treatment-related complications. This may create less opportunity to see the impact of improved rescue from these complications at HVF.

Multiple factors have been shown to impact survival in patients with salivary gland malignancies including tumor grade, stage, gland involved, histologic type, and margin status. The current standard of care for initial treatment is surgical resection. Although there have been no randomized controlled trials addressing this, adjuvant RT has been shown to reduce locoregional recurrence in patients with adverse features such as high-grade, locally advanced, positive nodal disease, and certain histologic types (adenoid cystic carcinoma) in retrospective studies. More recently, adjuvant radiation has been shown to offer a survival benefit to patients with these adverse features, in recent retrospective reviews of the NCDB. Unfortunately, systemic therapy has not yet been shown to offer improvements in survival and evidence for its use in salivary gland malignancies is very limited, although a Radiation Therapy Oncology Group clinical trial aiming to address the efficacy of adjuvant chemoradiotherapy is ongoing (NCT01220583).

There are multiple limitations of our study. The NCDB offers some benefits over other population databases, including a larger sample size, broader inclusion of ages, and the availability of adjuvant therapy details; however, as with all database studies, limitations include selection bias, incomplete/missing data, and coding errors. Adult patients <40 years old required exclusion, due to the suppression of treating facility type. Additionally, many patients were excluded due to imprecise histologic diagnoses (e.g., carcinoma NOS). With >20 different histologic subtypes of salivary gland malignancies, diagnosis can be challenging, and it is possible that pathologists uncomfortable establishing a diagnosis may be more prevalent at LVFs, which may have an impact on the findings of the study. Finally, the NCDB only contains data on OS, and we were unable to evaluate the effect of hospital volume on recurrence rates as well as relevant complications. Information on facial nerve outcomes would be of considerable interest to clinicians and may differ between HVFs/LVFs or high volume/low volume surgeons.

CONCLUSION
Regionalization of care is occurring in patients with major salivary gland malignancies. Patients treated at HVFs had greater rates of adverse clinical features and more commonly underwent neck dissections, although adjuvant RT rates were similar between facility types. There was no apparent survival benefit to patients treated at HVFs or academic/research institutions, although there were lower rates of positive margins at HVFs.

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BIBLIOGRAPHY


