Adjuvant Radiation Therapy for High-Grade and/or Locally Advanced Major Salivary Gland Tumors

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Objective: To examine the effect of adjuvant radiation therapy (RT) on survival of high-grade and/or locally advanced malignant major salivary gland tumors (MMSGT).

Patients: The study population comprised 2170 patients with high-grade (poorly differentiated or undifferentiated) and/or locally advanced MMSGT (T3/4 or N+).

Main Outcome Measures: The Surveillance, Epidemiology, and End Results registry was used to obtain data for all patients 20 years or older who underwent surgery for high-grade and/or locally advanced nonmetastatic MMSGT between 1988 and 2005. Univariate and multivariable regression analyses were performed to identify factors associated with improved survival.

Results: Seventy-two percent of patients received adjuvant RT, while 28% underwent surgery alone. Patients receiving adjuvant RT were younger and had higher T and N categories and grade. Multivariable analysis revealed significantly improved survival with adjuvant RT (HR for mortality, 0.76; 95% CI, 0.65-0.89; P < .001). Other factors associated with improved survival included younger age at diagnosis, less than radical surgery, certain histologic subtypes, lower grade, and lower T and N categories. Subset analyses found significantly improved survival with adjuvant RT among patients with both high-grade and locally advanced disease (P < .001), involvement of the parotid gland (P = .002), or squamous cell carcinoma (P = .004), with a survival benefit seen among patients with adenocarcinoma that did not reach significance (P = .06).

Conclusions: Adjuvant RT is associated with improved survival for high-grade and/or locally advanced MMSGT based on analysis of this large, population-based database. Further prospective studies are warranted to examine the role of RT in the management of this disease.

and survival in the United States.\textsuperscript{21} The SEER database is composed of 17 geographically distinct registries that house information from approximately 26\% of the US population, although the data it stores are thought to be representative of the US population as a whole. It stores information on patient demographics, tumor characteristics, treatment course, and patient survival.

The purpose of this study was to examine the effect of adjuvant RT on overall survival of patients with high-grade and/or locally advanced MMGST using this large, population-based database. We further hoped to elucidate which subgroups of patients benefit most from adjuvant RT.

**DATA COLLECTION**

The SEER database\textsuperscript{22} was queried using SEER\textsuperscript{Stat} software, version 6.5.1, to identify all adults (age $\geq 20$ years) diagnosed between 1988 and 2005, who underwent surgical resection of high-grade (poorly differentiated or undifferentiated) and/or locally advanced (T3/4 or N+) MMGST. We purposefully excluded patients with low-grade and nonlocally advanced MMGST because adjuvant RT is not typically recommended for such cases.

Data on survival, year of diagnosis, age at diagnosis, sex, tumor location, grade, histologic features, T and N categories, type of surgery, and administration of adjuvant RT were extracted for all patients. Survival was defined as time from date of diagnosis to date of death (in months). Tumor location and histologic subtype were analyzed according to the International Classification of Diseases for Oncology site and histology codes. Location was divided into the parotid gland (C07.9), the submandibular gland (C08.80), the sublingual gland (C08.1), and other (C008.89). Patients with minor salivary gland tumors were excluded. Grade was categorized as well differentiated, moderately differentiated, poorly differentiated, and undifferentiated/anaplastic. High grade included the latter 2 groupings. Histologic subtypes were categorized as adenocarcinoma (8140-7), adenoid cystic carcinoma (8200), mucoepidermoid carcinoma (8430), acinar cell carcinoma (8550-1), malignant mixed tumor/carcinoma in pleomorphic adenoma (8940-1), squamous cell carcinoma (8070-8), or other (all other codes). T and N categories were determined using extent of disease data available through the SEER Web site. The SEER database categorizes extent of surgical resection for salivary malignant neoplasms according to the following groupings: local tumor excision, less than total removal of the salivary gland, total removal of the salivary gland, or radical removal of the salivary gland. These designations are defined by the performing surgeon. For the purposes of comparison, we divided surgery into less than radical resection vs radical resection.

**STATISTICAL ANALYSIS**

Characteristics of patients receiving and not receiving adjuvant RT were compared using the unpaired t test for continuous variables and $\chi^2$ test for categorical variables. Univariate and multivariable Cox regression analyses were conducted to evaluate the effect of covariates on overall survival using year of diagnosis, age at diagnosis, sex, tumor location, grade, histologic subtype, T and N categories, type of surgery, and the presence or absence of adjuvant RT as plausible risk factors. Analysis was performed only on those patients with complete data available. Multivariable analyses were repeated on individual subgroups of patients (based on high-grade and/or locally advanced status, location, and histologic subtype) to assess plausible associations between adjuvant RT and survival within subsets.

Two-sided $P$ values, hazard ratios (HRs) for death and the corresponding 95\% CIs are reported herein. All statistical tests were done at the .05 level of significance. Data analyses were performed using SAS software (version 9.2; SAS Institute Inc, Cary, North Carolina).

**RESULTS**

**PATIENT CHARACTERISTICS**

A total of 2170 patients met the defined selection criteria: 51\% of cases were high grade and 63\% were locally advanced. In addition, 37\% were both high grade and locally advanced. The median age for the study population was 68 years (range, 20-99 years). Sixty-eight percent of patients were male, while 32\% were female. The majority of patients (84\%) had involvement of the parotid gland, while submandibular gland and sublingual gland involvement were less common (15\% and 1\%, respectively). In terms of treatment, 77\% had less than radical surgery, while 23\% had radical surgery. Seventy-two percent of patients received adjuvant RT, while 28\% underwent surgery alone. Patients receiving adjuvant RT were slightly younger and had higher T and N categories and grade. Moreover, the 2 groups were significantly different in terms of histologic subtypes (eg, patients with adenoid cystic were more likely to receive adjuvant RT). When analyzed by tumor location, the more aggressive histologic subtypes—adenocarcinoma, mucoepidermoid carcinoma, and squamous cell carcinoma—composed a larger proportion of cases in the sublingual (50\%) and submandibular glands (45\%) than in the parotid gland (36\%). Patient characteristics are summarized in Table 1.

**UNIVARIATE ANALYSIS FOR OVERALL SURVIVAL (ENTIRE COHORT)**

Univariate analysis revealed that younger age at diagnosis, female sex, less than radical surgery, lower grade, and lower T and N categories were significantly associated with improved survival. Also, there was significant variation in mortality based on histologic subtypes, with squamous cell carcinoma having the worst prognosis. Year of diagnosis, location, and adjuvant RT ($P = .14$) had no association with overall survival. The results of univariate analysis are summarized in Table 2.

**MULTIVARIABLE ANALYSIS FOR OVERALL SURVIVAL (ENTIRE COHORT)**

Multivariable analysis revealed a significant association between improved survival and adjuvant RT (hazard ratio [HR] for mortality, $0.76; 95\%$ confidence interval [CI], 0.65-0.89; $P < .001$). Moreover, significantly improved survival was associated with younger age at diagnosis, less than radical surgery, lower T and N categories, and...
There were statistically significant differences in mortality noted among the various histologic subtypes. Year of diagnosis, sex, and location had no association with survival. The results of multivariable analysis are summarized in Table 3.

SUBGROUP ANALYSES

When analyzed by high-grade and locally advanced status, multivariable analysis revealed significantly improved survival with use of adjuvant RT among patients with both high-grade and locally advanced disease ($P < .001$), but not among patients with high-grade, nonlocally advanced disease ($P = .28$) or locally advanced, non-high-grade disease ($P = .21$).

When analyzed by location, multivariable analysis revealed significantly improved survival with the use of adjuvant RT among patients with tumors involving the parotid gland ($P = .002$) but not among patients with tumors involving the submandibular gland ($P = .90$). There were an insufficient number of analyzable patients with involvement of the sublingual gland to make definitive conclusions regarding a possible survival benefit with adjuvant RT in this subgroup.

When analyzed by histologic subtype, multivariable analysis revealed significantly improved survival with use of adjuvant RT among patients with squamous cell carcinoma ($P = .004$) and a survival benefit among patients with adenocarcinoma that did not reach significance ($P = .06$). The association between adjuvant RT and improved survival among patients with mucoepidermoid carcinoma failed to reach statistical significance ($P = .22$). Although there were trends toward improved survival with adjuvant RT among patients with adenoid cystic carcinoma, acinar cell carcinoma, and carcinoma ex pleomorphic adenoma and/or mixed malignant tumor, there were limited numbers of analyzable patients in these subgroups to make definitive conclusions regarding possible survival benefits with adjuvant RT.

The associations between adjuvant RT and mortality in the various subgroups of patients are summarized in the Figure.

COMMENT

Our analysis of the SEER database demonstrates an association between improved survival and use of adjuvant RT among patients...
vant RT after surgical resection in patients with high-grade and/or locally advanced MMSGT. Given the higher T and N categories and grade seen among patients receiving RT, it is not surprising that this survival benefit was seen on multivariable rather than univariate analysis. The clearest survival benefits were seen among patients with both high-grade and locally advanced disease, involvement of the parotid gland, and squamous cell carcinoma or adenocarcinoma, although one must be cautious when interpreting the results of subset analysis because a number of subgroups had an inadequate number of analyzable patients to make definitive conclusions regarding the effect of adjuvant RT on survival in these subsets.

To our knowledge, our study represents the largest published data set examining the effect of adjuvant RT in patients with MMSGT. Bhattacharyya et al\textsuperscript{23} previously analyzed 903 patients extracted from the SEER database who were diagnosed between 1988 and 1998 and underwent surgery for parotid gland malignant tumors to identify determinants of survival. They found that adjuvant RT conferred survival benefit, which did not reach significance ($P=.09$). As opposed to our study, their subgroup analyses identified a significant survival benefit with adjuvant RT among patients with acinar cell carcinoma and squamous cell carcinoma in patients with squamous cell carcinoma that did not reach significance ($P=.08$). The discrepancies between their findings and ours are likely attributable to different patient inclusion criteria, with our study including patients with MMSGT involving the submandibular and sublingual glands but limited to patients with high-grade or locally advanced disease. Moreover, as our study spanned a longer period, it included a larger number of patients, yielding more statistical power to identify a survival benefit with adjuvant RT.

Only a few retrospective series have identified a significant survival benefit with adjuvant RT in patients with MMSGT.\textsuperscript{17-20} Armstrong et al\textsuperscript{17} performed a match-
paired analysis of 46 patients with previously untreated MMSGT, who received surgery followed by adjuvant RT (compared with 46 patients treated with surgery only during an earlier era). They found a significant 5-year survival benefit with adjuvant RT among patients with stage III/IV disease (51.2% vs 9.5%), with a nonsignificant trend toward improved 5-year survival among patients with high-grade disease (57% vs 28%). In an analysis of 87 patients with MMSGT, North et al reported a significantly improved 5-year survival among patients receiving postoperative RT compared with those undergoing surgery alone (75% vs 59%). The majority of patients in this series had either locally advanced (51%) or high-grade disease (62%). Finally, the remaining 2 retrospective series identified survival benefits with adjuvant RT in specific subsets of patients with MMSGT (T4 adenoid cystic carcinomas and N0 ex pleomorphic adenomas). Given the limited numbers of patients available in these retrospective series, however, they had insufficient statistical power to reliably and consistently identify precisely which subsets of patients experience survival benefits with adjuvant RT. Moreover, only 1 study identified a survival benefit with adjuvant RT on multivariable analysis, which controls for the simultaneous effects of multiple factors to assess the significance of each variable individually.

Although we adjusted for all available patient and tumor characteristics in our analyses, our study was, nonetheless, limited by the information available in the SEER database. The SEER database is dependent on individual physician reporting for classification of patient, tumor, and treatment characteristics. In this way, it is representative of national patterns of cancer care; however, it is also subject to inconsistencies. For one, there is considerable variation in the histologic classification of MMSGT. As an example, the ability to differentiate the generally aggressive histologic features of mucoepidermoid carcinoma and squamous cell carcinoma becomes more difficult with increasing grade. Errors in reporting may, therefore, partly explain the survival benefit seen with RT in one histologic subtype vs the other. However, our study included a small proportion of patients with acinic cell or adenoid cystic carcinomas, histologic subtypes traditionally thought to be less aggressive although known to have occasional aggressive variants. Ultimately, we decided to simply include all patients in the SEER database diagnosed as having either high-grade and/or locally advanced MMSGT and thereafter perform exploratory subset analyses according to grade/locally advanced status, location, and histologic subtype because there is no way to correct for these limitations in the SEER database. Moreover, the SEER database is also dependent on physician reporting to provide certain details of patient treatment. For example, as extent of surgery is somewhat subjective and defined by the performing surgeon, this is a potential source of error in our study, the exact impact of which is unknown.

In addition, as with all SEER studies, we were unable to include certain pathologic information such as margin status, presence of perineural or lymphovascular invasion, or intraoperative tumor spillage. The lack of such information may explain why those who underwent less than radical surgery fared better than those who underwent radical surgery, since the latter are more likely to have these high-risk pathologic characteristics. Intuitively, these high-risk pathologic characteristics were likely more prevalent among patients receiving adjuvant RT because these patients had higher T and N categories and
grade. Should this information have been available, perhaps the survival benefit seen with adjuvant RT would have been even more pronounced or significant among more patient subgroups. However, as with any nonrandomized study, there is the risk of a selection bias as physicians may be more likely to treat those who have better performance status and fewer comorbidities.

Similarly, local control and distant metastasis data were not available for analysis. As such, it should be pointed out that, although multivariable analysis did not confirm improved survival with adjuvant RT in certain subgroups, this does not exclude the possibility of a clinically important local control benefit with adjuvant RT in these subsets. Moreover, the lack of such data limits our ability to speculate as to the exact mechanism of improved outcomes with adjuvant RT (ie, whether from improved local control and/or decreased distant metastasis).

Finally, although there was no information available regarding the use of systemic therapy, given the poor responses seen with chemotherapy in this disease, it plays little role in the adjuvant setting. Therefore, inclusion of chemotherapy data would likely not alter our results significantly.

In conclusion, our analysis of the SEER database revealed a significant association between improved survival and use of adjuvant RT in the treatment of patients with high-grade and/or locally advanced MMSGT. Patients with the clearest benefit from adjuvant RT included those with both high-grade and locally advanced disease, involvement of the parotid gland, squamous cell carcinoma, or adenocarcinoma, although many of the other subsets likely had inadequate patient numbers. However, given the rarity of MMSGT, a randomized trial may be impractical; further prospective studies are warranted to examine the role of RT in the management of this disease.

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REFERENCES