NEUTRON RADIOTHERAPY FOR THE TREATMENT OF LOCALLY ADVANCED MAJOR SALIVARY GLAND TUMORS

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Abstract: *Background.* Malignant salivary gland tumors are rare tumors of the head and neck region. The treatment of these tumors has generally consisted of surgical extirpation, with postoperative radiotherapy improving locoregional control and survival in patients with high risk tumors. Neutron radiotherapy has been found to be more efficacious than conventional radiotherapy in the setting of inoperable or subtotally resected salivary gland tumors.

Methods. One hundred forty-eight patients with malignant salivary tumors of major salivary gland origin were treated at the University of Washington Medical Center with fast neutron radiotherapy between the years 1984 and 1995. One hundred twenty-eight patients were treated with curative intent, and of these, 120 patients had evidence of gross residual disease at the time of treatment. These patients constitute the main analysis of this paper. Of these patients, 19% had recurrent disease, 39% were initially seen with positive lymph nodes, and 11% had previously received full dose conventional radiotherapy. At the time of analysis, the median period at risk of survivors was 26 months.

Results. The 5-year actuarial locoregional control rate for all patients with gross tumor treated with curative intent was 59%. A tumor size $\leq$4 cm was associated with an excellent locoregional control rate (80%), and cause-specific survival (73%) at 5 years compared with patients with larger tumors (35% and 22%, respectively, $p < .001$ in both cases). On univariate analysis, there appeared to be an advantage in locoregional control for patients with smaller sized tumors ($\leq$4 cm) who underwent an attempted surgical extirpation. Locoregional control was excellent (100%) in patients having a complete surgical resection of their tumors and undergoing postoperative neutron radiotherapy because of the presence of other high risk factors. Lymph node status at the time of treatment, base of skull involvement, and male sex were associated with the development of distant metastasis, with 52% of node positive patients developing distant metastases by 5 years, compared with 32% of node negative patients ($p = .04$).

Conclusions. Neutron radiotherapy is an effective form of treatment for patients with high risk, locally advanced tumors of major salivary gland origin. An initial surgical resection appears beneficial in patients for whom such an approach is feasible. © 1999 John Wiley & Sons, Inc. *Head Neck* **21:** 255–263, 1999.

Keywords: salivary gland tumors; neutron radiotherapy

Primary malignant tumors of the major salivary glands are uncommon lesions, accounting for only 5% to 7% of all head and neck malignancies.[1,2] They also are characterized by a wide spectrum of histologies, with disparate biologic behavior. Historically, surgery has been the primary mode of

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treatment for these tumors,[3–6] although, more recently, the efficacy of conventional photon radiotherapy for microscopic residual disease in the postoperative setting or for the presence of other high risk factors has been demonstrated.[1,6–12] The reported results using low linear energy transfer (low-LET) conventional photon radiotherapy in the setting of more advanced disease, unresectable disease, or recurrent disease have been disappointing and have shown locoregional control rates of approximately 25% in numerous studies.[1]

High-LET particle irradiation, such as fast neutron irradiation, offers several potential advantages over conventional (low-LET) irradiation. High-LET irradiation deposits more energy as it traverses the cell, resulting in less dependence on the "indirect" mechanism of cell killing. In addition, cells which are irradiated by high-LET radiation are less able to repair sublethal and potentially lethal damage, which may be manifested by increased death of cells in the "resting" or G_0 portion of the cell cycle. Finally, radiobiologic studies have shown that there is less cell cycle specificity with regard to radiosensitivity for high-LET irradiation as compared with low-LET irradiation. The applicability of these observations to the clinical setting can be determined only through controlled studies.

In the 1970s and 1980s, numerous trials using high-LET neutron irradiation were performed. One of the highest relative radiobiologic effective factors (RBE, a measure of the relative efficacy of neutron radiation relative to photon radiation) was found for adenoid cystic carcinomas of salivary glands which was 8.0 with fractionated radiotherapy in contrast to an RBE of approximately 3–3.5 for late effects for most normal tissues.[13] This results in a therapeutic gain of approximately 2.5 over conventional radiotherapy and is thought to account for the improved outcome noted in studies using fast neutrons to treat tumors of salivary gland origin.[14–17] In a multiinstitutional, randomized study, fast neutron radiotherapy was conclusively shown to be superior to conventional irradiation in improving locoregional control in patients with inoperable or recurrent salivary gland tumors.[16,17]

In this paper, we describe our experience in treating tumors of major salivary gland origin with fast neutron radiotherapy over an 11-year period.

MATERIALS AND METHODS

The records of 148 patients with malignant tumors of major salivary glands treated with fast neutron radiotherapy at the University of Washington from 1984 to 1995 were reviewed. One hundred twenty-eight patients were treated with curative intent and constitute our evaluable data base. Eight of the 128 patients underwent complete surgical resection with negative margins achieved (four with <2 mm margins) and are not included in our major analysis but are analyzed separately. The remaining 120 patients had either unresectable disease or partially resected tumors with remaining residual disease as evidenced by multiple positive margins and/or postoperative imaging studies demonstrating residual masses. Follow-up data were obtained by contacting the patient's current physician and the patient and/or family member directly. The follow-up interval was calculated from the completion of radiotherapy. The median period at risk is defined as that time period from completion of treatment to the time of analysis of surviving patients.

Patient Characteristics. The median age at the time of treatment for the 120 curatively treated patients with gross residual disease was 61 years (range, 24–94 years). Sixty-three percent of patients were men, 37% women (ratio, 1.7:1). The median period at risk for surviving patients was 26 months (range, 4–125 months). Minimum follow-up period was 4 months. Eighty-five percent of patients had parotid gland tumors; the remaining 15% had submandibular or sublingual tumors. Eighty patients (66%) had attempted extirpative surgery prior to neutron radiotherapy, all with remaining microscopic or gross residual disease. Two patients were lost to follow-up (one had no documented posttreatment follow-up, and one was lost at 22 months). Nineteen percent of patients were treated for recurrent disease; 39% were initially seen with positive lymph nodes; 11% had previously received full dose conventional photon radiotherapy. Sixty-six patients (55%) had the presence or absence of perineural invasion documented in the pathology report, with 86% of these cases having evidence of perineural involvement. In the remaining 54 patients, the presence or absence of perineural invasion was not commented upon. Fifteen percent of patients had radiographic evidence of base of

skull involvement, with one having cavernous sinus involvement as well.

Histologic Classification. All patients had their pathologic specimens reviewed at our institution to confirm their diagnosis. The following histologic patterns and percentage of patients with that histologic pattern are as follows: adenoid cystic carcinoma, 32%; adenocarcinoma, 23%; mucoepidermoid carcinoma, 20%; carcinoma not otherwise specified, 8%; acinic cell carcinoma, 6%; squamous cell carcinoma, 4%; mixed malignant carcinoma, 3%; basaloid carcinoma, 2%; and other histologies, 2%.

Staging. All patients were staged according to the criteria of the fourth edition of the American Joint Committee on Cancer (AJCC) TNM group staging system (1993) at the time of presentation to our facility. Sufficient information was available to determine the group stage in 118 of the 120 patients, with the following results: stage I, 34%; stage II, 16%; stage III, 28%; stage IV, 22%. Data for T staging was available for 115 patients, with the following percentages: T1, 10%; T2, 44%; T3, 21%; T4, 25%.

Statistical Analysis. Locoregional control rates, survival rates, and rates of developing distant metastases were calculated using an actuarial, life-table method. The log rank test (two tailed) was used to evaluate the statistical significance of differences between two curves. Univariate and multivariate analyses were performed using the Statview 4.5 statistical package. All variables having a univariate *p* value .1 were entered into the multivariate analyses. A Cox stepwise procedure with a significance level of .05 was used to enter and/or eliminate variables in the multivariate analysis.

Description of Treatment. All patients were treated using a high energy, hospital-based, Scanditronix MC 50 cyclotron as has previously been described.[18] The cyclotron utilizes a 50 MeV p $\rightarrow$ Be reaction and is equipped with an isocentric rotating gantry and multileaf collimation system which permits the use of conformal field shaping. Fields were individualized according to the location and extent of the primary tumor. However, the majority of patients were initially treated using a three-field parotid technique, as previously described, to spare as much as possible the contralateral parotid gland.[19] A computed tomography (CT)-based, 3-dimensional conformal treatment planning system was generally used to configure the boost fields. Fraction sizes ranged from 1.7 neutron Gy given 3 times a week to 1.05 neutron Gy given 4 times a week. The most commonly used fractionation scheme over the past 5 years has been 1.2 neutron Gy given 4 times a week. The median dose per fraction was 1.2 neutron Gy, the median target dose 19.2 neutron Gy, and the median lowest target dose was 18.07 neutron Gy, with a median highest target dose of 20.09 neutron Gy. Thirteen percent of patients required a break in radiotherapy treatment due to acute mucositis reactions.

RESULTS

Overall Median Survival and Locoregional Control. Figure 1 shows the overall 5-year actuarial survival and cause-specific curves for the 120 analyzed patients. The 5-year actuarial survival rate was 39%, with a cause-specific survival rate of 50% at 5 years. The median survival was 50 months, with a median cause-specific survival of 63 months. Figure 2 shows the locoregional control curve for this group with a 5-year actuarial locoregional control rate of 59%. The median duration of locoregional control has not yet been reached for the curatively treated group. Five-year actuarial survival, cause-specific survival, and locoregional control for the eight patients with negative margins after surgical extirpation was 83%, 83%, and 100%, respectively.

Survival Analysis. Various factors were examined to determine prognostic variables related to improved survival outcome by univariate and mul-

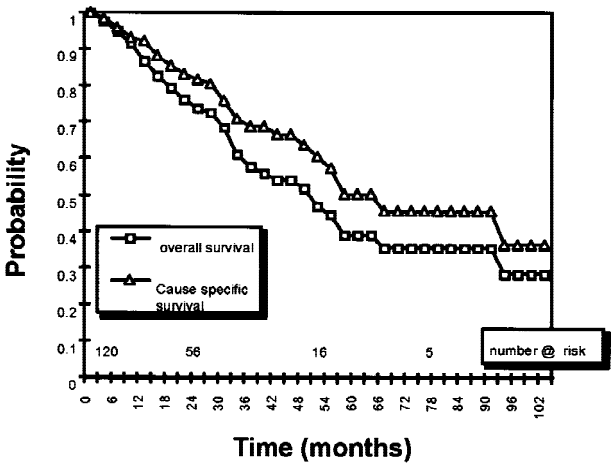

FIGURE 1. Actuarial overall and cause-specific survival.

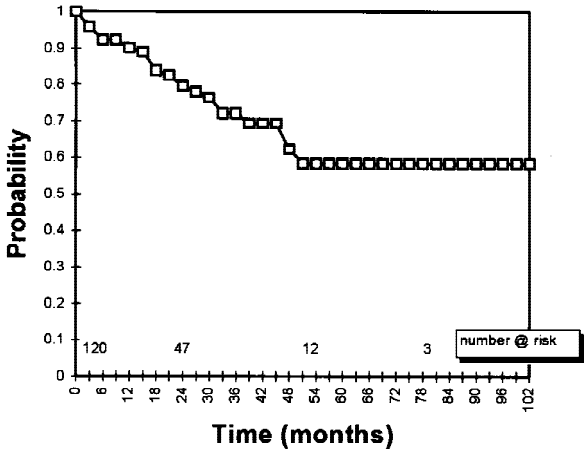

FIGURE 2. Actuarial locoregional control.

tivariate analysis and included the following variables: primary location, sex, tumor size, base of skull involvement, presenting status (primary versus recurrent), surgical resection status, histology (low grade defined as low grade mucoepidermoid, acinic cell, and low grade adenocarcinoma, high grade defined as all other histologies), prior conventional radiotherapy, presenting lymph node status, and whether an interruption in treatment was required during neutron radiotherapy. Results achieving statistical significance using a univariate analysis are shown in Table 1. Female sex, no lymph node involvement, low tumor histologic grade, a nonparotid primary site, a tumor size ⩽4 cm, and absent base of skull involvement were associated with improved overall survival. Upon multivariate analysis, however, only a tumor size ⩽4 cm and a sublingual/submandibular site of origin were statistically associated with improved survival (Table 1). Neither high grade histology, base of skull involvement, nor the presence of perineural invasion had a statistically significant negative impact on survival. The influence of histologic type on overall survival is shown in Table 2. Survival at 5 years was substantially better in patients with adenoid cystic and acinic cell histologies compared with all other histologic varieties.

Table 1. Overall survival.

	p Value	
Variable	Univariate	Multivariate
Sex (women vs men)	<.01	.08
Lymph node status (negative vs positive)	.01	.18
Tumor grade* (low vs high)	.03	.11
Tumor location (other vs parotid)	.02	.05
Tumor size (⩽4 cm vs >4 cm)	<.001	.004
Base of skull involvement	.05	0.57

**Low grade histology includes: low grade mucoepidermoid carcinoma, acinic cell, and low grade adenocarcinoma; high grade: all other histologies.*

Cause-specific survival was next examined by univariate and multivariate analysis (Table 3). Only tumor size >4 cm was associated with a statistically poorer outcome by multivariate analysis, with lymph node status and tumor location failing to achieve statistical significance. Figure 3 portrays the cause-specific survival by tumor size. Patients with a tumor size ⩽4 cm had a cause-specific survival rate of 75% at 5 years, compared with 23% for patients having larger tumors ($p = .002$).

Locoregional Control. Variables that potentially could effect locoregional control were next examined and included: primary location (parotid versus sublingual/submandibular), sex, tumor size, base of skull involvement, presenting status (primary versus recurrent), surgical resection status, tumor histology and histologic grade (as defined previously), prior radiotherapy, presenting lymph node status, and whether a treatment break was required. Results of the univariate analysis are shown in Table 4. A tumor size ⩽4 cm, a primary presentation, and previous surgical resection were associated with a statistically improved locoregional control, whereas base of skull involvement and prior radiotherapy were associated with a decreased locoregional control by univariate analysis. However, only tumor size 4 cm and a primary presentation remained significant ($p \leqslant .05$) upon multivariate analysis. The actuarial curves for locoregional control as a function of size is shown in Figure 4. We were unable to establish a dose response curve for this group of patients. Multivariate analysis showed only a tumor size ⩾4 cm and initial presenting status of a recurrent tumor to be statistically related with poorer locoregional control.

Several factors were then examined in the subgroup of patients who had undergone surgical resection of their tumors including tumor size and the presence of perineural invasion. No statistically significant difference was observed in patients with perinerual invasion versus no invasion (88% versus 75% 3-year actuarial locoregion-

Table 2. Five-year locoregional control and survival by histology.

Histology	No. of patients	Locoregional control (%)	Survival (%)	LN+* (%)
Adenocarcinoma	28	78	25	64
Adenoidcystic	38	53	78	26
Acinic cell	7	100	80	0
Mucoepidermoid	24	64	40	42
Squamous cell	6	42 (43 mos)	0 (56 at 40 mos)	30
Mixed malignant	4	0	0	25
Carcinoma NOS†	9	38	15 (40 mos)	22
Basaloid	3	50	0 (100 at 40 mos)	30

†*Not otherwise specified.*
**Lymph node–positive at presentation.*

al control). Tumor size was related to locoregional control rates in this group. Patients having a tumor size ⩽4 cm with a previous surgical resection had superior 5-year locoregional control rates compared with patients not undergoing surgical resection (89% versus 70% at 45 months, $p = .003$), but no statistically significant difference in overall survival or cause-specific survival was noted. Prior surgical resection was not found to be associated with improved locoregional control in patients with tumors ⩾4 cm (62% versus 33% at 45 months; $p = .32$) nor overall or cause-specific survival.

The influence of histologic type on locoregional control is shown in Table 2. Acinic cell carcinoma, adenocarcinoma, mucoepidermoid carcinoma, basaloid carcinoma, and adenoid cystic carcinoma histologies all had locoregional control rates that exceeded 50%. However, it should be noted that the seemingly good actuarial locoregional control rates observed in patients with adenocarcinomas and mucoepidermoid carcinomas is in part due to the poor overall survival for these histologic subtypes, ie, many patients died before being at risk long enough to fail locally. The number of patients initially seen with lymph node metastases by histologic type is also shown in Table 2. Adenocarcinoma and mucoepidermoid carcinomas were associated with a high likelihood of having lymph node metastases present at the time of treatment.

Table 3. Cause-specific survival.

Variable	*p* Value	
	Univariate	Multivariate
Sex (women vs men)	.08	.30
Tumor size (⩽4 cm vs >4 cm)	.001	.002
Tumor location (other vs parotid)	.06	.09
Lymph node status (negative vs positive)	.01	.07
Base of skull involvement	.03	.34

Development of Distant Metastases. Univariate analysis showed that patients who presented with positive lymph nodes at the time of treatment, a tumor size >4 cm, base of skull involvement or male sex were more likely to develop distant metastases at 5 years. By multivariate analysis lymph node involvement, base of skull involvement and sex achieved statistical significance (Table 5). Fifty-two percent patients presenting with nodal involvement developed distant metastases compared to 32% of patients who were node negative ($p = 0.04$) and the time to development of distant disease was abbreviated in lymph node positive patients compared to node

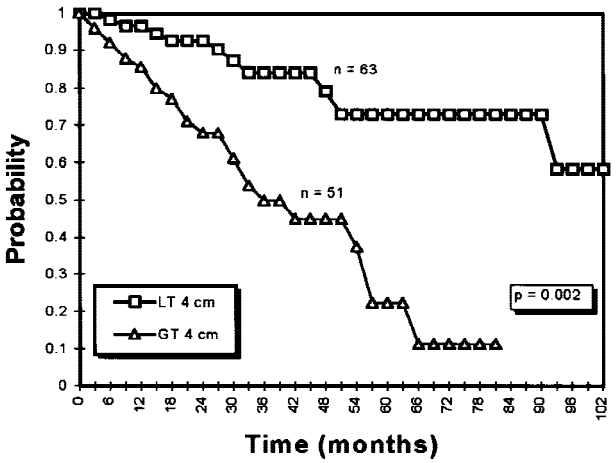

FIGURE 3. Actuarial cause-specific survival for patients with a tumor size ⩽4 cm versus tumor size >4 cm; the number of patients in each category is indicated in the figure. The *p* value for the difference between the two groups is .002.

Table 4. Locoregional control.

Variable	*p* Value	
	Univariate	Multivariate
Prior radiotherapy	.001	.16
Tumor size (≤4 cm vs >4 cm)	.001	.004
Surgical resection (yes vs no)	.001	.15
Primary vs recurrent	.001	.05
Base of skull involvement	.02	.14
Grade (low vs high)*	.08	.44

**Low grade histology includes: low grade mucoepidermoid carcinoma, acinic cell, low grade adenocarcinoma; high grade: all other histologies.*

Table 5. Development of distant metastasis.

Variable	*p* Value	
	Univariate	Multivariate
Lymph node status (negative vs positive)	.03	.04
Sex (women vs men)	.02	.02
Base of skull involvement	.01	.03
Tumor size (≤4 cm vs >4 cm)	.04	.18

negative patients (Fig. 5). Comparison of the of the 3 largest histologic types included in the "high grade" histology group by univariate analysis showed that patients with adenocarcinomas were more likely to develop distant metastases than the remainder of the group (adenoid cystic and mucoepidermoid carcinoma, $p < 0.01$). Patients having adenocarcinomas accounted for 54% of the group who developed distant metastases while only representing 23% of the patient cohort. Patients having adenoidcystic carcinomas, on the other hand, accounted for only 16% of patients developing distant metastases, while representing 32% of the entire patient cohort.

Radiation-Related Complications. The joint Radiation Therapy Oncology Group/European Organization of Radiation Treatment Centers (RTOG/EORTC) grading system was used to quantify the severity of untoward, radiation-related side effects. Seven of the 120 patients developed grade 3 or 4 late toxicities including osteoradionecrosis of the inner ear ossicles with subsequent deafness on the treated side and optic neuritis ($n = 1$), soft tissue necrosis or ulceration ($n = 2$), radiation-induced cervical myelopathy ($n = 1$), progressive sensory loss of the V2 branch of the trigeminal nerve ($n = 1$), radiation necrosis of the temporal/frontal lobe of the brain ($n = 1$), and degeneration of the right mandibular ramus ($n = 1$). Of these seven patients, only one had previously received conventional radiotherapy and was treated for recurrent disease; 1 additional patient was treated for recurrent disease; 5 of the 7 had attempted surgical extirpation just prior to neutron radiotherapy. Late effects related to the hearing apparatus are not specifically included in the RTOG/EORTC grading system. Nineteen of the 148 patients had some degree of hearing loss. Of these 19 patients, 1 had previously received conventional radiotherapy for a salivary gland tumor and 1 additional patient received radiotherapy for

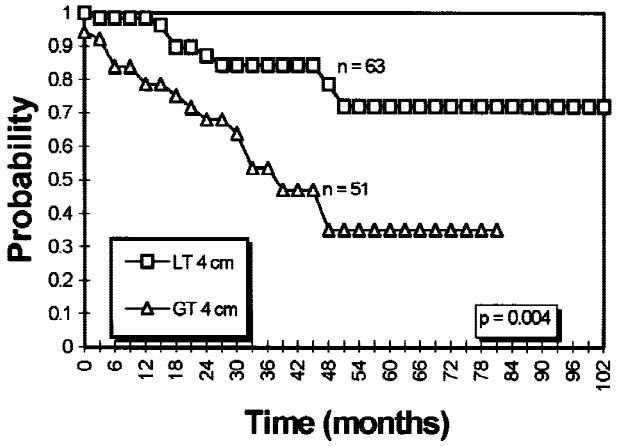

FIGURE 4. Actuarial locoregional control in patients with a tumor size ≤4 cm versus tumor size >4 cm; the number of patients in each category is indicated in the figure. The *p* value for the difference between the groups is .004.

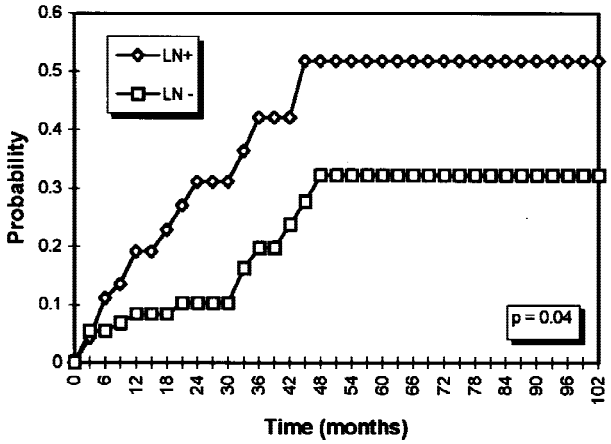

FIGURE 5. Time to development of distant metastases as a function of lymph node status at the time of presentation. The curves are statistically different at a $p = .04$ level.

otitis media as a child (dose unknown); 2 were treated for recurrent disease; and 12 had surgery prior to neutron radiotherapy. Perineural status was documented in 8 of the patients and was positive in 7. Six patients had complete unilateral hearing loss, with 1 of these patients, as previously mentioned, having an osteoradionecrosis of the ossicles of the middle ear, 2 patients having documented sensorineural hearing loss, whereas the etiology of the hearing loss in the remaining 3 patients is unknown.

DISCUSSION

The treatment of malignant salivary gland tumors has progressively changed over the past 50 years.[4] With the realization that tumor size, local extension, and nodal involvement adversely impact survival,[20] a new staging system was proposed and subsequently adopted by the AJCC. It became apparent that patients with more advanced stage disease and/or patients in whom a total resection of the tumor was not possible fared poorly without additional therapy.[2,5,6,11] Fu et al[7] reported a 54% local recurrence rate in patients with malignant salivary gland tumors of both major and minor origin, in whom margins were positive or close after surgical resection alone. They as well as others have clearly shown a benefit with the addition of conventional photon radiotherapy in patients in whom a complete resection cannot be achieved.[2,3,6–9] For the most part, these improved outcomes with the addition of conventional radiotherapy have been greatest in advanced stage disease (stages III and IV),[2,4,7] with substantial improvements noted in both locoregional control and survival. Despite these improved results from the addition of conventional radiotherapy in advanced stage disease, the overall survival and local control has been disappointing. Additionally, the outcome of patients treated for recurrent disease has been even worse.[8,21]

Neutron radiotherapy has been shown to be superior to conventional low-LET radiotherapy in the setting of locally advanced, inoperable, or recurrent salivary gland tumors.[1,2,14–17,22,23] This paper updates our experience treating patients with locally advanced malignant tumors of the major salivary glands. Fifty percent of the patients treated had stage III or IV disease, 100% had multiple positive margins or gross residual disease, and 24% were treated for recurrent tumors. Thus, these patients represent a high risk population, which must be kept in mind when these results are compared with those of other series.

The overall actuarial locoregional control for curatively treated patients was 58% at 5 years for all stages. On univariate analysis, attempted surgical extirpation of the tumor prior to neutron radiotherapy appeared beneficial. Patients who had a surgical resection prior to neutron radiotherapy had a locoregional control rate of 80%, despite the inability to completely excise the tumor, compared with 12% if no surgery was undertaken. This locoregional control rate of 80% is superior to that reported from other series for comparable patients.[1–5,7,9] The 100% locoregional control rate found in patients with negative margins, treated for other risk factors, is very encouraging, although the small number of patients in this group precludes making any definitive treatment recommendations. Prior resection, however, was not found to be statistically significant when included in a multivariate analysis of other factors found to be significant on univariate analysis including tumor size, presenting status, grade, base of skull involvement, and prior conventional radiotherapy. This most likely reflects the overwhelming influence of tumor size in this group (ie, patients with tumors $\leq$4 cm in size were more likely to have undergone surgical resection than were those patients with larger tumors, and most likely, less tumor bulk remained at the time of treatment). We found no difference in either locoregional control or survival in tumors $\leq$2 cm versus a size of 2 to 4 cm. Tumor size has also been reported by others to be a poor prognostic factor.[3,4,24] Our data also suggest that patients with recurrent disease have poorer locoregional control than do patients treated for primary tumors ($p = .05$). This again may be a reflection of bulk of disease at the time of treatment. The diminished locoregional control found by univariate analysis in patients with base of skull involvement and those having had previous radiotherapy may be related to dose constraints secondary to tumor location close to sensitive normal tissues (central nervous system) or prior full dose conventional radiotherapy. Similar findings have been reported for patients with adenoid cystic carcinoma of minor salivary glands treated with neutron radiotherapy.[25]

The presence of perineural invasion has been reported to have prognostic significance in some series, particularly adenoid cystic carcinomas,[26] but has been reported to be not significant in other reports.[25,27,28] We did not find any prognos-

tic significance to the presence or absence of perineural invasion in our cohort of patients. This may be because of a bias in our data base (only 53% of patients had documentation of perineural status). We are currently reevaluating the initial pathology from this patient cohort to clarify this issue. Furthermore, we routinely treat the base of skull to 12 neutron Gy in patients with documented perineural invasion as part of our initial treatment plan, and this may negate any deleterious effect perineural involvement might have.

The influence of histologic type and grade on locoregional control and survival has been examined by numerous investigators.[3,6,8,11,12,24] For the purpose of this analysis, tumor grade was divided into two categories: low grade, defined as low grade mucoepidermoid, acinic cell, and low grade adenocarcinoma; high grade, which included all other histologies. Although low grade tumors had a statistically improved overall survival compared with high grade tumors by univariate analysis, no difference was detected in cause-specific survival, locoregional control, or in the development of distant metastases, and on multivariate analysis, no statistically significant difference was noted in any of the aforementioned parameters. When specific histologic subtypes were evaluated, patients with adenoid cystic carcinomas, acinic cell carcinomas, and basaloid carcinomas had both good locoregional control rates and overall survival rates compared with other histologies. These results are consistent with the previously mentioned reports.[3,6,8,11,12,24]

Lymph node involvement has uniformly been found to be a poor prognostic factor.[8,11,21,24] Our analysis indicates that lymph node status alone was not a statistically significant risk factor for locoregional failure or diminished survival (both overall and cause-specific survival) by multivariate analysis. However, patients who were initially seen with lymph node involvement were more likely to develop distant metastases than were lymph node–negative patients (52% versus 32%; $p = .04$) and developed metastases sooner. The development of distant metastases was also found to be associated with male sex and base of skull involvement. The increased rate of metastases in men appears to be related to a specific histology, ie, adenocarcinoma. Patients with adenocarcinomas accounted for a proportionately higher percentage of patients who developed metastases (54%), and 80% of patients with adenocarcinomas were men. Base of skull involvement has also been shown to be a poor prognostic factor in adenoid cystic carcinomas of minor salivary glands.[25] The fact that lymph node involvement was associated with a higher likelihood of distant metastases but not with overall survival may be a reflection of the overwhelming effect of tumor size on survival outcome.

Six percent of patients developed grade 3 or 4 complications using the RTOG/EORTC grading system. An additional 15% of patients developed some degree of hearing loss on the treated side. The hearing loss was complete on the affected side in 6 of the 19 patients. Two had documented sensorineural hearing loss, 1 developed osteoradionecrosis of the middle ear ossicles, and in 3 patients, the etiology was not documented. Vertigo was reported to be present in 3 of the 19 patients and severe tinnitus in 1 patient. It thus appears that the hearing apparatus and the eighth cranial nerve are at risk for late complications. Of these 19 patients, perineural involvement was present in 7, not present in 1, and not documented in 11 patients. Other potential risk factors such as base of skull involvement, previous conventional radiotherapy, treatment for recurrent disease, prior surgery, and stage appeared to have a similar distribution in this group compared with the overall cohort of patients. Whether this complication is caused by neutron radiotherapy or whether other factors are involved, particularly perineural invasion of the eighth cranial nerve, cannot be determined from our data. We plan to begin obtaining pre- and posttreatment audiometric testing to ascertain the incidence and severity of this complication.

In summary, the overwhelming variable associated with favorable locoregional control and survival was tumor size. Patients treated with tumors ≤ 4 cm had excellent outcomes, with a locoregional control rate of 80% at 5 years and an overall survival rate of 61% for all histologic types. Neutron radiotherapy, thus, is an effective form of therapy for patients with high risk tumors of major salivary gland origin. Survival remains suboptimal largely because of the development of distant metastases. Fifty-two percent of patients initially seen with lymph node metastases at the time of initial presentation developed distant metastases which negatively impacted their overall survival. The need for effective, systemically active agents in this population is self- evident.

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