Objective: To evaluate the efficacy of fast neutron radiotherapy for the treatment of salivary gland neoplasms.

Design: Retrospective analysis.

Setting: University of Washington Cancer Center, Neutron Facility, Seattle.

Patients: The medical records of 279 patients treated with curative intent using fast neutron radiotherapy at the University of Washington Cancer Center were reviewed. Of the 279 patients, 263 had evidence of gross residual disease at the time of treatment (16 had no evidence of gross residual disease), 141 had tumors of a major salivary gland, and 138 had tumors of minor salivary glands. The median follow-up period was 36 months (range, 1-142 months).

Main Outcome Measures: Local-regional control, cause-specific survival, and freedom from metastasis.

Results: The 6-year actuarial cause-specific survival rate was 67%. Multivariate analysis revealed that low group stage (I-II) disease, minor salivary sites, lack of skull base invasion, and primary disease were associated with a statistically significant improvement in cause-specific survival. The 6-year actuarial local-regional control rate was 59%. Multivariate analysis revealed size 4 cm or smaller, lack of base of skull invasion, prior surgical resection, and no previous radiotherapy to have a statistically significant improved local-regional control. Sixteen patients without evidence of gross residual disease had a 100% 6-year actuarial local-regional control. The 6-year actuarial freedom from metastasis rate was 64%. Factors associated with decreased development of systemic metastases included negative lymph nodes at the time of treatment and lack of base of skull involvement. The 6-year actuarial rate of development of grade 3 or 4 long-term toxicity (using the Radiation Therapy Oncology Group and European Organization for Research on the Treatment of Cancer criteria) was 10%. No patient experienced grade 5 toxic effects.

Conclusions: Neutron radiotherapy is an effective treatment for patients with salivary gland neoplasms who have gross residual disease and achieves excellent local-regional control in patients without evidence of gross disease.


SALIVARY GLAND malignancies are relatively rare entities, accounting for approximately 5% of all head and neck cancers.1,2 Treatment of these tumors generally involves surgical resection followed by the use of postoperative radiotherapy for incompletely resected tumors or those with other high-risk factors such as perineural invasion, bone invasion, and lymph node involvement.3,4 The use of postoperative irradiation has been shown to improve local-regional control and survival, particularly in advanced-stage disease (stages III and IV).3,4,5

Conventional photon irradiation in the setting of locally advanced disease, recurrent disease, and/or surgically unresectable disease has demonstrated poor local-regional control rates of approximately 25%.6 Over the past 15 years, retrospective studies and a single prospective randomized trial have shown an advantage in local-regional control with the use of “high linear energy transfer (LET)” neutron radiotherapy compared with photons (low LET).7-10 This report updates our experience treating salivary gland neoplasms with fast neutron radiotherapy.

METHODS

The medical records of patients treated with fast neutron radiotherapy at the University of Washington Cancer Center, Seattle, were reviewed retrospectively, and 303 patients with salivary gland neoplasms were identified. During this period, all patients referred to our institution with salivary gland neoplasms were treated with neutron radiotherapy. Twenty-three of these patients presented with distant metastases at the time of treatment or were treated with local palliative intent and were removed from this analysis. One patient had no documented follow-up and was removed from this analysis, leaving 279 patients for evaluation.

PATIENT CHARACTERISTICS

Of the 279 patients, 263 had evidence of gross residual disease at the time of treat-
ment, which was defined as having 1 or more of the following findings: the presence of multiple positive margins, radiographic evidence for residual disease, and/or a surgical report documenting the presence of residual disease. Sixteen patients had no evidence of gross residual disease (defined as having 1 or more of the following findings: a locally positive margin and no radiographic evidence for residual disease and/or indeterminate margins with no clinical or radiographic evidence for gross residual disease). Patients not having gross residual disease had other high-risk factors including perineural invasion, recurrent disease, or bone or vascular invasion. The median age at time of treatment was 53.6 years. The female-male patient ratio was 1.2:1. Of the patients, 40% were treated for recurrent tumors; 24% had base of skull involvement; 22% presented with lymph node involvement; and 9% had previously been treated with full-dose photon radiotherapy. The median follow-up period was 36 months (range, 1-142 months). Four patients were lost to follow-up at 3, 6, 9, and 22 months.

SITES OF DISEASE

Tumors of a major salivary gland occurred in 141 patients with the following distribution: 118 parotid primary tumors and 23 submandibular or sublingual gland tumors. Tumors of minor salivary glands occurred in 138 patients with the following subsite distribution: 43 paranasal sinus tumors, 33 oral cavity tumors, 22 nasopharyngeal tumors, 19 oral pharyngeal tumors, 8 lacrimal gland tumors, 6 miscellaneous sites, 5 tracheal tumors, and 2 auditory canal tumors.

STAGING

Tumors arising in the major salivary glands were staged according to staging criteria as published by the American Joint Committee on Cancer (AJCC) in 1998. This staging system is primarily based on the size of the primary lesion and the presence or absence of lymph node involvement. Macroscopic evidence of invasion into other tissues (eg, nerve and bone) is secondarily used to subdivide the tumor stage (T stage).

Currently, there is no adequate staging system for tumors arising in minor salivary glands. The AJCC system stages such tumors by applying the same site-specific criteria as squamous cell carcinoma of the head and neck, and no accepted staging criteria have been developed for sites such as the trachea, nasal cavity, ethmoid sinuses, and sphenoid sinuses. No attempt has been made to subdivide the tumor stage by the presence or absence of tissue invasion as is used for major salivary gland tumors, and thus there is currently no uniformity for the staging of salivary gland tumors. In addition, the applicability of the AJCC staging system to patients with recurrent disease is uncertain.

Documentation was available to stage the primary tumor according to the 1998 AJCC criteria in 259 patients (93%) with the following distributions: T1, 8%; T2, 30%; T3, 20%; and T4, 42%. Documentation was present to classify patients by group stage in 267 patients (96%) with the following distribution: group 1, 20%; group 2, 15%; group 3, 20%; and group 4, 45%.

HISTOLOGY

The following histological distribution was found: adenoid cystic carcinoma, 68%; mucoepidermoid, 11%; adenocarcinoma, 10%; acinic cell, 3%; squamous cell, 2%; basaloid, 1%; and other, 5%. Squamous cell tumors were determined to be primary tumors of the salivary glands if no other primary tumor was found at the time of diagnosis and pathologic examination determined that the tumor was not a metastatic lesion to a salivary lymph node. The histologic type of all but 2 of 138 tumors in patients with minor salivary gland primary tumors was adenoid cystic carcinoma.

TREATMENT TECHNIQUE

All patients were treated with fast neutrons using a Scanditronix cyclotron (Scanditronix, Uppsala, Sweden) with a 50.5-meV proton → beryllium reaction as previously described. The depth-dose characteristics of this beam are similar to that of an 8-mV photon beam. The unit has isocentric capabilities with a rotating gantry. Conformal field shaping is accomplished by the use of multileaf collimation. Fraction sizes ranged from 1.05 to 1.7 nGy (neutron Gray) administered 3 or 4 times per week. The total dose delivered varied from 17.4 nGy to 20.7 nGy. The most commonly used fractionation schema was 1.2 nGy per fraction treated 4 days a week to a total dose of 19.2 nGy.

STATISTICAL ANALYSIS

Local-regional control rates, survival rates, rates of developing distant metastases, and complication rates were calculated using the Kaplan-Meier product-limit method. The log-rank test (2-tailed) was used to evaluate for statistically significant differences between outcome curves. Univariate and multivariate analyses were performed using the Statview 4.5 statistical package (Abacus Concepts Inc, Berkeley, Calif, 1996). All variables having a univariate P value of ≤ .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.

RESULTS

SURVIVAL

The 6-year actuarial overall survival was 59%. The 6-year actuarial cause-specific survival was 67% (Figure 1). Multiple factors were then examined by univariate and multivariate analysis to determine those associated with improved cause-specific survival and are shown in Table 1. By univariate analysis, group stage I and II disease, minor tumor sites, negative lymph nodes, size <4 cm or smaller, no base of skull involvement, previous surgical resection, and microscopic disease at time of treatment were found to be associated with an improved outcome. On multivariate analysis, group stage I and II disease, minor salivary sites, lack of base of skull invasion, and primary disease were statistically significant for improved survival.
The 6-year actuarial local-regional control was 59%. Multiple factors were then examined by univariate and multivariate analysis to determine those associated with improved local-regional control and the results are given in Table 2. Improved local-regional control was associated with primary disease, no base of skull involvement, prior surgical resection, group stage I and II disease, size 4 cm or smaller, no previous radiotherapy, and microscopic residual disease at the time of treatment. Lack of base of skull involvement, size 4 cm or smaller, no previous radiotherapy, and prior surgical resection remained significant on multivariate analysis for improved outcome. Patients having these characteristics (n=69) had a 6-year actuarial local-regional control rate of 90%. The 16 patients having no evidence for macroscopic disease had a local control rate of 100% (Figure 2).

**LOCAL-REGIONAL CONTROL**

The 6-year actuarial local-regional control was 59%. Multiple factors were then examined by univariate and multivariate analysis to determine those associated with improved local-regional control and the results are given in Table 2. Improved local-regional control was associated with primary disease, no base of skull involvement, prior surgical resection, group stage I and II disease, size 4 cm or smaller, no previous radiotherapy, and microscopic residual disease at the time of treatment. Lack of base of skull involvement, size 4 cm or smaller, no previous radiotherapy, and prior surgical resection remained significant on multivariate analysis for improved outcome. Patients having these characteristics (n=69) had a 6-year actuarial local-regional control rate of 90%. The 16 patients having no evidence for macroscopic disease had a local control rate of 100% (Figure 2).

**FREEDOM FROM METASTASES**

The 6-year actuarial freedom from metastasis was 64% (Figure 3). Factors associated with development of metastases by univariate analysis included primary size larger than 4 cm, lymph node involvement, base of skull invasion, and group stage III and IV disease (Table 3). On multivariate analysis, lymph node involvement and base of skull invasion were associated with an increased likelihood of developing distant metastases (Table 3). Patients not having these 2 high-risk factors (n=153) had a 6-year actuarial freedom from metastases of 74% (Figure 3).
ure 3). Figure 3 shows graphically the association of these 2 variables on the development of metastases.

HISTOLOGY

As mentioned previously, all but 2 patients with minor salivary gland tumors had adenoid cystic carcinomas. Historical analysis was performed for patients having major salivary gland tumors and the results are given in Table 4. Statistical analysis was not performed because of the small number of patients in several of the histologic groups.

TOXICITY

Toxicity was determined using the Radiation Therapy Oncology Group and European Organization for Research on the Treatment of Cancer (RTOG-EORTC) toxicity scale. The 6-year actuarial development of grade 3 or 4 toxic effects was 10%. No patient developed grade 5 toxic effects, either in the short or long term. Specific toxic effects involved the following: osteoradionecrosis of the inner ear ossicles with resulting deafness (1 patient), cervical myelopathy (1 patient), central nervous system radiation necrosis (4 patients), optic neuritis with subsequent blindness (3 patients), palatal fistula (1 patient), acute angle glaucoma requiring enucleation (1 patient), osteoradionecrosis of the mandible or facial bones (4 patients), and retinopathy with resultant blindness (2 patients). Multiple factors were examined by univariate analysis and multivariate analysis to determine any relationships with toxicity and the results are given in Table 5. On multivariate analysis, patients not having gross residual disease and those previously having conventional radiotherapy had a significantly less incidence of grade 3 or 4 toxic effects, with those with tumors of major sites having borderline lower incidence. On multivariate analysis, however, no factors remained statistically significant.

The overall local-regional control was 59% at 6 years and is quite superior to those results mentioned above. Four factors were associated with local-regional control rates: size (prior to surgery if surgery performed), extension into the base of skull region, attempted surgical resection, and prior radiotherapy. Two of these factors are most likely related to the dose of neutron radiation delivered. Prior full-dose conventional irradiation limits the ability to give full-dose neutron irradiation because of the accumulative effects on normal tissues. Base of skull extension is also dose limiting because of the sensitivity of central nerve system structures to neutron radiotherapy. We are currently investigating the addition of a single fraction stereotactic photon boost or proton boost to the area of base of skull invasion after completion of neutron radiotherapy in this cohort of patients.

The remaining 2 factors appear to be related to the amount of disease present at the time of treatment in that smaller tumors at presentation or tumors “debulked” had improved local-regional control. In addition, the excellent outcome of the 16 patients having only “microscopic” disease at the time of treatment substantiates this hypothesis. The outcome of patients with microscopic disease compares favorably to the series reported by Garden et al.3

Cause-specific survival was also influenced by the presence of base of skull invasion in a negative fashion, most likely explained by the increased local failure and increased rate of the development of distant metastases. In addition, higher group stage, recurrent disease, and site of disease (major vs minor) were associated with lower survival rates. The improved survival of patients with minor sites of disease was somewhat surprising in that most pa-

Table 4. Major Salivary Gland Tumor Outcomes by Histologic Type

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>No. of Patients</th>
<th>Local-Regional Control, %</th>
<th>Cause-Specific Survival, %</th>
<th>Freedom From Metastases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoid cystic</td>
<td>53</td>
<td>61</td>
<td>77</td>
<td>60</td>
</tr>
<tr>
<td>Acinic</td>
<td>8</td>
<td>100</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>28</td>
<td>78</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Mucoepidermoid</td>
<td>27</td>
<td>72</td>
<td>51</td>
<td>86</td>
</tr>
<tr>
<td>Basaloid</td>
<td>4</td>
<td>67</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>7</td>
<td>40</td>
<td>63</td>
<td>100</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>32</td>
<td>32</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 5. Six-Year Actuarial Incidence of Grade 3 and 4 Toxic Effects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Toxicity, %</th>
<th>Univariate P Value</th>
<th>Multivariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor/major site</td>
<td>10/7</td>
<td>.08</td>
<td>.11</td>
</tr>
<tr>
<td>Primary/recurrent</td>
<td>10/10</td>
<td>.54</td>
<td>NT</td>
</tr>
<tr>
<td>Male/female</td>
<td>7/10</td>
<td>.15</td>
<td>NT</td>
</tr>
<tr>
<td>Previous XRT, no/yes</td>
<td>10/0</td>
<td>&lt;.05</td>
<td>.94</td>
</tr>
<tr>
<td>GRD, no/yes</td>
<td>0/10</td>
<td>&lt;.05</td>
<td>.96</td>
</tr>
<tr>
<td>Previous surgery, no/yes</td>
<td>8/12</td>
<td>.4</td>
<td>NT</td>
</tr>
<tr>
<td>BOS −/+</td>
<td>7/10</td>
<td>.2</td>
<td>NT</td>
</tr>
<tr>
<td>Size ≤4/&gt;4 cm</td>
<td>8/12</td>
<td>.4</td>
<td>NT</td>
</tr>
<tr>
<td>Lymph node −/+</td>
<td>10/5</td>
<td>.61</td>
<td>NT</td>
</tr>
</tbody>
</table>

Abbreviations: BOS, base of skull; GRD, gross residual disease; NT, not tested; XRT, photon radiotherapy; −, negative; +, positive.
tients with base of skull invasion were in this group. However, almost all of patients with minor salivary gland tumors had adenoid cystic carcinomas and that histologic type is associated with an improved cause-specific survival. This is in agreement with other published series.4,5,20-25

The overall rate of development of distant metastases was 40% at 6 years. Base of skull involvement was associated with a higher rate of metastases, as was the presence of lymph nodes. In addition, patients with positive lymph nodes developed metastases at an abbreviated interval compared with patients presenting with negative nodes. This remains consistent with our earlier reports.12,14,18

As mentioned previously, all but 2 patients with tumors of minor sites had adenoid cystic carcinoma. For this reason, the effect of histologic type was examined only in patients with major salivary gland tumors. Different patterns of failure were observed among the varying histologic types, with the highest rates of distant metastases occurring in patients with adenocarcinomas; those not fitting into the more common histologic types (other) had rates of 60% to 65%. In patients with adenoid cystic carcinomas, 40% developed metastases. Low rates of metastases were observed in patients with acinic cell, mucoepidermoid, and basaloid histologic types, which was expected for patients with lower-grade lesions. Local-regional failure or progression was seen most often in patients with squamous cell and “other” histologic types. The apparent excellent actuarial local control observed for patients with adenocarcinoma may be attributed in part to the poor survival due to deaths from metastatic disease.

The 6-year actuarial incidence of grade III or IV toxic effects according to the RTOG-EORTC scaling system was 10%. One third of these complications were anticipated because of the location of the lesion. Patients were counseled regarding the likelihood of such complications before proceeding with treatment. We were not able to identify factors statistically associated with an increased risk of grade III or IV toxic effects, which was most likely owing to the small number of events limiting the power to detect such differences. This is an acceptable risk for these patients with poor prognoses.

CONCLUSIONS

Neutron radiotherapy is an effective treatment for patients with salivary gland neoplasms who have gross residual disease, and it achieves excellent local-regional control in patients without evidence for gross disease. Local-regional control and survival continues to be suboptimal in patients with base of skull invasion. Surgical resection prior to neutron radiotherapy improves local-regional control and is indicated when feasible. Even though local-regional control is poor in patients who previously were treated with photon irradiation, long-term survival can be achieved in many of these high-risk patients (6-year actuarial cause-specific survival, 40%) and should be considered as salvage therapy. Distant metastatic disease remains the major cause of death and morbidity. Strategies to prevent and/or treat distant spread must be developed, or there will be little change in overall survival in these patients. The expression of potential targets for chemotheraphy agents, such as C-erb2 and C-kit, on the surface of a proportion of salivary gland tumors may offer effective therapies for metastatic disease in the future.

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Corresponding author and reprints: James G. Douglas, MD, MS, Department of Radiation Oncology, University of Washington, PO Box 356043, Seattle, WA 98195-6043 (e-mail: drjay@uwashington.edu).

REFERENCES