ORIGINAL ARTICLE

GAMMA KNIFE STEREOTACTIC RADIOSURGERY FOR SALIVARY GLAND NEOPLASMS WITH BASE OF SKULL INVASION FOLLOWING NEUTRON RADIOTHERAPY

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Abstract: *Background.* Our aim was to examine the outcome of patients treated with a planned gamma knife boost after completion of neutron radiotherapy for salivary gland neoplasms involving the base of skull.

Methods. Thirty-four patients with salivary gland neoplasms involving the base of skull were treated from 2001 to 2005 at our institution. These results were compared with a similar historical group treated at our institution from 1984 to 2000. The patients had the following characteristics: median age: 54 years (range, 23–80); median follow-up period: 20.5 months (range, 4–55); women-to-men patient ratio: 1.1:1; histology: 29 adenoid cystic, 3 adenocarcinoma, 1 acinic cell, 1 mucoepidermoid; primary sites of disease: 6 nasopharyngeal, 14 paranasal sinuses, 4 parotid gland, 8 oral cavity, 1 lacrimal gland, and 1 auditory canal. All patients had gross residual disease at the time of treatment. The median neutron dose prescribed to isocenter was 19.2 nGy and the median dose to the effected temporal tip was 11.98 nGy. The median prescribed gamma knife dose was 12 Gy to the 50% isodose line. The median number of isocenters was 17. The median target volume treated was 12.4 cm^3 (range, 1.9–28.9) with a median total volume treated of 18.3 cm^3 (range, 5.9–53.9).

Results. The 24-month and 40-month Kaplan–Meier estimated local control was 82% versus 81% (24 months) and 82% versus 39% (40 months; $p = .04$) for the gamma knife treated group versus historical controls ($n = 61$). Two of the 4 failures in the gamma knife–treated group occurred outside the boosted area. Complications were no greater in the gamma knife–treated group than in those treated with neutron radiotherapy alone.

Conclusions. Patients with primary salivary gland neoplasms that involve the base of skull and are treated with neutron radiotherapy alone are at high risk of local recurrence. A gamma knife boost improves local control and adds little additional toxicity. These preliminary results suggest that all patients with salivary neoplasms and base of skull invasion should be considered for a gamma knife boost after primary treatment with neutron radiotherapy. *Head Neck* **30:** 492–496, 2008

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Salivary gland malignant tumors account for approximately 2% to 4% (incidence of 1–2 per 100,000) of all head and neck tumors.[1] The predominant histological variant for salivary glands malignancies involving the minor salivary glands is adenoid cystic carcinoma (ACC).[2] A Radiation Therapy Oncology Group (RTOG) study randomly

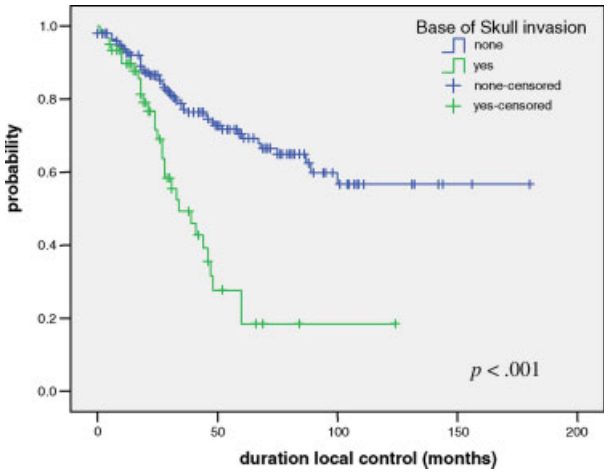

FIGURE 1. Kaplan–Meier plots comparing 198 patients treated with neutron irradiation and having no base of skull invasion versus 61 patients treated with neutron irradiation and base of skull invasion ($p < .001$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

assigned patients with gross residual disease with salivary gland neoplasms of all histologies concluded that neutron radiotherapy (NRT) was superior to photon irradiation (X-ray).[3,4] Thirty-two patients were enrolled, and the study was terminated after the criteria for early termination of the trial were reached, as monitored by the data safety committee.[3,4] Though controversy remains regarding the best form of therapy for these patients, we have treated patients having salivary gland malignancies with NRT for over 22 years at our current facility. Previously presented data from our group has identified several prognostic factors, both for tumors involving the major salivary glands and minor salivary glands.[5–7] In our analysis, 1 of the most significant prognostic factors identified was base of skull invasion.[8] Patients not having base of skull involvement ($n = 198$) had a Kaplan–Meier estimated 5-year local control rate of 70% versus those having base of skull invasion ($n = 61$) of only 19% at 5 years (Figure 1, $p < .001$). We postulated that because of the higher radiobiological effective dose (RBE) of neutrons for central nervous system structures (RBE = 4 to 4.5) versus an RBE of 3 to 3.5 for normal soft tissue,[9] areas of the tumors invading above the lower portion of the temporal lobes were relatively underdosed with NRT (median dose, 11.98 neutron Gray [nGy]). We further postulated that the addition of a single stereotactic boost using gamma knife technology might provide additional dose and as a result improve local control.

In 2001 we began boosting all patients with salivary gland malignancies and skull base invasion with a gamma knife boost. A description of the technique and rationale for dosing has previously been published.[10] Our early experience suggested no increase in the complication rate using this approach.[10] Based on our initial experience with doses ranging from 8 to 12 Gy, we have more recently used a dose of 12 Gy to the majority of the tumor volume, unless normal tissue constraints (most commonly the optic structures) and patients' desires to avoid late complications (blindness) intervened. We report our experience with 34 patients treated with a gamma knife boost and compared those results to 61 historical controls who did not receive a boost. All were treated similarly with NRT prior to the gamma knife boost.

MATERIALS AND METHODS

Patient characteristics are summarized in Table 1 and include the patients treated with a gamma

Table 1. Patient characteristics.

	Control patients ($n = 61$)	Gamma knife boosted patients ($n = 34$)
Median age (range), y	54.5 (22–80)	54 (23–80)
Male/female ratio	0.89:1	1:1.1
Primary site of disease		
Nasopharynx	16	6
Paranasal sinuses	16	14
Parotid gland	17	4
Oral cavity	4	8
Lacrimal gland	1	1
Auditory canal	0	1
Oral pharynx	2	0
Submandibular gland	1	0
Other	4	0
Histology		
ACC	47	29
ADNCA	3	3
ACN	0	1
ME	4	1
SCC	2	0
Other	5	0
Surgery, %	48	32
Residual disease		
GRD	61	34
Median follow-up, mo	56.5	20.5

Abbreviations: ACC, adenoid cystic carcinoma; ADNCA, adenocarcinoma; ACN, acinic cell carcinoma; ME, mucoepidermoid; SCC, squamous cell carcinoma; GRD, gross residual disease.

knife boost as well as the control patients. Briefly, patients treated with a gamma knife boost had the following characteristics: median age was 54 years (range, 23–80); median time of follow-up was 20 months (range, 4–55 months); men-to-women patient ratio was 1:1.1; primary sites of disease included nasopharynx ($n = 6$), paranasal sinuses ($n = 14$), oral cavity ($n = 8$), parotid gland ($n = 4$), 1 lacrimal gland ($n = 1$), and auditory canal ($n = 1$). Histology consisted of ACC ($n = 29$); adenocarcinoma ($n = 3$); acinic cell carcinoma ($n = 1$); and mucoepidermoid carcinoma ($n = 1$). Eleven patients (32%) underwent surgical resections prior to NRT, with the remaining 23 patient having biopsies only. At the time of gamma knife boost, all patients had gross residual disease as defined by imaging studies ($n = 33$) or by multiple positive margins ($n = 1$).

Treatment Parameters. Patients were treated with NRT to a median dose to isocenter of 19.2 nGy. The median dose to the temporal tip on the effected anatomic side was 11.98 nGy, resulting in relative underdosing of the superior tumor volume. The gamma knife boost was administered a median of 2 weeks from the completion of neutron irradiation (range, 0 days–3 months). The median dose prescribed was 12 Gy to the 50% isodose line (range, 8–14). The median number of isocenters was 17 (range, 1–24). The median target volume was 12.4 cm^3 (range, 1.9–28.9 cm^3). The median total volume treated was 18.3 cm^3 (range, 5.9–53.9 cm^3). The median conformity index (total volume receiving the prescribed dose divided by the total target receiving the prescribed dose) was 1.57 (range, 1.3–3).

Historical Controls. Sixty-one patients with base of skull invasion who were treated prior to March 2001 served as the historical controls. Patient characteristics are presented in Table 1 and are similar to the gamma knife boosted patients.

RESULTS

Local Control. The 24-month and 40-month Kaplan–Meier estimated local control was 82% versus 81% and 82% versus 39% (40 months; $p = .04$) for gamma knife boosted patients versus non-boosted controls (Figure 2). Four failures have occurred to date, 2 in the gamma knife boosted field and 2 outside the boosted area. One of the out-of-field failures occurred within the initial neutron field along the VIIth cranial nerve proximal to the gamma knife boosted region. The second out-of-field failure was out of the initial neutron field.

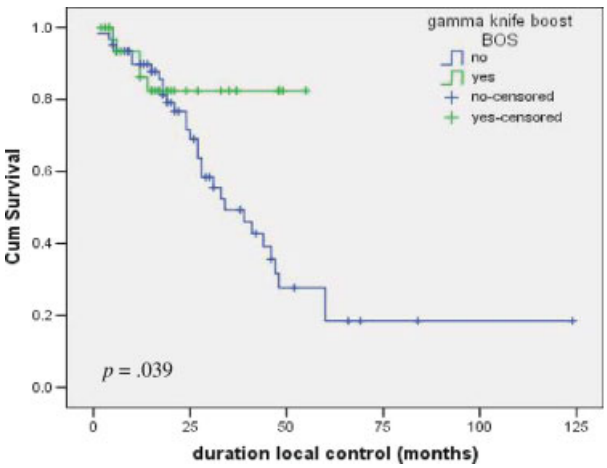

FIGURE 2. Kaplan–Meier plots comparing 34 patients with base of skull invasion treated with neutron irradiation and a gamma knife boost versus 61 patients with base of skull invasion treated with neutron irradiation alone ($p = .039$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Survival. One patient who received a gamma knife boost has died. An MRI scan prior to his death suggested progressive disease, which was well above the neutron field and gamma knife field. Upon autopsy there was no evidence for residual tumor, but rather an infectious process was felt to be responsible for the findings on the MRI and the cause of his death.

Toxicity. Acute complications including RTOG grade 3 to 4 toxicities, mostly consisting of skin reactions, mucositis, and oral candidiasis, were observed in all patients in both groups.

Late complications including RTOG grade 3 to 4 toxicities, mostly consisting of permanent xerostomia, trimus, and skin fibrosis, were also similar in both groups. Three patients in the gamma knife group developed enhancement along the medial, inferior temporal lobe on the affected side by MRI scans 12 to 18 months post–gamma knife. The changes were initially felt to represent tumor recurrence. Two patients had further evaluation with positron emission tomography (PET) scans, and the third patient had both a PET and MR spectroscopy, which were consistent with radiation-induced necrosis. Two patients were asymptomatic, and the third patient had headaches that

responded to low-dose steroid administration for several months. The enhancement resolved by 30 months posttreatment.

One patient died from a supraorbital infection with intracranial extension. The infected area was outside of the irradiated fields, and the role of irradiation as a possible inciting event is unknown.

DISCUSSION

The treatment of salivary gland neoplasms with base of skull invasion remains challenging with local control rates far below that for patient with the same tumors and no base of skull invasion. NRT appears to be more effective than photon irradiation for patients having gross residual disease after surgical resections or biopsies only.[2–7,11–15] In our analysis of factors affecting prognosis for this group of patients, we discovered that size > 4 cm, previous irradiation, and base of skull invasion were portenders of poor local control.[8] If surgical resection is possible to reduce the burden of disease, we currently recommend that approach, however, as is often the case with tumors invading the base of skull, and surgical resection is avoided because of the potential for significant facial disfigurement. Patients having base of skull invasion have a very high local failure rate compared with patients who have no base of skull invasion.[8] Reviewing the dosimetry of patients with base of skull invasion, it became clear that the superior portion of these tumors received only approximately 12 nGy of a prescribed dose of 19.2 nGy to areas of the tumor above the inferiormost portions, thus leading to a relative underdosing of those areas. This has led to unacceptable low local control rates for those patients (19%). In 2001 we began boosting the relatively "underdosed" area along the base of skull with a gamma knife boost. Treatment parameters have previously been described as was the rationale for the initial dose and volumes chosen. After the initial few failures with 1 recurrence occurring outside of the gamma knife boosted area along the course of a cranial nerve, we altered our treatment planning and thereafter traced the named nerve (usually the facial nerve or trigeminal nerve) to its insertion into the brain stem and treated that volume.

The local-control rate of 82% was statistically better than the rate with patients who did not receive the boost. Thus far, with fairly short follow-up, patients have a local failure rate of only 18% compared with 81% in the historical, nonboosted control group. We anticipate that there may[10] be local failures beyond the relatively short follow-up period reported. Despite that, our preliminary data suggest that the addition of a gamma knife boost for patients with salivary gland neoplasms and base of skull invasion may benefit from a single fraction, gamma knife boost. Further follow-up will be needed to confirm these results No additional toxicities have been noted.

CONCLUSIONS

Patients with primary salivary gland neoplasms that involve the base of skull and are treated with NRT alone are at high risk of local recurrence. A gamma knife boost appears to improve local control and adds little additional toxicity. Based on these preliminary data, all patients with salivary neoplasms and base of skull invasion should be considered for a gamma knife boost after primary treatment with NRT.

REFERENCES

1. Eisele D, Kleinberg L. Management of malignant salivary gland tumors. In: Harrison L, Sessions R, Hong W, editors. Head and neck cancer: a multidisciplinary approach. Philadelphia, PA: Lippincott Williams and Wilkins; 2004. pp 620–651.
2. Spiro R, Armstrong J, Harrison L, Geller N, Shiow-Yun L, Strong E. Carcinoma of major salivary glands. Recent trends. Arch Otolaryngol Head Neck Surg 1989;115:316–321.
3. Griffin T, Pajak T, Laramore G, et al. Neutron vs. photon irradiation of inoperable salivary gland tumors: results of an RTOG-MRC cooperative randomized study. Int J Radiat Oncol Biol Phys 1988;15:1085–1090.
4. Laramore G, Krall J, Griffin T, et al. Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. Int J Radiat Oncol Biol Phys 1993;27:235–240.
5. Douglas J, Laramore G, Austin-Seymour M, et al. Neutron radiotherapy for adenoid cystic carcinoma of minor salivary glands. Int J Radiat Oncol Biol Phys 1996; 36:87–93.
6. Douglas J, Laramore G, Austin-Seymour M, et al. Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy. Int J Radiat Oncol Biol Phys 2000;46:551–557.
7. Douglas J, Lee S, Laramore G, Austin-Seymour M, Koh W, Griffin T. Neutron radiotherapy for the treatment of locally advanced major salivary gland tumors. Head Neck 1999;21:255–263.
8. Douglas J, Koh W, Ausin-Seymour M, Laramore G. Treatment of salivary gland neoplasms with fast neutron radiotherapy. Arch Otolaryngol Head Neck Surg 2003; 129:944–948.
9. Laramore G, Austin-Seymour M. Fast neutron radiotherapy in relation to the radiation sensitivity of human organ systems. In: Altman K, Lett J, editors. Advances

in radiation biology. New York: Academic Press; 1992. pp 153–193.
10. Douglas J, Silbergeld D, Laramore G. Gamma knife stereotactic radiosurgical boost for patients treated primarily with neutron radiotherapy for salivary gland neoplasms. Stereotact Funct Neurosurg 2004;82:84–89.
11. Armstrong J, Harrison L, Spiro R, Fass D, Strong E, Fuks Z. Malignant tumors of major salivary gland origin. Arch Otolaryngol Head Neck Surg 1990;116:290–293.
12. Douglas J, Laramore G. Neutron radiotherapy for head and neck cancer. Adv Oncol 1998;14:24–29.
13. Duncan W, Orr J, Arnott S. Neutron therapy for malignant tumors of the salivary glands. A report of the Edinburgh experience. Radiother Oncol 1987;8:97–104.
14. Laramore G. Radiotherapy as the primary treatment for malignant salivary gland tumors. In: Johnson J, Didolkar M, editors. Head and neck cancer. New York: Elsevier Science Publishers B.V.; 1993. pp 599–617.
15. Saroja K, Mansell J, Hendrickson F, Cohen L, Lennox A. An update on malignant salivary gland tumors treated with neutrons at Fermilab. Int J Radiat Oncol Biol Phys 1987;13:1319–1325.