Stereotactic Radiation for Palliation of Skull Base Recurrences of Salivary Gland Carcinomas: Implications for Tumor Targeting

Zaid A. Siddiqui¹ Edward Melian^{1,2} Anil Sethi¹ Vikram C. Prabhu^{1,2} Iris Rusu¹ Bahman Emami¹
John P. Leonetti³ Douglas E. Anderson²

¹Department of Radiation Oncology, Loyola University Medical Center, Maywood, Illinois, United States

²Department of Neurological Surgery, Loyola University Medical Center Maywood, Illinois, United States

³Department of Otolaryngology, Loyola University Medical Center Maywood, Illinois, United States

Address for correspondence Edward Melian, MD, Department of Radiation Oncology, Loyola University Chicago, Stritch School of Medicine, 2160 South First Ave, Maguire Building Room 2944, Maywood, IL 60153, United States (e-mail: emelian@lumc.edu).

J Neurol Surg B 2017;78:82–88.

Abstract

Background Approximately 3 to 13% of salivary carcinomas recur at the skull base. We report our experience treating these recurrences with stereotactic radiation.

Methods In total, 14 patients with skull base recurrence of salivary gland carcinoma were identified. Patient characteristics, treatment parameters, response to treatment, local recurrence-free/overall survival, and patterns of failure were studied.

Results All 12 symptomatic patients experienced palliation of symptoms. Two grade 3 toxicities were observed. Local recurrence-free survival after skull base treatment was 28 months (74 months after allowing for additional course of salvage radiotherapy). Overall survival was 153 months from primary diagnosis and 67 months from first skull base failure. Of 13 treatment failures, 8 occurred at margins; the rest were infield. All intracranial failures occurred along meningeal surfaces.

Conclusions Stereotactic radiation provides well-tolerated palliation for the majority of patients, but with a high rate of local failure. Due to the propensity for meningeal failures, we suggest increasing margins along the meningeal surfaces when treating these patients.

Keywords

- ▶ salivary gland carcinoma
- ▶ skull base recurrence
- ▶ stereotactic radiation
- ▶ palliation
- ▶ radiosurgery

Introduction

Malignant salivary gland carcinomas make up a rare subset of head and neck cancer. Despite having indolent clinical courses, more than 30% of salivary carcinomas eventually relapse distally, often to the lungs.¹ A smaller, but still significant, subset of patients with high-risk salivary carcinomas recur in the tumor bed or in regional lymph nodes.^{1,2} Depending on disease characteristics, adjuvant radiotherapy is often indicated to decrease these recurrences.^{3,4} Salivary carcinoma recurrences are particularly challenging to treat because they may involve areas previously treated with surgery and radiation.

A third type of recurrence, skull base recurrence, has also been described for salivary gland carcinomas. Two of the histological subtypes of salivary carcinoma, adenoid cystic and squamous cell, have well known propensities to spread along perineural tracts. Tumor cells often track along major divisions of the facial and trigeminal nerves and follow their courses retrograde into the skull base. Depending on the population studied, the long-term rate of skull base metastases has been reported to be between 3 and 30%.^{4–6} Although adenoid cystic tumors have the greatest rate of skull base recurrences, these recurrences have been reported from all histological types and sites of primary disease (parotid,

received
December 4, 2015
accepted
May 25, 2016
published online
July 18, 2016

© 2017 Georg Thieme Verlag KG
Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0036-1584884>.
ISSN 2193-6331.

submandibular, or minor glands). Skull base recurrences can lead to a variety of neurological symptoms, including pain and visual changes. Patients with skull base recurrences also have a poor prognosis.⁵

Recent retrospective series have reported the results of stereotactic radiation with or without surgery in an attempt to treat these recurrent tumors. These studies report good short-term palliation of symptoms, but the long-term outcomes and patterns of failure remain unclear. Here we report on a series of patients treated for skull base recurrences of salivary gland cancer at our institution with stereotactic radiation. We include results on characteristics of patients with skull base recurrence, treatment response and toxicities, local control and survival after treatment, and patterns of failure.

Materials and Methods

Patient Record Review

The records of all patients treated at Loyola University Medical Center with stereotactic radiation to the skull base between 1995 and 2013 were reviewed after obtaining institutional review board approval. Of these patients, 14 were identified with salivary carcinoma as the primary disease. Demographic data and initial disease characteristics including tumor site, stage, and histology, as characterized by initial pathology review at Loyola or the referring hospital, were obtained. Additionally, the treatment for the primary disease was recorded.

Patient Evaluation

All patients were examined by a surgeon and radiation oncologist prior to treatment. Symptoms reported during initial evaluation and radiographic data including magnetic resonance imaging (MRI) of the head/neck were reviewed to characterize the location and size of the lesion.

The radiation dose fractionation method was decided upon on the basis of lesion size and proximity to critical structures such as optic chiasm and cranial nerves, taking into account the low tolerance of these structures for single fraction radiosurgery.⁷

Patient Follow-Up

After treatment, patients were followed with interval MRIs and physical examinations until the end of follow-up for this study (August 31, 2014) or patient death. Symptomatic responses were noted. Maximal radiographic responses were characterized as complete response (no evidence of lesion), partial response (interval decrease in lesion), or stable (no appreciable change). Radiographic recurrences were recorded on the basis of interval increase in lesion size (infield failure) or presence of a new adjacent (marginal failure) or distant lesion. All sites of metastases and causes of death were tracked. Significant treatment-related toxicities were also recorded for each patient.

Statistical Methods

Local recurrence-free survival was calculated from time of diagnosis of a skull base lesion to time of evidence of

radiographic disease progression. Survival times since diagnosis of the primary cancer and since first skull base metastasis were also recorded. Kaplan–Meier estimates for median survival are reported. Local recurrence-free survival times were censored at death or last follow-up. Overall survival and survival since first skull base metastasis were censored at last follow-up.

Results

Patient Characteristics

Patient demographics and the characteristics of their primary disease are shown in ►Table 1.

Of 14 patients, 12 were treated with adjuvant radiation for their primary disease with doses of 50.4 to 66 Gy in 1.8 to 2.0 Gy/fraction. The remaining two patients treated without radiation had early stage disease and were treated with wide local excision alone. The number of patients whose adjuvant radiation fields covered the skull base could not be determined.

A total of 21 lesions (including skull base treatment failures) were treated. Three patients underwent subtotal resection of their skull base disease prior to referral for radiation therapy of remaining gross disease. All patients except for one had a single skull base lesion at first treatment. These lesions are characterized in ►Table 2, with data involving time since initial diagnosis, location of lesion, and symptoms. The median duration between diagnosis of primary disease and time of treatment of first skull base metastatic lesion was 55 months (range: 13–248 months).

Treatment

All patients were treated with stereotactic localization. For patients treated with stereotactic radiosurgery (SRS; $n = 6$ lesions), frame-based localization was employed. These patients were treated with either the Radionics XKnife system (Integra LifeSciences, Plainsboro, NJ) or Novalis Radiosurgery platform (BrainLab Inc., Westchester, IL). After a frame was placed by a neurosurgeon under local anesthesia, a computed tomographic scan with 1.5 mm thickness was obtained for localization and fused with MRI scans (T1, with and without contrast, and T2). The single patient treated with the Radionics XKnife system was treated with 15 Gy to the 50% isodose volume. The other patients were treated with 15 to 22 Gy to 58 to 98% isodose volume using the BrainLab RT (Munich, Germany) planning software. After radiosurgery, all patients were observed for 1 to 2 hours prior to discharge. Dexamethasone, 20 mg, was given on the treatment day and patients were discharged home on an approximate 2-week taper.

The lesions treated with fractionated SRS ($n = 5$) were treated with 25 Gy in five fractions to approximately 85% isodose volume. The remaining lesions were treated with fractionated stereotactic radiotherapy (FSRT; $n = 10$), 45 to 66 Gy in 1.8 to 2.0 Gy/fraction (►Table 2). One of these patients also had a sequential SRS boost. Both of these sets of patients were treated with mask-based immobilization/localization on a linear accelerator system with the aforementioned software planning system.

Table 1 Initial disease characteristics of patients with skull base metastases of salivary carcinoma

Patient no.	Age (y)	Sex	Histology/site	Stage ^a (AJCC)	Initial therapy
1	78	Male	Acinic cell/left parotid	T1N0	Wide local excision
2	60	Male	Ductal/left parotid	T3N0	Total parotidectomy, neck dissection + radiation
3	45	Male	Adenocarcinoma/minor	–	Partial resection + radiation
4	36	Female	Adenoid cystic/minor	–	Wide local excision
5	65	Female	Adenoid cystic/ minor	–	Complete resection + radiation
6	40	Female	Adenoid cystic/left parotid	T2N2b	Total parotidectomy, neck dissection + radiation
7	24	Male	Adenoid cystic/minor	–	Complete resection + radiation
8	39	Female	Adenoid cystic/left submandibular	T2N0	Total submandibular gland resection + radiation
9	29	Male	Adenoid cystic/right parotid	T4N0	Total parotidectomy, neck dissection + radiation
10	24	Female	Acinic cell/right parotid	T3N0	Total parotidectomy + radiation
11	15	Female	Adenoid cystic/left parotid	T3N0	Total parotidectomy + radiation
12	62	Male	Adenoid cystic/left parotid	T4aN0	Total parotidectomy, resection of extension + radiation
13	58	Male	Mucoepidermoid/minor	T2N0	Complete resection + radiation
14	59	Female	Adenocarcinoma/right parotid	T4aN0	Total parotidectomy, sinus/temporal resection + radiation

Abbreviation: AJCC, American Joint Committee on Cancer.

^aT and N staging is pathologic if neck dissection was performed; otherwise N staging is clinical. All minor salivary sites in our series were located at or above the hard palate and do not have an AJCC-designated staging system.

Follow-Up

All patients were followed up until death or until the time of last data collection for this study, with no patients lost to follow-up. Median follow-up after radiotherapy treatment for first skull base lesion was 26.2 months (range: 6.3–75.4 months).

Treatment Response

Of the 14 patients treated, 12 presented with neurological symptoms during the course of their disease, most commonly pain and diplopia. All patients who presented with symptoms experienced symptom palliation (►Table 2). Radiographically, five lesions showed complete response, six lesions showed partial response, five lesions were stable, and the remainder (five lesions) could not be assessed. There were two grade 3+ toxicities, radiation necrosis for patient 9 (►Table 2) and possible contribution to meningitis in patient 3 (►Table 3).

Survival

The median local recurrence-free survival for lesions was estimated to be 28 months (95% confidence interval [CI]: 5–51 months) for initial treatment; allowing for salvage, this was extended to 74 months (7–141 months; ►Fig. 1). Allowing for salvage, 7 of the 14 patients were locally controlled until death or last follow-up. The median overall survival since primary diagnosis was estimated at 153 months (95% CI: 27–280 months; ►Fig. 2a), and survival since first skull base metastasis was estimated to be 67 months (95% CI: 0–159 months; ►Fig. 2b). The cause of death was determined to be neurological progression in at least three patients (►Table 3).

Patterns of Failure

As shown in ►Table 2, there were 13 local treatment failures, 8 of which failed at the margin (remaining were infield failures). An example of marginal failure is shown in ►Fig. 3. Upon radiographic review, all intracranial marginal failures occurred along the meningeal axes, that is, there were no failures by intraparenchymal extension. Distant metastases and cause of death for each patient are noted in ►Table 3.

Discussion

To our knowledge, this series represents the largest reported series of patients with skull base recurrences from salivary carcinoma primaries treated with radiation. The patients in our series generally had appropriate therapy for their primary disease. However, we could not verify the specific adjuvant radiation therapy parameters for some of our patients due to incomplete records. Specifically, we would have liked to ascertain how many of our patients had radiation fields extending into skull base during primary treatment as this may have predictive significance for skull base recurrences.⁵ The most common initial presentation (mode) in our series was a patient with advanced left parotid adenoid cystic carcinoma, a finding that agrees with other reports on salivary cancer. However, several patients had early stage disease (and therefore were not offered radiation or even total parotidectomy) that eventually recurred at the skull base. There were also a wide range of histologies observed (adenoid cystic, acinic cell, adenocarcinoma, ductal carcinoma, and mucoepidermoid).

Table 2 Palliation of skull base metastases in patients with salivary carcinoma

Patient no.	Lesion	Lesion site on MRI	Symptoms	Tx type ^a	Symptomatic/radiographic response	LRFS ^b (mo)	Failure site
1	1	Left infratemporal fossa	Palpable fullness/pain	FSRT	Resolution/complete	32.4	Marginal
	2	Right posterior fossa	Disequilibrium	FSRT	Resolution/complete	39.0	Infield
	3	Left zygoma	None	FSRS	No symptoms/complete	40.7 (censored)	None
2	1	Left infratemporal fossa	Facial pain	SRS	Reduction/stable	3.8	Marginal
	2	Left infratemporal fossa	Vision loss, left eye	FSRT	Partial vision return/no f/u imaging	0.9 (censored)	None
3		Right sphenoid/clivus	None	FSRS	No symptoms/stable	6.9 (censored)	None
4		Left cavernous sinus	Facial pain/blurry vision	FSRT	Resolution of blurry vision/partial	30.2 (censored)	None
5		Left pterygopalatine fossa	Facial pain	FSRS	Resolution/stable	7.0	Infield
6	1	Left infratemporal fossa	Diplopia/headache	FSRT	Reduction in pain and diplopia/partial	3.4	Infield
	2	Left infratemporal fossa	Diplopia	FSRT	Reduction/no f/u imaging	0.3 (censored)	None
7	1	Left infratemporal fossa	Seizure	FSRT	No further seizures (on medication); partial response	28.1	Marginal
	2	Left infratemporal fossa	None	FSRS	No symptoms/stable	15.2 (censored)	None
8		Left orbit	Diplopia/dizziness	FSRT	Resolution/complete	7.1 (censored)	None
9	1	Sella turcica	None	FSRT/SRS	No symptoms/complete	33.5	Marginal
	2	Clivus	None	SRS	No symptoms/complete	19.2	Marginal
	3	Left infratemporal fossa	Diplopia	SRS	Reduction/no interval imaging	21.5	Infield
10		Left pterygoid fossa	None	SRS	No symptoms/stable	95.8	Infield
11		Left temporal fossa	Palpable fullness	FSRS	Resolution/no f/u imaging	100.9 (censored)	None
12		Left cavernous sinus	Diplopia	SRS	Resolution/partial	9.1	Marginal
13		Right cavernous sinus	Diplopia	SRS	Reduction/partial	2.1	Marginal
14		Left orbit	Palpable fullness/pain	FSRT	Reduction of pain/stable	17.3	Marginal

Abbreviations: FSRS, fractionated stereotactic radiosurgery; FSRT, fractionated stereotactic radiation; LRFS, local recurrence-free survival; MRI, magnetic resonance imaging; SRS, stereotactic radiosurgery.

Note: Bolded lesions are treatment failures (salvage therapy).

^aTreatment: SRS(single fraction), FSRS (five fractions), FSRT (1.8–2 Gy/fraction).

^bLRFS data censored at death or last follow-up.

Our results show that stereotactic radiation effectively palliates patient symptoms, whether single-fraction SRS, multifraction SRT, or conventional FSRT is used. This high palliation rate is in agreement with prior studies showing effective palliation with Gamma Knife radiosurgery (Elekta, Stockholm,

Sweden).^{8,9} From a patient comfort viewpoint, which is of increased importance in a palliative setting, a hypofractionated SRT approach may be most suitable as it avoids both placement of a headframe and repeated trips to the treatment facility. We observed a 65% radiographic response rate (complete or partial

Table 3 Clinical course of patients treated for skull base metastases

Patient no.	Overall survival (mo)	Survival after skull base metastasis ^a (mo)	Cause of death
1	184.7 (censored)	79.2 (censored)	N/A
2	32.9	9.0	Spinal metastases
3	87.6	10.4	Meningitis ^b
4	233.4 (censored)	38.6 (censored)	N/A
5	89.2	29.0	N/A
6	25.6	9.4	Pulmonary metastases
7	314.8	67.1	Pulmonary metastases
8	21.8	8.6	Liver metastases
9	153.8	103.8	Pulmonary metastases/possibly skull base disease
10	186.0	111.6	Pulmonary metastases/skull base disease
11	190.1 (censored)	106.6 (censored)	N/A
12	41.6	19.4	Skull base disease
13	25.4	5.7	Unsure
14	95.6	76.4	N/A

^aSurvival data censored at last follow up.
^bMeningitis from cerebrospinal fluid leak after both surgery and stereotactic radiation.

response) compared with 62% reported by Lee et al⁸ and 80% reported in the adenoid cystic carcinoma series by Mori et al.⁹ In our study, there were patients within all the three treatment group types who eventually failed locally, and we did not have enough statistical power to discriminate between the three fractionation schedules.

One area of concern from our results is the large rate of marginal failures along meningeal surfaces after stereotactic radiation, a finding that has not been previously reported. Past series have not been clear as to whether the local failures

were true in field failures or marginal recurrences. Highly conformal stereotactic radiation may prevent toxicity to critical structures located in the skull base and allow for shorter fractionation schedules for similar doses. However, given our finding, extending the radiation field to include a “high-risk clinical target volume” by expanding into the meningeal surfaces may be appropriate. A possible hypothesis for this pattern of failure is that the purported mechanism for perineural invasion/spread¹⁰ is mimicked in meningeal spread. In addition to marginal failures, we also observed two cases of “skip” lesions along the meninges, with one of these patients having leptomeningeal involvement in the spinal cord (►Table 2, patients 1 and 2). These skip lesions contributed to mortality in at least one of our patients and may correlate with the deaths from “distant intracranial disease” reported by Mori et al.⁹ Since infield failures were approximately one-third of all local failures in this study, dose de-escalation is not a viable option for these patients.

In our series, as in the prior series, salvage re-irradiation seemed to be an effective treatment for local failure. Salvage therapy palliated new symptoms with acceptable toxicity and added a median of 46 months of local control. While the series by Lee et al⁸ and Mori et al⁹ do not distinguish between salvage treatment for infield versus marginal failures, in our series, only one infield failure was treated with salvage therapy. Although only 35% of patients were given salvage treatment compared with 63% in the study by Lee et al,⁸ our survival results suggest that we offered appropriate, early salvage therapy to our patients. Despite our high relapse rate after initial therapy, only one-third of patients died from intracranial disease compared with one-half⁸ to two-thirds⁹ of patients in prior series, suggesting that salvage therapy may have prevented some neurological deaths. We therefore

Fig. 1 Local recurrence-free survival curve for skull base recurrence of salivary cancer patients is shown, both after initial treatment only and allowing for salvage therapy. Estimated median local recurrence-free survival was 28 months (95% CI: 5–51 months) for initial treatment. Estimated median local recurrence-free survival allowing for salvage was 74 months (95% CI: 7–141 months).

Fig. 2 (a) Overall survival curve since primary diagnosis for salivary cancer patients with skull base metastases is shown. Estimated median overall survival since primary diagnosis was 153 months (95% CI: 27–280 months). (b) Survival curve after skull base recurrence in salivary cancer patients is shown. Estimated median overall survival since skull base disease was 67 months (95% CI: 0–159 months).

advocate serial imaging during follow up to catch early marginal failures, as offering salvage therapy may be of benefit even to asymptomatic patients.

Toxicity from treatment tended to be low in our study, which agrees with the current literature. One patient who

received three treatments (one for initial disease and then subsequently two salvage treatments) experienced symptomatic brain necrosis, causing seizure activity. Another patient who underwent both partial resection and stereotactic radiation developed meningitis after a cerebrospinal fluid

Fig. 3 Clinical course of illustrative patient showing marginal failure after treatment; (a) patient with biopsy-proven sellar recurrence after treatment for right parotid carcinoma, (b) showing complete response after SRS, (c) then showing a contralateral left temporal failure along meningeal surface, anterolateral to the original sellar lesion.

leak and succumbed to this complication (►Table 3, patient 3). Otherwise, patients tolerated the treatment without major adverse events.

In conclusion, this study suggests that the majority of patients who have skull base recurrences will be effectively palliated by radiation, but will often fail after first therapy, and may even succumb from neurological disease. In addition, we observe that survival following skull base recurrences may be greater than the local control at the skull base, suggesting that managing skull base recurrences following salivary cancer is not a trivial undertaking. Our study shows a unique pattern of failure along the meningeal surfaces after stereotactic skull base radiation for salivary gland cancer recurrence, suggesting that larger treatment fields or larger margins along the meningeal surfaces may be worth studying. Our results also confirm the importance of long-term follow-up in patients with salivary gland carcinoma.

Financial Disclosures

None.

Note

Presented at the 35th annual North American Skull Base Society Meeting.

Acknowledgments

We would like to thank Marguerite Kaminski in the Department of Radiation Oncology for help with collecting and managing patient charts, and Dr. Bahman Emami for his 17 years of support for the Loyola stereotactic radiation program.

References

- 1 Terhaard CHJ, Lubsen H, Van der Tweel I, et al; Dutch Head and Neck Oncology Cooperative Group. Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. *Head Neck* 2004;26(8):681–692, discussion 692–693
- 2 Chen AM, Granchi PJ, Garcia J, Bucci MK, Fu KK, Eisele DW. Local-regional recurrence after surgery without postoperative irradiation for carcinomas of the major salivary glands: implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* 2007;67(4):982–987
- 3 Terhaard CHJ, Lubsen H, Rasch CRN, et al; Dutch Head and Neck Oncology Cooperative Group. The role of radiotherapy in the treatment of malignant salivary gland tumors. *Int J Radiat Oncol Biol Phys* 2005;61(1):103–111
- 4 Garden AS, Weber RS, Morrison WH, Ang KK, Peters LJ. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. *Int J Radiat Oncol Biol Phys* 1995;32(3):619–626
- 5 Chen AM, Garcia J, Granchi P, Bucci MK, Lee NY. Base of skull recurrences after treatment of salivary gland cancer with perineural invasion reduced by postoperative radiotherapy. *Clin Otolaryngol* 2009;34(6):539–545
- 6 Kim J, Lee J, Wu H, et al. Impact of radiation therapy volumes on skull base recurrence in adenoid cystic carcinoma in the head and neck. *Int J Radiat Oncol* 2014;90(1):S545–S546
- 7 Tishler RB, Loeffler JS, Lunsford LD, et al. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. *Int J Radiat Oncol Biol Phys* 1993;27(2):215–221
- 8 Lee N, Millender LE, Larson DA, et al. Gamma knife radiosurgery for recurrent salivary gland malignancies involving the base of skull. *Head Neck* 2003;25(3):210–216
- 9 Mori Y, Kobayashi T, Kida Y, Oda K, Shibamoto Y, Yoshida J. Stereotactic radiosurgery as a salvage treatment for recurrent skull base adenoid cystic carcinoma. *Stereotact Funct Neurosurg* 2005;83(5–6):202–207
- 10 Zhang C-Y, Mao L, Li L, et al. Promoter methylation as a common mechanism for inactivating E-cadherin in human salivary gland adenoid cystic carcinoma. *Cancer* 2007;110(1):87–95