ORIGINAL ARTICLE

PROTON RADIATION THERAPY FOR PRIMARY SPHENOID SINUS MALIGNANCIES: TREATMENT OUTCOME AND PROGNOSTIC FACTORS

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Abstract: *Background.* The purpose of this study was to determine treatment outcome and prognostic factors in patients with locally advanced primary sphenoid sinus malignancy treated with proton radiation therapy.

Methods. Between 1991 and 2005, 20 patients with primary sphenoid sinus malignancy received proton beam to a median dose of 76 Gray equivalent.

Results. With a median follow-up of 27 months, the 2-year local, regional, and freedom from distant metastasis rates were 86%, 86%, and 50%, respectively. The disease-free and overall-survival rates at 2 years were 31% and 53%, respectively. In multivariate analysis, oropharyngeal involvement ($p = .005$) and anterior cranial fossa invasion ($p = .02$) were predictive for poor disease-free survival rate. Brain invasion was predictive for decreased overall-survival rate ($p = .05$).

Conclusions. Proton radiation therapy results in excellent local control in patients with advanced primary sphenoid sinus malignancy. Brain invasion, involvement of the oropharynx and anterior cranial fossa are important prognostic factors. *Head Neck* **31:** 1297–1308, 2009

Keywords: sphenoid sinus; paranasal sinus malignancies; skull-based malignancies; proton radiation therapy; craniofacial resection; radiation; staging; prognostic factors

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Primary sphenoid sinus malignancies are rare paranasal sinus tumors and represent approximately 1.5% to 8.3%[1–4] of all paranasal sinus and nasal cavity malignancies. Clinical presentation of sphenoid sinus malignancies often differs from other paranasal sinus malignancies because of frequent involvement of the base of skull, such that neurological symptoms including cranial neuropathies are often seen in addition to rhinological symptoms. Treatment is technically challenging for both the radiation oncologist and surgeon because of the close

proximity and relative radiosensitivity of adjacent critical structures including the orbit and central nervous system. Sphenoid sinus malignancies tend to have an unfavorable prognosis compared with other paranasal sinus sites,[1] with local failure being the main cause of death.[2,3]

Various staging systems have been defined for paranasal sinus malignancies and skull base tumors, depending on the anatomic site and histology. For paranasal sinus and nasal cavity sites, the American Joint Committee on Cancer (AJCC) has defined a staging classification for maxillary, ethmoid, and nasal cavity sites for squamous cell histology. For esthesioneuroblastoma, a system has been devised by Kadish et al[5] based on anatomic extension. For sphenoid sinus malignancies, when using the AJCC staging system, these tumors require categorization into other primary sites such as maxillary or ethmoid sites and are automatically defined as T4 tumors, rather than defining the primary site by the epicenter of the tumor.

A number of surgical approaches for sphenoid malignancies have been described ranging from endoscopic to open anterior craniofacial resections.[2,6–13] Recent reports show a trend toward more aggressive combined surgical approaches with the aim of achieving a maximal oncologic resection, while minimizing operative morbidity.[2,11,12] However, because primary sphenoid sinus malignancies are usually locally advanced at presentation, these tumors are often less amenable to a radical resection, and radiation therapy is often used as the primary treatment to achieve local control.

The challenge of radiotherapy for primary sphenoid sinus malignancies is achieving a tumoricidal dose, with sparing of adjacent critical normal structures such as the neurovascular structures traversing the cavernous sinus, and the optic structures. With conventional 2-dimensional (2D) radiotherapy techniques for paranasal sinus cancer, the incidence of bilateral blindness due to radiation-induced optic neuropathy is approximately 8%[3] and is dose dependent, with doses of 60 Gy or more to the optic nerves resulting in optic neuropathy in up to 50% of cases.[14] Attempts at dose escalation of radiation therapy had not been possible, until the advent of more conformal radiotherapy techniques, including 3D conformal radiotherapy and intensity modulated photon radiotherapy to achieve better sparing of adjacent critical normal tissues.

Proton radiation therapy consists of charged particles and has similar radiobiological effectiveness to photon radiotherapy. The physical properties of protons offers a unique advantage over photon radiation therapy, the dose deposited increases gradually with depth and then reaches a sharp peak (Bragg peak) with minimal exit dose. By modulating the Bragg peak, the high-dose region can be spread out to encompass the target volume, while minimizing dose to adjacent normal tissues. The superior physical properties of protons allows for dose escalation to the tumor and improved local control, while lowering the dose to adjacent normal tissue organs, thereby decreasing potential acute and late toxicities.[15]

In 1991, our institution began using proton radiation therapy for primary sphenoid sinus malignancies, to allow for dose escalation, while respecting the radiation tolerance doses to the adjacent critical normal structures. The purpose of this study was to report our results using proton radiation therapy for primary sphenoid sinus cancers. The second aim was to explore potential prognostic factors that determine outcome and develop a clinical staging system that can be applied to sphenoid sinus malignancies.

PATIENTS AND METHODS

Study Cohort. Between November 1991 and July 2005, 20 patients with newly diagnosed locally advanced primary sphenoid sinus malignancy were treated with proton radiation therapy at the Massachusetts General Hospital. The study was conducted as a retrospective review of patient records after approval from our Institutional Review Board. Patients with sinonasal malignancies were identified as having a primary sphenoid sinus malignancy if the tumor epicenter was centered on the sphenoid sinus on review of radiology films and operative reports. All available pathology slides were reviewed at our institution prior to treatment. Each patient was evaluated jointly by radiation oncologists, neurosurgeons, and otolaryngologists, and a multidisciplinary decision was made for the patient to undergo proton radiation therapy with or without surgery. The median follow-up of all patients in the study was 21 months. The median follow-up of all living patients was 27 months.

Table 1. Clinical symptoms and signs.

	No. of patients	% of patients
Symptoms		
Headaches	15	75
Vision change	9	45
Nasal congestion/obstruction	8	40
Epistaxis	6	30
Facial numbness or pain	8	40
Cranial nerve deficits*	12	60
CN II	5	25
CN III	4	20
CN IV	0	0
CN V 1	2	10
CN V 2	4	20
CN V 3	2	10
CN VI	5	25

**Patients may have had more than 1 cranial nerve deficit.*

Patient and Tumor Characteristics. The age range was 17 to 78 years, with a median of 53 years. There were 10 men and 10 women. The median Karnofsky Performance Scale score at the time of radiation was 90. The median duration between onset of symptoms and diagnosis was 4 months. Patient clinical signs and symptoms at presentation are described in Table 1. All patients were node negative at presentation, and 1 patient with adenoid cystic carcinoma had a pathologically confirmed asymptomatic small solitary pulmonary nodule at presentation. All patients had no prior history of radiation therapy.

The histology and the extent of the tumor were evaluated by Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) studies as well as operative and pathology reports (Table 2). Figure 1 shows a diagnostic MRI, T1 post-gadolinium coronal image, and an axial FLAIR image used for evaluation of primary tumor extent before treatment and is noted to have invasion of brain parenchyma.

Treatment

Surgery. Seven patients (35%) underwent partial resection of their tumors prior to proton radiation therapy. The surgical approach included craniofacial resection in 2, transfacial resection in 1, and endoscopic in 4 patients. The remaining 65% of the patients underwent biopsy alone. None of the patients underwent complete resection of the primary tumor or elective neck dissection. The median time interval between biopsy or surgery and the initiation of radiation was 1.7 months.

Radiotherapy Planning and Delivery. The majority of the patients were immobilized by means of a custom-made dental fixation technique and an integrated thermoplastic head mask.[16] This immobilization device limited the mean net 3D patient motion during the treatment to less than 1 mm. Thin-cut high-resolution CT scan with contrast was obtained in the treatment position. MRI was obtained to assist in target delineation. The gross tumor volume (GTV), clinical target volume (CTV), and surrounding critical structures were outlined. Dose-volume histograms were generated for the GTV, CTV, and surrounding critical structures.

For proton treatment planning, a patch combination (split-target volume) technique was used to optimize the proton dose distribution within an irregular volume in close proximity to critical normal structures.[17] The target volume was divided into multiple segments and each treated by a separate radiation field. Utilizing the sharp dose fall-off of the Bragg peak, each

Table 2. Tumor characteristics.

	No. of patients	% of patients
Histology		
Squamous cell carcinoma	10	50
Adenoid cystic carcinoma	7	35
Neuroendocrine tumor	2	10
Adenocarcinoma	1	5
Extension of tumor*		
Ethmoid sinus	16	80
Maxillary sinus	9	45
Nasal cavity	16	80
Nasopharynx	13	65
Oropharynx	3	15
Optic canal	12	60
Optic chiasm	3	15
Optic nerve	6	30
Lamina papyracea	7	35
Cavernous sinus—unilateral	13	65
Cavernous sinus—bilateral	6	30
Pituitary gland	11	55
Clivus	18	90
Infratemporal fossa	4	20
Pterygopalatine fossa	14	70
Anterior cranial fossa	3	15
Middle cranial fossa	13	65
Meckel's cave	15	75
Brain parenchyma	5	25
Dura	9	45

**Most patients had tumor extension into more than 1 location.*

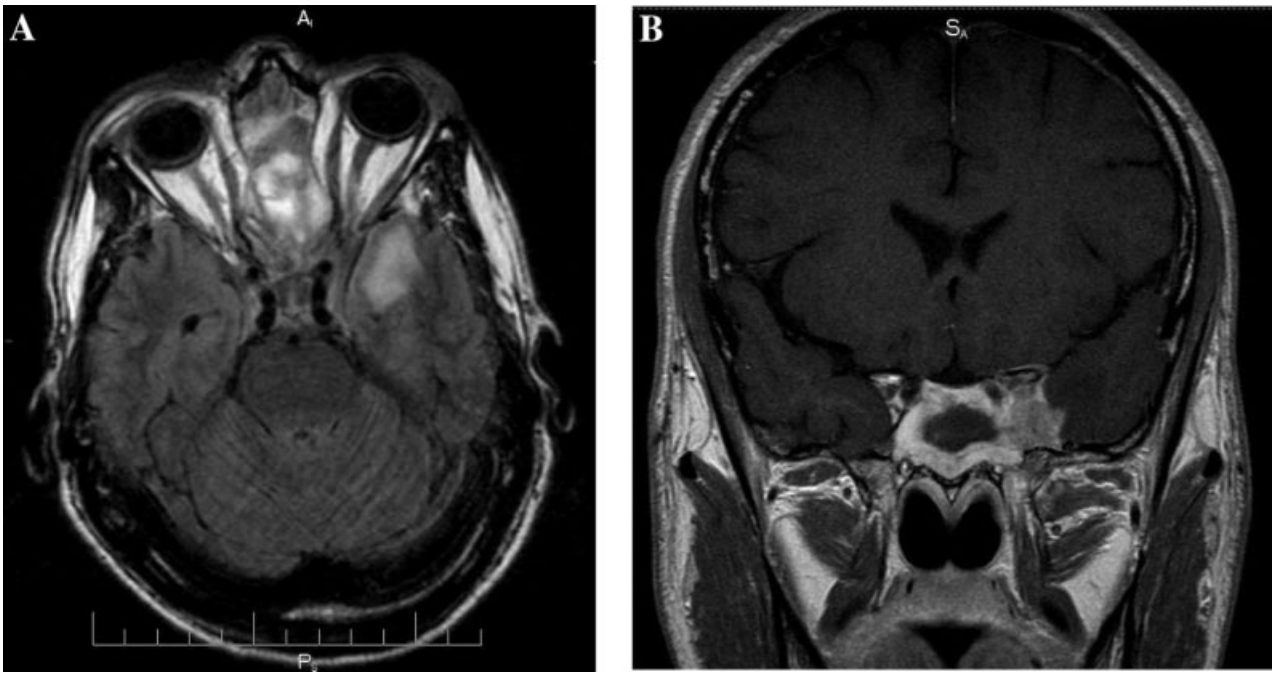


FIGURE 1. Axial (FLAIR) (**A**) and coronal T1-weighted (**B**) MR image of patient with sphenoid sinus squamous cell carcinoma with radiographic evidence of invasion of the brain parenchyma.

field was designed to stop in the penumbra of the other fields. Each treatment field was shaped by an individually designed brass aperture and a lucite range compensator. An appropriate modulator wheel was selected to spread out the Bragg peak. Pretreatment alignment radiographs were obtained daily and compared with CT-generated digitally reconstructed radiographs daily to ensure precise positioning of the treatment fields. Proton radiation was delivered at the Harvard Cyclotron Laboratory or the Francis H. Burr Proton Therapy Center at the Massachusetts General Hospital, using 160 and 230 MeV beams, respectively. Digital portal imaging was performed daily prior to treatment delivery to verify setup. For photon radiotherapy, a 5-field graduated block technique[18] was used to design the treatment plan, consisting of an anterior and 2 sets of right and left lateral beams designed to the CTV. These fields were matched to a lower photon neck field if indicated.

All patients were treated with proton radiation therapy with curative intent. Radiotherapy was delivered after biopsy or surgery in all patients. The radiation dose and fractionation schema, extent of resection, and histology are described in Table 3. The median proportion of proton was 61% (range, 23% to 100%). The median number of proton fields was 8 (range, 4–17).

Chemotherapy. Eleven patients (55%) received chemotherapy, of whom 6 (30%) received concurrent chemotherapy. The sequence of chemotherapy included induction chemotherapy in 4 patients, induction and concurrent chemotherapy in 4 patients, concurrent and adjuvant chemotherapy in 1 patient, concurrent chemoradiotherapy alone in 1 patient, and adjuvant chemotherapy alone in 1 patient Chemotherapy regimens included cisplatin-based regimens in 55%, carboplatin-based regimens in 36%, and doxorubicin-based regimens in 9%. Chemotherapy was used since 1994; concurrent chemotherapy was utilized from 2004.

Statistical Analysis. Locoregional control was measured from the end of radiation treatment to the date of local or regional relapse, censoring patients at last follow-up or death. Survival time was measured from the end of radiation therapy until death or last follow-up. The Kaplan-Meier product-limit method was used to estimate the probabilities of tumor control and survival rates. Local control and survival

Table 3. Total radiation dose by fractionation, extent of resection, and histology.

	No. of patients (%)	Median dose, Gy (range)	Median treatment duration in days (range)
All patients	20 (100)	76.0 (66–78)	45 (35–59)
Radiation fractionation			
Once-daily	7 (35)	72 (66–76)	57 (46–59)
Twice-daily	13 (65)	76.4 (67.6–78)	38 (35–48)
Elective nodal irradiation	12 (60)	44 (40–50)	38 (35–57)
Extent of resection			
Partial resection	7 (35)	75.6 (66–76.6)	50 (35–59)
Biopsy alone	13 (65)	76 (67.6–78)	40 (35–57)
Histological type			
Squamous cell carcinoma	10 (50)	76 (66–78)	47 (35–59)
Neuroendocrine tumors	2 (10)	68.8 (67.6–70)	42.5 (38–47)
Adenoid cystic carcinoma	7 (35)	76.4 (76–77)	42 (35–58)
Adenocarcinoma	1 (5)	75.6	57

Abbreviations: Gy, gray; GTV, gross target volume.

probabilities were compared in univariate analysis, using log-rank test for discrete variables or likelihood ratio test for proportional hazards model for continuous variables. The variables with p values less than .1 were then entered into the multivariate analysis using the Cox proportional hazards model.

Patient-related factors that were entered into analysis were sex, age at diagnosis, duration of symptoms, vision change at presentation, and cranial nerve deficits at presentation. Tumor-related factors that were entered into the analysis included the extent of tumor (by radiographic and operative information), as described in Table 2. Treatment-related factors used were extent of resection, duration of radiation therapy, percentage of proton radiation, and use of chemotherapy. Univariate analyses of patient, tumor, and treatment factors for tumor control and survival were performed. The primary endpoint was locoregional control. Secondary endpoints evaluated were overall survival, disease-free survival, and rate of freedom from distant metastasis. All statistical analyses were performed on SAS 9.1 system (SAS Institute, Cary, NC).

RESULTS

Locoregional Control and Survival. The actuarial local control rate was 86% at 2 years. The regional control rate was also 86% at 2 years. The rate of freedom from distant metastases at 2 years was 50%. Figure 2 shows the rates of local control, regional control, and freedom from distant metastasis. The disease-free and overall survival rates at 2 years were 31% and 53%, respectively.

Patterns of Failure. Local, regional, and distant recurrences occurred in 2, 2, and 8 patients, respectively, as their first site of failure. Of the distant recurrences, 6 were systemic, and 2 were leptomeningeal. The median time to recurrence was 6 months. Two patients with poorly differentiated squamous cell carcinoma developed local recurrence. One developed an isolated

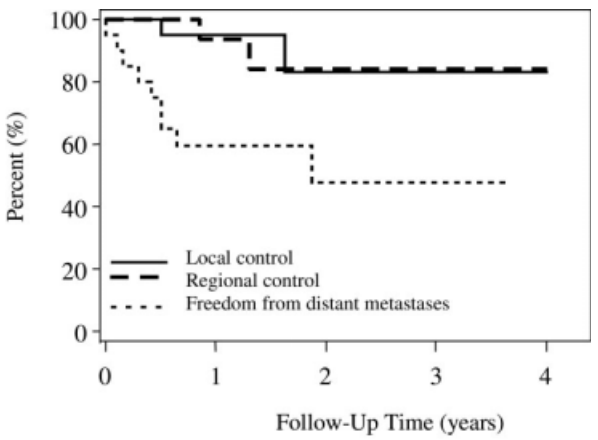
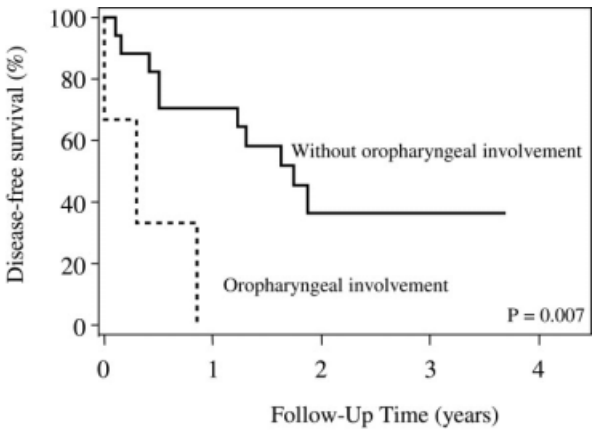


FIGURE 2. Kaplan-Meier curve illustrating local, regional, and freedom from distant metastases.



No. at risk by oropharynx involvement

Yes	3	0	0	0	0
No	17	12	7	7	7

FIGURE 3. Kaplan-Meier curve illustrating disease-free survival with or without oropharyngeal involvement.

local recurrence in the right Meckel's cave in the high-dose region of 75 Gray-Equivalent (GyE) at 19.6 months after completion of radiation therapy. The Meckel's cave was involved at presentation. This patient died at 26.6 months after radiation. Another patient experienced a local recurrence in the high-dose target volume (76 GyE) at 6 months after completion of radiation therapy. The patient was also found to have concurrent distant bone metastases and died from disease 8.4 months after radiation.

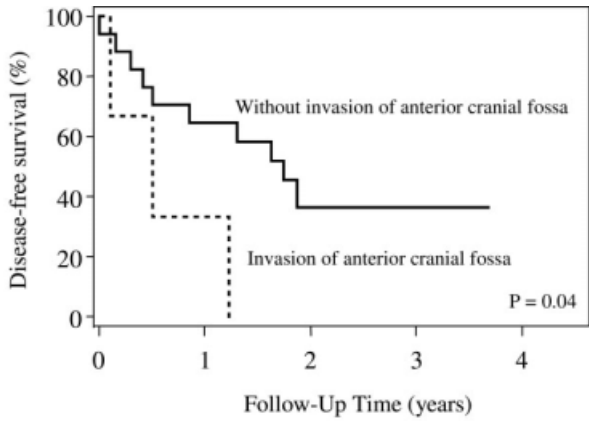
Two patients (10%) with squamous cell carcinoma histology experienced a regional recurrence at 10 and 15.6 months, respectively. One patient received bilateral neck irradiation to 59 Gy to the upper neck and 45 Gy to the low anterior neck, and the second patient received 45 Gy to the bilateral neck down to the supraclavicular fossa. Both patients died from progressive nodal disease at 19.2 and 21 months after radiation, respectively.

In total, there were 10 distant recurrences including first site of failure and subsequent failures, of which 7 (35%) were systemic and 3 (15%) were leptomeningeal. Sites of systemic metastases included osseous (3 patients), pulmonary (2 patients), and hepatic (2 patients) metastasis. Histology included squamous cell carcinoma (2 patients), small cell neuroendocrine carcinoma (1 patient), and adenoid cystic carcinoma (4 patients). Median time to the development of metastasis was 4.5 months. Five patients died from progressive disease, and 2 patients are alive with stable disease. For the 3 patients (15%) who experienced a leptomeningeal recurrence, the histology included squamous cell carcinoma in 2 and adenoid cystic carcinoma in 1 patient. Median time to recurrence was 7.8 months. Two patients died from leptomeningeal disease.

Salvage Treatment. One patient who developed local recurrence at 19.6 months, in the right Meckel's cave underwent salvage treatment with stereotactic radiosurgery to 13 Gy and died at 26.6 months (7 months after radiosurgery salvage). One patient underwent salvage surgery and partial brain irradiation for leptomeningeal disease with stable disease at last follow-up. Salvage neck dissection was performed in 1 patient with nodal recurrence; however, the patient died from progressive nodal disease.

Prognostic Factors

Disease-Free Survival. In univariate analysis, tumor involvement of the oropharynx (see Figure 3) and invasion of the anterior cranial fossa (see Figure 4) were significant predictive factors for decreased disease-free survival (Table 4). It is noted that patients who had oropharynx involvement also had tumor extension into the nasal cavity and nasopharynx. Other factors that showed a trend for decreased disease-free survival included lower Karnofsky performance status ($p = .06$, unadjusted hazard ratio (HR) 2.9), tumor size ($p = .08$, unadjusted HR 1.5), invasion of the optic chiasm ($p = .09$,



No. at risk by anterior cranial fossa invasion

Yes	3	1	0	0	0
No	17	11	7	7	7

FIGURE 4. Kaplan-Meier curve illustrating disease-free survival with or without invasion of the anterior cranial fossa.

Table 4. Univariate and multivariate analyses of disease-free survival rates of all patients.

Variable	No. of patients	No. of events	2-year actuarial rate, %	Univariate *p* value (log-rank)	Unadjusted hazard ratio (95% CI)	Multivariate *p* value	Adjusted hazard ratio (95% CI)
Optic Chiasm							
Involved	3	3	0	.09	3.3	.48	0.5
Not involved	17	10	36		(1–11)		(0.1–2.4)
Brain parenchyma							
Involved	5	4	20	.15	2.4	.07	3.8
Not involved	15	9	37		(0.9–6.7)		(1.1–12.9)
Oropharynx							
Involved	3	3	0	.007	5.9	.005	26.7
Not involved	17	10	36		(1.7–19.9)		(3.9–182.3)
Anterior cranial fossa							
Involved	3	3	0	.04	4.0	.02	8.0
Not involved	17	10	36		(1.2–12.8)		(1.8–36.0)

Abbreviation: CI, confidence interval.
p values are for the entire duration of the study. The relative risk is defined as the risk of the first group divided by the risk of the second group.

unadjusted HR 3.3), and invasion of the brain ($p = .15$, unadjusted HR 2.4).

In multivariate analysis of tumor extent, tumor involvement of the oropharynx and anterior cranial fossa were significant predictive factors for decreased disease-free survival. There was a trend for inferior disease-free survival for brain invasion. Table 4 shows the disease-free survival rates for patients with and without these prognostic factors.

Overall Survival. In univariate analysis of prognostic factors for overall survival, lower Karnofsky performance status ($p = .003$, unadjusted hazard ratio (HR) 5.4), invasion of the brain parenchyma, invasion of the anterior cranial fossa, invasion of optic chiasm, and larger tumor size ($p = .02$, unadjusted HR 1.6) were significant for decreased overall survival. The addition of concurrent chemotherapy showed a trend for improved overall survival. The 2-year overall survival rate was 64 and 36% with and without concurrent chemotherapy, respectively ($p = .11$).

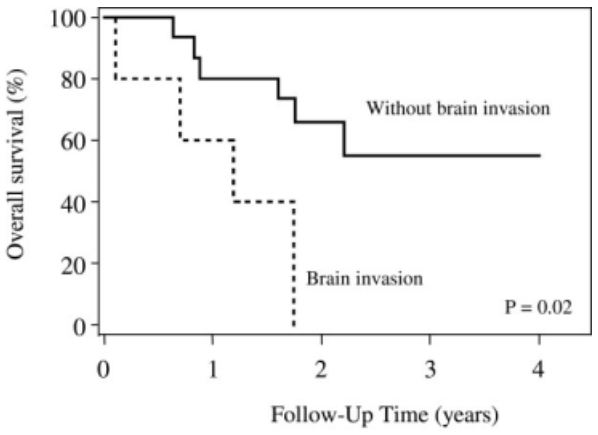
In multivariate analysis of tumor extent, only tumor invasion of the brain was predictive for an inferior overall survival (Table 5). Figure 5 depicts the overall survival of patients with and without invasion of the brain parenchyma.

Distant Metastases. In univariate analysis of prognostic factors for freedom from distant metastases, invasion of the anterior cranial fossa ($p = .02$, unadjusted HR 4.6) and invasion of the optic nerve ($p = .03$, unadjusted HR 4.0) were significant for increased risk for distant metastases. Involvement of the oropharynx ($p = .13$, unadjusted HR 3.2) showed a trend for increased risk for distant metastases. On multivariate analysis, only oropharynx involvement was significant for decreased freedom from

Table 5. Univariate and multivariate analyses of overall survival rates of all patients.

Variable	No. of patients	No. of events	2-year actuarial rate, %	Univariate *p* value (log-rank)	Unadjusted hazard ratio (95% CI)	Multivariate *p* value	Adjusted hazard ratio (95% CI)
Optic chiasm							
Involved	3	3	0	.03	4.2	.10	3.9
Not involved	17	7	63		(1.3–13.7)		(1.0–15.5)
Anterior cranial fossa							
Involved	3	2	0	.07	4.2	.50	2.1
Not involved	17	8	57		(1.0–16.7)		(0.4–12.6)
Brain parenchyma							
Involved	5	4	20	.02	5.0	.05	4.8
Not involved	15	6	66		(1.5–16.3)		(1.3–17.5)

Abbreviation: CI, confidence interval.
p values are for the entire duration of the study. The relative risk is defined as the risk of the first group divided by the risk of the second group.



No. at risk by brain invasion

Yes	5	3	1	1	1
No	15	12	10	9	9

FIGURE 5. Kaplan-Meier curve illustrating overall survival with or without brain invasion.

distant metastases ($p = .04$, adjusted HR 7.5) as shown in Table 6. The actuarial rates at 2 years for freedom from distant metastases with or without chemotherapy were 53% and 56%, respectively ($p = .64$). The corresponding rates with and without concurrent chemotherapy were 67% and 50%, respectively ($p = .29$).

Proposed Sphenoid Sinus Staging System. Based on the review of patterns of tumor extension and tumor-related prognostic factors determined in this study, a staging system relevant to primary sphenoid sinus cancer is proposed. This system includes: A, tumors confined to the sphenoid sinus; B, tumors extending beyond the sphenoid sinus, but not invading the brain parenchyma, anterior cranial fossa or oropharynx; and C, tumors extending beyond the sphenoid sinus and invading the brain parenchyma, anterior cranial fossa, or oropharynx (Table 7).

Patients from this series were categorized according to this system. The 2-year disease-free survival and overall survival rates according to this categorization are described in Table 7. Figures 6 and 7 show the Kaplan-Meier graph of disease-free and overall survival, respectively based on the proposed staging.

Toxicity. Toxicity was scored using the Common Toxicity Criteria (CTC) (version 3) of the U.S. National Institutes of Health (http://ctep.cancer.gov/reporting/ctc.html).

All patients tolerated treatment to completion without any treatment break. Oral mucositis occurred in 14 patients, including 8 patients with CTC Grade 2 (patchy ulceration), and 6 patients experienced CTC Grade 3 mucositis (confluent mucositis), of which 1 patient required hospitalization for placement of a gastrostomy. There were no acute CTC grade 4 or 5 aerodigestive toxicities. Acute skin reaction within the radiation portal occurred in 11 patients, 9 patients with CTC grade 2, and 2 patients with CTC grade 3 acute skin reactions.

Ocular and Visual Complications. There was no acute grade 3 or higher ocular or visual toxicity. Two patients experienced CTC grade 2 late ocular toxicity, including epiphoria, which was secondary to nasolacrimal duct obstruction. This required placement of a nasolacrimal stent at 7 and 9 months, respectively after radiotherapy. None of the patients developed CTC grade 3 or 4 late ocular or visual toxicity after radiation therapy. None required an orbital exenteration after radiotherapy.

Table 6. Univariate and multivariate analyses of freedom from distant metastasis rates of all patients.

Variable	No. of patients	No. of events	2-year actuarial rate, %	Univariate *p* value (log-rank)	Unadjusted hazard ratio (95% CI)	Multivariate *p* value	Adjusted hazard ratio (95% CI)
Optic nerve							
Involved	6	5	17	.03	4.0	.15	3.8
Not involved	14	4	71		(1.3–12.2)		(0.8–17.5)
Anterior cranial fossa							
Involved	3	3	0	.02	4.6	.32	2.6
Not involved	17	6	59		(1.4–15.4)		(0.5–13.2)
Oropharynx							
Involved	3	2	33	.13	3.2	.04	7.5
Not involved	17	7	54		(0.8–12.5)		(1.5–37.3)

Abbreviation: CI, confidence interval.
p values are for the entire duration of the study. The relative risk is defined as the risk of the first group divided by the risk of the second group.

Table 7. MGH-MEEI staging for primary sphenoid sinus cancer

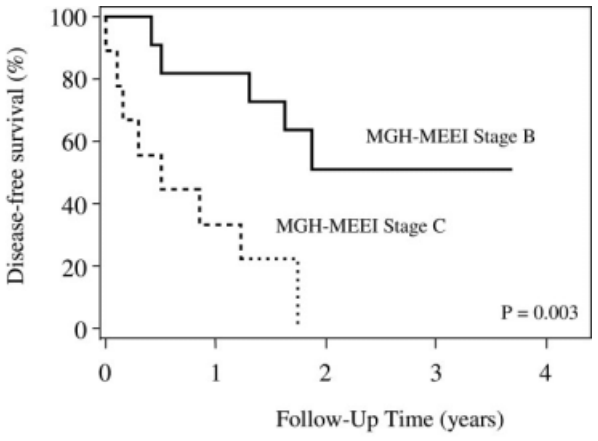
Group	Patient no.	Tumor extent	2-year disease-free survival	2-year overall survival
A	0	Limited to the sphenoid sinus	–	–
B	11	Extends beyond sphenoid sinus but does not involve brain, oropharynx, or anterior cranial fossa	51%	73%
C	9	Extends beyond sphenoid sinus and involves brain, oropharynx, or anterior cranial fossa	11%	19%

Abbreviation: MGH-MEEI, Massachusetts General Hospital-Massachusetts Eye and Ear Infirmary.

Nasal Complications. Three patients developed chronic nasal symptoms after radiotherapy, consisting of CTC grade 2-3 nasal obstruction secondary to fibrous adhesions. One patient required surgical removal of adhesions to relieve chronic nasal congestion. Median time for development of symptoms was 4.4 months.

Auditory Complications. Four patients developed late CTC grade 2 auditory complications, including serous otitis media; 3 of these patients required placement of tympanostomies. Median time to development of symptoms was 18.6 months (range, 0.7–38.9).

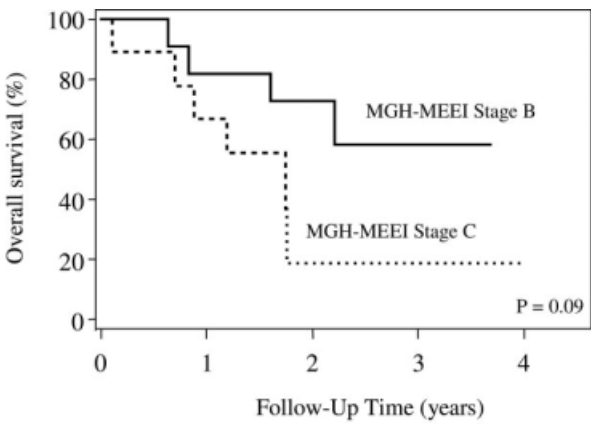
Neurological Complications. Radiographic change seen on MRI of the brain suggesting radiation change was defined by enhancement seen on T1-weighted MR images at any follow-up scan. Radiographic brain change was observed in 2 patients at a median time of 10.9 months (range, 8.5–13.2) after radiation. One patient with symptomatic CTC grade 2 brain toxicity experienced seizures and short-term memory loss. The seizures were controlled with anticonvulsant medication and a short course of steroids. Two patients experienced cerebrospinal fluid (CSF) leak after surgery and radiation. One patient developed a CTC grade 2 CSF leak from the external auditory canal, which developed secondary to tumor shrinkage and erosion of the petrous temporal bone 5 months after radiotherapy. The patient was offered surgery and declined treatment. One patient developed a CTC grade 5 CSF leak without evidence of tumor recurrence at 2 months after completion of radiotherapy. The patient underwent 4 surgical repairs including trans-ethmoid packing of the ethmoid and sphenoid sinuses and placement of a lumboperitoneal shunt. The patient subsequently died from infectious meningitis.



No. at risk for MGH-MEEI Staging

Stage B	11	9	6	6	6
Stage C	9	3	1	1	1

FIGURE 6. Kaplan-Meier curve illustrating disease-free survival by the MGH-MEEI staging system for advanced primary sphenoid sinus malignancies.



No. at risk for MGH-MEEI Staging

Stage B	11	9	8	7	7
Stage C	9	6	3	3	3

FIGURE 7. Kaplan-Meier curve illustrating overall survival by the MGH-MEEI staging system for advanced primary sphenoid sinus malignancies.

Endocrine Complications. One patient developed CTC grade 2 hypothyroidism requiring thyroid replacement at a time of 43 months. One patient had CTC grade 4 pituitary dysfunction at 6 months after completion of radiation therapy. The patient was seen with syndrome of inappropriate antidiuretic hormone secretion (SIADH); symptoms included apnea, respiratory acidosis, hyponatremia, and SIADH was confirmed on serum and urinary electrolytes. The patient was treated with fluid restriction, saline, and diuretics with complete recovery.

DISCUSSION

Sphenoid sinus malignancies pose a particular challenge compared with other paranasal sinus sites, because these tumors are often considered unresectable because of proximity to brain, structures within the cavernous sinus and optic structures, and often present at a locally advanced stage. Our study represents the first clinical report of radiotherapy management using proton radiation therapy for locally advanced primary sphenoid sinus malignancies. This study shows that this modality is feasible with excellent normal tissue sparing, due to the unique property of protons, which allow sharp dose delineation between tumor and normal critical structures from the Bragg Peak effect. A local control rate of 86% at 2 years with proton beam in our series is comparable to other series examining sphenoid sinus malignancies.[1,2,6,19,20]

Surgical management in our series consisted mainly of biopsy or partial resection. Craniofacial resection has been advocated for tumors of the skull base including paranasal sinus cancers.[7] Absolute contraindications to craniofacial resection include involvement of the cavernous sinus, or carotid artery encasement.[21] Sphenoid sinus malignancies often fall into the latter category; hence, radiation therapy often plays a definitive role. Partial surgical resection or surgical debulking,[22] however, may facilitate delivery of radiotherapy, by removing tumor away from critical structures, which may minimize complications from radiotherapy. In the DeMonte series, it is noted that 56% (14 of 25 patients) underwent surgical resection, with a trend toward more aggressive surgical resections using combined lateral and anterior approaches over time. Of the 14 patients undergoing surgical resection, a gross total resection with negative margins was performed in 6 patients (24%) and a subtotal resection with positive margins in 8 patients (32%).[2] In our series, none of the patients had undergone complete resection, and only 35% of patients had partial resection. Although it is difficult to make a direct comparison to the DeMonte series, the latter series had a greater number of completely resected patients compared to our series, suggesting that patients presented with earlier stage disease. Although a randomized comparison of surgery and radiation is unlikely to be performed, the relative role of surgery and radiation need to be individualized for each patient, and often locally advanced sphenoid malignancies require a combined modality approach, and where possible, a complete resection followed by postoperative radiation therapy may have a superior outcome. For patients with residual or unresectable disease, proton radiation therapy may offer the ability to escalate radiation dose to sterilize tumor and improve radiation dose coverage of tumor, although this does not necessarily replace the role of surgery in resectable cases.

In our study, chemotherapy was used in 11 (55%) patients, of which induction chemotherapy was used in 8 patients (40%) and concurrent chemotherapy in 30% of patients. On univariate analysis, the addition of chemotherapy did not affect survival; however, small numbers, heterogeneous histology, and short follow-up for patients receiving concurrent chemotherapy make it difficult to draw definitive conclusions. Licitra et al[23] has investigated primary chemotherapy for paranasal sinus malignancies of adenocarcinoma histology in a phase II study of 49 patients with cisplatinum, 5 fluorouracil, and leucovorin, with a complete pathological response rate achieved in 16% of patients. The 3-year overall survival was 69% for the whole patient cohort, in patients who achieved a pathologic complete response, their 3-year survival and event-free survival was 100%. In our series, it is noted that 4 of 7 patients who developed systemic, nonintracranial disease had adenoid cystic carcinoma histology, in which currently no effective chemotherapy regimen has been proven. Hence, defining the role of chemotherapy is difficult to conclude in this histologically heterogeneous population. The high rate of distant disease may reflect the predominance of adenoid cystic histology recurrences in our patient cohort, rather than because of the sphenoid sinus being the primary site.

In our series, optic or visual complications occurred in 10%, mainly consisting of epiphoria, strabismus, and photophobia. We did not observe optic neuropathy or radiation-induced visual loss, although longer follow-up may be required. Patients presenting with vision impairment secondary to tumor did not experience worsening of symptoms after radiation therapy. In our experience, limiting doses to the optic structures generally to a maximum of $\leq$2 CGE/day and to a total dose of 54 GyE,[24] utilizing 3D conformal planning is critical in evaluating the treatment plan, including critical appraisal of the dose volume histograms and isodose plans. Digital portal imaging was performed daily prior to treatment delivery to verify setup and ensure accuracy of delivery.

Finally, the current AJCC 2002[25] defines a staging system for paranasal sinus malignancies. This includes maxillary, ethmoid, and nasal cavity sites, but none exists for sphenoid sinus cancers. Although the AJCC defines the staging system for squamous cell histology only, many studies have applied this staging system for paranasal sinus malignancies of other histological types. Other staging systems exist for anterior skull base tumors,[26] such as the Kadish staging system for esthesioneuroblastoma[5] based on histology. One of the difficulties of comparison of our data to the literature is the lack of a staging system for sphenoid sinus malignancies and that tumors of the sphenoid sinus are not defined in the current AJCC staging system. If using the AJCC staging for the sphenoid sinus, another paranasal site is designated as the primary, with extension into the sphenoid sinus, this automatically categorizes the disease as stage IV. We attempted to find prognostic factors that may influence survival, and differentiate a potentially useful T staging system for malignancies of the sphenoid sinus. The only factors found to be significant for disease-free survival on multivariate analysis were oropharyngeal involvement and anterior cranial fossa invasion. Of note, patients who had oropharyngeal involvement also had invasion of the nasopharynx and nasal cavity, although nasopharyngeal and nasal cavity invasion alone were not significant for disease-free survival. Disease extension into the brain was a significant factor in multivariate analysis for decreased overall survival. This finding is also supported in other surgical series, showing decreased survival for patients with intracranial involvement of the brain. The 5-year disease-specific survival was 28.4% compared to 55.1% with and without brain invasion, respectively, in an international collaborative study examining craniofacial resection for paranasal sinus malignancies.[7] We did not find any survival difference for patients presenting with cranial neuropathies. This is in contrast to other series that have shown a worse survival with presentation of cranial neuropathies.[2]

CONCLUSIONS

Primary sphenoid sinus malignancies require a combined modality approach, with radiotherapy playing an important role in management. Disease presentation is often locally advanced, and the presentation and outcome differ from that of other paranasal sinus malignancies, thus warranting its own staging system. Proton radiation therapy provides an advantage over conformal photon therapy because of the potential to deliver higher dose while maintaining normal tissue dose constraints. Prospective multi-institutional studies are needed to further validate the use of proton radiation therapy for this rare paranasal sinus malignancy.

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