



Case Report

Cesium-131 Brachytherapy Seeds for the Treatment of Sinonasal Carcinosarcoma: A Case Report and Literature Review

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Abstract

Background

Radiation-induced tumors of the skull base pose a significant treatment challenge. Temporary Brachytherapy (BRT) with Cesium-131 (Cs-131) seeds is a novel therapeutic technique that holds significant potential for the achievement of local tumor control in patients with limited therapeutic options.

Methods

We report a 70 year-old patient with a history of anaplastic oligoastrocytoma who presented with recurrent left-sided epistaxis. Imaging and biopsy results revealed a high-grade carcinosarcoma of the paranasal sinuses and skull base. The Sinonasal Carcinosarcoma (SN-CS) was resected and the residual micro tumor was treated with Cs-131 BRT seeds attached to a vicryl mesh, which was removed 6 weeks later.

Results

Follow-up examination demonstrated no evidence of recurrence or metastasis for 9 months and the patient had an overall survival of 15 months after treatment with Cs-131 BRT.

Conclusion

Temporary BRT with Cs-131 seeds may play a pivotal role in achieving local tumor control and palliation in patients with aggressive skull base tumors who are precluded from receiving more extensive forms of radiotherapy.

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Citation: Patel KR, Talei B, Hsu AK, Parashar B, Scognamiglio T, et al. (2017) Cesium-131 Brachytherapy Seeds for the Treatment of Sinonasal Carcinosarcoma: A Case Report and Literature Review. J Otolaryng Head Neck Surg 3: 007.

Received: November 07, 2016; Accepted: March 14, 2017; Published: March 21, 2017

Keywords: Brachytherapy; Cesium-131; Cs-131; Sinonasal carcinosarcoma; Skull base

Introduction

Carcinosarcoma tumors have been noted to occur in numerous anatomic sites including the uterus, breast, thyroid, and various sub-sites of the head and neck [1-5]. The salivary glands are the most common location of carcinosarcoma within the head and neck region [6]. The incidence of carcinosarcoma within the nasal cavity and paranasal sinuses is extremely rare and previous studies have consequently been limited to small case series and a recent systematic review [7-11].

Sinonasal Carcinosarcoma (SN-CS) tumors often present with nonspecific symptoms such as facial pain and unilateral nasal obstruction and have a reported 5-year disease-specific survival of 48.5% [10,11]. Because SN-CS can cause rapid and extensive local destruction, achieving prompt local control is of utmost importance in order to preserve function, obtain pain relief and thereby reduce patient morbidity. A recent systematic review of 86 cases of sinonasal teratocarcinoma reported radical surgical resection followed by radiation therapy to be the most commonly used therapeutic approach resulting in a 26% recurrence rate and 57% survival rate at approximately 4 years follow-up [11].

The use of External Beam Radiotherapy (EBRT), however, is often precluded, as in this patient, because a large proportion of SN-CS tumors are believed to reside within previously irradiated fields. The use of EBRT can in these circumstances result in significant toxicity to surrounding vital structures such as the brain, spinal cord, orbit, internal carotid arteries and optic nerves and may result in cerebrovascular accidents or rupture of the carotid artery [12]. Additionally, resection of skull base tumors is also often complicated by proximity or extension into critical structures resulting in suboptimal outcomes [13,14]. Cesium-131 (Cs-131) Brachytherapy (BRT) is an effective and highly conformal contemporary technique for administering further radiation in a previously irradiated field while limiting toxicity in the treatment of head and neck cancer [15-20].

Cesium-131 is a novel radioisotope that has only recently been reported in the treatment of recurrent head and neck cancers as an effective adjuvant therapeutic modality to surgical resection with low rates of acute toxicity [19]. We hypothesize that temporary Cs-131 seed placement may hold significant therapeutic potential for the treatment of radiation-induced skull base tumors in the face of limited treatment options. Here, we report the first documented case of a primary skull base tumor treated with a temporary mesh containing Cs-131 BRT seeds after endoscopic resection and the resultant favorable outcome of local tumor control and no evidence of disease for 9-months post-treatment.

Case Report

Patient demographics and clinical presentation

A 70-year old male with poor cognitive function presented to an outside hospital in November 2010 with recurrent left-sided epistaxis. This patient had a history significant for anaplastic oligoastrocytoma

diagnosed in 1994 for which he underwent craniotomy with resection and partial brain irradiation. In 2001, he experienced tumor recurrence and was subsequently treated with stereotactic radiotherapy and chemotherapy. The patient had a medical history further complicated by chronic ventriculoperitoneal shunt malfunction, seizure disorder; prostate cancer treated with anti-androgen therapy and a factor II mutation with recurrent deep vein thrombosis.

The patient underwent nasal endoscopy and excisional biopsy at an outside hospital in December 2010, which revealed a high-grade carcinosarcoma in the left ethmoid and sphenoid sinuses. Chemotherapy and EBRT were not administered due to the patient's overall poor health status and he was discharged on January 9th, 2011. In February 2011, the patient presented to New York Presbyterian Hospital/Weill Cornell Medical Center with an admission diagnosis of aspiration pneumonia and upper gastrointestinal bleed. A brain MRI at this time for worsening cognitive function revealed a mass in the left paranasal sinuses (Figure 1). Following consultation with otolaryngology, the patient was taken to the operating room for a repeat biopsy, which confirmed the presence of a high-grade carcinosarcoma in the left ethmoid and sphenoid sinuses.



Figure 1: (a) Coronal and (b) Sagittal T1 with contrast MRI of sphenothmoidal carcinosarcoma.

Tumor characteristics and therapeutic management

The malignant epithelial component of the tumor specimen was positive with an immunohistochemical stain for p63 and negative for cytokeratin (AE1/AE3), chromogranin and synaptophysin; the malignant stromal component showed no heterologous differentiation and was negative for S100, myo-d1 and myogenin. This patient's case was discussed at a multidisciplinary tumor board meeting with otolaryngology and medical and radiation oncology, which yielded limited options. The patient's history of nearly toxic doses of irradiation for a prior brain neoplasm precluded him from receiving further EBRT and his poor overall functional status made him unsuitable for systemic chemotherapy. Given the location of the sinonasal malignancy proximal to the previously irradiated field and the timeline of the tumor being diagnosed 9 years after multiple brain radiotherapy treatments, it is most likely that the high-grade SN-CS was a long term sequela of his prior irradiation. He was taken back to the operating room on February 24, 2011 for a more definitive resection and placement of BRT seeds. A completion left endoscopic sinus surgery was performed with excision of a majority of the paranasal contents including the middle turbinate. Stereotactic navigation with Brain Lab[®] confirmed the removal of tissue bordering the skull base and orbit. The anterior and posterior ethmoid specimens demonstrated clear evidence of high-grade carcinosarcoma while all other sinus contents yielded chronically inflamed respiratory mucosa with or without bone (Figure 2).

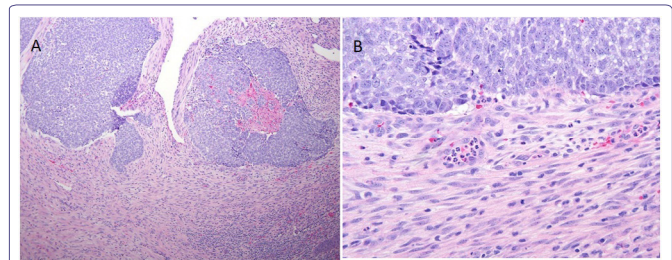


Figure 2: (a) 10x and (b) 40x representative views of the tumor specimen.

The remaining micro tumor was treated with 20 Cs-131 radiation seeds embedded 1 cm apart in suture strands attached to a vicryl mesh that was implanted utilizing stereotactic guidance and was secured to the tumor using surgical clips. The mesh was then further secured with a nasal tampon and absorbable packing, which were both removed at one week while leaving the mesh in place. The dose was determined based on a normogram developed by our radiation oncology department. The Cs-131 BRT seeds have a half-life of 9.7 days and an activity level of 1.57 U (2.29 mCi) was used given the patient's history of multiple prior radiation treatments adjacent to the implanted site. The total expected radiation dose was 60 Gy to the surrounding tissues within 0.5 cm of the mesh. Proper placement of the mesh and BRT seeds was monitored by endoscopy and serial skull x-rays (Figure 3). The implant was removed after 6 half lives resulting in a delivery of greater than 99% of the prescribed dose of 60 Gy (Figure 4). On April 4, 2011, the patient was taken back to the operating room for repeat sinonasal endoscopy and removal of the BRT seeds and vicryl mesh. There was no residual tumor noted at this time.

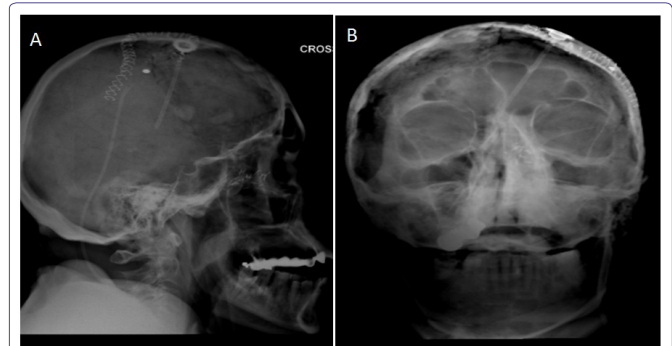


Figure 3: (a) Lateral and (b) Anteroposterior skull films after BRT seed placement.

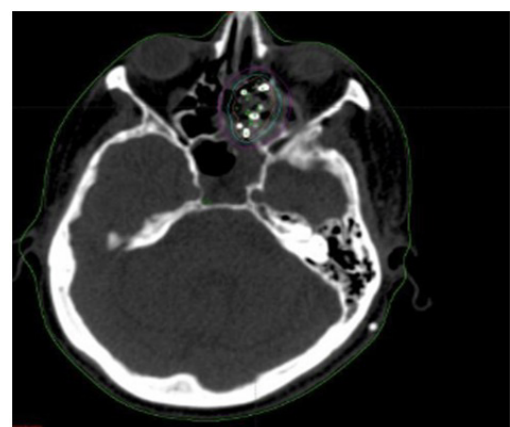


Figure 4: Radiation dosimetry diagram with green line representing the 60 Gy isodose line.

Patient outcome

The patient continued to show no evidence of disease on November 17, 2011-roughly 9 months after therapy-when a brain MRI was performed for a work-up of progressively worsening mental status. The MRI displayed extra soft tissue and associated bone destruction in the region of the anterior left cavernous sinus and left orbital apex consistent with post-surgical changes. Additionally, the patient had no evidence of disease upon thorough endoscopic evaluation in the office. The patient was devoid of any symptoms related to the sinonasal tract at this time and a decision was made to withhold further treatment. He was subsequently re-admitted for worsening mental status and based on *in-vitro* data at that time, a 4-week trial of erlotinib 150 mg daily was initiated on February 10, 2012. As the patient progressed to an unresponsive state in the setting of persistent hydrocephalus, treatment was ceased and the patient was discharged home with hospice care in April 2012 and died approximately one month later.

Literature Review and Discussion

For the treatment of SN-CS, surgery and radiotherapy are the most frequently employed treatment modalities but no standard has been defined due to the relatively rare and heterogeneous nature of this neoplastic entity. Historically utilized most frequently in the treatment of gynecologic malignancies [21-23], BRT is now also an established therapeutic modality in the management of residual, recurrent and metastatic tumors of the head and neck region [15,16,24-29]. EBRT of the sinonasal tract and nasopharynx may result in both acute and late toxicities due to secondary radiation exposure to the optic chiasm, optic nerve, orbit and brainstem, especially in the setting of prior skull base irradiation. Additionally, the difficulty of obtaining clear margins and a satisfactory aesthetic outcome for sinonasal tract tumors in the setting of advanced and locally destructive disease has made BRT a common therapeutic modality utilized by head and neck surgeons.

A variety of different isotopes have been used for brachytherapy including cesium-131, gold-198, iodine-125, iridium-192, cobalt-60 and palladium-103 [30]. Several factors must be considered when choosing the type of source to utilize including the half-life, tumoricidal range, energy, and the ability to protect medical personnel and caregivers. In addition, a removable, temporary instead of a permanent source may be used in order to provide a lower risk of toxicity [30]. The radiation source can be implanted within the tumor mass (interstitial brachytherapy) or placed within a body cavity (intracavitary brachytherapy) and deliver radiation doses with high precision [18]. Utilization of BRT can thereby minimize the incidence of complications associated with radiation-induced adjacent tissue damage while treating and preventing progression of residual micro tumor. Although toxicities associated with brachytherapy are relatively low in comparison to conventional EBRT, potential side effects are not negligible. Toxicities in the head and neck region may include subcutaneous fibrosis, mucositis, ulceration, infections, fistula formation and necrosis [25,31].

Methods for achieving local control within the nasal cavity, paranasal sinuses and skull base have varied widely. Combining surgical resection with radiotherapy is of utmost importance given the high recurrence rate of most tumors within these subsites. Furthermore, obtaining clear margins with paranasal space tumors is inherently difficult due to restricted bony access and proximity to vital structures despite advances in endoscopic and cranial base surgery. Teudt et al., recently described the outcomes of 35 patients with advanced stage sinonasal tract tumors treated with perioperative image-adapted

brachytherapy with or without EBRT and chemotherapy and reported a 72% survival rate at 3 years [32]. Their study and others [20,33-36] support the use of BRT to achieve local and regional control, to improve survival rates and to limit toxicity in patients with recurrent or advanced stage malignancies of the nasopharynx and paranasal sinuses. Local control rates for nasopharyngeal carcinoma treated with surgery and intracavitary Ir-192 brachytherapy have been found to be similar to those of wide-field irradiation with lower complication rates [37]. In the management of neoplasms of the paranasal sinuses, the European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) recommends BRT as sole therapy of residual disease following surgery with close margins, for superficial recurrences, for boost therapy following EBRT, and in combination with surgery for recurrent tumors [38].

For the management of skull base tumors such as those of the ethmoid and sphenoid sinuses, periorbital region, cribriform plate and maxillary antrum as well as the nasopharynx and nasal cavity, Intra-operative High Dose Rate BRT (IOHDR) maximizes local control and survival in patients with no previous radiation therapy, especially as a pre-EBRT boost [39]. The use of IOHDR in previously irradiated patients, however, resulted in poor outcomes [39]. Overall, the use of IOHDR with Ir-192 achieved 67% local control and 72% overall survival at 21 months for 29 patients diagnosed with recurrent or advanced skull base tumors [39]. Kumar et al., reported their experience using iodine-125 seed implantation as sole therapy for 5 recurrent, previously irradiated malignant tumors (clival chordoma, meningiomas, pituitary hemangiopericytomas and nasopharyngeal and parotid carcinomas) with extension into the skull base. All cases reported by this group were treated with 1 or 2 permanent seed iodine-125 implants and achieved complete tumor resolution without any acute or chronic complications [40]. Other authors have also demonstrated the value of BRT in the management of advanced stage skull base tumors due to favorable palliative results and the preservation of visual acuity [41].

Several previous studies have thus reported on the success of brachytherapy for treatment of various histological subtypes of sinonasal and skull base tumors (Table 1). However, to our knowledge, this is the first paper to report the use of temporary Cs-131 BRT seeds for the treatment of a primary skull base tumor. We propose a novel therapeutic approach to patients with primary or recurrent skull base tumors, who are precluded from receiving EBRT or systemic chemotherapy. In this case report, we preferred the use of Cs-131 radiation seeds in a vicryl mesh in treating the SN-CS due to its conformity, high dose rate, short half-life (9.7 days) that ensures therapeutic radiation being delivered in a short time (in comparison, iodine-125 has a half-life of 60 days) and limited exposure to staff and health care workers. Notably, the patient had no severe complications after BRT treatment.

The largest cohort of SN-CS patients studied (n=15), for which the primary treatment modality was surgery with conventional radiotherapy, reported a disease-specific survival rate at 15 months of approximately 65% [10]. This patient had an overall survival time of 15 months post-treatment, which is relatively prolonged given the patient's extremely poor prognosis at presentation due to the aggressive nature of his tumor, his limited treatment options and his poor functional status. Overall, evidence from prior studies and this case report demonstrates that a high rate of local tumor control and improved survival, palliation and aesthetic outcomes can be achieved while minimizing toxicity and patient morbidity through meticulous

Year	Journal	Reference	No. cases	Tumor site	Tumor histology	Brachytherapy type	Median or range of BRT doses	Outcomes	Mean follow-up (yrs)
1983	Cancer	Vikram et al. [31]	124	HN	Epidermod carcinoma (n=111) salivary gland carcinoma (n=10) thyroid carcinoma (n=3)	Permanent I-125 implants	120 Gy	64% local Control rate at 5 yrs, 27% overall survival rate at 1 yr	5
1988	Cancer	Kumar et al. [40]	5	Skull base	Meningioma, clivalchordoma, pituitaryhemangiopericytoma, nasopharyngeal carcinoma, parotid carcinoma (n=1)	Permanent I-125 implants	100 Gy	80% local control rate at 3 months, 100% overall survival rate at 3 yrs	1.75
1996	Radioth and Onc	Nag et al. [39]	29	Skull base	SCC (n=21) undifferentiated (n=3) chondrosarcoma, esethioneuroblastoma, adenocarcinoma, adenoidcystic carcinoma, mucoepidermoid carcinoma, basal cell carcinoma (n=1)	Intraoperative Ir-192 HDR	7.5-15 Gy	67% local control rate at 21 months, 72% overall survival rate at 21 months	N/A
2002	Laryngo-scope	Glatzel et al. [25]	90	HN	N/A	Interstitial or intracavitaryIr-192 HDR	17.5 Gy	46% complete remission rate, median overall survival of 7 months	N/A
2003	RadiothOncol	Hall et al. [37]	18	Nasopharynx	Undifferentiated or SCC (n=15) neuroendocrine carcinoma, malignant melanoma, adenocarcinoma (n=1)	Intracavitary-Ir-192 LDR & HDR	30-63 Gy	32% local control rate at 5 yrs, 34% overall survival rate at 5 yrs	5.7
2005	Hong Kong Med J	Ngan et al. [28]	13	HN	SCC (n=11) mucoepidermoid carcinoma (n=1) alveolar soft-part sarcoma (n=1)	InterstitialIr-192	70 Gy (BRT alone) 35 Gy (BRT + EBRT)	75% local control rate at 3 years, 89% overall survival rate at 3 years	3.5
2005	Strahlenth and Onk	Strege et al. [41]	18	Skull base	Paranasal sinus carcinoma (n=10) sarcomas (n=5) primitiveneuroectodermal tumor (n=2) parotid gland carcinoma (n=1)	Interstitial Ir-192 pulsed-dose-rate/ high dose rate afterloading	10-30 Gy	Median survival time of 16 months	1.2
2006	Radioth and Onc	Nutting et al. [29]	72	HN	SCC (n=63) adenocarcinoma (n=2) carcinoma ex pleomorphic adenoma (n=2) UCNT (n=2)	Interstitial Ir-192 LDR	60 Gy	37% local control rate at 2 yrs, 31% overall survival rate at 2 yrs	5
2007	Brachytherapy	Narayana et al. [26]	30	HN	N/A	Interstitial HDR	40 Gy (BRT alone) 34 Gy (Postoperative BRT) 20 Gy (BRT + EBRT)	63% overall survival rate at 2 yrs	1
2008	Radiat Oncol Biol Phys	Allen et al. [35]	9	Nasal cavity	SCC (majority) and non-SCC	Interstitial Ir-192	65 Gy	86% local control rate at 5 yrs, 82% overall survival rate at 5 yrs	11
2008	Laryngo-scope	Tselis et al/ [36]	2	Nasal vault	Esthesioneuroblastoma	Interstitial CT guided HDR	27 Gy	100% overall survival at 17 months	1.1
2012	Head and Neck	Gaztanaga et al. [27]	97	HN	SCC	HDR	32-40 Gy (no EBRT) 16-24 Gy (BRT + EBRT)	52% disease-free survival at 9 yrs	4.3
2013	J Contemp Brachytherapy	Scepanovic et al. [34]	1	Nasal cavity, nasopharynx	Malignant melanoma	Intracavitary Ir-192 HDR	72 Gy	Regional progression of disease at 6 months, AWD at 1 yr	1
2014	Brachytherapy	Teudt et al. [32]	35	Sinonasal tract	N/A	Perioperative image-adapted brachytherapy	N/A	72% overall survival rate at 3 yrs	2.3
2015	Eur Arch Otorhinolaryngol	Kadah et al. [18]	20	Nasal cavity, paranasal sinuses, nasopharynx	SCC (n=14) mixed tumors (n=2) adenocarcinoma (n=1) adenoid cystic carcinoma (n=1) mucosal melanoma (n=1) plasmocytoma (n=1)	Intracavitary Ir-192 HDR afterloading	10-20 Gy	57.3% overall survival at 2yrs	2

2015	Brachytherapy	Tagliaferri et al. [20]	9	Sinonasal, nasopharynx	N/A	Endoscopy guided BRT	30 Gy	Median disease-free survival of 12 months, median overall survival of 23 months	1.6
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Table 1: Summary of reviewed relevant studies.

AWD, Alive With Disease; BCC, Basal Cell Carcinoma; HDR, High Dose Rate; HN, Head And Neck (Subsites Unspecified); IMBT, Intensity-Modulated Fractionated Interstitial Brachytherapy; LDR, Low Dose Rate; N/A, Information Not Available; SCC, Squamous Cell Carcinoma; UCNT, Undifferentiated Carcinoma of the Nasopharynx.

implementation of temporary Cs-131 BRT seeds in the management of recurrent, residual or advanced skull base disease. However, no randomized trials have been performed and there is a paucity of literature regarding clinical guidelines for the use of BRT for specific head and neck subsites, such as the sinonasal tract [38]. This literature review was limited by the lack of randomized controlled analyses and prospective studies regarding the use of BRT for sinonasal and skull base malignancies. Future studies may wish to focus on a more rigorous analysis of BRT protocols for sinonasal tumors and patients outcomes.

Conclusion

Endoscopic surgical resection and subsequent implantation of a temporary mesh with Cs-131 BRT seeds resulted in a 9-month disease-free interval in a patient with SN-CS presenting with an otherwise poor prognosis. In the management of patients with aggressive skull base tumors, careful implementation of temporary BRT seeds has the potential to achieve local and regional tumor control and palliation in patients who are precluded from receiving more extensive forms of radiotherapy and chemotherapy.

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