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CASE REPORT

Management of recurrent alveolar soft-part sarcoma of the tongue after external beam radiotherapy with iodine-125 seed brachytherapy

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ABSTRACT: *Background.* Alveolar soft-part sarcoma (ASPS) is a rare type of soft tissue sarcoma. The infrequency of ASPS is such that it comprises <1% of all soft-tissue sarcomas and <0.1% of sarcomas concerning the head and neck, primarily those involving the orbit (48%) and tongue (25%). Traditional chemotherapy or radiotherapy of ASPS is often associated with poor outcome, even after comprehensive interventions.

Methods and Results. We performed iodine-125 (^{125}I) seed brachytherapy under ultrasound guidance through a submandibular puncture in a 4-year-old male patient with recurrent ASPS of the tongue. The prescription dose was 120 Gy; therefore, 35 ^{125}I seeds were implanted with 0.77 mCi per seed, the total amount of activity being 26.95 mCi. CT scans confirmed a complete response after the treatment.

Conclusion. Our patient now has a recurrent-free survival of >30 months, an amount of time longer than the median rate described in the literature. © 2014 Wiley Periodicals, Inc. *Head Neck* 00: 000–000, 2014

KEY WORDS: ^{125}I seed, brachytherapy, ultrasound guidance, alveolar soft-part sarcoma, outcome

INTRODUCTION

Alveolar soft-part sarcoma (ASPS) is an extremely rare cancer that arises mainly in young adults. Although sarcomas comprise about 1% of all newly diagnosed cancer and 15% for all childhood, ASPS comprises <1% of sarcomas. The low incidence of morbidity seriously impedes the development of specific treatment and makes clinical management very difficult.[1]

ASPS presents itself as a slow-growing, painless, nonulcerating mass. The tumor is usually encapsulated and well circumscribed, but there are no distinctive gross findings. As a highly vascular lesion, ASPS tends to spread hematologically. As a result, tumor cells may easily metastasize into the brain, lungs, and bone. Regional lymph node metastasis has only been seen in 7% of cases.[2] Simmons et al[3] reported that enlarged cervical lymph nodes are only related to follicular lymphoid hyperplasia in biopsy. A metastasectomy should be considered for operable metastatic disease because of the fact that ASPS tumors can enlarge rapidly and have a propensity for bleeding and obstructing airways.

ASPS is usually diagnosed by MRI or a CT scan and biopsy. MRI or CT scanning can be useful for determining the gross anatomic extent of the tumor, and may also be useful in executing the treatment plan. ASPS is a form of soft-tissue sarcoma whose tumor cells may arise from embryonic mesenchyme. In pathologic analysis, tumors in adults typically appear as nests of large cells with necrotic centers that resemble alveoli; however, alveoli are often absent in pediatric tumors. Lesions are generally characterized by vascular septae, round nuclei, and prominent nucleoli. They are periodic acid-Schiff positive and exhibit diastase-resistant inclusion crystals within the cytoplasm. Mitoses of a lesion's cells is rare.[4] AQ2

In young children, ASPS rarely occurs in the oral cavity. Only 12 cases of ASPS in the tongue have been reported as arising during the first decade of life.[4] Because ASPS in children is rare, no specific treatment guidelines have been developed, making treatment decisions in the clinical setting very difficult. In this study, we report a new case of tongue ASPS in a 4-year-old male patient whose tumor was located at the root of the tongue. He was successfully treated with permanent implantation of iodine-125 (^{125}I) seeds under ultrasound guidance. No recurrence was found after 30 months of follow-up procedures.

CASE REPORT

In 2007, a 4-year-old male patient suffered from dysphagia and partial airway obstruction. A CT scan of the tongue revealed a low density mass with a volume of 2.5 × 4.5 × 3.5 cm^3 located in the left tongue body, root, and base of the mouth. There was no cervical lymphadenopathy. The diagnosis of the tumor as a Langerhans cells tumor was confirmed by a biopsy and followed by a histological examination. This patient initially received 5

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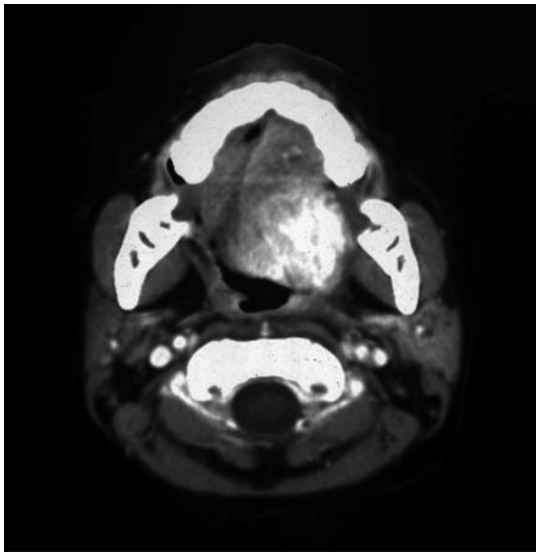

FIGURE 1. The recurrent tumor on CT scans before seed implantation.

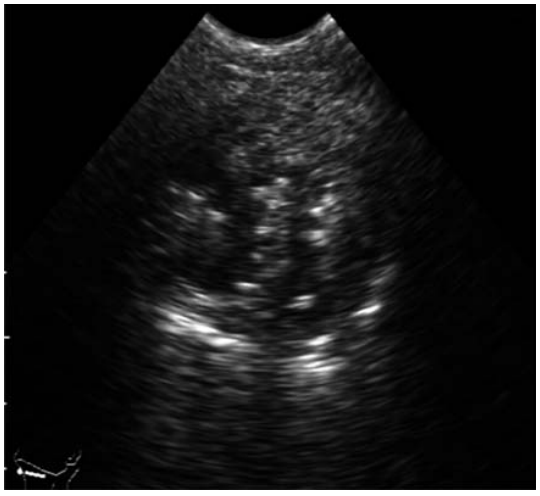

FIGURE 2. Ultrasound scans showing the distribution of seeds in the tumor after iodine-125 (^{125}I) seed implantation.

cycles of chemotherapy with etoposide and vincristine; however, no treatment response was observed. Another biopsy and an additional histological examination were performed at the same location 1 month after chemotherapy to reconfirm pathological types. Tumor cells identified by immunohistochemistry were as follows: MyoD1+, esmin+/-, vimentin+, KP1-, S100-, MSA-, CD34-, CgA-, and SY-. The patient was transferred to a pediatric medical center and received an additional 3 cycles of chemotherapy with vincristine and adriamycin. A CT scan demonstrated further mass progression with an enlarged tumor volume of 5.3 × 3.8 × 4.0 cm^3. The patient then received external beam radiotherapy (EBRT) (DT 57.5 Gy in 23 fractions) and 2 months later started and eventually completed 6 cycles of VAIA and 1 cycle of VAICE. However, at 6 months after completion of radiation, the tumor volume continued to enlarge with F1 partial airway obstruction (Figure 1). The patient had no option but to have radical surgery in a pediatric medical center; this surgery would make him lose swallowing and speech function. The patient's guardians refused the surgery plan and the patient was transferred to our department. ^{125}I seed brachytherapy was considered at this time. One week before seed brachytherapy, a tumor volume study was conducted using CT scans with a 5-mm thickness. Gross tumor volume and clinical tumor volume measured by CT was 40.8 cm^3 and 50.5 cm^3, respectively. The doses delivered to 90% of the target volume defined by the CT using dose – volume histograms of irradiation doses, or the number of ^{125}I seeds for implantation, was determined using a 3D Radiation Therapy Planning System (3D-TPS, Beijing Tianhang Kelin Industries, Beijing, China).

Ultrasound imaging (Aloka 5000, Japan) was performed to guide the placement of needles. Precautionary procedures, such as placing needles 1 cm away, were taken to avoid puncturing the large blood vessels. ^{125}I seeds were then implanted using a Mick applicator, and the space between the seeds was maintained at approximately 1.0 cm (center-to-center). The number of implanted ^{125}I seeds was 35. The specific activity of the ^{125}I seeds was measured at 0.77 mCi per seed and the total amount of activity was calculated at 26.95 mCi (Figures 2 and 3). The F2 F3 patient received perioperative prophylactic antibiotics to avoid infections. Follow-up examinations were scheduled for every 2 months after implantation, up to 30 months. Complications were evaluated by Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Score.

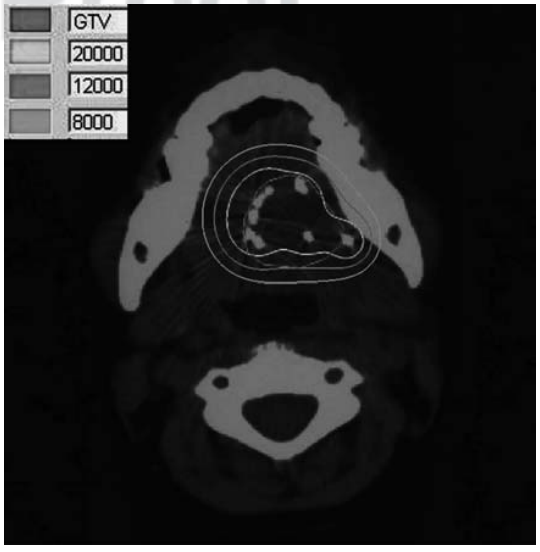

FIGURE 3. The CT scans isodose distribution after seed implantation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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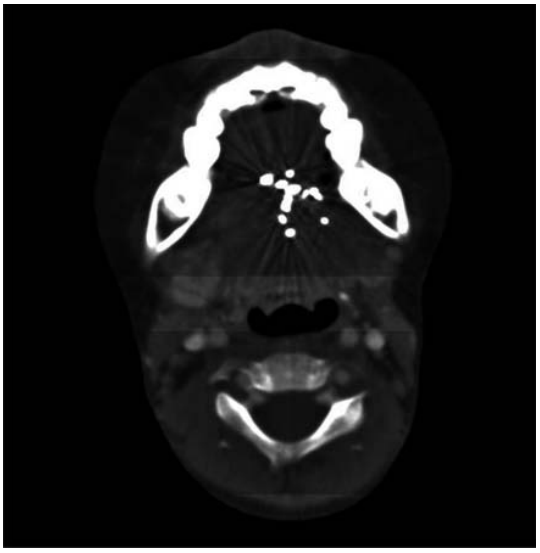

FIGURE 4. CT scans showing local response 32 months after iodine-125 (^{125}I) seed implantation.

No recurrent tumor was observed in the ultrasound examination or on the CT scan after 3 months of ^{125}I seed brachytherapy (Figure 4). Thirty-two months after the treatment, a physical examination and a CT scan confirmed that no recurrence of the tumor was found. The mouth had grade 3 mucositis and recovery from palliative treatment. The patient was able to open the mouth at a maximum 4 to 5 cm and had whisper speech ability.

DISCUSSION

ASPS is a rare malignant tumor with only 5% of the cases affecting the tongue. The characteristics of lingual ASPS include lower median age at diagnosis, lower rate of metastases, and lower death rate compared to nonlingual ASPS.[5]

The age for lingual ASPS is much younger than ASPS in other anatomic locations. Fanburg–Smith et al[5] analyzed the features of 14 cases of lingual ASPS in 8 male and 6 female patients. In their study, the median age was only 5 years old (range, 3–21 years). The age of our patient was consistent with this finding. The most common therapy for ASPS is radical surgery, which is difficult for anyone, especially for young children. Furthermore, commonly used anesthetic agents may damage a child's developing brain and increase the risk for developmental and behavioral disorders.

Lingual ASPS presents in difficult anatomic sites to perform radical surgery and may lead to disastrous consequences. Nevertheless, wide surgical excision with tumor-free margins is the standard curative treatment for ASPS. A precautionary tracheotomy should be considered before resection if there is a potential for blocking the airway. The tumor should be resected with minimal manipulation to avoid direct and hematologic seeding. Although several authors have suggested that a tumor-free zone of 1 to 1.5 cm is appropriate, this excision is often difficult, especially in the head and neck. Local recurrence is rare, unless the tumor is not completely resected, and there is no advantage to radical neck dissection. Preoperative angiographic embolization has been used to decrease intraoperative blood loss.[6] For large tongue lesions, similar to our patient, a safe oncologic surgical protocol is necessary. Our patient received a precautionary tracheotomy when the partial airway was obstructed. However, the potential risk of losing swallowing and speech function is not acceptable for some patients, especially young children.

The role of neoadjuvant and adjuvant EBRT is controversial. Roozendaal et al[7] achieved excellent local control in 6 adults who were administered EBRT before and after excision of ASPS tumors. However, a review of 102 cases at Memorial Sloan–Kettering Cancer Center found that local excision alone was adequate. In our case, EBRT was used for gross disease, and the dose of 57.5 Gy was likely ineffective. Although lower doses may be effective in other sarcomas of children, it is likely that the dose was too low to be effective for ASPS.

Several different chemotherapeutic treatment protocols, including combinations of vincristine, actinomycin D, cyclophosphamide, doxorubicin, and chlorambucil, have been attempted, but minimal success was achieved. Thiotepa monotherapy and the combination of ifosfamide and doxorubicin have both been shown to promote tumor regression in a limited number of cases. Antiangiogenic treatment as a preoperative management was reported by Conde et al.[8] The use of antiangiogenic drugs (bevacizumab and celecoxib) as a preoperative treatment may help achieve tumor resection leading to a reduction in postsurgical complications. Chemotherapy in this patient was performed for more than 10 cycles; however, no response was observed. This response may be related to the presence of chemotherapy-resistant tumor cells.

The selection of a treatment plan largely depends on the tumor type and location. Listing the sites in most to least favorable order, they are: the orbit, the tongue, the head, the neck, and the extremities. The prognosis is also affected by the size of the tumor; Casanova et al[9] reported that the rate for 5-year survival was 100% for patients with tumors 5 cm or smaller, but only 31% for patients with larger tumors. In this case, the patient suffered from ASPS with a volume of mass $2.5 \times 4.5 \times 3.5$ cm^3 located in the left tongue body, root, and base of the mouth. The location of the tumor is a very important factor, in this case, for the final treatment decision considering that ultrasound-guided EBRT is preferred rather than radical surgery.

^{125}I seed brachytherapy with ultrasound-guidance has the following advantages: (1) the implant setup can be performed easily with the patient under local anesthesia without severe pain or discomfort during hospitalization for patients; (2) the ultrasound-guided procedure reduces the corner of operation geometry; (3) and the half-life decay of a ^{125}I seed is about 60 days and half-layer value is 1.5 cm in tissue, providing a minimal radiation risk to the surrounding normal tissues because of the sharp decay outside the implanted target. Ultrasound guidance for ^{125}I

seed brachytherapy was already widely used in prostate carcinoma, pancreatic carcinoma, and metastatic carcinoma treatments.[10,11] In this case, the ultrasound-guided procedure resulted in a successful seed implant and the dose delivered to the target was satisfactory. The side effects were acceptable.

In our case report, ^{125}I seed brachytherapy was clinically effective and demonstrated safety. ^{125}I seed brachytherapy has the potential to be one of the most desirable therapeutic options for recurrent ASPS. The prospect of brachytherapy is highly promising and practical. We will not only consider it as a first-line adjuvant therapy for surgery with inadequate surgical margins, but, in some cases, as a first-line therapy for unresectable or recurrent ASPS. The patient in our study was noted to have a good performance status and a reasonable expectation of prolonged survival.

In conclusion, ultrasound-guided ^{125}I seed brachytherapy is an effective option for recurrent ASPS after surgery or EBRT. It minimizes the possibility of further surgery or EBRT, achieves reliable local control, and has acceptable side effects. Although further demonstration with a large number of patients with ASPS is needed, our report provides a successful direction or reference for future cases of ASPS.

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