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^{125}I interstitial brachytherapy in management of pediatric skull base tumors

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Abstract

Background: The purpose of this study was to present our preliminary assessment of the safety and efficacy of ^{125}I interstitial brachytherapy (IBT) in the management of pediatric skull base tumors.

Methods: Thirty pediatric patients with skull base tumors treated with ^{125}I IBT from April 2007 to May 2017 were included in this study. The probabilities of local control (LC) and overall survival (OS) were calculated by the Kaplan–Meier method.

Results: The one- and two-year LC rates were 96.7% and 74.8%, respectively. The one- and two-year OS rates were 93.3% and 72.2%, respectively. No severe acute toxicity was observed. Severe late toxicities were observed in one (3.33%) of 30 patients.

Conclusion: ^{125}I IBT is effective and safe in the management of pediatric skull base tumors, with satisfactory cosmetic and functional outcomes.

KEYWORDS

brachytherapy, pediatric, skull base tumor

1 | INTRODUCTION

Pediatric skull base tumors can originate from primary tumors of the skull base or tumors of adjacent structures, such as the maxilla, para pharyngeal, and parotid. They are rare but contain a variety of histology features.[1–3] Surgical resection is considered the primary treatment modality for solid tumors; however, skull base tumors are in close proximity to critical structures, such as cranial nerves (e.g., the facial nerve and the acoustic nerve) and critical organs (e.g., eyeballs, external auditory canal, internal carotid artery, and internal jugular vein). It is difficult to achieve complete tumor resection without facing a high risk for severe side effects. For at least 10 years after birth, the skull base of a child is not yet completely developed.[4] Skull base development may be affected by surgery, resulting in cosmetic and functional defects, which pose a considerable challenge to surgeons.

Postoperation radiotherapy or exclusive radiotherapy has been used for skull base tumors.[5–7] However, optimal sparing of surrounding organs at risk is difficult for conventional radiotherapy, and dose prescription is therefore limited by patients' tolerance to irradiation.[5] Radiotherapy-related toxicities and adverse effects are associated with dosage and the age when receiving radiotherapy. Radiotherapy has a far-reaching influence in pediatric patients; long-term radiotherapy reactions appear two to four years after radiotherapy in adults but five to 10 years after radiotherapy in pediatric patients[8]; these include mental decline, social dysfunction, and cosmetic alterations, along with function defects or even second primary tumors.[9,10]

^{125}I interstitial brachytherapy (IBT) is a modality of radiotherapy. In the early 1980s, Philip et al reported 13 recurrent tumors of skull base and spine patients treated with ^{125}I sources.[11] ^{125}I IBT delivers higher radiation doses to target areas while sparing surrounding normal tissue. There are several articles reporting the advantages of ^{125}I brachytherapy in treating pediatric head and neck tumors.[12–14]

The purpose of this study was to evaluate the feasibility and effectiveness of ^{125}I IBT in the management of pediatric skull base tumors.

2 | PATIENTS AND METHODS

2.1 | Patients

Thirty pediatric patients with skull base tumors treated with ^{125}I IBT from April 2007 to May 2017 in the Peking University School

Abbreviations: BTPS, brachytherapy treatment planning system; CSF, cerebrospinal fluid; GA/S, general anesthesia or sedation; GTV, gross tumor volume; IBT, interstitial brachytherapy; LC, local control; MPD, matched peripheral dose; MPO, maximum passive openness; OS, overall survival; PM-RMS, parameningeal rhabdomyosarcoma; PRT, proton radiotherapy; PTV, planning target volume

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TABLE 1 Characteristics of 30 pediatric patients treated with ^{125}I IBT for skull base tumors

Characteristic	Patients, *n*	Percent
Sex		
Male	22	73.3
Female	8	26.7
Age, years		
0–3	11	36.7
4–6	11	36.7
7–12	6	20.0
13–18	2	6.67
Histology grade		
High grade	9	30.0
Alveolar rhabdomyosarcoma	3	10.0
Malignant rhabdomyoid cancer	1	3.33
Ewing sarcoma	1	3.33
Synovial sarcoma	2	6.66
Poorly differentiated carcinoma	1	3.33
Poorly differentiated sarcoma	1	3.33
Immediate grade	17	56.7
Embryonal rhabdomyosarcoma	14	46.7
Giant cell malignant Histiocytoma	1	3.33
mucoepidermoid carcinoma	1	3.33
Fibrosarcoma	1	3.33
Benign or low grade	4	13.3
Sialoblastoma	1	3.33
Myofibroma	1	3.33
Inflammatory myofibroblastic tumor	1	3.33
Fibromyxoma	1	3.33
Tumor subsite		
Infratemporal fossa	13	43.3
Nasal maxillary region	4	13.3
External auditory Canal/mastoid process region	8	26.7
Clivus	5	16.7
Tumor size		
>5 cm	25	83.3
<5 cm	5	16.7

of Stomatology were included in this retrospective study. The inclusion criteria were as follows: diagnosis age < 18 years old, tumors were primary, and tumors involved the skull base structures, such as the infratemporal fossa, nasal maxillary region, clivus, and external auditory canal/mastoid process region. Patients with a history of radiotherapy before brachytherapy, a history of chemotherapy for other malignant tumors or severe systemic disease were excluded. At least six months follow-up time after ^{125}I IBT was required to get enough toxicity data. This retrospective study was approved by the Ethics Committee and was conducted under the guidance of international ethical standards, and all pediatric patients' guardians signed their informed consent, which has been properly documented. Table 1 describes the baseline information of patients. Twenty-two patients were male, and eight patients were female. The median age was five years (ranging from two to 17 years old). The median follow-up time was 26 months (ranging from 11 to 86 months). Twenty-five of the histologic types were sarcomas. The maximum tumor diameter ranged from 3.90 to 10.6 cm, with a mean of 5.99 cm. Patients were divided into three histologic groups according to tumor local invasiveness and metastasis potential: a benign or low-grade group, an immediate-grade group, and a high-grade group. Tumor location included infratemporal fossa, external auditory canal/mastoid process of temporal bone area, nasal maxillary region, parasellar region, and clivus. According to the main tumor body location, tumors were separated into four anatomic regions, as shown in Table 1.

TABLE 2 Treatment for 30 pediatric skull base tumor patients

Histological type	Treatment	Patients, *n* (%)
High grade		9 (30.0)
Soft-tissue sarcoma	CT + IBT	7 (23.3)
	CT + IBT	1 (3.3)
Salivary gland carcinomas	IBT	1 (3.3)
Immediate-grade		17 (56.7)
Soft-tissue sarcoma	CT + IBT	13 (43.3)
	S + CT + IBT	2 (6.7)
	S + IBT	1 (3.3)
Salivary gland carcinomas	S + IBT	1 (3.3)
Benign or low-grade	IBT	4 (13.3)

Abbreviations: CT, chemotherapy, IBT, interstitial brachytherapy, S, surgery.

2.2 | Treatment workflow

Surgical resection or biopsy was performed before ^{125}I IBT in all patients. Four malignant cases (13.3%) underwent surgical resection: one maxillary giant cell malignant histiocytoma underwent subtotal resection, one infratemporal fossa moderately differentiated mucoepidermoid carcinoma underwent complete resection, and one mastoid process synovial sarcoma, and one mandibular rhabdomyosarcoma underwent extensive resection. The remaining 26 patients were evaluated by experienced surgeons and were considered inoperable due to close proximity to critical structures in the skull base. Biopsy was done for only diagnosis, and ablative surgery was avoided for organ preservation. Thus, patients who were chosen for ^{125}I IBT presented with gross tumors. All sarcoma patients excluded one giant cell malignant histiocytoma patient received neoadjuvant and adjuvant chemotherapy before and after ^{125}I IBT. Four benign or low-grade tumors were treated exclusively by ^{125}I IBT (Table 2).

2.3 | ^{125}I IBT workflow

Before ^{125}I IBT, head and neck contrast-enhanced computed tomography (CECT, Siemens, AG, Munich, Germany, at 120 kV and 150 mA, with a slice thickness of 0.75 mm) was needed to evaluate the residual tumor. DICOM data were transferred into a brachytherapy treatment planning system (BTPS, Beijing Atom and High Technique

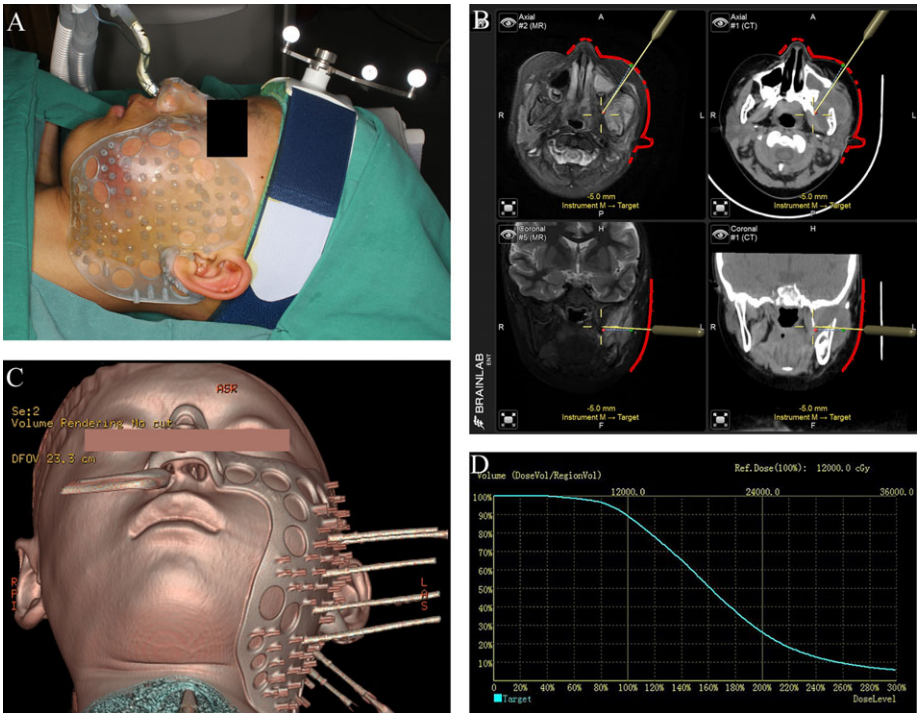

FIGURE 1 (A) 3D printing individual template used to guide needle insertion during ^{125}I radioactive seeds implantation. (B) Real-time navigation system used to guide needle insertion. (C) Needle position and depth verified by intraoperation CT. (D) Dose-volume histogram of quality verification

Industries), and target volume, as well as organs at risk, was delineated. Then, dose-volume histograms for all defined structures were generated. The gross tumor volume (GTV) was defined by CECT, along with magnetic resonance imaging (MRI) or PET/CT. Based on imaging findings, pathology reports, and surgery outcomes, as well as the tolerance doses of surrounding normal tissue and organs, the planning target volume (PTV) included the GTV as well as any suspected microscopic lesions, which was 0.5 to 1.5 cm beyond the margins of the primary tumor. The median matched peripheral dose (MPD) was 10 000 cGy (range, 9000–12 000 cGy).

All patients received ^{125}I IBT under general anesthesia. The ^{125}I radioactive seeds had a half-life period of 59.4 days and a surface radioactivity of 18.5 to 25.9 MBq per seed (type 6711, Beijing Atom and High Technique Industries, Beijing, China). Three-dimensional (3D)-printed individual templates were used in 21 patients; in detail, preoperative CT data were transferred into Mimics10.01 (Materialise, Belgium) and Geomagic8.0 (Geomagic Company, USA); then, a 3D-printed individual template for needle insertion guidance was designed prior to ^{125}I IBT, as was introduced previously in other articles.[15] A far-infrared navigation guidance system (iPlan 3.0, Brainlab, Feldkirchen, Germany) was used in eight patients, and intraoperative CT guidance was used in four patients (Figure 1).

2.4 | Follow-up

Patients were typically seen at two-month intervals for the first half year and at three- to six-month intervals thereafter. Follow-up contains physical examinations and appropriate CT and (or) MRI and (or) PET/CT scans. Toxicities associated with radiation were recorded and graded according to the Radiation Therapy Oncology Group (RTOG) grading system. Acute toxicity was defined as toxicity occurring within two months of the completion of brachytherapy. Six months and later recorded toxicities were defined as long-term toxicity. Local control (LC) was defined as the absence of further tumor growth following radiotherapy. Distant recurrence was defined as disease outside of the radiotherapy field.

2.5 | Statistical analysis

The probabilities of LC and overall survival (OS) were calculated by the Kaplan–Meier method, and outcomes between groups were compared by the log-rank test based on SPSS 20.0 for Windows. Sex, age, intracranial invasion, histology grade, and tumor subsite were considered to be risk factors and were analyzed by the classical log-rank test. The P values < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of pediatric skull base tumor

The most common main complaint of pediatric skull base tumor is mass or swelling (23/30, 76.7%). The other symptoms include snoring (3/30), sore throat (2/30), facial paralysis (1/30), and tongue numbness (1/30). The median symptom onset time was four months (range, 1–12 months). Adjacent structures were often involved when patients were referred to our hospital. Twenty-four patients (80.0%)

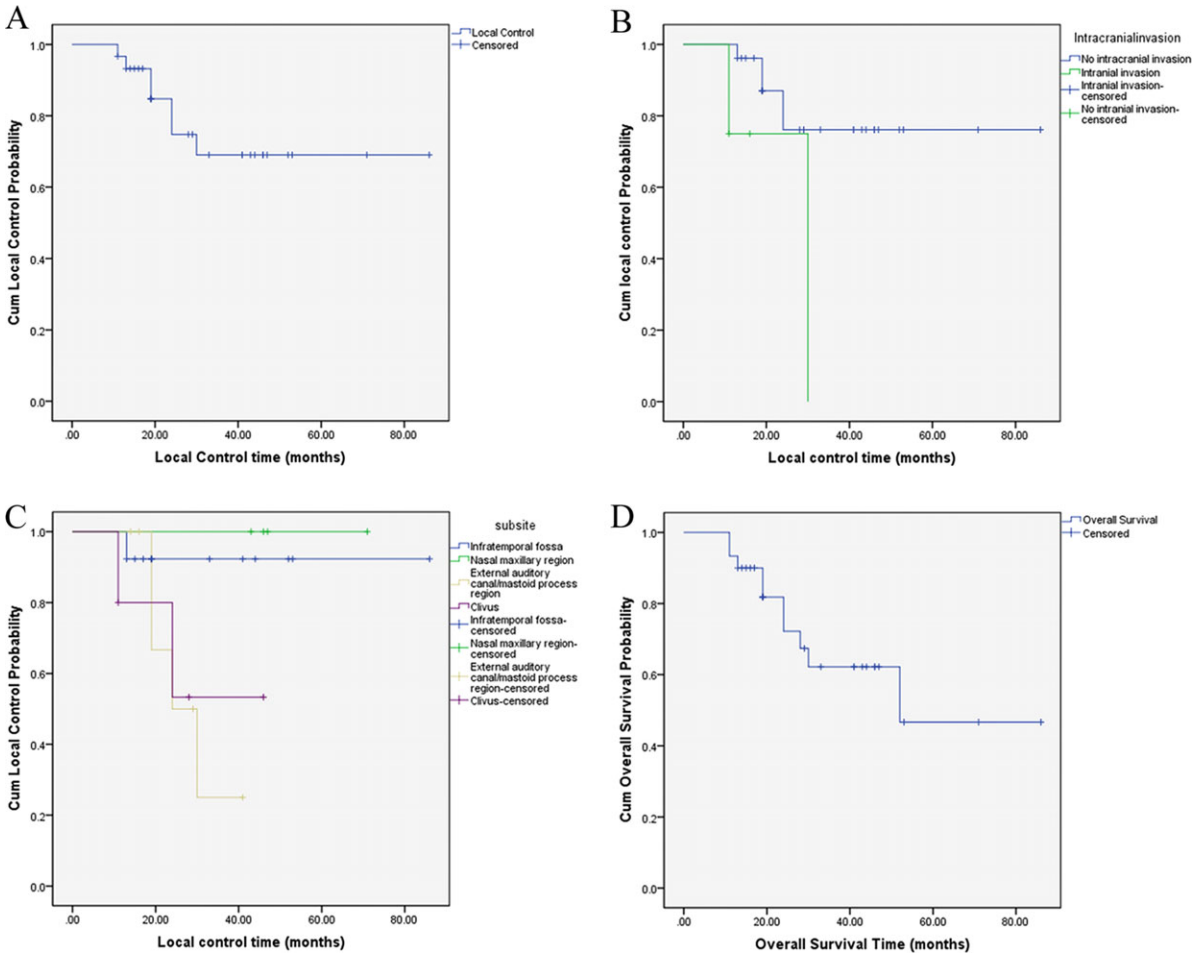

FIGURE 2 (A) Kaplan–Meier curves for local control. (B) Patients with intracranial invasion had a statistically significant poorer LC than patients without intracranial invasion ($P = 0.023$). (C) Tumors located in the external auditory canal/mastoid process region and clivus have a poorer LC. (D) Kaplan–Meier curves for overall survival

had skull base erosion at first visit, and four of them had an intracranial invasion.

3.2 | Implantation and distribution of ^{125}I radioactive seeds and postimplant dosimetry

All patients received ^{125}I IBT successfully. The average hospital stay was 6.87 days, ranging from three to 17 days. In contrast, the average hospital stay after ^{125}I implantation surgery was 2.0 days, ranging from one to six days.

The mean D90 (the doses delivered to 90% of the target volume) was 113.5 ± 14.8 Gy and was higher than the prescribed dose for all patients. V100 (the percentage target volume that receives at least the prescribed dose) was >90% for each patient (mean, 93.3% ± 3.4%), and the mean V150 was 60.9% ± 8.0%.

3.3 | LC rate

The one- and two-year LC rates were 96.7% and 74.8%, respectively (Figure 2A). Two patients were lost to follow-up at 14 months and 16 months, respectively, after ^{125}I IBT. CT scans before loss to follow-up showed LC for each patient.

The two-year LC for the 0–3-year-old group, 3–6-year-old group, 7–12-year-old group, and 13–18-year-old group was 76.2%, 60.6%, 60%, and 100%, respectively. The difference was not statistically significant ($P = 0.746$). The two-year LC rate for male and female was 78.2% and 51.9%, respectively. The difference was also not statistically significant ($P = 0.333$).

Patients without intracranial invasion ($n = 26$) had a two-year LC rate of 76.1%, while the two-year LC rate in patients with intracranial invasion was 0%. The difference was statistically significant ($P = 0.023$; Figure 2B).

Tumor subsite seems to play an important role in LC. The two-year LC for infratemporal fossa, nasal maxillary region, external auditory canal/mastoid process region, and clivus was 92.3%, 100%, 50%, and 53.3%, respectively ($P = 0.069$; Figure 2C). Tumors located in the external auditory canal/mastoid process region and clivus have a poorer LC.

3.4 | OS rate

The one- and two-year OS rates were 93.3% and 72.2%, respectively (Figure 2D). Four benign or low-grade patients remained disease-free throughout the follow-up period. The one-year and two-year OS rates for intermediate histological grade group were 94.1% and 73.3%,

respectively. The one-year and two-year OS rates for the high-grade group were 88.9% and 62.2%, respectively. The difference between different histological grade was not statistically significant ($P = 0.189$).

Eleven patients died during follow-up, seven of whom died of local recurrence and four of whom died of distant metastasis. The high-grade group presented higher incidences of local recurrence and distant metastasis, which leads to a lower survival rate. Those patients who failed during follow-up were treated with chemotherapy or ^{125}I brachytherapy again. One infratemporal fossa synovial sarcoma was found to have developed lung metastasis one year after treatment and was treated with chemotherapy; she was still alive at follow-up. Except for this patient, all the other patients who found local recurrence or distant metastasis during follow-up died soon after. The median survive time from recurrence was seven months (ranging from one to 23 months).

3.5 | Side effects and toxicity

Two patients (6.67%) experienced cerebrospinal fluid (CSF) leakage after ^{125}I seed implantation. No other complications, such as meningitis or facial weakness, were observed.

All patients experienced acute minor toxicities, including erythema or dry desquamation (n = 27 patients, 90.0%), mild dysphagia or odynophagia ($n = 2$ patient, 6.66%), mild/moderate external otitis ($n = 3$ patients, 10%), or patchy mucositis (n = 2 patient, 6.66%), which was RTOG grades 1 to 2 in all cases. No severe acute toxicities (RTOG grades 3–4) were observed. Two patients with patchy mucositis were treated symptomatically. The other ones healed without treatment within four to six weeks.

Ninety percent of this cohort experienced late toxicities. Severe late toxicities were observed in one (3.33%) of 30 patients. He had maxillary sialoblastoma treated exclusively with ^{125}I IBT, and he developed severe keratitis and hypopsia one year after ^{125}I IBT and was treated in the ophthalmology department. Slight atrophy or pigmentation change was observed in 26 (86.7%) of 30 patients.

Notably, two months after brachytherapy, 10 (33.3%) patients developed a limited opening; the median maximum passive openness (MPO) was 12 mm (ranging from 5 to 22 mm). Most of them had a slight improvement in MPO at the end of follow-up. However, another nine patients developed a limited opening. The MPO of the 19 total patients was 18.5 mm (ranging from 5 to 30 mm). One patient with a limited opening was treated by surgery after seven years of follow-up. The others were left untreated considering the limited follow-up time and that these pediatric patients are not grown.

Facial asymmetry due to ^{125}I IBT was observed in five patients (16.7%): two of them presented temporal depression, and the other three patients developed mandibular lateral deformity. A plastic surgery will not be considered until they are grown up.

4 | DISCUSSION

Pediatric skull base tumors are rare and consist of a variety of histology types.[1,16] Malignant tumors account for 27% to 54% of all pediatric skull base tumors, of which sarcoma is the most common type.[3,17,18] There is no consensus in treatment for pediatric skull base tumors; thus, they are a challenge for oncologists, pediatric surgeons, and radiation practitioners. Multidisciplinary therapy, including surgery, radiotherapy, and chemotherapy, has become a treatment modality for pediatric skull base tumors.[16,17,19,20] However, children are known to be more sensitive to radiation-induced malignancies than adults by a factor of more than 10 times, and long-term radiotherapy-related complications, such as facial growth disorders and dental abnormalities in pediatric patients, have been frequently reported.[21,22] Ideal dose distribution is difficult by conventional radiotherapy techniques, especially in the head and neck region.

Proton radiotherapy (PRT) had been used to treat pediatric skull base tumors.[23,24] It is well known that, due to its Bragg peak effect and its finite range, PRT can allow high doses of radiation to be delivered near critical structures. Hug et al reported 29 children and adolescents treated with conformal PRT.[25] Of the 20 patients with malignant tumors, five (25%) had a local failure; of the patients with benign tumors, one patient (giant cell tumor) had a local failure at 10 months. Severe late effects (motor weakness and sensory deficits) were observed in two (7%) of 29 patients. Childs et al also reported 17 children with parameningeal rhabdomyosarcoma (PM-RMS) treated with PRT.[24] After a median five-year follow-up time, the five-year failure-free survival estimate was 59% (95% confidence interval, 33%–79%), and the OS estimate was 64% (95% confidence interval, 37%–82%), which is comparable with that in historical controls. Another recent study investigated acute toxicities and early outcomes following PRT for pediatric head and neck malignancies.[26] That study concluded that PRT appears safe for this patient population, with LC rates similar to historical reports. However, due to limited follow-up time and cases, most studies are unable to provide sound data on long-term treatment-related side effects, such as growth and development impairment and secondary malignancies.

Cost is another important factor that parents face when choosing treatment modalities. There are only two proton facilities available to treat patients in China; one started in the year 2004 in Shandong Province and another started in the year 2014 in Shanghai City. The construction and equipment servicing costs are high and comprise a large proportion of proton therapy costs. Goitein estimated that intensity-modulated proton therapy costs two to three times than intensity-modulated photon therapy.[27] In China, it was estimated that intensity-modulated photon therapy costs two times than ^{125}I IBT. Shen et al analyzed 12 101 children in the National Cancer Data Base who had been diagnosed with a solid malignancy and had received photon- or proton-based radiotherapy, and they found that a higher median household income and educational attainment were associated with increased proton use.[28] More than half of this cohort were from rural China; they are struggling to be economically stable due to the children's disease. A highly expensive PRT may destroy a family's stability. It is recommended that families be assessed on their ability to house, transport, feed, clean, clothe, and care for the child, because this stability is the key to providing continuous and effective therapy and follow-up.[29]

Another unique aspect of providing radiotherapy (both PRT and intensity-modulated radiation therapy) to children is the fact that

children under three years uniformly require general anesthesia or sedation (GA/S). This requires not only professional pediatric anesthesiologists but also sufficient nursing support. Furthermore, children are required to fast (NPO) before GA/S. Seilei et al identified that fasting requirements can be burdensome because they can affect nutritional intake in already nutritionally depleted pediatric patients.[30] In contrast, ^{125}I IBT requires only one general anesthesia, reducing the adverse effects of the above aspects.

^{125}I IBT, as a radiotherapy modality, increases local dose while sparing surrounding normal tissues, which is highly conformal, even for tumors closely surrounded by critical structures. ^{125}I IBT is increasingly being found to be effective for patients with head and neck malignant tumors and in improving LC and survival rate, so it is being used for pediatric soft-tissue sarcoma treatment.[31–33] Laskar et al treated 50 pediatric soft-tissue sarcomas with brachytherapy as a monotherapy or combined with external radiotherapy. The lower extremities were most commonly involved (66%), followed by the upper extremities (18%), the chest and abdominal walls (14%), and the head and neck region (2%). After a median follow-up of 51 months, the LC, disease-free survival, and OS were 82%, 68%, and 71%, respectively.[34] Our study consists of a variety of histology. The one- and two-year LC rates were 96.7% and 74.8%, respectively. The modern brachytherapy techniques improve the target dose coverage (i.e., 3D template[15] or navigation system[35]). Four benign or low-grade tumors survived throughout the follow-up. For malignant tumors, PM-RMS accounted for 56.7% (17/30) of all cases; 14 patients were in the IRS group III and three were in the IRS group IV, and the two-year OS was 58.8% for PM-RMS. In another six-year-old boy with maxillary giant cell malignant histiocytoma, tumor size was 5 cm with periorbital skull base bone erosion (group III), extensive resection was rather difficult without facing severe complications. The reported five-year survival rate for group III malignant histiocytoma is 53%.[36] We treated this patient with postoperative ^{125}I IBT after subtotal resection; no tumor recurrence nor complications were observed after 71 months of follow-up. Another two synovial sarcomas, one malignant rhabdomyoid cancer, and one Ewing sarcoma, which were locally invasive and had a high potential for distant metastasis, and thus a high mortality rate were reported; these tumor types remain a challenge for clinicians.[37–40] Seven of 10 patients died of local recurrence, which indicated that an improved LC rate may improve the OS rate.

Ablative surgery was avoided in 26 inoperable cases (86.7%) for organ preservation. Hayhurst et al treated 23 pediatric skull base tumor patients with skull base surgery combined with adjuvant treatment when required.[16] Complete resection was achieved in 12 patients (52%). Thirteen patients (57%) had benign histology, with a median follow-up duration of 60 months; the progression-free survival was 68% at five years (70% malignant disease and 66% benign disease). Surgery-related complications occurred in seven patients (30.4%), including CSF leakage, meningitis, facial weakness, hearing loss, and memory loss. Additionally, three (13%) of 23 children required a ventriculoperitoneal shunt following surgery. Three (15%) of the 20 surviving children have permanent pituitary dysfunction. In our study, no intraoperative complications, such as CSF leakage, massive hemorrhage, facial nerve injury, hearing loss, or meningitis, were observed. Compared with surgical resection, the complications were much less common, and the corresponding functions of mastication, pronunciation, and swallowing could be preserved without mutilating surgery. Although all patients experienced acute and late minor side effects after ^{125}I IBT, severe adverse radiotherapy side effects (RTOG 3–4) were observed only in one maxillary sialoblastoma patient (3.33%) with severe keratitis. The side effects were small, and the patients tolerated well, with a satisfactory cosmetic and functional outcomes. In a four-year-old boy with para pharyngeal and skull base embryonal rhabdomyosarcoma who was treated with ^{125}I IBT combined with chemotherapy, a slight limited opening and facial asymmetry were observed at four years of follow-up (Figure 3). He remains in mainstream schooling, without special educational assistance.

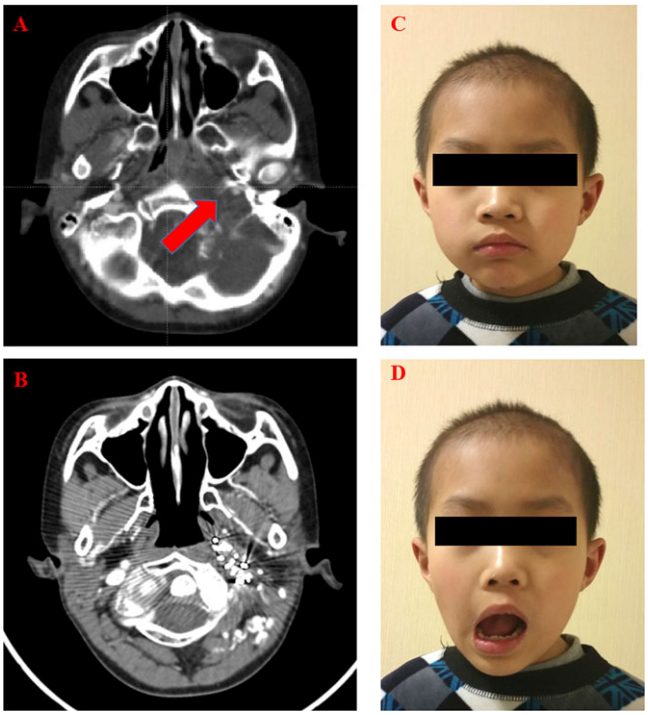

FIGURE 3 (A) Rhabdomyosarcoma with skull base erosion. (B) Complete response four years after ^{125}I IBT. (C, D) A satisfactory cosmetic and functional outcomes four years after ^{125}I IBT

This study has several limitations. First, the follow-up time is limited. As long-term radiotherapy reactions may appear 5 to 10 years after radiotherapy in pediatric patients, the increasing follow-up time might compromise the survival rate. Furthermore, our data are not sufficient for evaluating a real side effect of IBT because of the small sample size.

5 | CONCLUSION

^{125}I IBT combined with chemotherapy and/or surgery is effective and safe for pediatric skull base tumors, with satisfactory cosmetic and functional outcomes. Due to the limited follow-up time, long-term efficacy and adverse reactions still need further observation.

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CONFLICTS OF INTEREST

On behalf of all the authors, the corresponding author states that there are no conflicts of interest.

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