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RESEARCH ARTICLE

Long-term result of ^{125}I seed brachytherapy for pediatric desmoid tumor in the head and neck

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Abstract

Background: Desmoid tumor (DT) is rare and challenging, often affects the head and neck (HN) region in children, and its appropriate treatments are under-discussed. This study aimed to retrospectively evaluate the long-term effectiveness and safety of ^{125}I seed brachytherapy for pediatric DT in HN.

Procedure: Seven pediatric patients with a median age of three years who suffered from DT in HN treated with ^{125}I brachytherapy from January 2008 to June 2018 were included. Among these, five underwent sole brachytherapy and the others combined with surgery under prescription doses ranging from 10,000 to 12,000 cGy. The rate of local control (LC), complete response (CR), and partial response (PR) was calculated after evaluation by radiological and pathological means. Radiation-associated toxicities were also evaluated.

Results: The LC rate was 7/7 during the follow-up time ranging from 43 to 135 months and with a mean of 57 months. No recurrent lesion was found in the patients receiving surgery combined with brachytherapy. In patients treated with sole brachytherapy, the radiological PR rate and CR rate were 4/5 and 1/5, respectively. In those reaching radiological PR, 3/4 were pathological CR. Slight acute radiation-associated toxicities were observed in all patients, and no late or severe acute toxicity was observed.

Conclusion: ^{125}I brachytherapy is effective and safe in the management of pediatric DT in HN as the sole modality or combined with surgery in the long term.

KEYWORDS
Brachytherapy, desmoid tumor, head and neck, pediatrics

Abbreviations: BTPS, Brachytherapy treatment planning system; CR, Complete response; CT, Computed tomography; CTV, Clinical target volume; D_{90}, The doses delivered to 90% of the target volume; DICOM, Digital Imaging and Communications in Medicine; DT, Desmoid tumor; GTV, Gross tumor volume; HI, Homogeneity index; HN, Head neck; LC, Local control; MRI, Magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NSAIDs, Nonsteroidal anti-inflammatory drugs; PR, Partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RTOG, Radiation Therapy Oncology Group; $T_{1.5ref}$, The volume of clinical target volume that receives 150% of the prescribed dose; TKIs, Tyrosine kinase inhibitors; T_{ref}, The volume of clinical target volume that receives 100% of the prescribed dose; V_{100}, The percentage of target volume that receives at least 100% of the prescribed dose; V_{150}, The percentage of target volume that receives at least 150% of the prescribed dose.

1 | INTRODUCTION

Desmoid tumor (DT), also known as aggressive fibromatosis, is a rare intermediate fibroblastic neoplasm derived from mesenchymal tissues with an annual incidence of approximately 2 to 4 per million, and two peaks of age 6-15 years and age 40 years.[1] Locally infiltrative growth is the nature of DT and a threat to the vital structure around the tumor. Especially for cranial nerves (e.g., the facial nerve), critical vessels (e.g., internal carotid artery and internal jugular vein), and organs (e.g., salivary gland and maxillofacial bone) in the head neck (HN) region, which accounts for 7%-15% of all the DT, and higher in the pediatric population (26%-33%) than the adult (7%-9%),[2–4] DT would cause severe morbidity.

Observation was advocated as the first treatment for DT by the guideline of the National Comprehensive Cancer Network (NCCN)[5] and the Desmoid Tumor Working Group[6] under the consideration of spontaneous regression. However, interventions are unavoidable for the relatively low spontaneous regression rate[7,8] and potential risk for further adjacent vital tissue destruction and affecting growth by progression.

Complete resection is often the primary intervention for most DTs other than those in HN of pediatric patients for the difficulty to get a negative margin, and the demand for aesthetic and function.[9] Chemotherapy, radiotherapy, or medical therapy can be performed as supplementary treatment with a positive margin after surgery, or sole therapy, in the HN region.[6,9,10] Among these, the use of radiotherapy is limited in children due to the long-term complication and toxic effects caused by external-beam radiation therapy such as secondary cancers and growth retardation of craniofacial bone.[9,10]

However, brachytherapy, the minimally invasive radiation method with the strength of minimizing growth retardation or second primary cancer in children,[11] has the potential to offer a selection of either supplementary or definitive methods for pediatric DT in HN, whereas long-term follow-up outcome is requested.

Therefore, this study attempted to retrospectively evaluate the long-term effectiveness and safety of ^{125}I seed brachytherapy for pediatric DT in HN.

2 | MATERIALS AND METHODS

2.1 | Patients

Under the guidance of the Ethics Committee of Peking University School and Hospital of Stomatology, seven pediatric patients with DT in HN treated with ^{125}I seed brachytherapy from January 2008 to June 2018 in the Peking University School of Stomatology were included in this study. All the pediatric patients' guardians signed their informed consents, which were well documented. Among the included patients, four were male and three were female. The median age was 3 years, ranging from 3 to 8 years. The median of maximum diameter of the primary tumor was 6.0 cm, ranging from 2.5 to 10.0 cm. The median follow-up time was 57 months, ranging from 43 to 135 months. The site tumor involved including four at the parapharyngeal region and three at the skull base region. Detailed patient characteristics are listed in Table 1. The R stage was classified as R0 with microscopically negative margin according to pathological examination, R1 with macroscopically negative margin according to the surgeon but microscopically positive margin, and R2 with a macroscopically positive margin.

2.2 | Treatment

After evaluation by an experienced medical group, four to six weeks before brachytherapy, two patients underwent surgery with R2 margin for vital organ preservation, and one to two weeks before brachytherapy, biopsies were performed on the other five patients with tumors invading the critical structures in HN, such as skull base, facial nerves and any other vital nerves or vessels. The pathological specimens were examined and diagnosed by two centers with expert pathologists in consensus. Then, the computed tomography (CT) scanning of the HN with a slice thickness of 0.75 mm, tube voltage of 120 kV, and tube current of 225-300 mA was performed on all patients using a GE Optima CT680 scanner. Then, all the Digital Imaging and Communications in Medicine (DICOM) data were transferred into a brachytherapy treatment planning system (BTPS, Beijing Atom and High Technique Industries). Referring to the tumor boundary based on magnetic resonance imaging (MRI), the clinical target volume (CTV) was contoured by extending the gross tumor volume (GTV) with a distance of 0.5 to 1.0 cm in any possible direction in the BTPS based on CT imaging. The prescription doses were set from 10,000 to 12,000 cGy according to the size, subsite, and tolerance doses of the adjacent vital structures, with a median of 12,000 cGy, in the BTPS. The prescription doses were optimized to reduce the mean parotid dose ($\leq$ 2600 cGy), the maximal eyeball dose ($\leq$ 5000 cGy), the mean eyeball dose ($\leq$ 3500 cGy), the maximal optic nerve dose ($\leq$ 5400 cGy), the maximal optic chiasm dose ($\leq$ 5400 cGy), and the maximal spinal cord dose ($\leq$ 4500 cGy) to an optimal level.[12] The ^{125}I seeds with surface radioactivity of 18.5 MBq and an air-kerma strength of 0.635 μGy·m^2·h^{-1} per seed (type 6711, t1/2, 59.4 days, Beijing Atom and High Technique Industries, Beijing, China) were used.

Three-dimensional printed individual templates[13] along with intraoperative CT or a far-infrared navigation guidance system (iPlan 3.0, Brainlab, Feldkirchen, Germany) were used to assist the distribution of the ^{125}I seeds. The individual templates helped constrain the direction of the inserting needles and kept them still, and then the depth was confirmed by the distance scale on the needle. Both direction and depth were verified by CT and the navigation guidance system. After placing all the needles, ^{125}I seeds were then inserted. ^{125}I brachytherapy was performed under general anesthesia according to the previous design. Finally, the post-implant dosimetry parameters of CTV and critical structures within the 1000 cGy

TABLE 1 Patient characteristics

Patient	Age (years)	Sex	Primary or recurrent	Previous treatments and outcomes	Current site	Current size (cm)	Current treatment	Follow-up time (months)
1	3	M	Primary		Parapharyngeal region	6.0	Surgery and brachytherapy	57
2	3	F	Primary		Skull base region	6.0	Brachytherapy	62
3	7	M	Primary		Parapharyngeal region	7.0	Brachytherapy	43
4	8	M	Primary		Parapharyngeal region	2.5	Surgery and brachytherapy	122
5	3	F	Recurrent	Recurrence occurred 3 months after surgery with R2 margin for facial nerve preservation	Parapharyngeal region	3.5	Brachytherapy	135
6	3	F	Recurrent	Recurrence occurred 2 years after surgery with R2 margin for skull base invasion	Skull base region	10.0	Brachytherapy	51
7	3	M	Recurrent	Recurrence occurred 2 years after surgery with R2 margin for facial nerve preservation	Skull base region	5.5	Brachytherapy	44

isodose line were calculated based on the post-implant CT by BTPS (Figure 1).

2.3 | Follow-up

Patients received a physical examination, CT and (or) MR every two months in the first half year, and every three or six months thereafter, and core-needle biopsy when confirmation for tumor response was needed. Safety was evaluated with radiation-relevant toxicities according to the Radiation Therapy Oncology Group (RTOG) grading system.[14] Effectiveness was evaluated with the local control (LC) rate. And LC was defined as the absence of tumor after surgery combined with brachytherapy, or complete response (CR) and partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[15] after sole brachytherapy.

3 | RESULTS

3.1 | Post-implant parameter and dosimetry

The median of the amount of ^{125}I seeds used for each patient was 60, with a range from 21 to 109. As for CTV, the mean ± standard deviation of post-implant D_{90}(the doses delivered to 90% of the CTV) of the patients was 115.1 ± 19.9 Gy, higher than the prescribed dose for each patient. The V_{100}(the percentage of CTV that receives at least 100% of the prescribed dose) was more than 85% for every patient with a median of 94.5% ranging from 87.7% to 96.1%, and the mean ± standard deviation of V_{150}(the percentage of target volume that receives at least 150% of the prescribed dose) was 50.2% ± 11.7%. The mean ± standard deviation of the homogeneity index[16] (HI; $HI = (VT_{ref} - VT_{1.5ref}) / VT_{ref} \times 100\%$, T_{ref} and $T_{1.5ref}$, were the volume of CTV that receives 100% and 150% of the prescribed dose, respectively) was 47% ± 12%. As for critical structures spared from the tumor destruction and within the 1000 cGy isodose line, the mean parotid dose ranged from 707 to 2442 cGy, the maximal eyeball dose ranged from 2759 to 4325 cGy, the mean eyeball dose ranged from 966 to 1615 cGy, the maximal optic nerve dose ranged from 1003 to 2411 cGy, the maximal optic chiasm dose ranged from 1322 to 1367 cGy and the maximal spinal cord dose ranged from 1336 to 3071 cGy. No critical structures suffered from a dose higher than the acceptable level.

3.2 | Local control

During the follow-up, the LC rate was 7/7. No recurrent lesion was found in the patients undergoing surgery combined with brachytherapy. In patients treated with sole brachytherapy, 4/5 were radiological partial response and 1/5 was radiological complete response. In those reaching radiological partial response, 3/4 were pathological complete response. Among all five patients undergoing sole brachytherapy, the LC condition was also described as the changes in tumor maximum diameter, MR signal evaluation, and pathological examination by core-needle aspiration as follows.

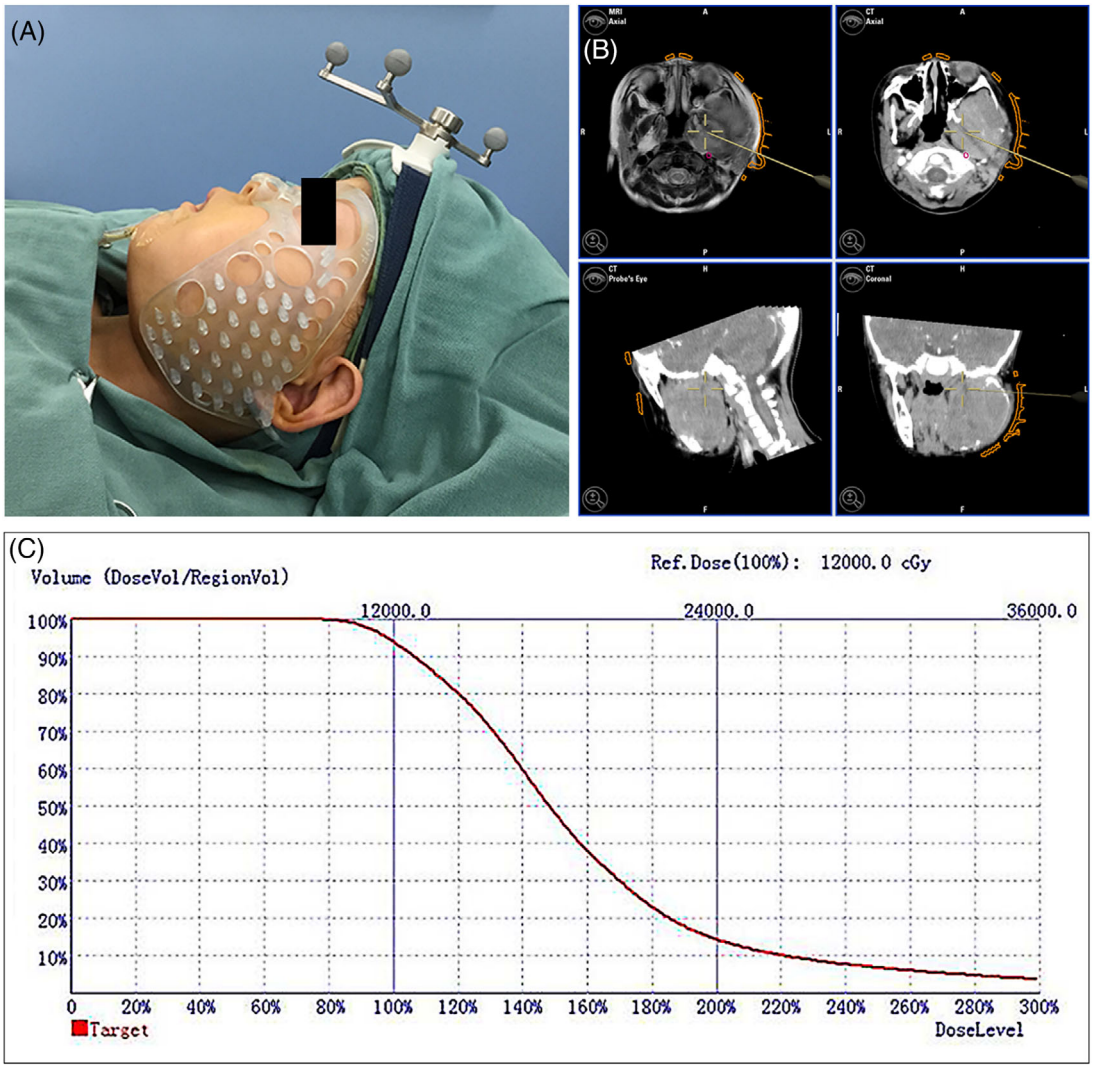

FIGURE 1 The procedure of brachytherapy. (A, B) Brachytherapy was performed with the help of a far-infrared navigation guidance system and three-dimensional printed individual templates, and (C) post-implant dosimetry parameters were then calculated.

3.3 | Tumor maximum diameter

There was only one lesion in every patient. And tumor maximum diameters at the first visit, two months' follow-up, six months' follow-up, and last follow-up were demonstrated in Figure 2. All the lesions were stable at the first follow-up and reached partial regression or complete regression at six months' follow-up (Figure 3).

3.4 | MR signal evaluation

Of the patients treated with sole brachytherapy, 3/5 underwent MR examination before and after brachytherapy. MR was performed no more than one month before preoperative or postoperative biopsy. All lesions presented hyperintense compared with muscle in preoperative T2-weighted images, and two lesions turned to hypointense and one lesion turned to isointense compared with muscle in postoperative T2-weighted images (Figure 4).

3.5 | Core-needle aspiration

Pathological examination by core-needle aspiration was performed on 3/4 of the lesions reaching partial regression, and specimens from at least five spots in the radiological tumor volume were taken under the guidance of the far-infrared navigation guidance system mentioned before. No tumor cell was found in all the specimens (Figure 5). Thus, all the patients receiving core-needle aspiration were regarded as pathological complete regression.

3.6 | Side effects or toxicity

No operative complication such as cerebrospinal fluid leakage, hematoma, or infection was observed. Radiation-related acute toxicities, including dry desquamation, edema, and erythema on the skin, were observed in all the patients, whereas 6/7 were classified as RTOG grade 1 and 1/7 was classified as RTOG grade 2, and no RTOG grade

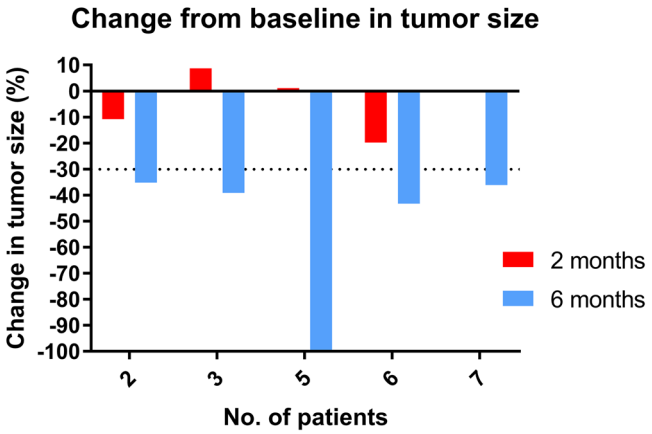

FIGURE 2 Change from baseline in tumor size. Five cases with desmoid tumor underwent sole brachytherapy, and the number of cases with radiological partial and complete responses was 4 and 1.

3 or 4 toxicity was observed. None experienced late toxicity. Notably, no radiation-related growth retardation and secondary cancer were observed.

4 | DISCUSSION

DT is a rare intermediate tumor characterized by infiltrative growth and a tendency to local recurrence,[6] with an annual incidence of approximately 2-4 per million per year, and two peaks of age 6-15 years and 40 years.[1] Infiltrative growth is a threat to the vital structure around the tumor, especially in the HN, which accounts for 7%-15% of all DT, and is higher in the pediatric population (26%-33%) than in the adult population (7%-9%).[2–4] The treatment was challenging in the pediatric DT in HN, for the stronger demand for organ and tissue preservation than those of adults and the limit of treatment modality.[9] Although the treatment varied, in recent years, the strategy of the treatment changed in the trend from surgery and radiotherapy to conservative methods, with the development of targeted therapy and knowledge of the nature of DT.[6] But for DT in HN of the pediatric population, treatment modalities used now are not satisfactory.

Observation, also described as the "wait and see" approach, was proved reasonable for the indolent nature of DT, with evidence of stabilization and even regression in the absence of therapy.[17] Since 2020, observation had been listed as first-line management, whereas both NCCN guidelines and Desmoid Tumor Working Group stressed that initial observation was recommended only for cases not causing morbidity even if progressed.[5–7] With the threat to functional or cosmetic preservation from progression, observation was suitable only for small DT in HN, which would often be managed by surgeons with complete resection at first. The condition for choosing observation is strict in HN, as all cases in this study underwent intervention and none took observation for organ preservation.

Complete resection with a clear margin used to be regarded as the mainstay treatment before 2000, and the five-year LC rate was up to 80% according to several retrospective studies.[18] While in the region of HN, the LC rate declined to between 24% and 70%.[19] And for the pediatric patient involved HN, a systematic review demonstrated a 27.2% recurrence rate of 125 patients treated with surgery in reports from 1982 to 2015. However, the pursuit of complete resection or at least R1 margin, which was regarded as acceptable,[20] at a price of excessive long-term functional or cosmetic sequelae was not recommended in tumors located at HN of the pediatric population.[9] Therefore, sole surgery has been abandoned as a choice for most DTs in the HN.[5] And in this study, patients with R2 margin after surgery were treated supplementarily with brachytherapy for LC.

External-beam radiotherapy was considered to be either the sole modality for inoperative cases of DT or complementary therapy for resectable ones, and the latter was regarded as a better solution than sole surgery by a review of 22 articles.[21] However, while considering on pediatric population, the long-term sequelae and adverse effects of external-beam radiation exposure in children, such as secondary malignancy and inhibition of the cranial-facial bone, caused the limited use of radiotherapy on pediatric DT.[22–24] Besides, the efficacy of radiotherapy on pediatric DT was uncertain according to a study reporting 10 of 13 children recurrent and 3 of 13 dead.[25]

Medical therapy, including antihormonal therapies, nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapy, and tyrosine kinase inhibitors (TKIs), was another way the clinicians turned to.[6] Antihormonal agents such as tamoxifen or toremifene, along with or without NSAIDs, were reported retrospectively effective.[26] However, a phase II study in the pediatric population using tamoxifen[27] showed limited activity for a progression-free rate of 36%, and notable safety problem with 40% of females developing ovarian cysts. Chemotherapy including a "low-dose" regimen with methotrexate plus vinblastine or vinorelbine was evaluated and proved well efficacy and acceptable toxicity.[6] TKIs seemed hopeful with progression-free survival ranging from 59% to 89% and low toxicity according to several phase II and III studies.[28] Therefore, chemotherapy and TKIs were advocated as active treatments.[5,6] Meanwhile, there was still a need for a backup therapy as the effectiveness of TKIs might be related to certain genome type[29] and also a solution for relapse from medical therapy.

Brachytherapy is a minimally invasive radiotherapy modality with a high local dose while sparing surrounding normal tissues.[30] Late radiation-induced toxicity complications like growth retardation and second primary malignancies, with a strong relation to a dose-volume effect, can be kept to a minimum by brachytherapy for its smaller target volume than external-beam radiotherapy.[11] Previous studies in our department had reported the application of brachytherapy on the pediatric population in HN and showed its good effectiveness and safety.[31–33] Besides, the study on pediatric survivors with parotid gland carcinoma after brachytherapy showed mild affection for the mandible growth.[34] The use of brachytherapy on DT in adults had also been reported with well LC.[35,36] However, the application of brachytherapy on pediatric DT in HN remained unclear, with long-term effectiveness and safety needing to be reported.

In this study, during the long-term follow-up time, it was inspiring that no recurrence was observed. Despite the limit of the amount

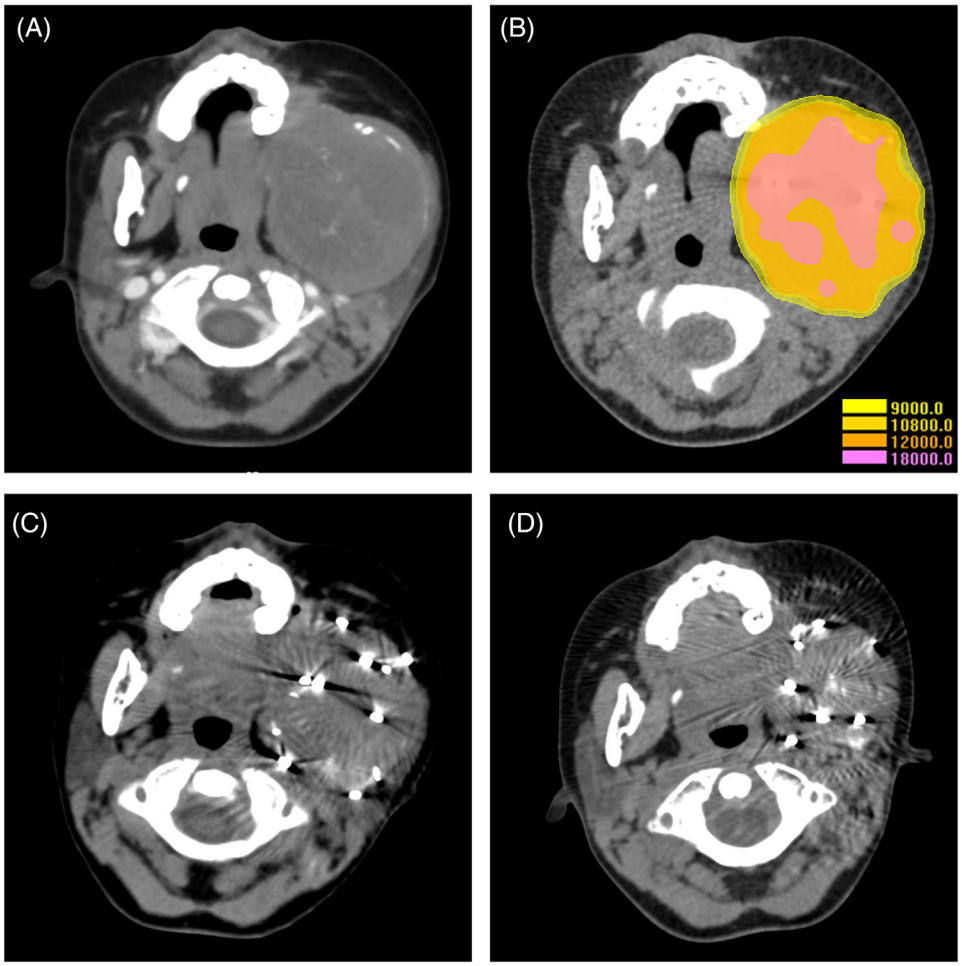

FIGURE 3 The follow-up CT image and postoperative isodose line (9000 cGy/75%, 10,800 cGy/90%, 12,000 cGy/100%, and 18,000 cGy/150%) of case with partial response. (A) Baseline, (B) 2 days after brachytherapy, (C) 2 months follow-up, and (D) 6 months follow-up

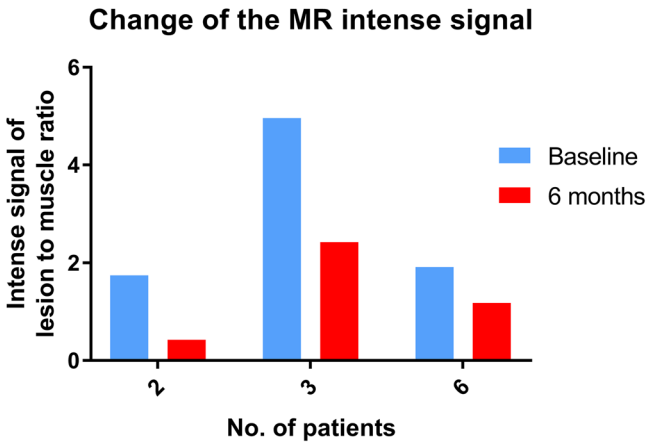

FIGURE 4 Change of the magnetic resonance intense signal. Magnetic resonance images from 3 cases that underwent sole brachytherapy showed a decline in the intense signal of the lesion-to-muscle ratio.

of cases, we could still conclude that brachytherapy as an effective method for pediatric DT in HN for much other evidence we collected. There were several methods the Desmoid Tumor Working Group recommended for assessment of treatment effect.[6] And we adopted the dimensional criteria, MR signal, and the gold standard, core-needle aspiration.

All the lesions in this study reach partial regression six months after brachytherapy, with dimensional change evaluated using CT or MR. Although CT examination was advised for the measurement of dimensional change according to the Desmoid Tumor Working Group[6] and NCCN guidelines,[5] the ^{125}I seeds would affect the observation of the tumor outline on CT with a radiological artifact. As an alternative, clinicians will measure the cluster volume of ^{125}I seeds, and a general volumetric shrinkage tendency indirectly showed the shrinkage of tumor volume.[37] However, that was not a common parameter to use for comparison with other studies. Another alternative was measurement using MR, with artifact still but would not affect the measurement, because the ^{125}I seeds showed as a small black area. But as for children, the time consumed on MR examination was a problem for their weak obedience ability, and they often needed sleeping pills. Therefore, in this study, we still used CT as an assessment of tumor diameter change and accomplished it with other methods.

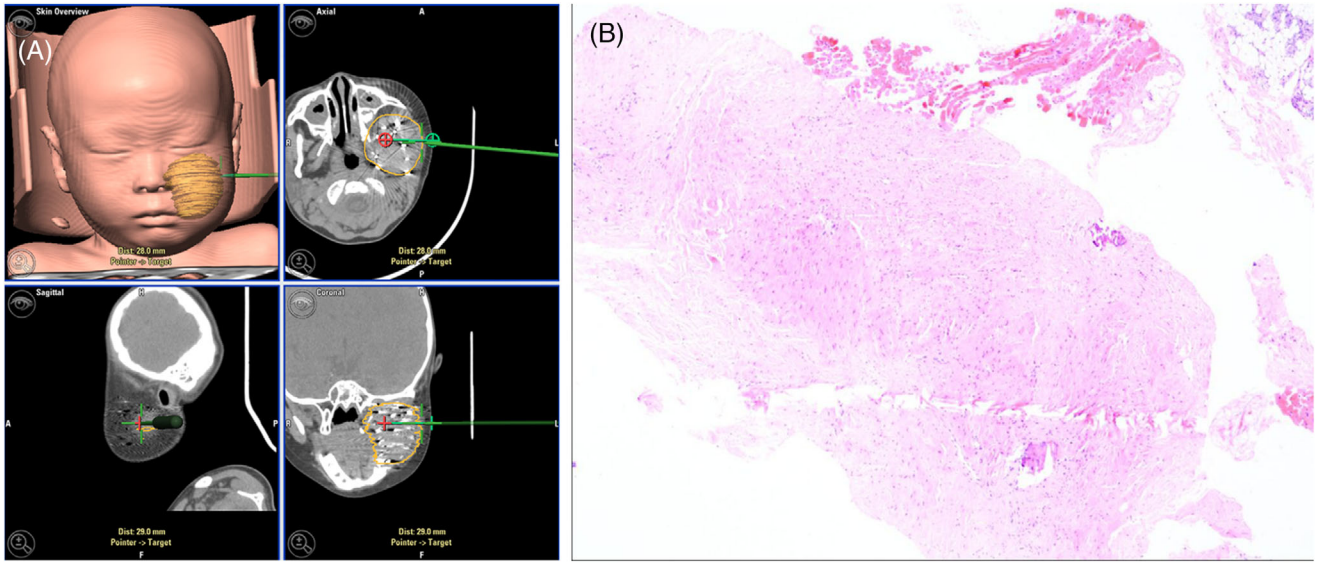

FIGURE 5 The procedure of pathological examination. (A) Core-needle aspiration was performed with the help of a far-infrared navigation guidance system, and (B) no tumor cells were found in the specimen.

Changes in the T2-weighted intensity signal of MR image are useful for the evaluation of the activity of DT, because a low T2-weighed signal corresponds to relatively lower cellularity and higher collagen content.[6,38] In this study, all cases with preoperative and postoperative MR showed a clear reduction in the T2-weighted intensity signal. The change in the T2-weighted signal can be evaluated, even though the artifact existed after brachytherapy, and therefore can be added as an ancillary criterion for treatment evaluation, following the diameter change. However, the acquisition of MR from children remained difficult. And to ensure the treatment effect, some cases in this study underwent core-needle aspiration for pathological examination, and no tumor cell was found, which further confirmed the result concluded from the change of T2-weighed signal and diameters.

All children in this study experienced mild acute side effects after brachytherapy (RTOG1-2), and no late or severe toxicity (RTOG 3-4) or second primary cancer was observed. Besides, except for cases that already had massive bone defects before therapy, no growth retardation was observed. Based on the long-term follow-up, the safety of brachytherapy could be shown as only mild and short-term toxicity was observed and no severe or late radiation-induced toxicity complications occurred.

However, as discussed above, because of the relatively indolent nature of DT, the more conservative methods should be considered first, such as TKIs or observation if suitable, and then aggressive methods like surgery and brachytherapy if needed and possible. Brachytherapy could be turned to for unresectable lesions with looming unacceptable destruction, or as salvage after the failure of the former treatments, or a combination with them as a potential alternative for external-beam radiation in pediatric DT in HN.

Even though DT is rare, the number of cases in this study is still obviously limited, whereas more cases reported were expected. Besides, the data for toxicity evaluation are limited also because of the small sample size.

5 | CONCLUSION

^{125}I Brachytherapy is effective and safe as a sole modality or combined with surgery, for pediatric DT in the HN region proven by multidimensional evaluation and can be adopted as an alternative therapy in certain situations.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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