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 head neck (HN) region in children, and its appropriate treatments are under discussed. This study aimed to retrospectively evaluate long-term effectiveness and safety of 125I seed brachytherapy for pediatric DT in HN. Procedure: Seven pediatric patients with median age of 3 years old suffered from DT in HN treated with 125I brachytherapy from January 2008 to June 2018 were included. Among which, 5 underwent sole brachytherapy and the others combined with surgery under a prescription doses ranging from 10 000 cGy to 12 000 cGy. The rate of local control (LC), complete response (CR) and partial response (PR) were calculated after evaluation by radiological and pathological means. The 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: 125I brachytherapy is effective and safe in the management of pediatric DT in HN as sole modality or combined with surgery in long term.

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 per year, and two peaks of age 6-15 years and age 40 years¹. Locally infiltrative growth is the nature of DT, and a threat to the vital structure around the tumor. Especially for cranial nerve s (e.g., the facial nerve), critical vessel (e.g., internal carotid artery and internal jugular vein) and organ (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 National Comprehensive Cancer Network (NCCN)⁵ and the Desmoid Tumor Working Group ⁶ under the consideration of the spontaneous regression. However, interventions are unavoidable for the relatively low spontaneous regression rate⁷,⁸ and potential risk for further adjacent vital tissue destruction and affecting growth by progression.

Complete resection is often the primary intervention for most DT other than those in HN of pediatric patients for the difficulty to get negative margin, and the demand of aesthetic and function⁹. Chemotherapy, radiotherapy or medical therapy can be performed as supplementary treatment with positive margin after surgery, or sole therapy, in the HN region⁶,⁹,¹⁰. Among which, 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 bone⁹,¹⁰.
However, brachytherapy, the minimally invasive radiation method with strength of minimizing the growth retardation or second primary cancer in children\(^{11}\), has the potential to offer selection of either supplementary or definitive method for pediatric DT in HN, while 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, 7 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, 4 were male and 3 were female. The median age was 3 years old, ranging from 3 to 8 years old. 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 4 at the parapharyngeal region and 3 at the skull base region. The detailed patients’ characteristics were 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 macroscopically positive margin.

### 2.2 Treatment

After evaluation by an experienced medical group, 4 to 6 weeks before brachytherapy, 2 patients underwent surgery with R2 margin for vital organ preservation, and 1 to 2 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 the magnetic resonance imaging (MRI), the planning target volume (PTV) were contoured by extending the gross tumor volume (GTV) with a distance of 0.5 to 1.0 cm in the BTPS based on CT imaging. The prescription doses were set from 10 000 cGy to 12 000 cGy according to the size, subsite and the tolerance doses of the adjacent vital structures, with a median of 12 000 cGy, in the BTPS, using the \(^{125}\)I seeds with a surface radioactivity of 18.5 MBq per seed (type 6711, t1/2, 59.4 days, Beijing Atom and High Technique Industries, Beijing, China).

Three-dimensional printed individual templates\(^{12}\) along with intraoperative CT or a far-infrared navigation guidance system (iPlan 3.0, Brainlab, Feldkirchen, Germany) were used to assist the \(^{125}\)I seeds distribution. Then the \(^{125}\)I brachytherapy were performed under general anesthesia according to the previous design. Finally, the post-implant dosimetry parameters were calculated based on the post-implant CT by BTPS (Figure 1).

### 2.3 Follow-up

Patients received 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. The safety were evaluated with radiation-relevant toxicities according to the Radiation Therapy Oncology Group (RTOG) grading system\(^{13}\). The effectiveness was evaluated with local control (LC) rate. And LC were 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\(^{14}\) after sole brachytherapy.
3 Results

3.1 Post-implant dosimetry

The mean ± standard deviation of post-implant $D_{90}$ (the doses delivered to 90% of the target volume) of the patients was 115.1 ± 19.9 Gy, and higher than the prescribed dose for each patient. The $V_{100}$ (the percentage of target volume 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%.

3.2 Local control

During the follow-up, the local control 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 5 patients undergoing sole brachytherapy, local control condition was also described as the changes of tumor maximum diameter, MR signal evaluation and pathological examination by core-needle aspiration as follow.

3.2.1 Tumor maximum diameter

There was only one lesion in every patient. And the tumor maximum diameter at first visit, 2 months’ follow-up, 6 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 6 months’ follow-up (Figure 3).

3.2.2 MR signal evaluation

Of the patients treated with sole brachytherapy, 3/5 underwent MR examination before and after the brachytherapy. The MR were performed no more than 1 month before the pre-operative or post-operative biopsy. All lesions presented hyper-intense compared with muscle in the pre-operative T2 weighted images, and 2 lesions turned to hypo-intense and 1 lesion turned to isointense compared with muscle in the post-operative T2 weighted images (Figure 4).

3.2.3 Core-needle aspiration

Pathological examination by core-needle aspiration was performed on 3/4 of the lesion 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.

3.3 Side effects or toxicity

No operative complication such as cerebrospinal fluid leakage, hematoma or infection was observed. Radiation related acute toxicity, including dry desquamation, edema and erythema on skin were observed in all the patients, while 6/7 were classified as RTOG grade 1 and 1/7 was classified as RTOG grade 2, and no RTOG grade 3 or 4 toxicity were observed. None experienced late toxicity. Notably, no radiation related growth retardation and secondary cancer were observed.

4 Discussion

Desmoid tumor is a rare intermediate tumor characterized by infiltrative growth and a tendency to local recurrence, with an annual incidence of approximately 2 to 4 per million per year, and two peaks of age 6-15 years and age 40 years. Infiltrative growth is a threat to the vital structure around the tumor, especially in the HN, which accounts for 7-15% of all the DT, and higher in the pediatric population (26-33%) than the adult (7-9%)\(^2\). The treatment was challenging in the pediatric DT in HN, for the stronger demand of organ and tissue preservation than those of adults and limit of treatment modality. 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 to the nature of DT\textsuperscript{6}. But for DT in HN of pediatric population, the treatment modalities used now are not satisfactory.

Observation, also described as “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 \textsuperscript{15}. Since 2020, observation had been listed as first-line management, while both NCCN guideline and Desmoid Tumor Working Group stressed that initial observation was only recommended for cases not causing morbid even if progressed \textsuperscript{5-7}. With the threat to functional or cosmetic preservation from progression, observation was only suitable 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 clear margin used to be regarded as mainstay treatment before 2000, and the 5-years local control rate were up to 80\% according to several retrospective study\textsuperscript{16}. While in the region of HN, the local control rate declined to between 24 and 70\%\textsuperscript{17}. And for 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 acceptable\textsuperscript{18}, at price of excessive long-term functional or cosmetic sequelae was not recommended in tumors located at HN of pediatric population\textsuperscript{9}. Therefore, sole surgery have been abandoned as a choice for most DT in the HN\textsuperscript{5}. In this study, patient with R2 margin after surgery were treated supplementarily with brachytherapy for local control.

External beam radiotherapy was considered to be either sole modality for inoperative cases of DT or complementary therapy for resectable ones, and the latter was regarded as better solution than sole surgery by a review of 22 articles\textsuperscript{19}. 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\textsuperscript{20-22}. Besides, efficacy of radiotherapy on pediatric DT was uncertain according to a study reporting 10 out of 13 children recurrent and 3 out of 13 dead\textsuperscript{23}.

Medical therapy including anti-hormonal therapies, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapy and tyrosine kinase inhibitors (TKIs) was another way the clinicians turned to\textsuperscript{6}. Anti-hormonal agents such as tamoxifen or toremifene, along with or without NSAIDs were reported retrospectively effective\textsuperscript{24}. However, a phase II study in pediatric population using tamoxifen\textsuperscript{25} showed limit activity for an progression free rate of 36\%, and notable safety problem with 40\% 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 \textsuperscript{6}. Tyrosine kinase inhibitors seemed hopeful with progression-free survival ranging from 59\% to 89\% and low toxicity according to several phase II and III studies\textsuperscript{26}. Therefore, chemotherapy and Tyrosine kinase inhibitors were advocated as active treatments\textsuperscript{5,6}. But meanwhile, there was still a need for a back-up therapy since the effectiveness of tyrosine kinase inhibitors might related to certain genome type \textsuperscript{27}, and also a solution for relapse from medical therapy.

Brachytherapy is a minimally invasive radiotherapy modality with high local dose while sparing surrounding normal tissues\textsuperscript{28}. 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 the brachytherapy for its smaller target volume than external beam radiotherapy\textsuperscript{11}. Previous studies in our department had reported the application of brachytherapy on pediatric population in HN, and showed good effectiveness and safety\textsuperscript{29-31}. Besides, the study on pediatric survivors with parotid gland carcinoma after brachytherapy showed mild affection on the mandible growth\textsuperscript{32}. The use of brachytherapy on DT in adult had also been reported with well local control\textsuperscript{33,34}. 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. In spite
of the limit of the amount of cases, we could still concluded that brachytherapy as an effective method for pediatric DT in HN for many other evidence we collected. There were several methods the Desmoid Tumor Working Group recommended for assessment of treatment effect\textsuperscript{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 month visit after brachytherapy, with dimensional change evaluated using CT or MR. Although CT examination was advised for measurement on dimensional change according to the Desmoid Tumor Working Group\textsuperscript{6} and NCCN guideline\textsuperscript{5}, the\textsuperscript{125}I seeds would affect the observation on the tumor outline on CT with radiological artifact. As an alternative, clinicians will measure the cluster volume of \textsuperscript{125}I seeds and a general volumetric shrinkage tendency indirectly showed the shrinkage of tumor volume\textsuperscript{35}. 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\textsuperscript{125}I seeds showed as small black area. But as for children, the time consuming on MR examination was a problem for their weak obedience ability and often needed sleeping pill. Therefore, in this study, we still used CT as an assessment on tumor diameter change, and accomplished with other methods.

Changes in T2 weighed intensity signal of MR image is useful for evaluation on activity of DT, because low T2 weighed signal corresponds to relatively lower cellularity and higher collagen content\textsuperscript{6,36}. In this study, all cases with preoperative and postoperative MR showed clearly reduction in T2 weighed intensity signal. The change in T2 weighed signal can be evaluated even though artifact existed after brachytherapy, and therefore can be added as an ancillary criteria for treatment evaluation, following the diameter change. However, the acquisition of MR from children still 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 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 were observed. Besides, except for cases already had massive bone defect 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, since the relatively indolent nature of DT, more conservative method should be considered firstly, such as TKIs or observation if suitable, and then aggressive method like surgery and brachytherapy if needed and possible. Brachytherapy could be turned to for unresectable lesion with looming unacceptable destruction, or as a salvage after 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, while more cases reported was expected. Besides, the data of toxicity evaluation is limited also because of the small sample size.

5 Conclusion

\textsuperscript{125}I Brachytherapy is effective and safe as sole modality or combined with surgery, for pediatric desmoid tumor in the head and neck region proven by multi-dimensional evaluation, and can be adopted as an alternative therapy in certain situation.

6 Conflict of Interest statement

None.

7 Acknowledgements

None.

References


Figures

Figure 1

![Image of a person with a device on their head and brain scans]

Figure 2

![Bar chart showing change in tumor size from baseline for 2 and 6 months]
Figure 3

Figure 4

Change of the MR intense signal

- Baseline
- 6 months

No. of patients

Intense signal of lesion to muscle ratio

0 1 2 3 4 5 6

9
Figure 1 The procedure of the brachytherapy. A,B) Brachytherapy was performed with the help of far-infrared navigation guidance system and three-dimensional printed individual templates, C) The post-implant dosimetry parameters were then calculated.

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 response were 4 and 1.

Figure 3 The follow-up computed tomography image of case with partial response. A) Baseline, B) 2 days after brachytherapy, C) 2 months follow-up D) 6 months follow-up.

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

Figure 5 The procedure of pathological examination. A,B) Core-needle aspiration was performed with the help of far-infrared navigation guidance system, C) No tumor cell was found in the specimen.

Table 1 Patients’ characteristics.

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Table 1.docx available at https://authorea.com/users/495193/articles/577006-long-term-result-of-125-i-seed-brachytherapy-for-pediatric-desmoid-tumor-in-the-head-and-neck