Received: 3 October 2017 | Revised: 10 April 2018 | Accepted: 11 April 2018
DOI: 10.1002/pbc.27223

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer SIOP aspho The American Society of Pediatric Hematology/Oncology

Mandibular growth in survivors of pediatric parotid gland carcinoma treated with interstitial brachytherapy

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The related study was presented as a poster display at the 2017 American Brachytherapy Society Annual Meeting in Boston, MA, USA.

Funding information
National Natural Science Foundation of China (81502652)

Abstract

Background: The aim of the study was to present long-term results of mandibular growth in pediatric parotid gland carcinoma survivors treated with interstitial brachytherapy.

Procedure: Twenty-five survivors of pediatric parotid gland carcinoma treated with iodine-125 seed interstitial brachytherapy were included for quantitative analysis, including three dimensional (3D) cephalometry and measurement of mandibular volume.

Results: 3D cephalometry showed that the median fore-and-aft increments of the lengths of the condyle, the ramus, and the body of the mandible were 1.23, 0.19, and 1.66 mm for the affected side, respectively, and were 1.37, 1.95, and 3.42 mm for the unaffected side, respectively. The difference in increments of the ramus was statistically significant between the affected side and the unaffected side ($P = 0.003$; $P < 0.05$). Moreover, mandibular volume measurements showed that the median fore-and-aft increments of the volumes of the condyle, the ramus, and the body of the mandible were 290.62, 220.14, and 1706.40 mm^3 for the affected side, respectively, and were 269.15, 370.40, and 1469.86 mm^3 for the unaffected side, respectively. The difference in increments was statistically significant between the affected side and the unaffected side for the ramus ($P = 0.005$; $P < 0.05$) and the body ($P = 0.043$; $P < .05$).

Conclusion: Mandibular growth was affected by interstitial brachytherapy, especially for the ramus, in pediatric parotid gland carcinoma survivors treated with interstitial brachytherapy. Nevertheless, the impact was mild in these survivors.

KEYWORDS
brachytherapy, cancer survivor, mandibular growth, parotid gland carcinoma, pediatric

1 | INTRODUCTION

Salivary gland carcinomas are rare in children and adolescents, representing 0.5% of all malignancies reported in this population.[1] The parotid gland is the most common organ involved in the pediatric population.[2,3] Moreover, about half of the parotid gland tumors are malignant in the pediatric population;[3] of these, mucoepidermoid carcinoma is the most common.[1,3–5] Nevertheless, pediatric patients with this malignancy have favorable prognosis, with 5 year overall survival above 80%.[1,4–9] The rates of nodal involvement and systematic metastasis are relatively lower in the pediatric population than is the case for salivary gland carcinomas in the adult population.[1,4] Surgery is the mainstay treatment, but the effects of radiotherapy are unclear.[2–4] Nevertheless, adjunctive radiotherapy may be indicated for high-risk cases, including tumors with high grades, perineural invasion, incomplete resection, or nodal involvement.[2–4,7,10] There is no clear dose–effect relationship; nevertheless, it is noteworthy that subsequent asymmetry deformity is one of the complications of radiotherapy.[4,6] Arrested mandibular growth requiring reconstructive surgery may occur because of mandibular and maxillary growth retardation.[6,11] Interstitial brachytherapy is effective and safe for pediatric patients with parotid gland carcinomas, according to our previous study.[12,13] The aim of the study was to present long-term results of mandibular growth in pediatric parotid gland carcinoma survivors

Abbreviations: 3D, three dimensional; BTPS, brachytherapy treatment planning system; cGy, centigray; CT, computed tomography; CTV, clinical target volume; D90, the dose delivered to 90% of the target volume; Gy, gray; MBq, megabecquerels; mm^3, cubic millimeter; V100, the percentage of the target volume receiving at least 100% of the prescription dose treated with interstitial brachytherapy. Quantitative analysis, including three dimensional (3D) cephalometry and measurement of mandibular volume, was used to evaluate the mandibular growth.

2 | METHODS

2.1 | Patient characteristics

Twenty-five pediatric patients with parotid gland carcinoma treated with iodine-125 seed interstitial brachytherapy as the sole (5/25) or adjuvant (20/25) modality from February 2006 to December 2014 were included retrospectively. The study was approved by the Ethics Committee and was conducted under the guidance of international ethical standards. These patients met the following inclusion and exclusion criteria: no history of radiotherapy before brachytherapy, no history of craniofacial bone fracture, no history of recurrence after brachytherapy, unilateral parotid gland carcinoma adjacent to the condyle of the mandible, and age < 19 years old. Ranging from 2 to 18 years old at the time of brachytherapy, the patients had a median age of 12 years. Fourteen patients were male and 11 were female. Up to December 2017, the follow-up time ranged from 36 to 141.4 months (median 79.3 months). None of the 25 patients received external-beam radiotherapy or chemotherapy as adjuvant treatment. During the follow-up, no osteomyelitis or fracture of the mandible was observed.

According to the staging criteria of the Union for International Cancer Control, seventh edition, 8 of the 25 patients were T2, 2 were T3, and 15 were T4 classification. All the patients were N0 M0. Mucoepidermoid carcinoma was the most common histologic type (17/25), followed by acinic cell carcinoma (4/25) and sialoblastoma (2/25). There was one patient for each of the other two types: epithelial-myoepithelial carcinoma and myoepithelial carcinoma. Among the 17 cases of mucoepidermoid carcinoma, 10 were intermediate and 7 were low grade. The other risk factors included facial nerve involvement (13/25), recurrent tumor (3/25), and T4 classification with residual tumor or positive margin (5/25). The detailed information of patients' characteristics is shown in Table 1.

TABLE 1 Patients characteristics

Characteristics	Number
Sex	
Male	14
Female	11
Age (years)	
Median	12
Range	2–18
T classification	
T1	0
T2	8
T3	2
T4	15
Risk factors	
Facial nerve involved	13
Recurrent tumor	3
T4 with residual tumor or positive margin	5
Histology	
Mucoepidermoid carcinoma	17
Acinic cell carcinoma	4
Sialoblastoma	2
Epithelial-myoepithelial carcinoma	1
Myoepithelial carcinoma	1

2.2 | Brachytherapy parameters

Brachytherapy was performed with iodine-125 seeds (type 6,711; Beijing Atom and High Technique Industries, Beijing, China), which had a half-life of 59.4 days and a radioactivity of 22.2–29.6 MBq per seed. The preoperative planning and postoperative quality verification with preoperative and postoperative computed tomography (CT) data were performed in the brachytherapy treatment planning system (BTPS; Beijing Atom and High Technique Industries, Inc., Beijing, China). Iodine-125 seeds were implanted into the target area according to the preplan with an individual template made via a rapid prototyping technique or combined with CT guidance, demonstrated in detail in our previous study.[14] The clinical target volume (CTV) was defined as gross tumor volume and its surrounding potential subclinical disease that was 1–1.5 cm beyond the margins of the primary tumor. Nevertheless, the condyle was inevitably covered by the CTV. The condyle of the affected side was delineated as organ at risk, and the dose was calculated in the BTPS. The median D90 (the dose delivered to 90% of the target volume) of the CTV was 11,550 cGy (8,320–13,650 cGy), and the median V100 (the percentage of the target volume receiving at least 100% of the prescription dose) was 92.8% (91–95.2%), whereas the V150 (the percentage of the target volume receiving at least 150% of the prescription dose) was <50% for all patients. The median D90 of the condyle was 5,760 cGy (1,323–1,5510 cGy). CT images and dose–volume histogram of quality verification of a patient are shown in Figure 1.

2.3 | Cephalometry

The CT data were available for all patients before and up to a median of 79.3 months after brachytherapy. The CT data before brachytherapy up to last follow-up were imported into ProPlan CMF software (Materialise, Leuven, Belgium), in which the linear mandibular measurements (the lengths of the condyle, the ramus, and the body of the mandible) and 3D cephalometry were analyzed. The fore-and-aft variations of the mandible were measured and calculated. Measurements were recorded to two decimal fractions of millimeter. To minimize the error in placing the landmarks and obtaining the measurements, two experienced researchers measured them according to the definitions three times. The detailed definitions of the landmarks and planes are shown in Table 2 and Figure 2.

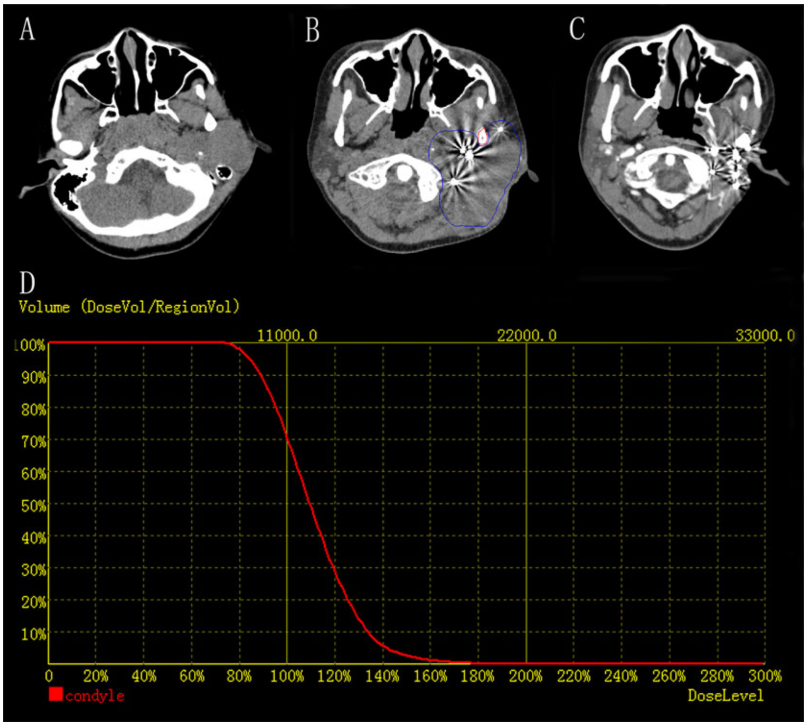

FIGURE 1 (A) CT image showing a T4 parotid carcinoma. The patient was treated with iodine-125 seed interstitial brachytherapy as a sole modality at the age of 8. (B) The condyle (the red line) of the affected side was delineated as the organ at risk. (C) The CT image after 112.1 months showed no sign of tumor recurrence. (D) Dose–volume histogram of quality verification in the brachytherapy treatment planning system showed the D90 of the condyle was 9785.8 cGy

TABLE 2 Definitions of cephalometric landmarks and linear mandibular measurements

Landmarks	Abbreviation	Description
Gnathion	Gn	Most inferior point on the mental symphysis
Mental foramen	Me	Point on mandibular base directly inferior to the mental foramen
Gonion	Go	The most inferior point on the angle of mandible
C-point	C	The lowest point of the semilunar incisure of sigmoid notch
Condyle length	Co	Distance between point Co and point C
Ramus length	R	Distance between point C and point Go
Body length	B	Sum of the two distances: distance between point Go and point Me; distance between point Me and point Gn

2.4 | Measurement of mandibular volumes

The same CT data were imported into Geomagic software (Geomagic Studio 2012, 3D System, SC, Morrisville, USA), in which the volume of the condyle, the ramus, and the body of the mandible were analyzed. The three parts of mandible were segmented by C-point plane, mandibular angle plane, and median landmarks plane.[15–19] Measurements were recorded to two decimal fractions of a cubic millimeter. Two experienced researchers segmented the mandibles and measured them according to the definitions three times. The teeth were removed in order to calculate the volume of the mandibular bone only, avoiding the influence of dentition at various stages. The coronoid process was also removed, since it is not considered to be part of the condyle or the ramus. The detailed definitions of the landmarks and planes are shown in Table 3 and Figure 2.

2.5 | Statistical analysis

The variables were the mean of the six measurements by the two experienced researchers. The mean fore-and-aft increments of the lengths and the volumes of the condyle, the ramus, and the body were calculated for the affected side and the unaffected side. The paired-samples *t*-test was used to compare the mean of the fore-and-aft increments between the affected side and the unaffected side. The partial bivariate correlation procedure was used to analyze the relationship between the D90 of the condyle and the difference of the increments of the two sides, controlling for age at onset. The age at onset and the difference of the increments were also analyzed by the partial bivariate correlation procedure, controlling for the D90 of the condyle. The two-sample *t*-test was used to compare the mean differences of the condyle, the ramus, and the body increments for the onset age ≤ 6 group and the onset age > 6 group. A *P*-value of <0.05 was considered statistically significant. The statistical analysis was carried out on SPSS 13.0 for Windows.

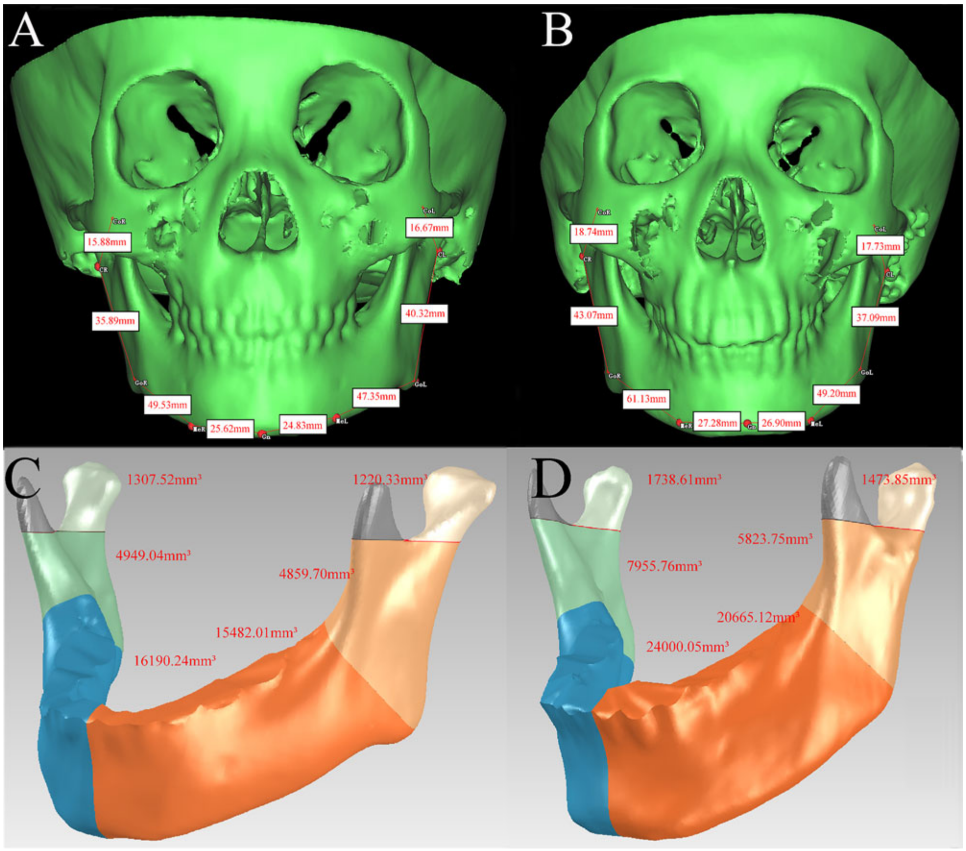

FIGURE 2 (A) 3D cephalometry before brachytherapy of the patient (the same patient as in Figure 1) showed that the lengths of the condyle, the ramus, and the body of the mandible were 16.67, 40.32, and 72.18 mm (47.35 + 24.83 mm) for the affected side and 15.88, 35.89, and 75.15 mm (49.53 + 25.62 mm) for the unaffected side, respectively. (B) 3D cephalometry 112.1 months after brachytherapy showed that the lengths of the condyle, the ramus, and the body of the mandible were 17.73, 37.09, and 76.10 mm (49.20 + 26.90 mm) for the affected side and 18.74, 43.07, and 88.41 mm (61.13 + 27.28 mm) for the unaffected side, respectively. (C) The measurement of mandibular volumes before brachytherapy showed that the volumes of the condyle, the ramus, and the body of the mandible were 1220.33, 4859.70, and 15482.01 mm^3 for the affected side and 1307.52, 4949.04, and 16190.24 mm^3 for the unaffected side, respectively. (D) The measurement of mandibular volumes 112.1 months after brachytherapy showed that the volumes of the condyle, the ramus, and the body of the mandible were 1473.85, 5823.75, and 20665.12 mm^3 for the affected side and 1738.61, 7955.76, and 24000.05 mm^3 for the unaffected side, respectively

3 | RESULTS

3.1 | Cephalometry

The median fore-and-aft increments of the lengths of the condyle, the ramus, and the body of the mandible were 1.23, 0.20, and 2.69 mm for the affected side, respectively. The median fore-and-aft increments of the lengths of the condyle, the ramus, and the body of the mandible were 1.37, 1.95, and 3.42 mm for the unaffected side, respectively. The difference of increments of the ramus between the affected side and the unaffected side was statistically significant ($P = 0.003$; $P < 0.05$). Nevertheless, there was no statistically significant difference between the affected side and the unaffected side for the increments of the length of the condyle or the body. The median differences of the condyle, the ramus, and the body increments were 0.26, 3.13, and 0.68 mm, respectively. The partial correlation coefficient was −0.454 ($P = 0.026$; $P < 0.05$) for the difference of the body increments and the age at onset, controlling for the D90 of the condyle. The other results for partial correlation coefficients showed no statistically significant difference. Moreover, there was no statistically significant difference between the onset age ≦ 6 group and the onset age > 6 group for the three parts.

3.2 | Mandibular volumes

The median fore-and-aft increments of the volumes of the condyle, the ramus, and the body of the mandible were 290.62, 220.14, and 1706.40 mm^3 for the affected side, respectively. The median fore-and-aft increments of the volumes of the condyle, the ramus, and the body of the mandible were 269.15, 370.40, and 1469.86 mm^3 for the unaffected side, respectively. The difference of increments of the ramus between the affected side and the unaffected side was statistically significant ($P = 0.005$; $P < 0.05$). Moreover, the difference of increments of the body between the affected side and the unaffected side was statistically significant ($P = 0.043$; $P < 0.05$). Nevertheless, there was no statistically significant difference between the affected side and the unaffected side for the increments of the volume of the condyle. The median difference of the condyle, the ramus, and the body increments were 27.13, 282.86, and 515.21 mm^3, respectively. The partial correlation coefficient was −0.707 ($P = 0.010$; $P < 0.05$) for the difference of

TABLE 3 Definitions of mandibular volume measurements and segmentation planes

Measurement	Description
F–H plane	The plane through the left and right infraorbital point, and the midpoint between the left and right porion
C-point plane	The plane through the C-point and parallel to the F–H plane
Jmed	The most medial and deepest point of the curvature formed at the junction of the ramus and body
Jlat	The most lateral and deepest point of the curvature formed at the junction of the ramus and body
Gopost	The most posterior point on the mandibular angle
Goinf	The most inferior point on the mandibular angle
Gomid	The midpoint between Gopost and Goinf
Mandibular angle plane	The plane through the points Jmed, Jlat, and Gomid
Median landmarks plane	The plane through the Menton, B-point, and the Genial Tubercle

TABLE 4 Length and volume increments of different parts of mandible

	Affected side		Unaffected side		
Measurements	Median	Mean	Median	Mean	*P*-value
Length increment of condyle	1.23	1.29	1.37	1.53	0.413
Length increment of ramus	0.19	0.13	1.95	2.90	0.003
Length increment of body	1.66	2.35	3.42	4.17	0.082
Volume increment of condyle	290.62	289.58	269.15	323.63	0.482
Volume increment of ramus	220.14	67.47	370.40	866.45	0.005
Volume increment of body	1706.40	2236.04	1469.86	2866.15	0.043

the body increments and the onset age, controlling for the D90 of the condyle. The other results of partial correlation coefficients showed no statistically significant difference. Moreover, there was no statistically significant difference between the onset age≦6 group and the onset age > 6 group for the three parts.

The detailed length and volume increments of the different parts of the mandible are shown in Table 4.

4 | DISCUSSION

Radiotherapy has played an important role in the management of head and neck cancer. Nevertheless, radiotherapy can cause severe impairments in the pediatric population, including osteoradionecrosis, eye problems, xerostomia, poor occlusion, radiation caries, and growth retardation of craniofacial bones.[20,21] Approximately 74% of pediatric patients who received radiotherapy in the craniofacial region presented with delayed growth or facial asymmetry.[22,23] Quality of life primarily depends on the cosmetic and functional outcomes for the survivors of pediatric head and neck carcinomas. For the pediatric patients, developing bones are radiosensitive, and growth retardation may occur postirradiation. Radiotherapy-related retardation of craniofacial bone growth remains a significant side effect of therapeutic radiation in survivors of pediatric head and neck cancer. However, few studies have evaluated growth retardation of craniofacial bones after radiotherapy by quantitative analysis.

The mandible plays an important role in facial appearance and occlusion. Radiotherapy often causes unilateral bone deformities. The growth of the body and ramus of the mandible has been substantially attributed to the growth center within the condylar cartilage.[24] For pediatric patients with parotid gland carcinoma, the condyle was inevitably covered in the target volume. Thus, mandibular growth was thought to be affected. Growth in the pediatric patient population should be followed carefully, and severe mandibular deformity may require reconstructive surgery. The study of mandibular growth in pediatric carcinoma survivors is relatively simple for craniofacial bones. In a similar fashion, clavicle growth after asymmetric mantle irradiation in pediatric patients was evaluated.[25] These results were similar to those of our study, where quantitative analysis, including 3D cephalometry and measurement of mandibular volumes, was shown to be a reliable method for evaluation of mandibular growth.

Using 3D cephalometry, we found that growth retardation occurred in the ramus of the mandible. However, according to the results of the measurement of mandibular volumes, we found that growth retardation occurred in the body and the ramus of the mandible, possibly because of buccolingual growth retardation of the body. Despite the difference, the mild growth retardation was barely recognizable in terms of facial appearance.

The minimal dose that may cause growth retardation in the growing facial bones was unknown in 1975.[26] Subsequently, it was reported that severe deformity occurred only in patients who received a dose greater than 50 Gy for the tumor,[27] whereas 30 Gy was the harmful dose for the bone.[28] Nevertheless, there was no clear dose–effect relationship in our study. However, the calculating methods in the BTPS were based on a homogeneous tissue structure and did not account for the complex structures in the head and neck region including bone and soft tissue.[29,30] The presence of bone affecting dose distributions in brachytherapy requires further study.

Other than radiation dosage, the severity of growth retardation was related to age, especially when the patients were less than 6 years old[31] or 5 years old[32] at the time of treatment. The growth rate of the ramus was maximal at 5 or 6 years of age.[24] The overall size of the mandible increased markedly between the ages of 11 and 17.[24] In our study, the ramus was the affected part of the mandible, according to 3D cephalometry and measurement of the mandibular volume. The difference of the body increments was negatively correlated with the age at onset controlling for the D90 of the condyle, and the partial correlation coefficients (−0.454 in 3D cephalometry and −0.707 in mandibular volumes) were significant at the 0.05 level (P value = 0.026 in 3D cephalometry and P value = 0.010 in mandibular volumes). However, growth retardation was not significantly different between the two groups (≦6 and >6). All in all, in our study, the age of the patient at the onset of treatment with brachytherapy may have been a more important factor than the radiation dosage in terms of the severity of mandibular growth retardation. Due to the small sample size of the current study, more patients and longer follow-up data are needed.

5 | CONCLUSION

Preliminary results revealed that mandibular growth was affected particularly for the ramus in pediatric parotid gland carcinoma survivors treated with interstitial brachytherapy. Nevertheless, mandibular growth retardation was mild. At least yearly surveillance for a prolonged period is recommended for these patients.

ACKNOWLEDGMENTS

The authors are deeply grateful to Jie-Ni Zhang (Department of Orthodontics, Peking University School and Hospital of Stomatology) for her contributions to discussion of this article.

This study was supported by the National Natural Science Foundation of China (81502652).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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How to cite this article: Wu W-J, Huang M-W, Zhang G-H, et al. Mandibular growth in survivors of pediatric parotid gland carcinoma treated with interstitial brachytherapy. *Pediatr Blood Cancer*. 2018;65:e27223. https://doi.org/10.1002/pbc.27223