Received: 7 February 2020 | Revised: 1 April 2020 | Accepted: 2 April 2020

DOI: 10.1002/pbc.28343

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

ONCOLOGY: RESEARCH ARTICLE

Efficacy of surgery combined with postoperative ^{125}I interstitial brachytherapy for treatment of acinic cell carcinoma of the parotid gland in children and adolescents

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Abstract

Background: Acinic cell carcinoma (AciCC) is rare in children; therefore, reaching a consensus on its management is challenging and radiotherapy is limited by concerns about long-term toxicity. The purpose of this study is to analyze the effectiveness and safety of surgery plus postoperative ^{125}I interstitial brachytherapy (IBT) for children and adolescents with AciCC of the parotid gland (PG) treated at a single institution.

Procedure: Sixteen patients ≤ 18 years old with AciCC of the PG treated with surgery plus ^{125}I IBT from 2007 to 2018 were included. Surgery was the primary treatment; ten patients underwent total gross excision and six subtotal gross excision. The matched peripheral dose was 60-120 Gy. Overall survival, disease-free survival (DFS), local control rate, distant metastasis, and radiation-associated toxicities were analyzed, and factors influencing outcomes were evaluated.

Results: During follow-up (1.8-12.6 years; mean, 6.3 years), lymph node metastasis was observed in one case, 2.6 years after ^{125}I IBT treatment. The five-year overall and DFS rates were 100% and 91.7%, respectively. On univariate analysis, tumor size ≥ 3 cm (100% vs 50%; $P = 0.025$) and extraglandular extension (100% vs 50%; $P = 0.025$) were significant prognostic indicators for DFS. No severe radiation-associated complications occurred.

Conclusions: Children and adolescents with AciCC of the PG with high-risk features can be managed using surgery plus postoperative ^{125}I IBT with excellent local control. Radiation-related complications were minor. Patients with facial nerve involvement can have their facial nerves preserved. Residual tumors can be safely managed using adjuvant ^{125}I IBT.

KEYWORDS

acinic cell carcinoma, adolescent, brachytherapy, children, parotid gland

1 | INTRODUCTION

Acinic cell carcinoma (AciCC) is a sparse, low-grade malignant epithelial carcinoma of the salivary glands, with an average annual incidence of 0.13 cases per 100 000 individuals,[1] and is far less common in children than adults.[2-6] The reported five-year survival rate of patients with AciCC ranges from 88.6% to 90%.[7-9] Due to its rarity, previous studies of AciCC in children and adolescents have predominately been reported as case series,[10-14] and it is challenging to develop a consensus on its management.

According to the literature, surgical resection remains the mainstay treatment for AciCC of the parotid gland (PG), and patients with low-grade, early T stage (T1/T2) disease, without high-risk clinicopathological features, can be managed using surgery alone.[15-18] Zenga et al. reported that, if the only risk factor was close (≤ 1 mm) margins, AciCC

Abbreviations: AciCC, acinic cell carcinoma; DFS, disease-free survival; FNI, facial nerve involvement; IBT, interstitial brachytherapy; LCR, local control rate; MPD, matched peripheral dose; OS, overall survival; PG, parotid gland; PRT, proton radiotherapy; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

can be treated with surgery alone, resulting in excellent locoregional control; [15] however, adjuvant radiotherapy (RT) is still required for cases with high-grade tumors, recurrent disease, positive surgical margins, advanced T stage (T3/T4), perineural invasion, gross residual disease, or regional metastasis.[7,17,19]

Despite the survival benefits of RT suggested in previous reports, this therapeutic approach is often limited by concerns about long-term toxicity in children, such as xerostomia, trismus, development of secondary cancers, and craniofacial growth abnormalities.[20,21] ^{125}I interstitial brachytherapy (IBT) is an RT modality, where postoperative ^{125}I IBT delivers a high dose of radiation directly to target areas, minimizing nontarget dose dispersal to adjacent normal structures, and is increasingly reported as effective and safe for treating children with malignant PG tumors.[22-24]

The aim of this retrospective study was to analyze the effectiveness and safety of surgery combined with postoperative ^{125}I IBT among children and adolescents with AciCC of the PG with high-risk features.

2 | METHODS

2.1 | Patients

We retrospectively reviewed pathology records from between 2007 and 2018 at the Peking University School of Stomatology to identify all cases of AciCC of the PG with high-risk features in children and adolescents less than 18 years of age at diagnosis. All patients received surgery plus postoperative ^{125}I IBT. This retrospective study was approved by the Ethics Committee of Peking University School and Hospital of Stomatology, and all patients' guardians signed their informed consent. Clinical records were reviewed for demographic data, patient and tumor characteristics, and therapeutic management. Diagnosis followed the classification system for salivary gland malignancies of the World Health Organization and was performed by experienced head and neck pathologists. R stage was classified into three degrees: R0 indicated no evidence of residual tumor, whereas R1 indicated tumor tissue within 1 mm of the resection margin, and macroscopically visible tumor at margins was classified as R2. Pathological data were obtained from pathology reports.

2.2 | Treatment workflow

All patients received surgery as the primary treatment. For patients with facial nerve involvement (FNI) (6/16), subtotal gross excision was performed, and for patients without FNI (10/16), total gross excision was conducted. FNI was defined intraoperatively as facial nerve adhering to or passing through the tumor. Elective neck dissection was not performed, as there was no evidence of lymph node metastases.

All patients received ^{125}I IBT at four to six weeks after surgery. Based on preoperative imaging results, pathology reports, surgery records, and tolerance doses of surrounding normal tissue, the planning target volume included the preoperative gross tumor volume, as well as 1 to 1.5 cm beyond the margins of the primary tumor. The matched peripheral dose (MPD) was 6000-10 000 cGy for patients with negative surgical margin (R0) and 10 000-12 000 cGy for patients with residual tumors (R1/R2). The MPD is defined as the dose for which the computed isodose volume matches the target volume, and it is numerically equal to prescription dose.[25] ^{125}I seeds (type 6711; Beijing Atom and High Technique Industries Inc, Beijing, China; t1/2, 59.4 days; energy level, 27.4-31.4 keV) with surface radioactivity of 18.5 to 22.2 MBq were implanted.

2.3 | Follow-up and assessment

Following the completion of ^{125}I IBT treatment, patients were assessed every two months for the first six months, every three months until the third year, and every six months thereafter. At each visit, clinical examinations were performed to evaluate for recurrence and, if suspected, confirmed by computed tomography. Facial nerve function was evaluated by the House-Brackman grading system before surgery, before brachytherapy, and six months after brachytherapy. Radiation-associated toxicities were assessed by the Radiation Therapy Oncology Group (RTOG) grading system.

2.4 | Statistical analysis

IBM SPSS Statistics for Windows, version 24.0 (IBM Corp, Armonk, New York), was used for statistical analyses. Univariate analysis was performed using the Kaplan-Meier method. The following parameters were examined: sex, age $\geq$ 14 years, stage T3/T4, tumor size $\geq$ 3 cm, extraglandular extension, recurrence history, margin status, R stage, surgical extent, tumor spillage, FNI, matched peripheral dose, and extracapsular spread. The Cox proportional hazards regression model was used for multivariate analysis to identify predictors of outcome. Statistical significance was set at $P \leq 0.05$. The Kaplan-Meier method was also used for analysis of overall survival (OS), disease-free survival (DFS), and local control rate (LCR) at 5 and 10 years. OS was calculated from the date of ^{125}I IBT to the date of last follow-up or death. LCR was calculated as the proportion of patients not developing recurrence at the parotid site. DFS was calculated from the date of ^{125}I IBT to the time of local or regional recurrence, distant metastasis, or death.

3 | RESULTS

3.1 | Clinicopathologic characteristics of the study cohort

The clinicopathologic characteristics of our patient cohort are presented in Table 1. Sixteen cases were identified, aged 3-18 years (mean, 13.7 years; median, 15 years), with equal sex distribution. All patients presented with palpable swelling in the PG region. Features including pain, rapid growth, and facial paralysis were absent. Advanced T stage (T3/T4) was found in 8 (50%) of patients. The maximum tumor diameter ranged from 1.2 to 5.0 cm (mean, 2.4 cm). Ten patients underwent total gross excision (R0/R1), whereas six received subtotal gross excision (R2), and the largest residual tumor diameter was 1 cm. The tumor

TABLE 1 Characteristics of 16 patients with parotid AciCC

Characteristics	*n* (%)
Sex	
Male	8 (50%)
Female	8 (50%)
Age (years)	
< 14	6 (37.5%)
≥ 14	10 (62.5%)
T stage	
T_2	8 (50%)
T_3	2 (12.5%)
T_4	6 (37.5%)
Tumor size (cm)	
≥ 3	4 (25%)
< 3	12 (75%)
Extraglandular spread	
Yes	2 (12.5%)
No	14 (87.5%)
Recurrent history	
Present	2 (12.5%)
Absent	14 (87.5%)
Margin status	
Positive	14 (87.5%)
Negative	2 (12.5%)
Surgical extent	
Total gross excision	10 (62.5%)
Subtotal gross excision	6 (37.5%)
Tumor spillage	
Present	1 (6.25%)
Absent	15 (93.75%)
Extracapsular extension	
Yes	7 (43.75%)
No	9 (56.25%)
R stage	
R0	2 (12.5%)
R1	8 (50%)
R2	6 (37.5%)
Matched peripheral dose (Gy)	
60-100	2 (12.5%)
100-120	14 (87.5%)
Facial nerve involvement	
Yes	6 (37.5%)
No	10 (62.5%)

of the two patients with recurrent disease presented as diffuse mass during surgery. The intervals between primary diagnosis and recurrence were 6 and 10 months. Other characteristics of the two patients with recurrent disease are presented in Table 2.

3.2 | Clinical outcome and predictors of DFS

At the end of the observation period, all patients were alive. During the follow-up period of 1.8-12.6 years (mean, 6.3 years), OS and LCR were both 100% and no patient developed distant metastasis. DFS was 91.7% at both 5 and 10 years (Figure 1A). Lymph node metastasis was observed in one case 2.6 years after ^{125}I IBT. After receiving elective neck dissection without adjuvant treatment, no relapse occurred during the follow-up period of five years. On univariate analysis, the most significant parameters predicting DFS were tumor size ≥ 3 cm (50% vs 100%; $P = 0.025$; Figure 1B) and extraglandular extension (50% vs 100%; $P = 0.025$; Figure 1C) at diagnosis; however, neither parameter retained their prognostic value in the Cox regression model for multivariate analysis.

The patient who developed lymph node metastasis was a 12-year-old male, with primary AciCC of PG, and a maximum tumor diameter of 3.7 cm, with extraglandular extension. A facial nerve branch was found passing through the tumor, with another branch adhering to the tumor. The branch passing through the tumor was accidentally excised and then reconstructed, whereas the other branch was preserved. Surgical margin status in this patient was R2; hence, an MPD of 110 Gy was administered. No recurrence was observed in the parotid site during the follow-up period of 95 months.

3.3 | Facial nerve function

Although no patients had facial nerve paralysis before surgery (Table 3), four (25%) patients suffered facial nerve injury during surgery. Functional improvements were observed in three patients within six months, except one sacrificed part of a nerve branch (House-Brackmann grade 3).

3.4 | Side effects and toxicity

No patients experienced acute toxicity beyond RTOG grade 3. Grade 1 and 2 skin reactions were experienced by 11 (68.75%) and 1 (6.25%) patients, respectively. No patient had oral mucositis, trismus, or hypoacusis during follow-up. All acute reactions resolved within six months. No patients suffered from late toxicities such as edema, xerostomia, pain, hearing loss, trismus, dental caries, osteoradionecrosis, or radiation-induced malignancies. No other serious late toxicity was recorded.

4 | DISCUSSION

Salivary gland tumors are rare in the general population, accounting for approximately 1% to 3% of all head and neck malignancies.[6] In children, AciCC is the second most common epithelial malignancy, following mucoepidermoid carcinoma.[5,6,13,26,27] The trend of literature reported is a feature of institutional series[10-14]; thus, a comparison of outcomes with other institutions is pretty difficult because all the patients had high-risk features in our study. However, OS was 100% in our cohort, with excellent local control. As a consequence of the rarity

TABLE 2 Characteristics of two patients with recurrent disease treated in our cohort

Patient	Gender	Age (years)	Size (cm)	R stage	FNI	Surgery type	Tumor spillage	MPD (Gy)	Follow-up months	Relapse
1	female	16	1.8	2	+	SGE	No	110	150	No
2	male	10	2	2	-	SGE	Yes	110	47	No

FNI, facial nerve involvement; MPD, matched peripheral dose; SGE, subtotal gross excision.

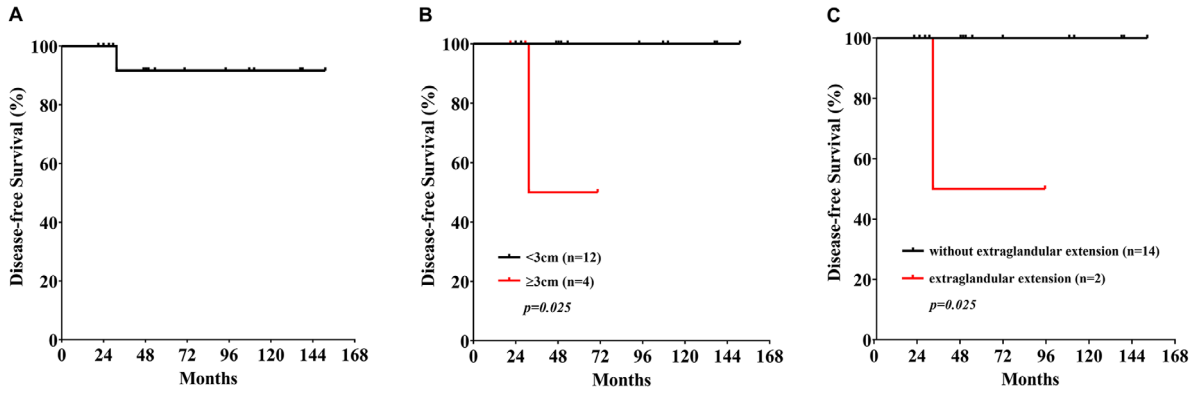

FIGURE 1 (A) Kaplan-Meier curves for DFS. (B) DFS according to tumor size (≥3 cm vs<3 cm, $P = 0.025$) and extraglandular extension (absent vs present, $P = 0.025$) (C)

TABLE 3 Facial nerve function evaluated using the House-Brackman grading system

Variable	I	II	III	IV	V
Before surgery	16				
Before ^{125}I IBT	12	3	1		
6 months after ^{125}I IBT	15		1		
1 year after ^{125}I IBT	15	1			

IBT, interstitial brachytherapy.

of AciCC in children and the limited data available, features assumed to indicate high-risk are based on extrapolation from adult data. Several population-based analyses of AciCC have been reported. On multivariable analysis of 2362 patients with AciCC from the National Cancer Database, tumor size between 3 and 6 cm was identified as a significant high-risk feature (hazard ratio, 1.53).[7] In our study, tumor ≥ 3 cm (50% vs 100%; $P = 0.025$; Figure 1B) was a significant prognostic indicator for DFS, consistent with the conclusions of Neskey et al.[28] Further, extraglandular extension (50% vs 100%; $P = 0.025$; Figure 1C) was a prognostic factor for DFS in our study; however, when these factors were included in multivariate analysis, neither was found to significantly influence DFS. We speculate that is because of the small sample size, which limited the value of multivariate analysis in further elucidating this issue.

In the literature, many surgeons have reported sacrificing functioning facial nerves to obtain clear surgical margins in children with AciCC. In a study of 215 patients (≤ 19 years) with AciCC in the PG identified using the National Cancer Database and managed using different modalities, 13% underwent surgery resulting in facial nerve sacrifice.[3] Similarly, another study using data from the Surveillance, Epidemiology and End Results database reported that six (7%) children (≤ 19 years) had sacrificed facial nerves.[6] Hence, special precautions should be taken when treating AciCC in children and adolescents, due to their ongoing facial growth and development. Extended surgery and facial nerve sacrifice lead to significant cosmetic and functional morbidity. Facial nerve dysfunction following surgery is profound for patients, because it leads to psychological distress, anxiety, and depression[29]; anxiety and depression rates caused by permanent facial nerve dysfunction are reported as 32.7% and 31.3%, respectively.[30] Mao et al. analyzed 24 mucoepidermoid carcinomas of the PG in children. Although FNI was found in 10 patients during surgery, facial nerves were preserved in all cases, resulting in reliable facial nerve function. No patients suffered from recurrence during the median follow-up period of 7.2 years,[23] in broad agreement with our findings. Therefore, in this study, less-invasive surgical modalities were undertaken to preserve the function of facial nerves, followed by treatment with ^{125}I IBT. Although transient facial nerve weakness was observed in four (25%) cases, three recovered within six months.

Literature on the treatment and outcomes of recurrent salivary gland neoplasms in children is sparse. Qureshi et al. reported six children with recurrent parotid malignancies.[31] Extended surgery of recurrent sites was undertaken to obtain clear surgical margins, and postoperative RT was also adopted. This may lead to complications of both surgery and RT, although these were not mentioned. In our cohort, two patients with recurrent disease received subtotal tumor excision, combined with postoperative ^{125}I IBT. During follow-up periods of 150 and 47 months, respectively, no recurrence was observed, and facial nerve function was satisfactory (House-Brackmann grade 1). These results emphasize the need for the extent of surgery to be carefully considered, so as to be therapeutically sufficient, but

not overtly radical, as cosmetic and functional considerations are paramount in children and adolescents. Hence, we recommend less-aggressive surgery combined with postoperative ^{125}I IBT for patients with recurrent AciCC.

Diverse RT modalities have been reported for the management of head and neck cancers in children. Cockerill et al. reviewed six children with a PG malignancy treated at the Mayo Clinic and receiving adjuvant RT. Complications from radiation in this series included facial lymphedema, xerostomia, paresthesia, external auditory canal stenosis, and arrested mandibular growth requiring reconstructive surgery.[26] A larger series of 26 children treated at the MD Anderson Cancer Center was also reported. After receiving external beam radiation, children suffered from long-term morbidities, including xerostomia (4%), dental caries (13%), mandibular osteoradionecrosis (4%), and second primary cancers in the treated field (8%).[19] As a modern conformal radiation method, intensity-modulated RT is also associated with late sequelae, such as facial asymmetry, jaw hypoplasia, trismus, and hearing loss, when used to treat head and neck carcinoma.[20,21] Proton RT (PRT) has been suggested to improve the side-effect profile because of its characteristic energy deposition profile (the Bragg curve), which eliminates exit dose and reduces exposure to surrounding normal tissue. A study of 13 children (≤ 18 years) with PG carcinoma, reported by Grant et al., showed that PRT was associated with favorable acute toxicity relative to conventional photon/electron-based RT; however, long-term treatment-related side effects, such as growth and development impairment, require further observation.[32] ^{125}I IBT is an alternative conformal RT, which can deliver a cumulative dose directly into the target tumor with acceptable radiation-related effects. Wu et al. reported a series of cases, including 25 children with PG cancers receiving ^{125}I IBT, where radiation-related side effects on mandibular growth were mild.[33] Consistent with previous studies on the application of postoperative ^{125}I IBT for treatment of PG cancer, this RT method is well tolerated as there is no evidence of severe late radiation-related complications (RTOG grades 3-4).[23,24,34]

In conclusion, lessaggressive surgery combined with postoperative ^{125}I IBT appears to be an effective and safe modality for the treatment for AciCC of the PG in children and adolescents. This method may be particularly suitable for children developing the disease, because of their long life expectancy. Our study illustrates that patients with FNI can have their facial nerves preserved, and residual tumors can be safely managed using adjuvant^{125}I IBT; however, the safe volume of residual tumors still needs further study. Our data indicate that, for children with recurrent AciCC of the PG, conservative surgery plus ^{125}I IBT is a reliable choice to avoid adverse effects caused by surgery and RT.

CONFLICTS OF INTEREST

None.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Yan Shi and Dr. Ming-hui Mao for their contributions to the preplanning of brachytherapy and collection of the data.

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How to cite this article: Li J, Zhang J, Lyu X-M, Huang M-W, Zheng L, Zhang J-G. Efficacy of surgery combined with postoperative I interstitial brachytherapy for treatment of acinic cell carcinoma of the parotid gland in children and adolescents Title page. *Pediatr Blood Cancer*. 2020;67:e28343. https://doi.org/10.1002/pbc.28343