Received: 14 November 2018 | Revised: 18 April 2019 | Accepted: 13 May 2019
DOI: 10.1002/hed.25813

ORIGINAL ARTICLE

WILEY

Efficacy of combined surgery and ^{125}I seed brachytherapy for treatment of primary mucoepidermoid carcinoma of the parotid gland

Zhi-Yuan Wu MD | Wen-Jie Wu MD | Lei Zheng MD | Ming-Wei Huang PhD | Yan Shi MD | Xiao-Ming Lv MD | Shu-Ming Liu MD | Jian-Guo Zhang BSMed | Jie Zhang MD

Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, China

Correspondence
Jie Zhang, Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, 22# Zhongguancun South Avenue, Beijing 100081, China.
Email: zhangjie06@126.com

Abstract

Background: This study aimed to determine the effectiveness and safety of surgery combined with postoperative ^{125}I seed brachytherapy for treatment of primary mucoepidermoid carcinoma (MEC) of the parotid gland.

Methods: Retrospective analysis of data of patients with MEC (n = 108) treated with surgery plus postoperative ^{125}I seed brachytherapy between 2004 and 2016. Overall survival (OS), disease-free survival (DFS), local control rate (LCR), distant metastasis, and radiation-associated toxicities were analyzed, and factors affecting outcomes were evaluated.

Results: The 5- and 10-year OS were 98.8% and 95.8%, respectively. The DFS and LCR at 5 and 10 years were all 91.4%. Age ≥ 60 years (hazard ratio [HR] = 6.86, 95% confidence interval [CI]: 1.54-30.55) and T4 disease (HR = 7.15, 95% CI: 1.40-36.52) were poor prognostic factors. Acute radiation-associated toxicities were minor.

Conclusion: Surgery plus ^{125}I seed brachytherapy appears to be an effective treatment for parotid gland MEC, capable of providing satisfactory outcomes with few complications.

KEYWORDS

^{125}I seed, brachytherapy, mucoepidermoid carcinoma, parotid gland, risk factor

1 | INTRODUCTION

Mucoepidermoid carcinoma (MEC) accounts for 40% to 50% of malignant tumors of the parotid gland.[1] Although surgical resection is the main treatment for these tumors,[2] postoperative radiotherapy is used to reduce the risk of recurrence. Treatment decisions are influenced by the histological grade as clinical prognosis varies between low-, intermediate-, and high-grade MECs. According to the National Comprehensive Cancer Network 2017 Guidelines, postoperative radiation therapy should be considered for MEC when there are adverse features such as intermediate or high grade, close or positive margins, perineural invasion, lymph node metastases, or lymphatic/vascular invasion.[3] However, external radiotherapy of the parotid region is associated with many toxicities, including skin and auditory toxicity, xerostomia, and osteoradionecrosis.[4-8] Theoretically, most of these toxicities of parotid region could be minimized with the use of ^{125}I seed brachytherapy, with which it is possible to deliver high dose to the tumor volume while sparing surrounding tissue.[9,10] The aim of this retrospective study was to explore the efficacy and safety of surgery combined with postoperative ^{125}I seed brachytherapy for treatment of MEC of the parotid gland and to identify the factors influencing outcomes.

2 | MATERIALS AND PATIENTS

2.1 | Patients

A total of 180 adult patients with a histological diagnosis of MEC of the parotid gland were treated at the Peking University School of Stomatology Hospital between February 2004 and December 2016. Patients treated for recurrence (n = 41) and those treated with surgery alone or surgery plus external radiotherapy (n = 31) were excluded. Finally, 108 patients with primary MEC of the parotid gland who were treated with surgery and postoperative ^{125}I seed brachytherapy were included in this retrospective study. All data related to these patients were retrieved from the hospital records. Tumors were staged according to the American Joint Committee on Cancer 2016 classification.

2.2 | Surgery and seeds implantation

Surgery included resection of tumor and parotid gland (part, superficial lobe, or total gland), with the extent of resection decided by tumor site and size. The facial nerves were preserved whenever possible and damaged nerves were reconstructed. None of the patients receive neck dissection as all of the patients had clinically negative neck nodes; patients who had clinically positive neck at presentation were treated with external radiotherapy and were excluded from the study. Radioactive seeds implantation was performed approximately 2 weeks after surgery, after wound healing was complete. The brachytherapy treatment planning system (Beijing Atom and High Technique Industries Inc, Beijing, China) was used for pretreatment planning. The planning target volume included a 1 to 1.5 cm margin around the preoperative gross tumor volume. The matched peripheral dose was 100 to 120 Gy. Implantation was performed with CT or template guidance. Hollow interstitial needles (18-gauge, 150 mm) were inserted into target area, and the ^{125}I seeds (model 6711; Beijing Atom and High Technique Industries Inc, Beijing, China; $t_{1/2}$, 59.6 days; energy level, 27.4-31.4 keV) with activity of 22.2 to 29.6 MBq (0.6-0.8 mCi) were implanted.

2.3 | Follow-up

Patients were evaluated every 2 months for the first 6 months, every 3 months until the third year, and every 6 months from the third year to the fifth year. Recurrence was evaluated by clinical examination and confirmed by CT. Facial nerve function was evaluated by the House-Brackman grading system before surgery, before brachytherapy, and 6 months after brachytherapy. Radiotherapy-associated toxicities were assessed by the Radiation Therapy Oncology Group (RTOG) grading system.

2.4 | Statistical analysis

Overall survival (OS), disease-free survival (DFS), local control rate (LCR), and incidence of complications were analyzed. OS was calculated from the date of brachytherapy to the date of death from any cause. LCR was calculated as the proportion of patients not developing recurrence at the treated site. DFS was calculated from the date of brachytherapy to the date of local failure, distant metastases, or death from any cause. The Kaplan-Meier method was used for analysis of OS, DFS, and LCR at 5 and 10 years. The Cox proportional hazards regression model was used for multivariate analysis to identify the predictors of outcome. Descriptive statistics was used for analysis of the complications of treatment. IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, New York) was used for statistical analysis. Statistical significance was at $P \leq .05$.

This study was approved by the Ethics Committee of Peking University School and Hospital of Stomatology.

3 | RESULTS

Table 1 lists the demographic and clinical characteristics of all patients. The 108 patients included 48 men (44.4%) and 60 women (55.6%), aged 18 to 79 years (mean age, 41.7 years). T classification was T1 in 36 patients, T2 in 34 patients, T3 in 6 patients, and T4 in 32 patients. There were 30 low-grade tumors, 54 intermediate-grade tumors, and 8 high-grade tumors; the histologic grade of 16 patients was unclear.

Table 2 lists the surgery characteristics. The operative procedure included partial tumor resection (9 patients), superficial parotidectomy (8 patients), total parotidectomy (7 patients) and extensive local excision (84 patients). The margins were clear in 31 patients, positive in 33, and close in 44. No patient underwent radical parotidectomy. Facial nerve paralysis was present in three patients before treatment and, during surgery, the facial nerves were seen traversing the tumor. The same was also seen in 12 other patients who did not have facial palsy. In all of these 15 patients, during resection of the tumor, a small part of the tumor surrounding the nerve was left in situ. The facial nerves of 19 patients were adherent to the tumors and had to be carefully separated from the growth. In the process, the temporal branch was damaged in three patients and had to be anastomosed.

TABLE 1 Patient and tumor characteristics

Characteristic	Patients (n = 108)
Sex	
Men	48 (44.4%)
Women	60 (55.6%)
Ages	
18-44	58 (53.7%)
45-59	38 (35.2%)
>60	12 (11.1%)
Mean age	41.7
T stage	
T1	36 (33.3%)
T2	34 (31.5%)
T3	6 (5.6%)
T4	32 (29.6%)
Histological grade	
Low	30 (27.8%)
Intermediate	54 (50%)
High	8 (7.4%)
Unknown	16 (14.8%)
Facial nerve palsy	
Absent	105 (97.2%)
Present	3 (2.8%)
Perineural invasion	
Negative	74 (68.5%)
Positive	34 (31.5%)

TABLE 2 Surgery characteristics

Characteristic	Patients (n = 108)
Surgery type	
Partial tumor resection	9 (8.3%)
Extensive local excision	84 (77.8%)
Superficial parotidectomy	8 (7.4%)
Total parotidectomy	7 (6.5%)
Cut margins	
Negative	31 (28.7%)
Close (<5 mm)	44 (40.7%)
Positive	33 (30.6%)
Facial nerve	
Preserved	105 (97.2%)
Sacrificed and reconstruct	3 (2.8%)

3.1 | Local control rate

Median follow-up was for 50.0 months (range, 5-157 months). The LCR was 91.4% at both 5 and 10 years after treatment (Figure 1). A total of eight patients developed local recurrence (Table 3): these included four patients with low-grade tumors, two with intermediate-grade tumors, and two with high-grade tumors. Among these patients T classification was T1 in two patients and T4 in six patients. Positive margins were recorded in six patients. The median time to recurrence was 25.5 months. Treatment of recurrence was with a second surgery (four patients), ^{125}I seed brachytherapy (two patients), or surgery plus ^{125}I seed implantation (one patient).

On univariate analysis, age (≥60 years vs <60 years), T classification (T4 vs T1-T3), and perineural invasion (positive vs negative) were significantly associated with LCR. The 5-year LCR was significantly higher in patients <60 years than in those ≥60 years (93.8% vs 71.3%; P = .008; Figure 2A); in T1-T3 disease than in T4 disease (96.9% vs 81.5%; P = .01; Figure 2B); and in patients without perineural invasion than in patients with perineural invasion (95.1% vs 82.6%; P = .03). The 5-year LCR was 85.8%, 95.9%, and 71.4%, respectively, in patients with low-grade, intermediate-grade, and high-grade tumors (P = .10). The 5-year LCR was higher in patients with negative margins than in patients with close/positive margins, but the difference was not statistically significant (100% vs 88.3%; P = .08).

On multivariate analysis performed using the Cox proportional hazard model, advanced T classification, close/positive margins, perineural invasion, and age ≥ 60 years were independent predictors of poor LCR. Age ≥ 60 years (P = .01) and T4 disease (P = .02) were strong predictors of poor local control. The hazard ratio for mortality was 6.86 (95% confidence interval [CI]: 1.54-30.55) for patients with age ≥ 60 years and 7.15 (95% CI: 1.40-36.52) for patients with T4 disease.

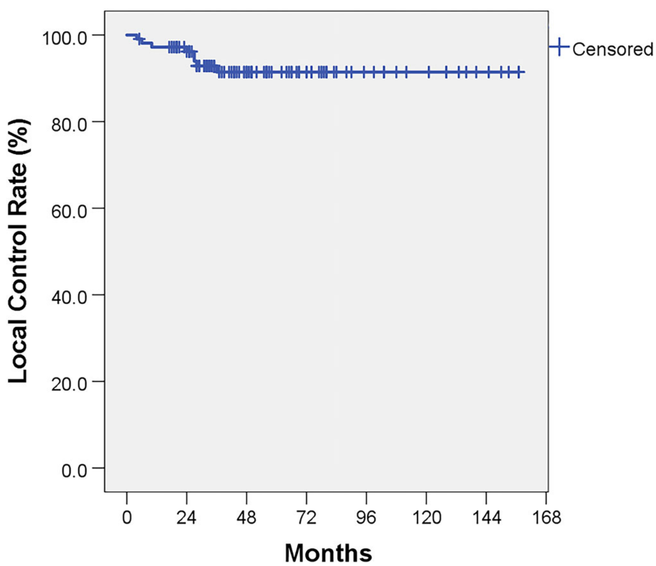

FIGURE 1 Kaplan-Meier curve for local control rate [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Characteristics of the eight patients who had recurrence

Patient	Age	Sex	T stage	Histological tumor grade	Cut margin	Time to relapse (mo)	Second operation	Alive or Deceased
1	79	M	4	HG	Positive	28	Resection	Alive
2	33	W	4	IMG	Positive	6	Resection + ^{125}I	Alive
3	72	W	4	LG	Positive	4	Resection	Alive
4	39	W	1	LG	Close	10	Resection	Alive
5	44	M	4	HG	Positive	36	Resection	Died
6	22	W	1	LG	Close	27	^{125}I	Alive
7	74	W	4	LG	Positive	24	^{125}I	Alive
8	55	M	4	IMG	Positive	27	None	Died

Abbreviations: HG, high grade; IMG, intermediate grade; LG, low grade; M, men; W, women.

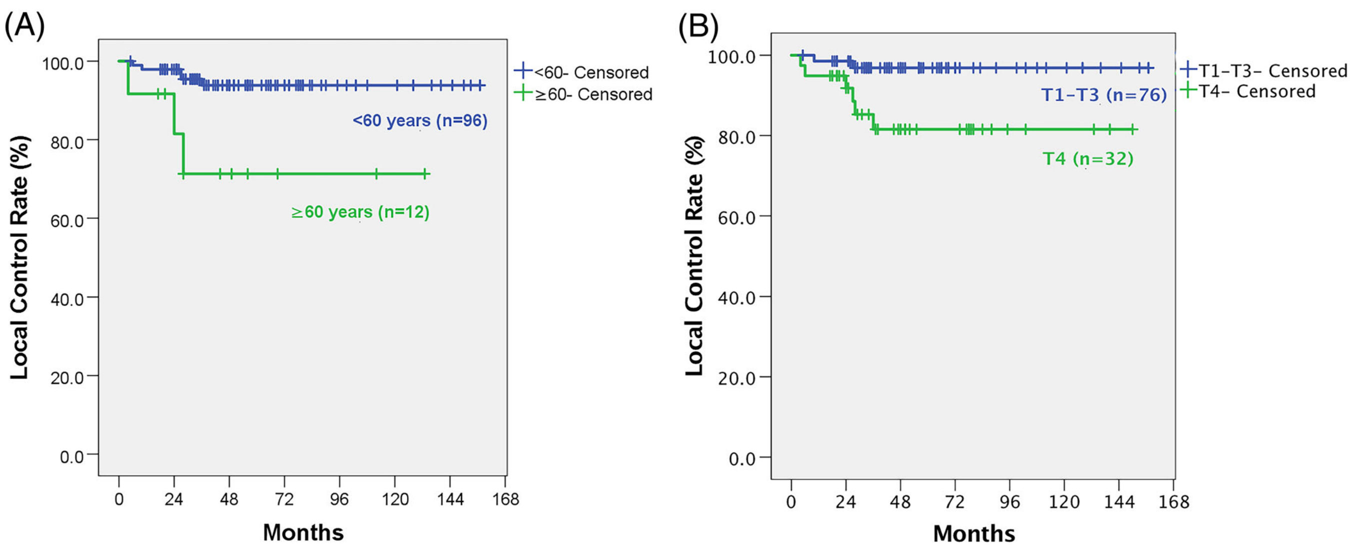

FIGURE 2 Local control rate according to age (<60 vs ≥60 years, $P = .008$) (A) and Local control rate according to T stage (T1-T3 vs T4, $P = 0.01$) (B) by Kaplan-Meier analyses [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Survival rate

OS at 5 and 10 years was 98.8% and 95.8%, respectively (Figure 3). DFS was 91.4% at both 5 and 10 years. OS at 5 years was 100% in patients with low-grade tumor, 97.5% in patients with intermediate-grade tumor, and 66.7% in patients with high-grade tumor. Only two patients died due to MEC during the follow-up period: one patient had high-grade disease, T4 tumor, and positive margin, whereas the other patient had intermediate-grade disease, T4 tumor, and negative margin. The first patient developed recurrence 3 years after ^{125}I seeds implantation and underwent three further surgeries. The second patient discontinued treatment after being diagnosed with recurrence and distant metastasis at 2 years after seeds implantation.

Age, histologic grade, T classification, cut margin status, and perineural invasion were not associated with OS on univariate analysis.

3.3 | Facial nerve function

Although 3 patients had facial nerve paralysis before surgery (Table 4), 37 (34.2%) patients suffered facial nerve injury during surgery. Most of the symptoms relieved within 6 months.

3.4 | Lymph node or distant metastasis and complications

No patient had confirmed N^+ disease before treatment, and no patient developed lymph node metastasis during follow-up. One patient was diagnosed with lung metastasis 2 years after seeds implantation.

No patients experienced acute toxicity beyond grade 4. Grade 0, grade 1, grade 2, and grade3 skin reaction were experienced by 23 (21.3%), 70 (64.8%), 12 (11.1%), and 3 (2.8%) patients, respectively. No patient had hypoacusis,

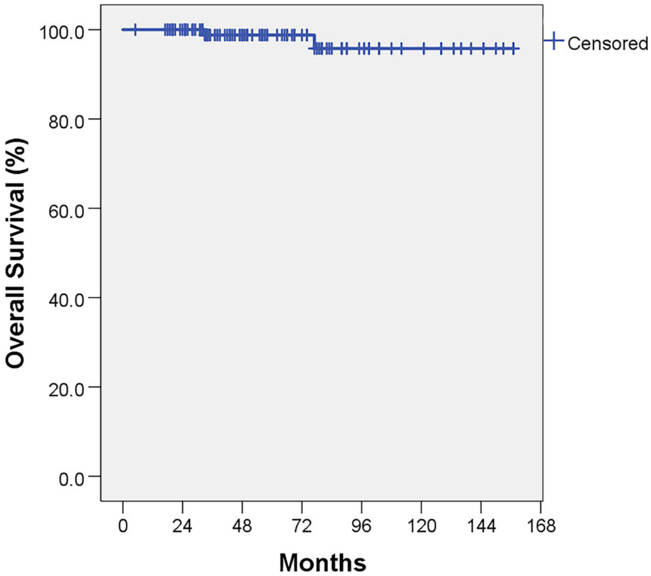

FIGURE 3 Kaplan-Meier curve for overall survival [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Facial nerve function according to the House-Brackmann grading system

Time	Grade				
	I	II	III	IV	V
Before surgery	105	-	3	-	-
Before brachytherapy	71	11	13	11	2
6 mo after brachytherapy	93	10	2	2	1

trismus, or oral mucositis during follow-up. All acute reactions resolved within 6 months. All patients were evaluated for late toxicities including pain, edema, xerostomia, hearing loss, trismus, osteoradionecrosis, and radiation-induced malignancies. One patient developed external auditory canal squamous cell carcinoma 1 year after ^{125}I seeds implantation. No other serious late toxicity was recorded.

4 | DISCUSSION

In an earlier study, the OS of patients with MEC of the parotid gland treated by surgery and postoperative radiation therapy were 85% and 79%, respectively at 3 and 5 years.[11] In other studies, the 5-year OS rates have ranged from 79.3% to 92.4% and the 10-year OS rates from 86.3% to 91.3% (Table 5), with the rate generally tending to be lower in patients with high-grade tumors. However, not all patients in these studies received postoperative radiation. As for LCR, Chen et al reported the 3- and 5-year LCRs of patients with MEC treated with surgery plus external radiotherapy to be 89% and 84%, respectively.[11] In another study on 113 patients with MEC, 61% of whom were treated with external radiotherapy, the 5- and 10-year LCRs were 77.8% and 75.5%, respectively.[12]

The OS and LCR of patients treated with surgery plus ^{125}I seeds brachytherapy are encouraging. In our study, OS at 5 and 10 years was 98.8% and 95.8%, respectively, and LCR was 91.4% at both 5 and 10 years. The result is consistent with Mao et al who reported 100% OS and LCR among 24 pediatric patients with MEC treated by surgery combined with postoperative ^{125}I seeds brachytherapy; the follow-up in their study was 5 to 13.4 years.[15] Zhang et al treated 12 patients with malignant parotid tumors (6 with MEC) with postoperative ^{125}I seeds implantation and reported no tumor recurrence in any patient after follow-up of 50 to 74 months.[16]

Our study included a large proportion of patients with low-risk disease characteristics, (eg, primary tumor and clinically node negative neck) and a large ratio of low-/intermediate-grade cases, which makes comparison with other studies difficult. Our results were consistent with that of Boahene et al[13] who reported OS at 5 and 10 years of 96.6% and 91.3%, respectively, and LCR at 5 and 10 years of 96.6% and 95.2%, respectively. They too selected patients with low risk (ie, primary tumor, 93% low- and intermediate-grade disease, and 97% clinically node negative neck). Only 8% of their patients received postoperative radiotherapy. However, the surgical treatments in their study were relatively aggressive. The rates of total parotidectomy, subtotal parotidectomy, and radical parotidectomy were 54%, 36%, and 10%, respectively. Moreover, 15 patients (16.7%) in their study underwent neck dissections. In our study, 84 patients (77.8%) received extensive local excision. This is why all of our patients were recommended postoperative adjuvant ^{125}I seed brachytherapy. Our results suggest that conservative resection combined with ^{125}I seed brachytherapy can provide excellent local control.

Neck dissection is recommended for patients with high-grade tumor and advanced stage. However, none of our patients received neck dissection. Several reports have shown that lymph node metastasis of MEC is associated with high-grade tumor. Aro et al studied 52 cases of major salivary gland tumor and reported lymph node metastasis in 50% of patients with high-grade MEC; however, they did not find tumor-positive lymph nodes in patients with low-grade MEC.[17] Nance et al investigated 20 patients who underwent neck dissection and reported that 12 of the 13 patients with confirmed N1 disease had high-grade tumors.[18] In our study, most patients had intermediate- and low-grade tumors. We therefore preferred to omit neck dissection and keep the patients under close follow-up.

On multivariate analysis, we found age $\geq$ 60 years and T4 disease to be independent predictors of local control failure. Earlier studies have shown high histological grade, advanced T classification, positive surgical margins, and older age to be prognostic factors.[10,12,14,17] In one study of

TABLE 5 Overall survival in patients with MEC of parotid reported in previous studies

Study	N	Research style	Tumors located in parotid (%)	Patients received PORT (%)	Overall survival (%)				
						Total	HG	IMG	LG
Chen et al[11]	61	Retrospective	100	100	5 y	79	52	80	84
Ghosh-Laskar et al[12]	113	Retrospective	100	61	5 y	92.4	73.3	94.1	96.8
					10 y	86.3	73.3	82.4	96.8
Boahene et al[13]	89	retrospective	100	8	5 y	96.6	-	-	-
					10 y	91.3	-	-	-
McHugh et al[14]	125	Retrospective	86.4	59.2	5 y	79.3	51	95.1	92.8

Abbreviations: HG, high grade; IMG, intermediate grade; LG, low grade; MEC, mucoepidermoid carcinoma; PORT, postoperative radiotherapy.

TABLE 6 Local control rate of MEC of parotid reported in previous studies

Study reference	N	Study design	Tumors located in parotid (%)	Patients receiving PORT (%)	Local control rate (%)				
						Total	HG	IMG	LG
Chen et al[11]	61	Retrospective	100	100	5 y	84	79	84	85
Ghosh-Laskar et al[12]	113	Retrospective	100	61	5 y	77.8	52.5	80.7	84.6
					10 y	75.5	35.0	80.7	84.6
Boahene et al[13]	89	Retrospective	100	8	5 y	96.6	-	-	-
					10 y	95.2	-	-	-

Abbreviations: HG, high grade; IMG, intermediate grade; LG, low grade; MEC, mucoepidermoid carcinoma; PORT, postoperative radiotherapy.

primary parotid gland carcinoma treated with ^{125}I seed brachytherapy alone, the survival rate of older patients (≥60 years) was significantly lower than that of younger patients (<60 years).[10] Cederblad et al[19]investigated 144 patients with parotid gland carcinoma and reported the 5-year survival rate in patients >65 years to be significantly lower than that of patients <65 years ($P < .01$). T classification has also been identified as a significant prognostic factor in MEC.[20] Chen et al found that the locoregional control at 5 years after treatment with surgery plus postoperative radiation was 88% for patients with T1-T3 tumors and 64% for those with T4 tumors ($P = .001$).[11] Their result was in line with that of our study, in which the 5-year LCR was 96.9% for T1-T3 tumors and 81.5% for T4 tumors.

High-grade MEC is usually associated with poor OS and LCR in literature (Tables 5 and 6). In some studies, histological grade has been shown to be a statistically significant predictor of DFS and OS.[14,21] Furthermore, patients with high-grade disease are usually advised adjuvant radiotherapy.[3] Chen et al investigated 24 patients with high-grade MEC, who received surgery and postoperative external radiation therapy.[11] The 5-year OS and LCR in their study was 52% and 79%, respectively. Patients in their cohort had high-risk characteristics, including lymph-node metastasis and distant metastasis, but they also received more aggressive surgery such as locoregional resection and neck dissection. Their results are similar to ours. In our study, the 5-year OS and LCR for high-grade MEC were 66.7% and 71.4%, respectively. These outcomes suggest that our approach is a feasible option for treatment of high-grade MEC—especially for patients with primary tumors and clinically node negative neck—but this needs to be confirmed on larger samples.

Radiation-induced toxicities were minor in our study. Although 97.2% of the patients experienced RTOG grade 0-2 acute skin reaction, all recovered completely. Only one patient (0.9%) developed external auditory canal squamous cell carcinoma. We believe that the low levels of toxicity in our cohort are related to the limited anatomic volumes that were treated. A large proportion of the toxicities seen with external beam radiotherapy is due to the inclusion of the neck in the treatment field. Thus, ^{125}I seed brachytherapy appears to be relatively safe for the treatment of parotid region tumors.

Our study has several important limitations. First, we did not have data on patients treated with surgery plus external radiotherapy during the same period; a comparison of the outcomes in the two cohorts would have more clearly demonstrated the benefits of brachytherapy. Second, toxicities were retrospectively determined by review of medical records; it is likely that not all complications were captured. Third, the histological grade of a small proportion of tumors was not known; this may have affected our results. Lastly, by excluding patients with clinically node negative necks we may have introduced a selection bias. Patients with relatively poor prognosis were under-represented in our sample, making comparison with patients treated by external beam radiotherapy difficult. We further sought to establish survival statistics for MEC of parotid gland treated by ^{125}I brachytherapy combined with surgery.

In conclusion, the combination of surgery and ^{125}I brachytherapy appears to be an effective and safe treatment option for MEC of parotid gland with clinically node negative neck, especially when the tumor is of low/intermediate grade. The OS and LCR are acceptable, and radiation-related complications are few. Older age and T4 disease are adverse prognostic indicators after treatment.

ORCID

Zhi-Yuan Wu https://orcid.org/0000-0001-6021-9344
Wen-Jie Wu https://orcid.org/0000-0001-5888-1208
Jian-Guo Zhang https://orcid.org/0000-0002-4793-3823

REFERENCES

1. Ho K, Lin H, Ann DK, Chu PG, Yun Y. An overview of the rare parotid gland cancer. *Head Neck Oncol*. 2011;3:40.
2. Rapidis AD, Givalos N, Gakiopoulou H, et al. Mucoepidermoid carcinoma of the salivary glands. Review of the literature and clinicopathological analysis of 18 patients. *Oral Oncol*. 2007;43:130-136.
3. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Head and Neck Cancers, version 2. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed May 8, 2017.
4. Pota M, Scalco E, Sanguineti G, et al. Early prediction of radiotherapy-induced parotid shrinkage and toxicity based on CT radiomics and fuzzy classification. *Artif Intell Med*. 2017;81:41-53.
5. Yang X, Tridandapani S, Beitler JJ, et al. Diagnostic accuracy of ultrasonic histogram features to evaluate radiation toxicity of the parotid glands: a clinical study of xerostomia following head-and-neck cancer radiotherapy. *Acad Radiol*. 2014;21:1304-1313.
6. Lambrecht M, Nevens D, Nuyts S. Intensity-modulated radiotherapy vs. parotid-sparing 3D conformal radiotherapy. Effect on outcome and toxicity in locally advanced head and neck cancer. *Strahlenther Onkol*. 2013;189:223-229.
7. Soleymanifard S, Toossi MT, Khosroabadi M, Noghreiyan AV, Shahidsales S, Tabrizi FV. Assessment of skin dose modification caused by application of immobilizing cast in head and neck radiotherapy. *Australas Phys Eng Sci Med*. 2014;37:535-540.
8. De Felice F, Thomas C, Patel V, et al. Osteoradionecrosis following treatment for head and neck cancer and the effect of radiotherapy dosimetry: the Guy's and St Thomas' head and neck cancer unit experience. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016;122:28-34.
9. Pham A, Arora S, Wernicke AG, et al. Cesium-131 brachytherapy in high risk and recurrent head and neck cancers: first report of long-term outcomes. *J Contemp Brachyther*. 2015;7:445-452.
10. Zhou C, Zhang J, Zhang JG, et al. Iodine-125 brachytherapy alone for advanced primary parotid gland carcinoma. *Int J Oral Maxillofac Surg*. 2017;038:1-7.
11. Chen AM, Lau VH, Farwell DG, Luu Q, Donald PJ. Mucoepidermoid carcinoma of the parotid gland treated by surgery and postoperative radiation therapy: clinicopathologic correlates of outcome. *Laryngoscope*. 2013;123:3049-3055.
12. Ghosh-Laskar S, Murthy V, Wadasadawala T, et al. Mucoepidermoid carcinoma of the parotid gland: factors affecting outcome. *Head Neck*. 2011;33:497-503.
13. Boahene DK, Olsen KD, Lewis JE, Pinheiro AD, Pankratz VS, Bagniewski SM. Mucoepidermoid carcinoma of the parotid gland: the Mayo clinic experience. *Arch Otolaryngol Head Neck Surg*. 2004;130:849-856.
14. McHugh CH, Roberts DB, El-Naggar AK, et al. Prognostic factors in mucoepidermoid carcinoma of the salivary glands. *Cancer*. 2012;118:3928-3936.
15. Mao MH, Zheng L, Wang XM, et al. Surgery combined with postoperative ^{125}I seed brachytherapy for the treatment of mucoepidermoid carcinoma of the parotid gland in pediatric patients. *Pediatr Blood Cancer*. 2016;00:1-7.
16. Zhang J, Zhang JG, Song TL, et al. ^{125}I seed implant brachytherapy-assisted surgery with preservation of the facial nerve for treatment of malignant parotid gland tumors. *Int J Oral Maxillofac Surg*. 2008;37:515-520.
17. Aro K, Leivo I, Mäkitie AA. Management and outcome of patients with mucoepidermoid carcinoma of major salivary gland origin: a single institution's 30-year experience. *Laryngoscope*. 2008;118:258-262.
18. Nance MA, Seethala RR, Wang Y, et al. Treatment and survival outcomes based on histologic grading in patients with head and neck mucoepidermoid carcinoma. *Cancer*. 2008;113:2082-2089.
19. Cederblad L, Johansson S, Enblad G, Engstrom M, Blomquist E. Cancer of the parotid gland; long-term follow-up. A single centre experience on recurrence and survival. *Acta Oncol*. 2009;48:549-555.
20. Ozawa H, Tomita T, Sakamoto K, et al. Mucoepidermoid carcinoma of the head and neck: clinical analysis of 43 patients. *Jpn J Clin Oncol*. 2008;38:414-418.
21. Byrd SA, Spector ME, Carey TE, Bradford CR, McHugh JB. Predictors of recurrence and survival for head and neck mucoepidermoid carcinoma. *Otolaryngol Head Neck Surg*. 2013;149:402-408.

How to cite this article: Wu Z-Y, Wu W-J, Zheng L, et al. Efficacy of combined surgery and ^{125}I seed brachytherapy for treatment of primary mucoepidermoid carcinoma of the parotid gland. *Head & Neck*. 2019;41:3219–3225. https://doi.org/10.1002/hed.25813