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BRACHYTHERAPY

Brachytherapy 15 (2016) 240–245

Physics

^{125}I interstitial brachytherapy for the treatment of myoepithelial carcinoma of the oral and maxillofacial region

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ABSTRACT

PURPOSE: This study evaluated the treatment of myoepithelial carcinoma (MC) of the oral and maxillofacial region with radioactive iodine (^{125}I) seed implantation.

METHODS AND MATERIALS: Twenty-seven patients with MC in the oral and maxillofacial region were treated with ^{125}I seed implantation between March 2006 and October 2012. Thirteen of the 27 patients (8/8 patients with primary disease and 5/19 patients with recurrent disease) were treated on an adjuvant setting after resections, and the other 14 patients were treated by brachytherapy after a recurrence precluding a surgical resection for salvage. The sites of the MC were the parotid for 18 patients, oral cavity for 2 patients, and base of skull for 7 patients. Recurrence-free survival (RFS), overall survival (OS) rates, and side effects were retrospectively reviewed.

RESULTS: Patients were followed for 6–105 months (median 37 months). The 3- and 5-year RFS rates were 51.9% and 46.1%, respectively. The 3- and 5-year OS rates were 68.6% and 51.5%, respectively. The OS and RFS were significantly better among the 8 patients treated upfront in comparison with the 19 patients treated for salvage at relapse. The OS was worst for the 7 patients with base of skull region disease. No severe complications were observed during followup.

CONCLUSIONS: This study showed ^{125}I brachytherapy is a feasible and effective modality for the treatment of MC. These findings should be interpreted cautiously due to the small number of patients and the relatively short followup.

Keywords: Myoepithelial carcinoma; Salivary gland tumor; Oral and maxillofacial; Iodine-125; Brachytherapy

Introduction

Myoepithelial carcinoma (MC) is a relatively rare tumor type that accounts for approximately 0.4–0.6% of all salivary gland tumors and 1.2–1.5% of salivary gland carcinomas (1, 2). Because of its rarity, the clinical and biological behavior of MC is not well characterized, although some researchers believe that MC should be classified as a high-grade malignancy (3, 4). The main treatment for MC is complete surgical excision with free margins, with or without nodal dissection (4, 5). Adjuvant radiotherapy does not seem to significantly improve prognosis (5); however, the value of chemotherapy has not yet been fully established in patients with MC.

Radioactive iodine (^{125}I) seed brachytherapy has emerged as an attractive option for improving local control (LC) in patients with malignant salivary gland tumors, as this technique can irradiate a limited area by delivering high doses of radiation directly to the tumor, while simultaneously sparing adjacent normal tissues (6–8). The objective of this retrospective report was to assess the outcome of a cohort of patients with MC of the oral and maxillofacial region who received ^{125}I seed implantation.

Methods and materials

Patients

Twenty-seven patients (15 males and 12 females) aged between 6 and 74 years who were treated between March 2006 and October 2012 were included in this retrospective study. MC was pathologically diagnosed in all patients before ^{125}I seed implant brachytherapy. Eight patients (29.6%) had primary MC; the other 19 patients (70.4%) had recurrent disease. No patients had neck lymph node

Received 10 August 2015; received in revised form 12 November 2015; accepted 12 November 2015.

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1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2015.11.002

metastases or distant metastases before ^{125}I seed implantation. The clinicopathological features of the patients are summarized in Table 1. The treatment plans for all cases were approved by the Ethical Committee of Peking University School and Hospital of Stomatology.

Treatment

Thirteen of the 27 patients had a tumor size less than 4 cm (8/8 patients with primary disease and 5/19 patients with recurrent disease) and underwent conservative surgical resection followed by ^{125}I seed implantation; the other 14/19 patients with recurrent disease had a tumor size greater than 4 cm and underwent biopsy without tumor resection followed by ^{125}I seed implantation.

Seed implantation treatment planning

The brachytherapy treatment plan for all patients was designed using a computerized treatment planning system (RT-RSI; Beijing Atom and High Technique Industries Inc., Beijing, China) based on computerized tomography (CT) images. The planning target volume was defined as a 10–15 mm extension of the preoperative gross tumor volume and the postoperative bed on the basis of CT scans in combination with imaging of the target area by intraoperative photography. The ^{125}I seed activity was 0.7–0.8 mCi. The matched peripheral dose (MPD) was 90–120 Gy and was adjusted according to previous treatments and adjacent structures. The dose was prescribed as the MPD encompassing the planning target volume.

Table 1
Clinicopathological features of the 27 patients with myoepithelial carcinoma

Characteristic	Number
Sex (*n*) (%)	
Male	15 (55.6)
Female	12 (44.4)
Age (y)	
Median	46
Range	6–74
Tumor size (cm) (%)	
2–4	13 (48.1)
4–6	7 (25.9)
≥6	7 (25.9)
Tumor site (%)	
Parotid gland	18 (66.7)
Primary tumor	6 (22.2)
Recurrent tumor	12 (44.4)
Skull base region (all recurrent)	7 (25.9)
Minor salivary glands of oral cavity (both primary)	2 (7.4)
Prior treatment (%)	
None	8 (29.6)
Surgery	14 (51.9)
Surgery and radiotherapy	5 (18.5)
Previous surgeries (%)	
One	9 (33.3)
Two	5 (18.5)
Three or more	5 (18.5)
Previous external beam radiotherapy (%)	
Once	4 (14.8)
Twice	1 (3.7)
Cumulative dose of external beam radiotherapy (%)	
50 ~ 70 Gy	4 (14.8)
>70 Gy	1 (3.7)
Median (Gy)	60

^{125}I seed implantation

Implantation of radioactive seeds was performed approximately 2 weeks postoperatively in all patients after wound healing had been achieved. The distribution of ^{125}I seeds (Beijing Atom and High Technique Industries Inc; Model 6711; $t_{1/2}$, 59.4 days; energy level, 27.4–31.4 KeV) was determined from CT scans in combination with the target area as recorded by intraoperative photographs. Based on the implantation scheme, 20–150 ^{125}I seeds (mean, 73) were implanted (Table 2). The space between seeds (center to center) was maintained at 10 mm. Evaluation of the postplan was routinely performed for

Table 2
Summary of treatment and outcomes for the 27 patients with myoepithelial carcinoma

Treatment/outcome	Number
Treatment type (%)	
Surgery plus ^{125}I seed implantation	13 (48.1)
Primary tumor	8 (29.6)
Parotid gland	6 (22.2)
Minor salivary	2 (7.4)
Recurrent tumor	5 (18.5)
Parotid gland	2 (7.4)
Skull base	3 (11.1)
^{125}I seed implantation alone	14 (51.9)
Parotid gland	10 (37.0)
Skull base	4 (14.8)
^{125}I seed activity (mCi)	0.7–0.8
Number of ^{125}I seeds implanted	
Median	73
Range	20–150
Matched peripheral dose of ^{125}I seed implantation (Gy)	
For patients without previous radiotherapy	120
For patients with previous radiotherapy	90
Followup (mo)	
Median	37
Range	6–105
Status (%)	
No evidence of disease	13 (48.1)
Alive with disease	3 (11.1)
Related death	11 (40.7)
Local progression-free time (mo)	
Median	23
Range	1–105
Toxicities after ^{125}I seed implantation (%)	
Skin pigmentation	5 (18.5)
Skin ulceration	1 (3.7)
Hearing loss	7 (25.9)
Trismus	3 (11.1)
Salvage treatment after relapse	
Surgery (neck dissection)	3
Reimplantation	5
Cause of death	
Local recurrence	5
Distant metastasis	6

each patient immediately after seed implantation to confirm the seed location and dose distribution (Fig. 1).

Followup and assessment of toxicity

All patients underwent a followup assessment every 2 months or earlier if new clinical signs or symptoms appeared, including a complete history and physical examination and CT scan. LC was defined as lack of tumor recurrence either in or adjacent to the implanted volume on physical and radiographic examination. A computerized treatment planning system was used to analyze the dose at the target area and calculate the dose remaining. Toxicities were graded according to the Radiation Therapy Oncology Group grading system and the National Cancer Institute common toxicity criteria (version 3.0) (9).

Statistical methods

Descriptive statistics were calculated for the patient and tumor characteristics, treatment features, and toxicities. LC was defined as a lack of tumor progression either in or adjacent to the implanted area. Overall survival (OS) was calculated from the date of seed implantation to the date of last followup or death. Recurrence-free survival (RFS) was calculated from the date of seed implantation to the time of locoregional recurrence, distant metastasis, or death. Time was calculated from the date of seed implantation to the event of interest. Statistical analysis was performed using Statistical Package for the Social Sciences (version 14; SPSS 2006 Inc., Chicago, IL). The Kaplan–Meier method was used to calculate survival estimates and times to progression; differences in survival estimates were tested using the log-rank test. Statistical significance was considered at $p < 0.05$.

Results

Followup, OS, and RFS

Median followup was 37 months (range, 6–105 months). At the end of followup, 13/27 (48.1%) patients were alive without disease, 3 (11.1%) were alive with disease, and 11 (40.7%) patients had died of disease.

At the time of analysis, the 3- and 5-year OS rates were 68.6% and 51.5%, respectively (Fig. 2). The 3- and 5-year actuarial survival rates were also 68.6% and 51.5%, respectively. Tumor size and previous external beam radiotherapy were not statistically significant factors for OS ($p = 0.179$ and $p = 0.625$, respectively). Patients with primary disease had a 5-year OS rate of 100%, which was significantly higher than the 5-year OS rate of 35% observed for patients with recurrent disease ($p = 0.016$). Tumor site was also statistically significant for OS; patients with salivary gland tumors had a 5-year OS rate of 67.4%, which was significantly higher than that of patients with tumors in the skull base region with a 5-year OS of 15.6% ($p = 0.017$).

The 3-year RFS for all patients was 51.9%, and the 5-year RFS was 46.1% (Fig. 3). Patients with primary disease ($n = 8$) had a 5-year RFS rate of 100%, whereas patients with recurrent disease ($n = 17$) had an RFS rate of 25.3%; this difference was statistically significant ($p = 0.002$).

Recurrence and metastasis

There were no relapses among the 8 patients treated after resection at the initial diagnosis. Five of the 19 patients with recurrent tumor treated with surgery plus seed implantation suffered local recurrence; the mean time to recurrence was 9 months after seed implantation. Three of 19 patients with recurrent tumor treated with seed implantation developed cervical metastasis 3, 6, and 53 months after the seed implantation. Six of 19 patients with recurrent tumor treated with seed implantation developed distant metastasis to the lung and brain; the mean time to distant metastasis was 17 months after seed implantation.

Salvage treatment after relapse

Three of the 6 patients with cervical metastasis underwent neck dissection; 4 of the 5 patients with local recurrence after seed implantation underwent seed reimplantation. None of the 6 patients with distant metastasis underwent further treatment.

Complications

Five of the 27 (18.5%) patients developed local skin pigmentation, 1 (3.7%) patient suffered local skin ulceration, 3 (11.1%) patients with a parotid tumor suffered limited ability to open their mouth, and 7 (25.9%) patients (including 3 patients who previously received external beam radiotherapy) suffered ipsilateral hearing loss.

Discussion

MC, first described by Stromeyer *et al.* (10) in 1975, is a rare malignant salivary gland neoplasm that was included as a distinct entity in the second edition of the World Health Organization's classification of salivary gland tumors (11). MC represents only 0.4–0.6% of all salivary gland tumors and undergoes exclusive myoepithelial differentiation and a pattern of infiltrative growth into the adjacent tissues (12). Owing to its rarity and the lack of comprehensive reports of large case series, the clinical profile and behavior of MC are not well characterized and our knowledge of the management of this tumor type is deficient. No clear guidelines exist for the management of MC. The use of radiation therapy in combination with surgery has improved locoregional control and the rate of survival for patients with major salivary gland carcinoma (13–15); however, chemotherapy does not seem to significantly improve the prognosis of patients with MC (16, 17).

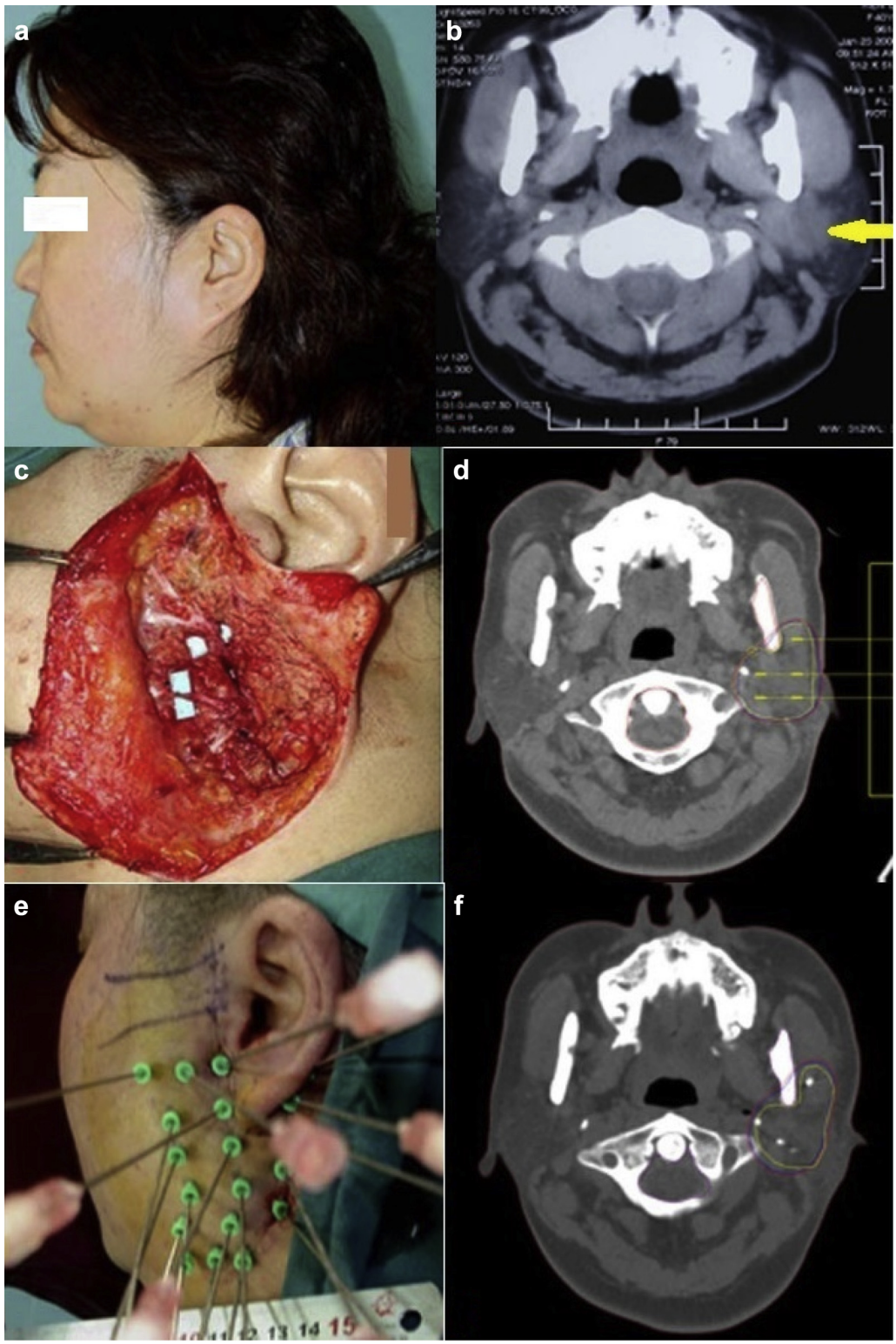

Fig. 1. (a) The profile of 1 patient before the treatment; (b) CT scan showing the tumor in the parotid gland (yellow arrow); (c) 1 patient had a reconstruction of the facial nerve after tumor resection during surgery; (d) the preplanning of seed implantation after surgery; (e) seeds implantation after surgery; (f) a typical transverse slice showing the distributions of the ^{125}I seeds and isodose curves of the patient who underwent the facial nerve reconstruction. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Until recently, MC was considered a low-grade carcinoma with a low tendency for local recurrence and metastasis (17, 18). However, one study reported that MC was clinically aggressive, with 47% of patients developing metastasis, and a mortality rate of 29% after a mean followup of 32 months (2). Another study reported a

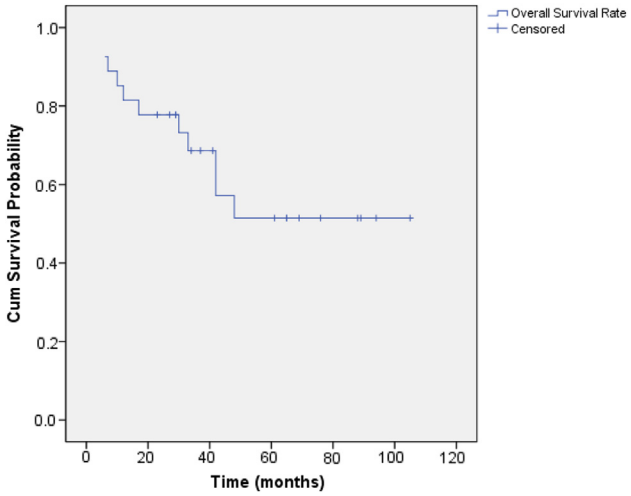

Fig. 2. The overall survival for 27 patients with MC after ^{125}I seeds implantation. MC = myoepithelial carcinoma.

recurrence rate of 50%, metastasis to the lung and the scalp, and a rate of metastasis of 40% (19). Recurrence and metastasis are more common in children with MC than in adults with MC, even when negative surgical excision margins are achieved (20). Therefore, Yu *et al.* (4) suggested MC of the salivary gland should be classified as a high-grade malignancy. The rates of recurrence and metastasis in this study were lower than those of the aforementioned reports; the 3-year and 5-year RFS rates were 51.9% and 46.1%, respectively. Patients with primary disease (n = 8) had a 5-year RFS rate of 100%, whereas those with recurrent disease (n = 17) had a 5-year RFS rate of 25.3%, and the 3- and 5-year OS rates were 68.6% and 51.5%, respectively. As most of the patients in this study had recurrent or advanced disease, ^{125}I seed implantation appears to lead to a good treatment outcome in patients with MC.

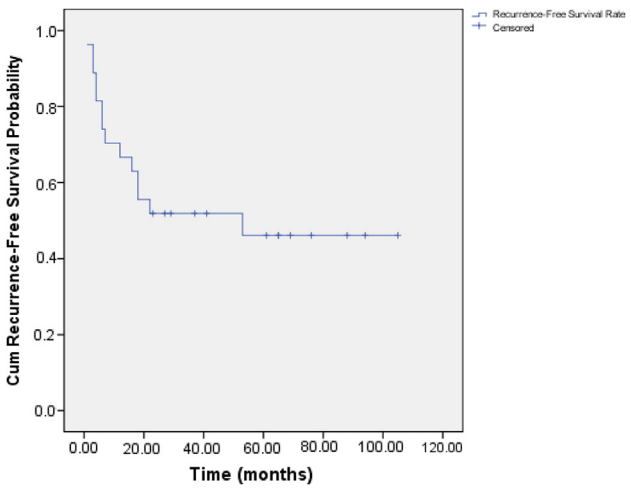

Fig. 3. The recurrence-free survival rate of the 27 patients with MC after the implantation of ^{125}I seeds. MC = myoepithelial carcinoma.

Because of its rarity, the clinical parameters and pathological factors which determine the prognosis of patients with MC are not well established, although cellular pleomorphism, p53 overexpression, and high levels of cell proliferation may correlate with a poor clinical outcome (5, 16). In our series, patients with adjuvant brachytherapy upfront experienced a better survival than patients having brachytherapy at time of relapse. The relapse-free survival was worst in patients having base of skull disease but did not differ by tumor size, keeping in mind the limitations from a small number of patients.

Radiotherapy-induced serious complications in patients with head and neck cancer include hearing loss, trismus, and osteonecrosis, along with other toxicities. In this cohort, ^{125}I seed implantation did not result in any other additional complications. The total radioactive dose received may be the major factor determining the occurrence of hearing loss. The rate of hearing loss after two-dimensional radiotherapy techniques ranges from 36% to 43% (21, 22). In this study, the incidence of hearing loss was 7/27 (25.9%). The low incidence of hearing loss may not reflect the true risk as many patients did not survive long enough to present this impairment. Additionally, the patients who suffered hearing loss had large tumors which required implantation of a larger number of seeds, and most of these patients had previously received external beam radiotherapy. In general, the complications observed in this study were acceptable, probably due to the use of lower activity seeds, application of the MPD, and the characteristics of the ^{125}I seeds, and seed implantation did not seem to increase the risk of further complications.

In this study, we present our experience of treating MC by ^{125}I seed implantation alone. Considering the advanced disease stage of the patients in this series, the RFS and OS rates are encouraging and suggest that ^{125}I brachytherapy is a feasible and effective modality for the treatment of MC. In addition, patients with primary disease and salivary gland tumors had significantly higher RFS and survival rates than patients at relapse and patients with disease in the base of skull region.

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