Int J Clin Exp Med 2017;10(1):1561-1566
www.ijcem.com /ISSN:1940-5901/IJCEM0026254

Original Article

Clinical characteristics, therapy and prognosis of parotid acinar cell carcinoma

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Received February 19, 2016; Accepted May 15, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: Objective: This study was aimed to investigate the clinical characteristics, therapy and prognosis of parotid acinar cell carcinoma (ACC). Methods: We retrospectively reviewed 72 patients with parotid ACC who were treated in Zhejiang Cancer Hospital from January 1999 to December 2011. Results: There were 35 males and 37 females with the median age of 40 years. In addition, 34 patients received initial therapy in our hospital and 38 patients received further treatment after surgery in other hospitals. Of 38 patients undergoing non-initial therapy, 6 patients suffered recurrence after surgery in other hospitals and 32 patients needed extended resection after only enucleation in other hospitals. Fifty-two patients underwent superficial parotidectomy and 16 patients underwent total parotidectomy. Five patients had surgery and postoperative radiotherapy in our hospital. Four patients who developed local recurrence refused reoperation and then received radiation therapy instead of surgery. Chemotherapy (cisplatin) was performed in 1 patient with lung and pleura metastasis. Sixty-six patients were available for follow-up with a median time of 24 months (range: 3-192 months). The post-operative 3-year and 5-year survival rate were 95.5% and 90.9%, respectively. Conclusion: The initial surgery is crucial for the prognosis of parotid ACC. Non-standard enuclration may cause the implantation of tumor cells, leading to post-operative local recurrence. Parotid ACC patients with lymph node metastasis have high risk for post-operative recurrence. Surgery with superficial or total parotidectomy and postoperative radiotherapy could achieve the satisfying disease control.

Keywords: Acinic cell carcinoma, parotid gland, prognosis, parotidectomy

Introduction

Acinar cell carcinoma (ACC) is a relatively rare malignancy of the salivary gland and accouts for 6-8% of salivary gland tumors and 17% of parotid malignancies [1]. ACC is often found in parotid (80-90%) and occasionally identified in submandibular gland and minor salivary gland [2, 3]. Parotid ACC is usually initially presented with infra-auricular mass, pain, or facial palsy. Although ACC is a low-grade malignancy and has slow progression, the non-standard treatment may increase the risk of recurrence due to incomplete resection. The local recurrence rate ranged from 20 to 50%; cervical lymph node metastasis ranged from 3 to 9%; distant metastasis ranged from 10 to 20% and it may metastasize to the liver, lung, stomach and brain [4]. In the present study, 72 patients with parotid ACC who received treatment in our department from 1999 to 2011 were recruited for analysis.

Materials and methods

A total of 72 patients pathologically diagnosed with parotid ACC were admitted in this study and all patients were treated in the Department of Head and Neck Surgery of Zhejiang Cancer Hospital from January 1999 to December 2011. Of these patients, 68 received surgical intervention, and 4 patients received non-surgery treatment due to recurrence after surgical intervention in other hospitals. Pathological examination in our hospital confirmed the diagnosis of ACC in these 4 patients who refused surgical intervention and they finally received radiotherapy in our hospital. Following information was recorded: age, gender, presenting symptoms, results of fine-needle aspiration cytology (FNAC), findings from pre-operative ultrasonography and radiography, methods of therapy, complications, survival and recurrences. The pathological staging was performed according to the American Joint Committee

on Cancer (AJCC) criteria (7th). Patients with advanced ACC, positive surgical margin or lymph node metastasis received postoperative radiotherapy. For patients with concomitant distant metastasis, radiotherapy and chemotherapy was performed as palliative treatment. This study was approved by the Ethics Committee of Zhejiang Cancer Hospital.

SPSS version 21.0 software (SPSS, Inc., Chicago, IL) was employed for the statistical analysis. Univariate analysis by the Pearson's chi-square test or Fisher exact test was performed to investigate the relationship between clinical parameters and metastasis or recurrence. A value of $P<0.05$ was considered statistically significant.

Results

Clinical information

A total of 72 patients were pathologically diagnosed with parotid ACC in the present study. There were 35 males and 37 females with the ratio of male to female of 1:1.06. The median age was 40 years (range: 17-77 years). Most patients presented with painless mass in parotid with slow growth at initial diagnosis. Mass in pre-auriculararea and in infra-auriculararea was found in 24 and 48 patients, respectively (ratio: 1:2). The median size of the mass was 2.0 cm (range: 0.5-8.0 cm). Moreover, 5 patients suffered facial paralysis with a median duration of 3 years (ranged from 1 month to 15 years). Of 72 patients, only 34 were initially treated in our hospital. The remaining 38 patients received further treatment in our hospital due to recurrence (n=6) or incomplete resection (n=32) after initial surgery in other institutions.

Treatment

In our series, 68 patients received surgical intervention including superficial parotidectomy (n=52), total parotidectomy (n=12, resection of residual parotid after initial surgery in 4 patients), total parotidectomy + partial temporal bone resection (n=1), total parotidectomy + partial temporal bone resection + repair with pectoralis major flap (n=1), total parotidectomy + partial mandible resection (n=1) and supraomohyoid lymphadenectomy due to recurrence at neck lymph nodes (n=1). In addition, 25 patients received elective neck dissection, including peri-parotid lymphadenectomy (n=11) and supraomohyoid lymphadenectomy (n=14).

Facial nerve dissection and preservation were accomplished during parotid surgery. However, resection of facial nerve was performed due to involvement of ACC in the trunk (n=4) and inferior branch (n=3), without nerve anastomosis during surgery. These patients experienced the symptom of facial paralysis. In patients with nerve dissection and preservation, the facial paralysis was transient and recovered after surgery.

Of patients initially treated with surgery in our hospital, 5 received postoperative radiotherapy with a median dose of 58.8 Gray. Four patients who suffered recurrence and refused surgery have received radical radiotherapy at the median dose of 55 Gy (range: 52-60 Gy). Chemotherapy (cisplatin) was performed in 1 patient with lung and pleura metastasis.

Histopathology

Patients undergoing surgical intervention also received pathological examination which confirmed the diagnosis of ACC. However, ACC was not further classified for various subtypes. According to the AJCC criteria (7th edition), the T classification was as follows: T1: 45.8% (n=33); T2: 30.6% (n=22); T3: 4.2% (n=3) and T4: 4.2% (n=3). Moreover, 5 (8.2%) patients had cervical lymph node involvement (N1), and the T stage was not available to assess in 11 patients who received initial surgery in other hospitals. The tumor stage distributions of the patients were 44%, 26%, 10%, and 4% for stages I, II, III, and IV, respectively.

Postoperative complications

Salivary fistula occurred in 10 patients after surgery, and salivary fistula was cured by pressure dressing in 8 patients and by radiotherapy (12 Gray) in 2 patients. Seven patients had facial paralysis due to resection the facial nerve involved by tumor.

Follow up

A total of 66 patients were available for follow up (91.7%), and the median time of follow-up was 24 months (range: 3-192 months). The

Table 1. Relationship between clinical parameters and metastasis or recurrence

Clinical parameters	No. of patients with metastasis or recurrence	P
Gender		0.561
Male	5/29 (17.2%)	
Female	7/37 (18.9%)	
Tumor Site		0.525
Pre-auriculararea	4/20 (20.0%)	
Infra-auriculararea	8/46 (17.4%)	
First surgery		0.008
Yes	2/34 (5.9%)	
No	10/32 (31.2%)	
Reason for a further surgery		0.008
Enucleation only at first surgery	7/32 (21.9%)	
Recurrence after treatment	5/6 (83.3%)	
Surgical options		0.577
Superficial parotidetomy	6/45 (13.3%)	
Total parotidetomy	2/15 (13.3%)	
T stage		0.588
T1-2	10/55 (18.2%)	
T3-4	2/6 (33.3%)	
N stage		0.048
N0	9/56 (16.1%)	
N1	3/5 (60.0%)	

postoperative 3-year and 5-year survival rate were 95.5% and 90.9%, respectively. Of 66 patients receiving surgery in our hospital, 12 developed recurrence (18.2%) including 7 cases with local recurrence and 5 cases with metastasis to cervical lymph nodes. Two patients with advanced ACC died of diseases related with tumor after treatment (1 died of liver metastasis, 1 died of lung metastasis). One patient died of unrelated illness with no evidence of tumor disease during the study period.

In the present study, we also investigated whether the initial surgery was associated with the recurrence and metastasis of ACC. Results showed the incidence of recurrence and metastasis in patients with complete resection of tumor at initial surgery was significantly lower than that in patients who needed a further surgery after enucleation only or a reoperation due to post-operative recurrence ($P<0.05$, **Table 1**). This suggested that incomplete enucleation may cause implantation metastasis, leading to local recurrence after surgery. In respect of the location of ACC, there was no significant difference in the incidence of recurrence and metastasis between patients with ACC in pre-auriculararea and those with ACC in infra-auriculararea. The tumor in pre-auriculararea was more closed to facial nerve than in infra-auriculararea. So for patients with ACC in pre-auriculararea, the manipulation of facial nerve during surgery is difficult, which may prolong the time of surgery and lead to incomplete resection of the mass, resulting in the increased risk of recurrence and metastasis. The risk of recurrence and metastasis significantly increased in patients with positive lymph node at initial surgery ($P<0.05$, **Table 1**). The rate of recurrence and metastasis of ACC was not significantly associated with gender, tumor size and method of surgery.

Discussion

Parotid ACC is a rare malignancy of the salivary gland and typically presents with a slowly enlarging painless mass in the parotid region. Pain (7.5%) and facial nerve palsy (3.0%) were seldom reported [5]. Although parotid ACC has a low-grade behavior, it tends to grow aggressively and has high potential for recurrence, metastasis and even death. Females were more frequently diagnosed with ACC than males [4, 5]. However, our sample showed that the incidence of parotid ACC was comparable between males and females (1:1.06). Our study series had a median age of 40 years, with a range of 17-77 years. It was younger than that seen in previous study, where suggested that ACC frequently occurred in the fifth and sixth decades of life [6]. In addition, our findings showed parotid ACC was more likely to occur in the superficial lobe of the parotid and had a slow course of disease, which was consistent with previously reported [7]. Moreover, the ratio of patients with parotid ACC in pre-auriculararea to those with parotid ACC in infer-auriculararea was 1:2 (24:48), which also supports above findings. However, the location of parotid ACC had no influence on the metastasis and recurrence of ACC.

The histological origin of ACC is still controversial. Abram *et al.* used alkaline particles in the cytoplasm of serous acini as a morphological

marker of ACC, and proposed that ACC cells were derived from intercalated duct cells [8]. In recent years, studies on ultrastructures also supported that ACC was derived from intercalated duct cells or non-specific reserve pluripotent cells which were localized between duct and intercalated duct in normal acinar tissues [8]. The pathological features of ACC are diverse and mainly divided into 6 types: solid, microcyst, papillary cystic, ductal, follicular and undifferentiated type [9]. Spiro *et al.* reported that patients with ACC of microcyst type had a poor prognosis [5], but similar finding was not reported in other studies. In our study, ACC was not further classified for pathological subtype.

Although ACC was a low-grade malignancy, it has a significant tendency to recur, to produce metastases (cervical lymph nodes and lungs), and may have an aggressive evolution [10]. It has been reported that the incidence of recurrence, lymph node metastasis and distant metastasis is 20-50%, 3-9% and 10-20%, respectively, and ACC may metastasize to the lung, stomach and brain [4]. In the present study, results showed the rate of local recurrence, lymph node metastasis and distant metastasis was 10.6% (7/66), 7.6% (5/66) and 3.0% (2/66), respectively. The site of distant metastasis was lung (1 case) and liver (1 case) and the local recurrence occurred more frequently than lymph node metastasis and distant metastasis. Treatment failure more likely occurred at the primary site rather than the neck or distant organs. Thus, to decrease the local recurrence of ACC is crucial for the treatment of parotid ACC [4, 7, 11, 12].

In general, the management of ACC consists of complete surgical removal of the tumor, by superficial or total parotidectomy. An adequate superficial parotidectomy with sparing of the facial nerve could be quite effective in removing the tumor in the superficial lobe. Conversely, a total parotidectomy appears to be necessary for recurrent tumors or primary tumors located in the deep lobe [7]. Facial nerve preservation should be attempted for each patient. However, a total parotidectomy with removal of facial nerve may be necessary for patients with preexisting facial nerve palsy indicating tumor involvement already, or with the presence of macroscopic invasion of the nerve during surgery. Nerve grafting after total nerve resection is recommended for a better quality of life [7, 13]. As the invasion of skin, bone or surrounding soft tissue, a comprehensive resection and reconstruction as a part of surgery was necessary. In our study, one patient had skin involvement of parotid ACC, and received reconstruction with pectoralis major flap after resection of the tumor and involved skin.

The role of neck dissection in ACC remains controversial. Therapeutic neck dissection is necessary for patients with clinically obvious cervical nodal involvement. Stennart *et al.* reported a high rate of node-positive disease (47.4%) in ACC patients, with a 44% rate of occult metastasis was found [14]. Therefore, several authors recommended routine elective neck dissection for patients with clinically negative neck, although the survival benefit was not shown [14, 15]. However, the neck lymph node metastatic rate in ACC was 2.86% with N1 and 5.71% with N2b lesions in the study by Gomez [16]. In our study, the incidence of metastasis to the neck lymph nodes was only 7.6% (5/66). The role of elective neck dissection was not evident in our study or in other studies. Thus we do not suggest prophylactic resection of neck lymph nodes for patients with the clinically negative neck. However, neck dissection is recommended in patients with suspicious of cervical nodal involvement [17].

The role of radiotherapy in acinic cell salivary tumors also remains controversial. Radiotherapy is not favoured as a primary mode of treatment, as ACC has generally been regarded as not radiosensitive [14]. However, fast neutron beam radiation, has shown promising and effective results, especially for cases of inoperable or unresectable tumors, incomplete tumor removal, residual disease, and recurrences. That means that it is a viable alternative to surgery, not just a postoperative adjunct [18]. Others have suggested that postoperative radiation therapy was indicated for ACC in cases of (1) recurrent tumors, (2) equivocal or positive margins or tumor spillage, (3) tumors adjacent to the facial nerve, (4) deep-lobe involvement, (5) lymph node metastases, (6) extraparotid extensions, and (7) large tumors (>4 cm) [19]. Radiation therapy for parotid may cause serious complications, including secondary malignancy, bone necrosis, brainstem necrosis, cerebellar necrosis, fistula formation, hearing loss,

or xerostomia [20-23]. The balance between toxicity and survival benefit should be emphasized during postoperative radiotherapy for parotid ACC.

Chemotherapy for ACC has largely been considered ineffective, except for pain-relief or partial responses [1]. There has been no prospective randomized study to evaluate the effectiveness of chemotherapy for parotid ACC. Lin *et al.* reported that concomitant chemoradiotherapy (CCRT) with cisplatin-based agents was administered to patients with positive resection margins [24]. Kim *et al.* also reported that the ACC patient with a concomitant adenocarcinoma received chemotherapy with 5-fluorouracil and eisplatinum in addition to radiation therapy [7]. It remains further investigation to evaluate the use of chemotherapy for malignant salivary gland tumors.

Conclusions

Parotid ACC is a rare malignant tumor with slow-growing nature, less aggressive behavior, and good prognosis. Our findings showed that the recurrence and metastasis of ACC are not associated with the gender, tumor location and tumor size, but related to the initial surgery and status of lymph node metastasis. These results indicate that initial treatment is essential for the prognosis of parotid ACC. Incomplete resection or enucleation will increase the risk of local recurrence. The radical neck dissection is necessary to patients with definitive or suspicious involvement of cervical lymph nodes. Some patients may benefit from adjuvant radiation therapy.

Disclosure of conflict of interest

None.

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