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Original Article

The Study on Prognosis in Patients with Adenoid Cystic Carcinoma of the External Auditory Canal

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BACKGROUND: Adenoid cystic carcinoma of the external auditory canal is a rare primary malignancy, and surgery is the primary management strategy. This study aims to optimize management strategies and improve prognosis of adenoid cystic carcinoma of the external auditory canal.

METHODS: Seventeen patients with adenoid cystic carcinoma of external auditory canal who had been admitted to a single institution from January 2008 to March 2019 were recruited and retrospectively reviewed. Among patients with T1 tumors, 2 underwent local external auditory canal resection, 1 received lateral temporal bone resection + superficial parotidectomy. Among patients with T2 tumors, all 5 patients underwent lateral temporal bone resection + superficial parotidectomy. Among patients with T3 tumors, 3 underwent subtotal temporal bone resection + superficial parotidectomy, 2 underwent subtotal temporal bone resection + superficial parotidectomy + radiotherapy, and 1 underwent extended temporal bone resection + superficial parotidectomy + radiotherapy. Among patients with T4 tumors, 2 underwent subtotal temporal bone resection + superficial parotidectomy and 1 underwent extended temporal bone resection + total parotidectomy + radiotherapy.

RESULTS: The common manifestations included otalgia (82.4%), hearing loss (23.5%), external auditory canal mass (23.5%), otorrhea (17.6%), and aural fullness (5.9%). In the study, 5/17 (29.4%) patients had been misdiagnosed preoperatively, 5/17 (29.4%) patients revealed local recurrence, and 3/17 patients (17.6%) were identified with distant metastasis postoperatively. The 3- and 5-year overall survival rates were 88.2% and 82.3%, respectively. There was no significant difference in overall survival ($P = .746$) and disease-free survival ($P = .933$) between patients receiving different surgical approaches. Three out of 17 patients (17.6%) died of T2, T3, and T4 diseases, respectively.

CONCLUSION: Otalgia is the most common manifestation of adenoid cystic carcinoma of the external auditory canal, and misdiagnosis is frequently encountered. Surgery is the preferred therapy, and local resection is associated with relapse, lateral temporal bone resection is strongly recommended in patients with early-stage tumor. Regular follow-up should be routinely conducted postoperatively to early identify local recurrence.

KEYWORDS: ACC, EAC, surgery, prognosis

INTRODUCTION

Adenoid cystic carcinoma (ACC) of the external auditory canal (EAC) is a rare primary malignancy, which is noted for its indolent course and high recurrence risk. Primary cancers in the EAC are not common, and 80% of carcinomas in the EAC are squamous cell carcinomas, while ACC in the EAC accounts for 5%-20%.[1,2] Adenoid cystic carcinoma of the EAC grows slowly and usually has a history of up to several years. Perineural invasion is common, while lymph node metastasis is rare. It is characteristically susceptible to local recurrence and distant metastasis, and pulmonary metastasis was frequently identified in patients with ACC in the EAC. In addition to local image study of ACC in the EAC, the patients should be reviewed carefully to exclude pulmonary, brain and liver metastasis preoperatively, even during postoperative follow-up.

The clinical manifestations of ACC in the EAC commonly include otalgia, hearing loss, otorrhea, and mass in the EAC. Adenoid cystic carcinoma of the EAC often has intermittent ear pain in the early stage and can be converted into persistent severe pain in the late stage and spread to the temporal part and the periauricular area. Tumor penetration into the EAC can block the EAC and

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consequently causes conductive hearing loss. The course of the disease is longer and can be accompanied by secondary infection and otorrhea; in this case, it is easy to be misdiagnosed as external otitis or otitis media.[2]

The tumor size, location, and involved surrounding anatomic structures are mainly determined in terms of imaging findings. Temporal bone computed tomography (CT) is excellent in defining bony erosion and magnetic resonance imaging (MRI) with enhancement is better in displaying the lesions of soft tissue involvement. Even though in early stage of ACC in the EAC, temporal bone CT scan might show no temporal bone erosion, temporal bone MRI is still mandatory and it can display possible soft tissue involvement.

Surgery is the primary management strategy of ACC in the EAC; adjuvant radiotherapy (RT) was applied in patients with advanced stage tumor postoperatively. Adenoid cystic carcinoma of the EAC is characterized by low degree malignancy without capsule, invasive growth, predilection for local recurrence, and poor prognosis. In this case, extensive resection to achieve free margins is suggested. Patients with early stage of ACC in the EAC were encouraged to receive lateral temporal bone resection (LTBR). Patients with extensive lesions, that is, patients with advanced ACC of the EAC, should be treated with subtotal temporal bone resection (STBR), superficial parotidectomy (SP) or total parotidectomy (TP), mandibular condylar process resection, and superior cervical lymph node dissection if necessary. Radiotherapy may be helpful for some patients, however; in general, the tumor is less sensitive to RT.[3]

In this study, we retrospectively reviewed 17 patients with ACC of the EAC who were treated by variable surgical strategies or surgery plus RT between January 2008 and March 2019 at our institution. The study was directed toward reviewing the symptoms of patients that had been diagnosed with ACC of the EAC and management at our institution. These findings might help to understand this disease and instruct diagnosis and treatment.

METHODS

This study was approved by our Ethics Review Board (Approval no: n065). Written informed consent was obtained from all patients who participated in this study.

Study Design and Subjects

This was a single-center retrospective study of 17 cases of histopathologically confirmed ACC in the EAC treated at our department between January 2008 and March 2019. All patients in this series were diagnosed with primary ACC in the EAC; no patients had a previous diagnosis of ACC in other organs. The diagnosis of ACC was based on histopathological and immunohistochemical analysis. The subjects included 7 males and 10 females (median age: 59 years, 38-79 years). The course of the disease was 0.5-5.0 years (range, 2.5 years).

T: Tumor (Topography), N: Lymph Node, M: Metastasis (TNM) Staging

All subjects were graded based on the Pittsburgh staging system modified by Moody et al[4] in 2000. T1: tumor was confined to the EAC without obvious bone or soft tissue invasion; T2: tumor had erosion of the bone wall of the EAC but did not infiltrate the whole layer or had limited soft tissue invasion; T3: tumor broke through the bony wall of the EAC with limited soft tissue invasion (<0.5 cm) or involved in the mastoid cavity of the middle ear; T4: tumor invaded the cochlea, petrous apex, dura mater, parotid gland, carotid artery, jugular foramen, facial nerve, and surrounding structures like the temporomandibular joint and styloid process.[5,6]

Treatment

In the study, the surgeries were conducted on all 17 patients including local EAC resection (LEACR), LTBR, SP, TP, STBR, and extended temporal bone resection (ETBR). According to preoperative image findings and tumor staging, the appropriate surgical approach was determined. For patients with early-stage cancer, local resection, LTBR was performed. The STBR or ETBR was conducted for patients with advanced-stage tumor. Additionally, adjunctive procedures like SP and TP were conducted when noted. Total parotidectomy was conducted for tumors which showed extensive superficial parotid gland involvement or deep lobe parotid gland infiltration. An SP was conducted for patients with limited superficial parotid gland involvement or to achieve a free margin in case of tumor in the anterior or inferior wall of the EAC.

All patients received temporal bone high-resolution CT (Figure 1) and contrast-enhanced temporal bone MRI (Figure 2) to define the location and extension of the tumor. Pulmonary CT was routinely conducted on all patients to rule out lung metastasis. If an imaging study demonstrated mandibular condyle or temporomandibular joint involvement, then these anatomic structures should also be resected.

For tumors infiltrating dura mater, the involved dura mater was removed and repaired with artificial dura, and the defect cavity was packed with abdominal fat following LTBR or STBR. If the facial nerve was involved, the facial nerves should be sacrificed and grafted with the great auricular nerve. Postoperatively, RT with a dose of 60-70 Gy

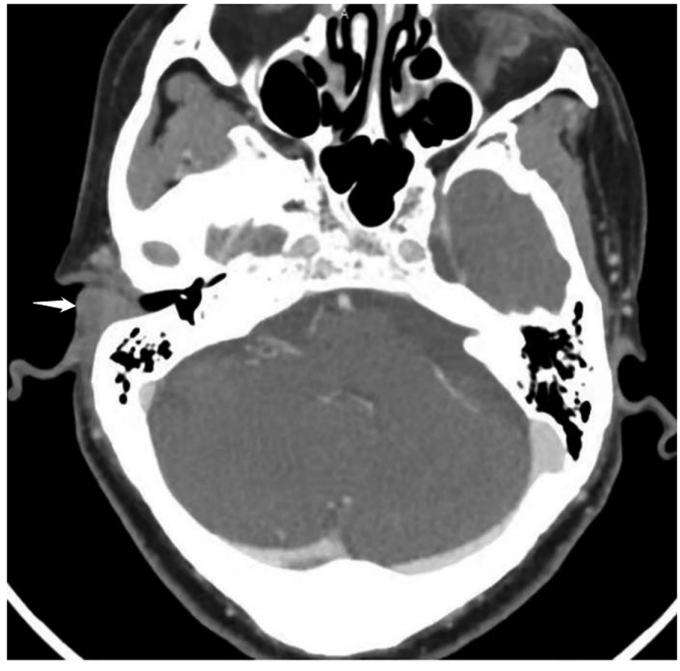

Figure 1. T he axial enhanced computed tomography of temporal bone shows enhanced soft tissue in the right cartilage segment of the posterior wall of the external auditory canal (white arrow).

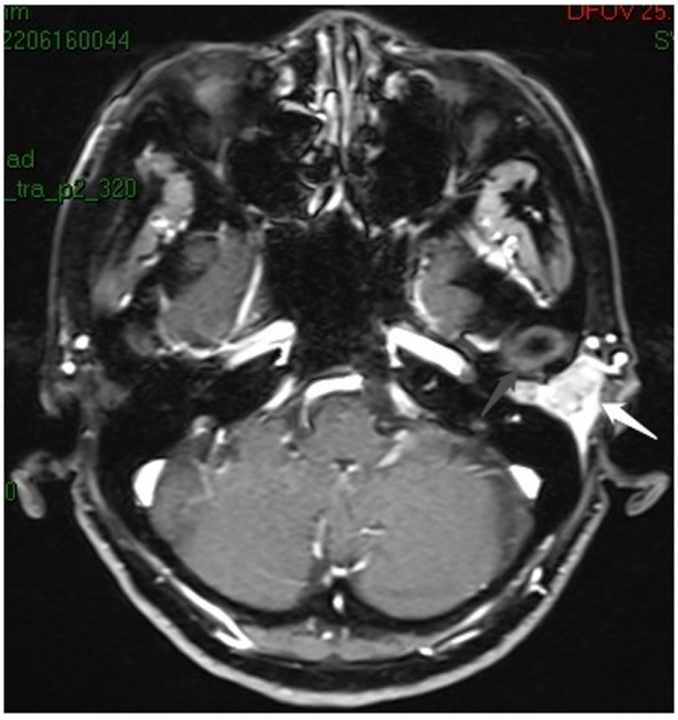

Figure 2. The axial T1-weighted enhanced magnetic resonance image showed T4 adenoid cystic carcinoma in the external auditory canal, tumor predominately locates in the cartilaginous segment (white arrow) and involves the temporomandibular joint anteriorly (gray arrow).

was administrated in patients with T3 or T4 tumors. Great efforts were made to achieve a negative surgical margin with frozen section examination intraoperatively.

Follow-Up

Regular follow-up with temporal bone MRI with enhancement was routinely conducted once every 3 months for the first year, twice a year for the second and third years, and once a year afterward. Suspicious recurrence was confirmed histopathologically following biopsy. In addition, pulmonary CT was conducted annually given the predilection of pulmonary metastasis in patients with ACC in the EAC.

Statistical Analysis

The results were analyzed through Statistical Product and Service Solutions 25.0 (IBM, Armonk, NY, USA). The KaplanMeier method was applied to analyze the survival rate. Continuous variables were displayed as mean ± standard deviation (SD). Categorical variables were displayed as numbers and percentages.

RESULTS

All 17 patients were diagnosed with ACC of the EAC following pathological examination preoperatively. Patients' characteristics including gender, age, presentations, tumor stage, surgery, adjunctive treatment, and outcomes are shown in Table 1.

Clinical Data

The study included 7 males and 10 females, and the course of the disease was 0.5-5.0 years (range, 2.5 years). The follow-up period ranged from 3 to 144 months (median, 36 months), and 2 patients failed to be followed up (11.8%). The age at diagnosis ranged from 38 to 79 years (mean, 58.4 ± 2.6 years). Otalgia (82.4%) was the most common manifestation, observed in 14 patients, followed by hearing loss (n = 5), mass (n = 4), otorrhea (n = 3), and aural ear fullness (n = 1) (Table 1).

Table 1. Detailed Patient Data

Patient No.	Pittsburgh Stage	Age (Years)/ Sex	Previous Operations/ Times	Symptom	Treatment	Follow-Up and Outcome (Months)
1	T1	38/M	0	Otalgia, otorrhea	LEACR	LR (54); A (60)
2	T1	61/M	0	Otalgia	LEACR	A (60)
3	T1	46/F	1	Otalgia, hearing loss	LTBR + SP	A (144)
4	T2	72/F	1	Otalgia, otorrhea	LTBR + SP	DM (12); DWD (18)
5	T2	55/M	1	Otalgia	LTBR + SP	LR (1); A (60)
6	T2	61/M	0	Otalgia	LTBR + SP	A (36)
7	T2	46/F	0	Otalgia	LTBR + SP	A (72)
8	T2	59/F	0	Otalgia	LTBR + SP	A (48)
9	T3	58/F	1	Otalgia, mass	STBR + SP	LR (9); DM (8); DWD (36)
10	T3	56/M	1	Mass, otalgia, hearing loss	STBR + SP + RT	A (36)
11	T3	54/F	1	Otalgia, mass	ETBR + SP + RT	A (36)
12	T3	61/F	1	Aural fullness	STBR + SP	LR (30); A (36)
13	T3	60/F	1	Otalgia, hearing loss	STBR + SP + RT	A (48)
14	T3	73/M	0	Otalgia	STBR + SP	LFU (3)
15	T4	68/F	0	Mass, otorrhea	STBR + SP	LFU (8)
16	T4	79/F	0	Mass, hearing loss	STBR + SP	LR (6); DM (8); DWD (12)
17	T4	45/M	1	Otalgia	ETBR + TP + RT	A (36)

A, alive; DM, distant metastases; DWD, dead with disease; EACR, external auditory canal resection; ETBR, extended temporal bone resection; F, female; LEACR, local external auditory canal resection; LFU, lost to follow-up; LR, local/regional recurrence; M, male; RT, radiotherapy; SP, superficial parotidectomy; STBR, subtotal temporal bone resection; TP, total parotidectomy.

Misdiagnosis

In 17 cases, 5 (29.4%) patients had been misdiagnosed. Two were diagnosed as otitis externa, 2 as ceruminoma despite the attempted surgical removal, and 1 as neuralgia. Nine patients were suspected of ACC in the EAC and a biopsy was conducted. The pathological examination demonstrated the diagnosis of ACC in the EAC.

Tumor Stages

Tumors were staged in line with the modified Pittsburgh staging system based on imaging findings and postoperative pathological examination. Among these patients, 3 with stage I tumor, 5 with stage II tumor, 6 with stage III tumor, and 3 with stage IV tumor. No patients had lymph nodes and distant metastasis preoperatively (Table 1).

Management

All subjects received surgical intervention. Two patients with T4 disease received STBR and SP, and 1 patient with T4 received ETBR, TP, and RT. Five patients with T3 received STBR and SP, 2 of them received RT, and 1 patient with T3 received ETBR, SP, and RT. Five patients with T2 received LTBR and SP. One patient with T1 disease received LEACR and another 2 T1 patients underwent LTBR (Table 1).

Follow-Up Results

The 3- and 5-year overall survival rates were 88.2% and 82.3%, respectively. There was no significant difference in overall survival ($P = .746$) and disease-free survival ($P = .933$) between patients receiving different surgical approaches (Figure 3A). The survival rate of patients in the early stage was better than that of patients in the advanced stage (Figure 3B).

Among the 17 patients, 5 patients had local recurrence and 1 (5.9%) patient who received LEACR without RT exhibited recurrence. No other treatments were conducted after recurrence; currently, the patient still survived the disease. One case had tumor progression at the ninth month postoperatively, the skull base was invaded extensively, showing dysphagia and progressive facial paralysis. Two cases had local tumor recurrence infiltrating the internal carotid artery with cachexia. One patient developed cervical lymph node metastasis 1 month postoperatively. After receiving neck dissection and RT, there was no recurrence during 5 years of follow-up. No perioperative deaths occurred in this series. In the study, 3 patients (17.6%) who suffered from T2, T3, and T4 diseases, respectively, died. One patient with T2 relapsed and then died in the 18th month following the surgery due to multiple metastases in the lungs and bilateral neck lymph nodes, the mass invaded the internal carotid artery. One patient with T3 who received STBR and SP died of multiple lung, liver, and bone metastases at the 36th month postoperatively. One patient with T4 who received STBR and SP died of liver metastasis at the 12th month postoperatively.

Two patients failed to be followed up since 3 and 8 months postoperatively, respectively, one was diagnosed with a T3 tumor and another was diagnosed with a T4 tumor; both received STBR and SP. Eleven patients survived without showing the signs of disease at an average 4-year follow-up (range from 3 to 12 years).

DISCUSSION

Adenoid cystic carcinoma is a very rare disorder which mostly originated from salivary glands, lacrimal glands, upper digestive tract,

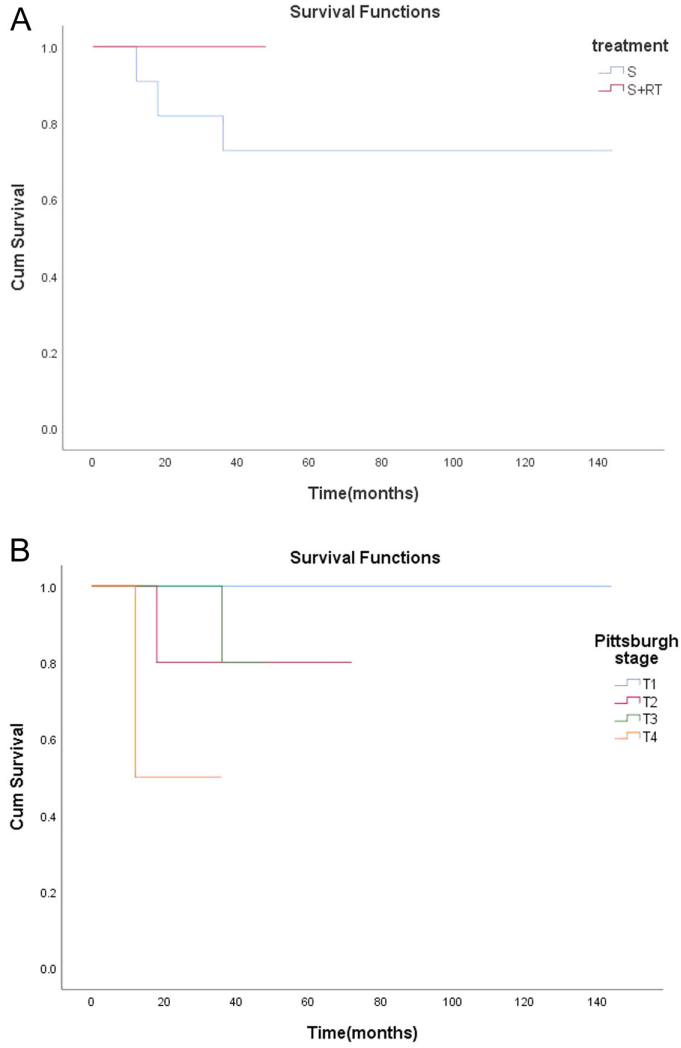

Figure 3. (A, B) Overall survival of patients with ACC of the EAC: (A) with different surgical strategies; (B) with various tumor stages. ACC, adenoid cystic carcinoma; EAC, external auditory canal; RT, radiotherapy; S, surgery.

and respiratory mucosal glands, occasionally originated from EAC and is considered more aggressive and can lead to poor prognosis.[7] Adenoid cystic carcinoma of the EAC can occur at any age, it has preponderance at 40-60 years old. The median age was 59 years in this series. The correlation between ACC and sex is controversial. Chen et al[8] revealed a female predilection for ACC, while Jiang et al[9] demonstrated the opposite situation. This study indicated that there were more females with ACC of the EAC than males.

In our study, the most common symptom was otalgia (82.4%), which was consistent with the works of literature.[2,4,10,11] Other symptoms included hearing loss, EAC mass, otorrhea, and aural fullness. In this case, patients who complained of consistent otalgia with or without mass in the cartilaginous segment of the EAC should order temporal bone MRI with enhancement to rule out ACC in the EAC.

Five of the 17 patients were initially misdiagnosed as otitis externa or ceruminoma or neuralgia owing to limited knowledge of EAC carcinoma.[12] Those who have the following manifestations should be highly alert to the possibility of ACC in the EAC: (i) ear pain is severe and otitis external was suspected, without response to

anti-inflammation therapy; (ii) EAC mass with severe ear pain; (iii) Ear discharge with bloody secretion; and (iv) Granulation tissue was persistent in the EAC concurrence with otalgia even after anti-inflammation.[13] In this case, a biopsy was strongly recommended.

Temporal bone MRI with contrast enhancement and temporal bone CT should be mandatory to conduct in patients with ACC in the EAC, which are helpful not merely to evaluate the location and extent of tumor but also to guide surgical plan. Adenoid cystic carcinoma of the EAC mostly originates from the cartilaginous segment of the EAC and grows subcutaneously. Temporal bone MRI and CT can be useful for defining the invasion of ACC in the EAC. Zhang et al[14] suggested that ACC in the EAC can infiltrate the surrounding soft tissues such as the parotid gland and temporomandibular joint through the Santorini notch or cartilaginous junction of the EAC without obvious destruction of bony structures in the early stage. In this case, if only high-resolution CT examination of the temporal bone was performed, the bony structures of the temporal bone can show normal, leading to misdiagnosis. Enhanced temporal bone MRI is able to define soft tissue involvement. In the case of ACC of the EAC, enhanced temporal bone MRI can localize masses in the EAC even at an early stage. At advanced-stage tumor, the invasion of the surrounding soft tissue can be well displayed, especially when the tumor further involved the dura mater and intracranial infiltration through the middle cranial fossa and the posterior cranial fossa. It is suggested that suspected ACC of the EAC patients should undergo routine temporal bone MRI-enhanced examinations.

Even though previous studies indicated that surgical excision was the major management strategy for patients with ACC of the EAC, the optimal surgical approach that should be applied remained unclear. The surgical approaches include LEACR, LTBR, STBR, and ETBR. In this study, 1 patient who received LEACR displayed recurrence, suggesting that even an early-stage tumor could demonstrate subcutaneous infiltration and that LEACR could not ensure a safe margin and could lead to recurrence.

Moffat et al[15] indicated that aggressive primary surgical management should be applied even to a tumor at an early stage to secure a negative margin. He also initially proposed ETBR for patients with advanced-stage tumor. The resection should include the total temporal bone, a supraomohyoid neck dissection, and parotidectomy which is performed with excision of the ascending ramus and head and coronoid process of the mandible and partial excision of the pterygoid muscles. Middle and posterior fossa craniotomies are then carried out. Some authors[4,16] strongly recommended patients with ACC of the EAC undergo STBR or ETBR to improve the prognosis; that is, early ACC of EAC patients, can undergo temporomandibular resection + LTBR, the resection should include cartilaginous and osseous parts of the EAC, tympanic annulus and membrane, malleus, incus, mastoid, zygomatic arch root, and SP. Patients with extensive lesions, that is, patients with advanced ACC in the EAC, should be treated with temporal bone subtotal or total resection, SP or TP, mandibular condylectomy, and elective neck dissection if necessary. Nonetheless, patients with early-stage tumor are recommended to receive SP and LTBR at the same time. The parotid gland can be partly excised to guarantee a free surgical margin. If it is obviously involved, it can be totally excised. In this study, our team applied this principle to most of our patients.

The effect of RT on ACC is still controversial. It is considered that ACC is not very sensitive to RT, previous studies showed that RT is only applied for patients who are unoperable in advanced stage or free surgical margin was not able to be achieved intraoperatively.[17] Surgery combination of postoperative supplementary RT is an effective intervention for controlling the tumor. Evidence showed that except for the early-stage tumor that does not invade the bony structure, the rest are treated with RT, and the dose is generally 60 Gy. Cristalli et al[18] indicated that chemotherapy would not significantly impact the survival of ACC patients; consequently, chemotherapy is not recommended in our clinical practice. The findings of the study displayed that the 3-year survival rate was 100% after using the combined treatment of surgery and RT, the 5-year survival rate of surgery alone is 81.8%, and the 5-year overall survival rate of surgery and combined treatment of surgery and RT is 86.7%. In short, RT may be helpful for some patients who have undergone surgery.

Study Limitations

This study has several potential limitations. First, selection bias may exist, as the choice of the surgical procedure depended on the experience of the surgeon. Second, surgeries were performed by different surgeons, with various levels of experience in otological surgery. Third, due to a relatively small sample size, the present study may have failed to reveal statistically significant differences in some results. In general, the conclusions of this single-institution analysis need to be validated in cohorts treated at other institutions.

CONCLUSION

In conclusion, ACC of the EAC is mostly characterized by otalgia, hearing loss, and smooth mass in the EAC. Given no specific symptom in patients with ACC in the EAC, patients were frequently misdiagnosed.

Preoperatively, high-resolution temporal bone CT, contrast enhancement of temporal bone MRI, and lung CT should be performed to determine the size, extent, and involvement of the surrounding anatomic structures as well as lung metastasis. Surgical approach should be considered to obtain safe surgical margin, Local resection is associated with high incidence of recurrence, LTBR is strongly recommended even in early-stage tumor. Regular follow-up should be indicated postoperatively to early reveal recurrence.

Data Availability: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Yangzhou University (Approval No: n065).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.W. ; Design – Y.W., L.X.; Supervision – Y.W., B.G.; Funding – B.G., Y.W.; Materials – Y.W., B.G.; Data Collection and/or Processing – B.G., T.T.; Analysis and/or Interpretation – B.G., L.C.; Literature Review – Y.W., L.X.; Writing – Y.W., L.X.; Critical Review – Y.W., L.X.

Declaration of Interests: The authors declare that they have no competing interest.

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