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OTOLOGY

External auditory canal carcinoma: clinical characteristics and long-term treatment outcomes

Pedro Correia-Rodrigues[1] · Sara Ramalho[2] · Pedro Montalvão[2] · Miguel Magalhães[2]

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Abstract

Purpose Evidence-based treatment recommendations for external auditory canal (EAC) carcinoma are lacking in available literature. This study aims to evaluate the clinical characteristics and long-term outcomes of EAC carcinoma in a tertiary referral centre in a period of 15 years and identify independent prognostic factors.

Methods Retrospective observational study enrolling all patients with primary EAC carcinoma who underwent primary surgical treatment at the Portuguese Institute of Oncology (Lisbon) between 2004 and 2018. Epidemiological, clinical, histopathological and surgical data were retrieved from clinical records and analysed.

Results Twenty-seven patients were identified, with a median age of 77 years (range 29–92 years) and a slight female predominance (59.3%). Squamous cell carcinoma (55.6%) was the most common histological type, followed by basal cell carcinoma (40.7%) and ceruminous adenocarcinoma (3.7%). Pittsburgh tumour staging was distributed as early stage in 51.9% (I: 40.7%; II: 11.1%) and advanced stage in 48.1% (III: 29.6%; IV: 18.5%). Median follow-up period was 21 months (interquartile-range: 47). Four patients (14.8%) showed recurrence; recurrence rate was significantly higher in individuals aged < 60 years ($p = 0.025$) and with lymphovascular invasion ($p = 0.049$). Median overall survival was 88 months and estimated 2-year and 5-year overall survival rates were both 66%. Survival rates were higher in early stage patients ($p = 0.021$) and in those without facial palsy ($p = 0.032$).

Conclusion Based on the available evidence in this review, individuals aged < 60, facial nerve impairment, advanced stage lesions, presence of lymphovascular invasion and squamous cell carcinoma histology are all associated with poor outcome and may be considered when discussing optimal treatment strategies in patients with EAC carcinoma.

Keywords External auditory canal carcinoma · Ear canal cancer · Petrosectomy · Temporal bone resection

Introduction

Primary carcinoma of the external auditory canal (EAC) represents an extremely rare malignant tumour originating from the temporal bone [1]. This neoplasm accounts for only 0.3% of all head and neck tumours and its estimated worldwide incidence is one case per 1 million people annually [2]. The first description of EAC carcinoma dates back to 1775 by Schwartze and Wild, but the confirmation of its existence only took place in the 1880s by Kretschmann et al. [3–5]. Several histological subtypes have been recognized over the years, with squamous cell carcinoma (SCC) being by far the most common form (80%), followed by basal cell carcinoma (BCC); adenocarcinoma variants are much rarer [6].

Carcinomas of the EAC occur in people with 40–60 years of age, with some reports of carcinomas that originate from ceruminous glands somewhat earlier [7]. Clinically, EAC carcinoma often simulates other benign and inflammatory otologic entities, which contributes to its difficult and late diagnosis. Additionally, the prognosis seems to be directly determined by the extent of the disease, with locally advanced staged tumours having an aggressive behaviour and reserved outcomes [8]. In some series, the estimated 5-year survival rates range from as low as 10–15% for advanced cases to 80–85% for early disease [9]. Combined surgery with variable temporal bone resections and

✉ Pedro Correia-Rodrigues
mcrpedro@gmail.com

[1] Department of Otorhinolaryngology, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, EPE, Lisbon, Portugal

[2] Department of Otorhinolaryngology, Instituto Português de Oncologia de Lisboa Francisco Gentil, EPE, Lisbon, Portugal

postoperative radiotherapy remains the treatment of choice for the majority of these malignancies [10, 11].

Detailed knowledge of clinical, histological and radiographic presentation of EAC carcinoma is essential to its accurate diagnosis and management, to optimize therapeutic guidelines and improve the prognosis. However, the available literature on this topic remains scarce and evidence-based treatment recommendations are lacking, because most studies have only reported on small sample sizes with heterogeneous populations. Despite the scientific and technological advances occurring during the last decades—namely the development of advanced diagnostic imaging systems and modern skull base microsurgical techniques—this clinical entity still represents a demanding challenge for otolaryngology surgeons.

The objective of this study was to report and evaluate the clinical characteristics, diagnostic approach, management and survival outcomes for patients with EAC carcinoma treated surgically at a single tertiary-care institution of reference in the field of otolaryngology oncology for the last 15 years, with a specific focus on identifying independent disease factors linked to poor prognosis and recurrence.

Materials and methods

Study population

A retrospective observational study was designed and implemented by reviewing data from the clinical records of all consecutive patients diagnosed with histopathologically confirmed primary EAC carcinoma who underwent primary surgical treatment (with or without adjuvant therapy) at the Department of Otolaryngology of the Portuguese Institute of Oncology—Lisbon between January 2004 and June 2018 (15 years). Minimum follow-up period was of 12 months. All patients were operated on with the intention to cure. Cases were identified by searching hospital-maintained patient databases for International Classification of Diseases—Ninth Revision [12] codes corresponding to temporal bone carcinoma (160.1; 170.0; 171.0; 173.20; 173.29).

Exclusion criteria were patients with tumours originating primarily from anatomical adjacent areas other than the external auditory canal itself—such as the pinna, periauricular skin or the parotid gland—that secondarily invaded the ear canal and temporal bone; secondary disease from metastatic spread; non-carcinoma histological subtypes, such as malignant mesenchymal tumours for example; and individuals with incomplete or insufficient data available on the records.

Data extraction

Clinical data of age, gender, smoking and alcoholic drinking habits, history of prior head and neck radiation, past medical history, initial symptoms, laterality, tumour location and extent, facial nerve function, histological diagnosis, staging, type and extent of surgical resection, postoperative complications including recurrence, postoperative histopathological examination (including presence of perineural and lymphovascular invasion and margins status), adjunctive therapy, length of follow-up and current patient status included in charts were collected for analysis.

Available preoperative clinical examination records, radiological findings from computed tomography (CT) scans and/or magnetic resonance imaging (MRI), surgical reports and definitive pathology reports were reviewed for cancer staging. For this purpose, the modified TNM system from the University of Pittsburgh—initially proposed by Arriaga in 1990 and revised by Moody in 2000—was considered (Table 1) [1, 13, 14].

Treatment protocols

Decisions regarding primary and adjuvant management plans for EAC carcinoma in this department were formulated and formally discussed at a multidisciplinary tumour board

Table 1 University of Pittsburgh revised TNM staging system proposed for external auditory canal carcinoma; of note, in the absence of metastatic lymph nodes or distant metastasis, T status defines the clinical stage

T status	
T1	Tumour limited to the external auditory canal without bony erosion or evidence of soft tissue involvement
T2	Tumour with limited external auditory canal bone erosion (not full thickness) or limited (< 0.5 cm) soft tissue involvement
T3	Tumour eroding the osseous external auditory canal (full thickness) with limited (< 0.5 cm) soft tissue involvement or tumor involving the middle ear and/or mastoid
T4	Tumour eroding the cochlea, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen or dura, or with extensive soft tissue involvement (< 0.5 cm), such as involvement of the temporomandibular joint of styloid process, or evidence of facial paresis
N status	The presence of lymph node metastases is a poor prognostic finding and any node involvement should promptly be considered as advanced disease (T1N+ = stage III and T2, T3, T4 N+ = stage IV)
M status	Distant metastases imply a very poor prognosis and should be classified as stage IV disease

consultation meeting including otolaryngologists, medical oncologists, radiologists and pathologists.

Surgery extent for malignancy resection was determined by staging and included microsurgery techniques from limited local sleeve excision and lateral temporal bone resection (indicated to patients with early stage tumours involving the osseous EAC without extension medial do the tympanic membrane) to subtotal petrosectomy (indicated to patients with advanced stage tumours extending beyond the EAC such as middle ear, skull base or temporomandibular joint). In view of the aggressive nature of this disease, pinna resection was indicated whenever needed to achieve clear surgical margins.

Selective or modified radical neck dissection and/or superficial or total parotidectomy were additionally performed concurrently with primary tumour resection when indicated by clinical and/or radiographic obvious tumour invasion, based on staging or for staging purposes or to obtain negative margins. Customized reconstruction of defects after malignancy excision was performed in a tailored fashion and included local and regional flaps.

Selected patients received adjuvant treatment of radiation therapy (RT) determined by tumour staging and postoperative histopathological examination (advanced stage disease, margin positivity, nodal disease, extracapsular invasion) with total doses up to 60 Gy to the primary tumour bed and neck.

Patient surveillance

In accordance with the clinical practice guidelines published by the National Comprehensive Cancer Network [15], postoperative follow-up visits at our centre occurred approximately every 1–3 months during the first year, every 2–6 months during the second, semiannually until the fifth and then annually.

Length of follow-up was determined based on the date of the patients' last visit at our centre. Date of recurrence corresponded to the patients' first visit with evidence of clinical or radiographic locoregional or distant recurrence after 6 months of initial surgery. Date of death was extracted from patient charts and considered to estimate overall survival. Except for legal purposes, Portuguese death registries do not allow for the cause of death to be directly accessed, making it impossible to determine disease-specific and disease-free survivals.

Statistical analysis

Statistical analysis of data was performed by Statistical Packages for the Social Sciences (SPSS) software—version 23.0 (IBM Corporate, Armonk, NY, USA). Recurrence rate and impact of risk factors for recurrence were determined using the Fishers exact test. Two-year and 5-year overall survival (OS) rates were calculated using the Kaplan–Meier time-to-event method. Stratified analyses and significant differences in survival rates between groups were determined by log-rank analysis of survival function equality. For multivariate analysis, the technique of Cox regression was applied for controlling multiple and potentially interacting covariates on survival. Interquartile range (P75–P25) was used whenever Shapiro–Wilk normality test evidenced non-normal distribution of data. Results were considered statistically significant for p values < 0.05.

Results

Demographic and clinical findings

Twenty-seven patients were identified in the final study population, with a median age at diagnosis of 77 years [interquartile range (IQR) of 14; range 29–92 years]. Gender distribution of the enrolled individuals revealed a slight predominance of female sex ($n = 16$; 59.3%). Regarding their past medical history, six patients (22.2%) presented with significant alcoholic habits; five patients (18.5%) were smokers; three patients (11.1%) had history of prior head and neck cancer (one case of oral cavity cancer and two cases of larynx cancer); three patients (11.1%) had previously been irradiated for conditions unrelated to the temporal bone carcinoma; and only one patient had previously been diagnosed with chronic otitis media (cholesteatomatous).

The most common symptom at presentation was a visible progressive growing lump or ulceration in the EAC observed in more than half of the patients ($n = 14$; 51.4%), followed by ear pain in 12 individuals (44.4%); otorrhea—defined as any serous, serosanguineous or purulent ear discharge from EAC—in ten individuals (37.0%); and subjective hearing loss in nine individuals (33.3%). Facial palsy was the first sign of disease in three patients (11.1%) and facial nerve (FN) status was assessed at presentation according to the House–Brackmann scale (HB) as follows: one case of incomplete palsy (grade IV) and two cases of complete palsy (grade VI).

The right side was more frequently affected, corresponding to two-thirds of cases (66.7%). All patients underwent diagnostic biopsy and imaging with CT and/or MRI prior to surgery. The most common histological type was squamous cell carcinoma ($n = 15$; 55.6%), followed by basal cell carcinoma ($n = 11$; 40.7%). One case of ceruminous adenocarcinoma was also identified (3.7%).

According to the modified Pittsburgh TNM classification, definitive tumour staging considering clinical and pathology data was distributed as follows: early stage in 14 cases (51.9%; stage I—40.7%; stage II—11.1%) and

advanced stage in 13 cases (48.1%; stage III—29.6%; stage IV—18.5%). There were no registered cases of distant metastatic spread in this study population.

The detailed demographic, clinical and surgical data of study subjects are shown in Table 2.

Surgical data

All patients enrolled in this study underwent primary surgical treatment with intention to cure. Lateral or subtotal petrosectomy was performed for malignancy resection in the majority of patients ($n=25$; 92.6%) and only two individuals (7.4%) were eligible for limited local excision.

Concurrent with temporal bone malignancy resection, additional procedures were also performed in selected individuals. Fourteen patients (51.8%) were submitted to parotidectomy, with partial and total resections distributed equally (seven cases of superficial parotidectomy and seven cases of total parotidectomy). Regarding neck dissection, ten patients (37.0%) were submitted to some kind of cervical lymph node excision, distributed as follows: seven cases of selective lateral neck dissection (levels II–IV), two cases of selective supraomohyoid dissection (levels I–III) and one case of type I radical modified neck dissection (levels I–V; internal jugular vein and sternocleidomastoid muscle resection with XI nerve preservation).

In 12 patients (44.4%), there was no possibility to primarily close the surgical defect, and different reconstructive techniques were concurrently performed in the following distribution: simple local flaps (rotation or transposition) in six patients (50.0%); pedicled pectoralis major myocutaneous flap in three patients (25.0%); cervicothoracic flaps in two patients (16.7%); and tie-over partial thickness free skin graft in one patient (8.3%).

Eight patients presented with at least one complication after surgery, corresponding to an overall rate of postoperative complications of 29.6%. The most frequent complications included: (1) early superficial necrosis of the locoregional flaps designed for reconstruction after pinna resection ($n=4$), with necrosis occurring in two pedicled pectoralis major myocutaneous flaps and two cervicothoracic flaps, managed conservatively with wet topic dressings with Manuka honey and frequent ointment, resulting in superficial crusting that fell off left without visible scarring; and (2) early surgical wound infection after cavity obliteration with fat and primary closure of the skin ($n=2$), successfully treated with intravenous piperacillin/tazobactam and ertapenem after identification of multidrug-resistant Pseudomonas aeruginosa and multidrug-resistant Escherichia coli, respectively.

There were eight cases of peripheral facial palsy installed de novo after surgery: four of them were expected and resulted from intraoperative sacrifice of the VII nerve

Table 2 Patient distribution according to demographic, clinical and surgical variables

	$N=27$
Median age at diagnosis	77 years (IQR 14; range 29–92)
Gender	
Female	16 (59.3%)
Male	11 (40.7%)
Past medical history	
Alcoholic habits	6 (22.2%)
Smoking	5 (18.5%)
Prior head and neck cancer	3 (11.1%)
Previous radiotherapy	3 (11.1%)
Chronic otitis media	1 (3.7%)
Presentation	
EAC growing lump or ulceration	14 (51.4%)
Ear pain	12 (44.4%)
Otorrhea	10 (37.0%)
Hearing loss	9 (33.3%)
Facial palsy	3 (11.1%)
Laterality	
Right	18 (66.7%)
Left	9 (33.3%)
Histology	
Squamous cell carcinoma	15 (55.6%)
G1	4 (26.7%)
G2	7 (46.7%)
G3	4 (26.7%)
Basal cell carcinoma	11 (40.7%)
G1	7 (63.6%)
G2	3 (27.3%)
G3	1 (9.1%)
Ceruminous adenocarcinoma	1 (3.7%)
Specimen invasiveness	
Margins invasion	15 (55.6%)
Perineural invasion	5 (18.5%)
Lymphovascular invasion	3 (11.1%)
Lymph node pathology-confirmed invasion	1 (3.7%)
Parotid pathology-confirmed invasion	6 (22.2%)
Stage	
Early	14 (51.9%)
I	11 (40.7%)
II	3 (11.1%)
Advanced	13 (48.1%)
III	8 (29.6%)
IV	5 (18.5%)
Surgery	
Primary malignancy resection	27 (100%)
Lateral or subtotal petrosectomy	25 (92.6%)
Limited local excision	2 (7.4%)
Concurrent parotidectomy	14 (51.9%)

Table 2 (continued)

	$N=27$
Partial parotidectomy	7 (25.9%)
Total parotidectomy	7 (25.9%)
Concurrent neck dissection	10 (37.0%)
Lateral neck dissection	7 (25.9%)
Selective supraomohyoid dissection (I–III)	2 (7.4%)
Type I radical modified neck dissection (I–V)	1 (3.7%)
Closure	
Primary closure of the defect	15 (55.6%)
Concurrent reconstructive procedure	12 (44.4%)
Adjuvant radiotherapy	17 (63.0%)

IQR interquartile range, *G1* grade I, well differentiated, *G2* grade II, moderately differentiated, *G3* grade III, poorly differentiated

without reconstruction; the other four were not related to direct manipulation of the nerve (one case of limited paresis of the temporal branch; two cases of incomplete palsy that eventually improved over the months and one case of persistent complete palsy).

Pathology results

Surgical specimens' anatomical and histopathological analysis reports were assessed. Regarding histological subtype, the results were totally concordant with the preoperative biopsy. Tumour grading distributed as following: for squamous cell carcinoma ($n=15$; 55.6%), 26.7% were well-differentiated grade I, 46.7% were grade II and 26.7% were poorly differentiated grade III; for basal cell carcinoma ($n=11$; 40.7%), 63.6% were grade I, 27.3% were grade II and 9.1% were grade III. At least one margin was invaded in 55.6% ($n=15$) of specimens resected. Perineural and lymphovascular invasion was found in five (18.5%) and three (11.1%) cases, respectively. One case of neck lymph node metastases was registered, corresponding to 3.7% of all patients included in the study and 10.0% of patients submitted to neck dissection. Six cases of parotid gland invasion were detected, corresponding to 22.2% of all patients included in the study and 42.9% of patients submitted to any extent of parotidectomy.

Regarding tumour invasion of the parotid gland, ten of the 27 patients presented with preoperative clinical and/or radiographic suspicion of invasion. Fourteen parotidectomies were performed, corresponding to these ten individuals plus four additional ones due to intraoperative decision. Considering the 14 specimens analysed, only six were confirmatory of gland invasion. None of the individuals submitted to parotidectomy without preoperative suspicion of invasion had a positive pathological result. The majority of cases of confirmed invasion occurred in total parotidectomy specimens (five out of six). All individuals with compromised facial nerve function underwent total parotidectomy and all showed evidence of invasion of the gland in the specimen.

Regarding cervical lymph nodes metastases, preoperative clinical suspicion of invasion was present in two patients and ten were submitted to neck dissection. Only one confirmatory case of neck invasion was reported, corresponding to the patient submitted to type I-modified radical neck dissection and staged as N2b. None of the individuals submitted to neck dissection with preoperative suspicious invasion obtained a positive pathologic result and the positive case did not present preoperative suspicion of metastases.

Adjuvant therapy

Adjuvant treatment with RT after surgery was purposed and performed in 17 patients (63.0%), from which 14 cases (82.3%) had positive margins, 11 cases (64.7%) were advanced stage tumours, five cases (29.4%) showed perineural invasion and three cases (17.6%) showed lymphovascular invasion. There were no cases of patients submitted to neoadjuvant therapy within our population sample, since it is not routinely performed at our centre for this specific malignancy.

Oncological outcomes

Median follow-up period of the enrolled patients was 21 months (IQR of 47). After the initial surgical treatment, four patients (14.8%) showed recurrence, with a median time for recurrence of 31 months (IQR of 47). All of them were re-operated and in one case, rescue radiation therapy was also performed. All the recurred patients died during the study period. Detailed characteristics of this subgroup of patients are summarized in Table 3.

Recurrence rate was significantly higher in individuals aged <60 years [$p=0.025$; relative risk 10.5 (1.3–83.5)] and in tumours with evidence of lymphovascular invasion [$p=0.049$; relative risk 1.3 (1.1–5.9)] according to Fischer's exact test, identifying these features as potential risk factors for recurrence. Additional factors analysed, such as histological type, staging, margin status and adjuvant radiotherapy, did not achieve statistical significance when related with recurrence.

Regarding prognosis, Kaplan–Meier statistical analysis was performed regarding patient-related, tumour-related and treatment-related factors that could possibly have an impact on survival. Considering the entire study population, median overall survival was 88 months and estimated 2-year and 5-year overall survival rates were both 66% (Fig. 1). Stratified analysis of data was also performed considering specific subgroups. Median overall survival and

Table 3 Characterization of the subgroup of patients with disease recurrence

Gender	Age	Histology	Stage	Primary surgery	Margins	PNI	LVI	Parotid invasion	Neck invasion	Radiotherapy	Time to recurrence	Management	Outcome
Male	56	BCC	III	P + Par	Invaded	+	+	+	–	Yes	54 mo	Surgery (R2) + RT	Death
Male	78	BCC	I	P	Free	–	–	–	–	No	55 mo	Surgery (R0)	Death
Female	49	SCC	III	P + Par + ND	Free	–	–	–	–	Yes	8 mo	Surgery (R2)	Death
Male	50	SCC	IV	P + Par	Invaded	+	+	+	–	Yes	8 mo	Surgery (R1)	Death

PNI—perineural invasion; LVI—lymphovascular invasion; P—petrosectomy; Par—parotidectomy; ND—neck dissection; mo—months; RT—radiotherapy; R0—complete resection; R1—microscopic positive margin; R2—macroscopic positive margin (palliative surgery)

5-year cumulative survival rates were higher in early stage patients than in advanced stage patients (12 months *versus* 88 months and 91.0% *versus* 37.0%, respectively) and this difference was statistically significant ($p = 0.021$, log-rank test) (Fig. 2). Patients with preserved facial nerve function had more favourable survival function than those with facial palsy and this difference was also statistically significant ($p = 0.032$, log-rank test) (Fig. 3). All patients with facial palsy at diagnosis died during follow-up and death occurred early (before 24 months). Although Kaplan–Meier curves' visual analysis suggest a trend towards worse prognosis with SCC pathology comparing to BCC—at least during the first 2 years of follow-up—these results did not reach statistical significance, likely due to the limited sample size of the study and/or incomplete survival data (Fig. 4). Additional subgroup analysis was limited by their respective sample size, which likely accounts for the lack of statistical significance in other characteristics expected to affect survival (variables that did not reach significance included e.g. age, margin status, adjuvant radiotherapy, specimen features). To control for confounding, multivariate regression analysis for overall population was performed, but none of the variables were found to have statistically significant odds ratios.

Discussion

Carcinomas of the EAC are very rare tumours of the head and neck, with highest prevalence among individuals in the seventh decade of life (mean age reported in the literature of 61.5 years) [7, 16, 17]. Available studies are somewhat contradictory regarding to gender ratio, with some reporting a similar incidence and others showing a tendency for a male predisposition [6]. We presented the data from 27 patients with temporal bone malignancy diagnosed as EAC carcinoma from our tertiary referral centre and we found a median age of 77 years with a slight predominance of female sex (59.3%).

Late diagnosis is typical for EAC malignancies. The disease may be masked by common unspecific ear symptoms such as long-lasting ear discharge, hearing loss, pain and/or bleeding and frequently mimics other otologic diseases [18]. Differential diagnosis typically includes more frequent and benign clinical entities, delaying the definite diagnosis and its adequate and timely management. Previous studies report a misdiagnosed rate of EAC carcinoma of up to 70% and time to diagnosis of up to almost 4 years in some series [1, 17]. In our population, we did not study the time of symptoms before diagnosis due to charts inconsistency with respect to this information but these factors could explain the high age at diagnosis of our cohort that is similar to data reported in other series of patients with EAC carcinoma [2, 7, 16, 17]. We found that pain, ear

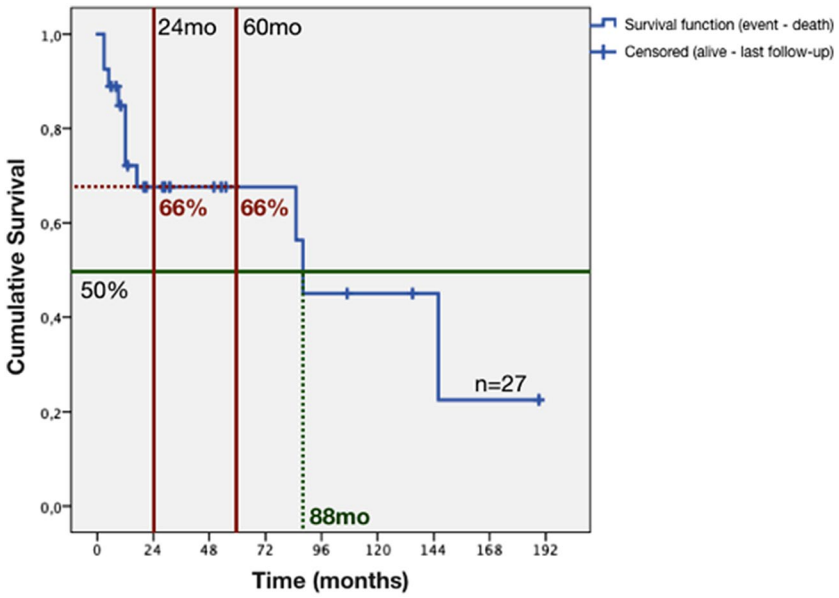

Fig. 1 Kaplan–Meier survival analysis of the overall population. Median overall survival was 88 months (green line) and estimated 2-year and 5-year overall survival rates were both 66% (red lines). Censored refers to people still alive at last the follow-up visit; the Y-axis represents cumulative survival and the X-axis refers to the time (in months)

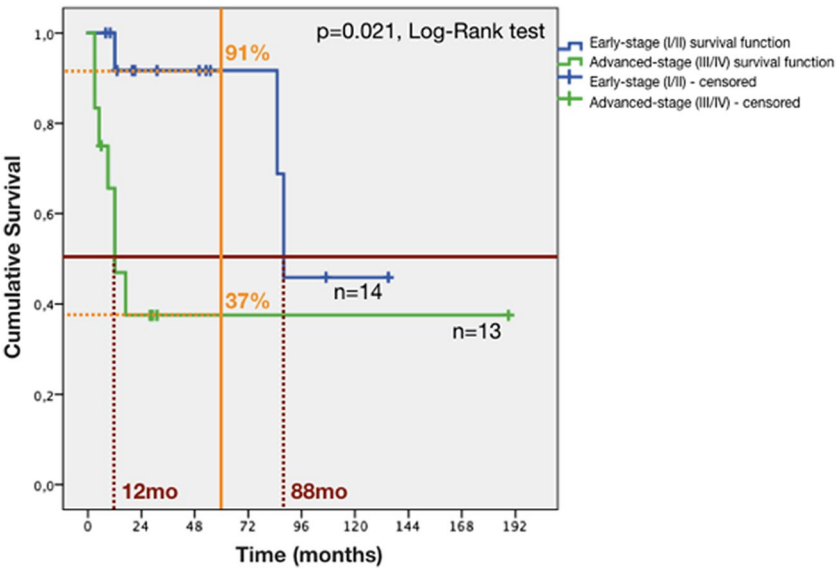

Fig. 2 Kaplan–Meier survival analysis of the overall population according to staging subgroups (early versus advanced). Stratified analysis of data revealed that median overall survival and 5-year cumulative survival rates were higher in early stage patients than in advanced stage patients (12 months versus 88 months [red line] and 91.0% versus 37.0% [yellow line], respectively) and this difference was statistically significant ($p=0.021$, log-rank test). Censored refers to people still alive at last the follow-up visit; the Y-axis represents cumulative survival and the X-axis refers to the time (in months)

discharge and hearing loss were present in one-third to half of the population at diagnosis, although the most frequent-reported symptom was a visible progressive growing lump or ulceration in the EAC, present in more than 50% of patients. It is known that delayed diagnosis seems to be related with unawareness of the symptoms both by the patient and the attending physician [18]. Our findings suggest that tumours of considerable size growing laterally in the EAC and/or into other pinna regions aware more the patients than the other non-specific symptoms commonly reported, although this does not necessarily imply tumours with high T staging. We reported three patients with facial palsy at initial diagnosis, namely one case of incomplete HB IV palsy lasting for 12 months in a patient evacuated from an underdeveloped country and two cases of complete HB VI palsy both lasting for about 1 month. These findings directly imply an advanced stage tumour according to the modified Pittsburgh classification for EAC carcinomas that classify lesions associated with facial palsy as T4 tumours [1, 19]. In our point of view, facial nerve impairment should be reminded as an important red flag in this population of patients and imply immediate examination. Other signs that should prompt careful investigation include out of proportion ear pain and refractory persistent ear discharge, although we also recognize these symptoms as a manifestation of another potentially life-threatening infectious entity known as malignant otitis externa [20].

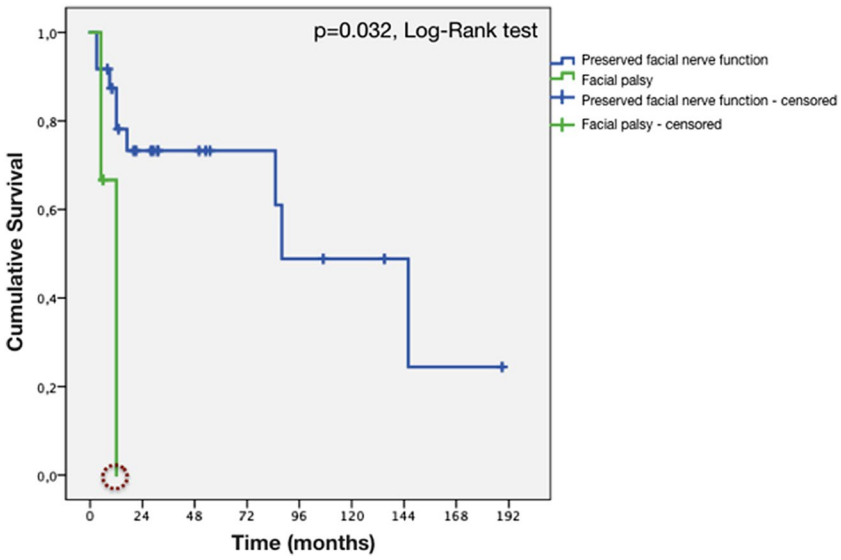

Fig. 3 Kaplan–Meier survival analysis of the overall population according to facial nerve function. Patients with preserved facial nerve function had more favourable survival function than those with facial palsy (difference statistically significant—$p = 0.032$, log-rank test). All patients with facial palsy at diagnosis died during follow-up and death occurred early (before 24 months–dotted red circle). Censored refers to people still alive at last the follow-up visit; the Y-axis represents cumulative survival and the X-axis refers to the time (in months)

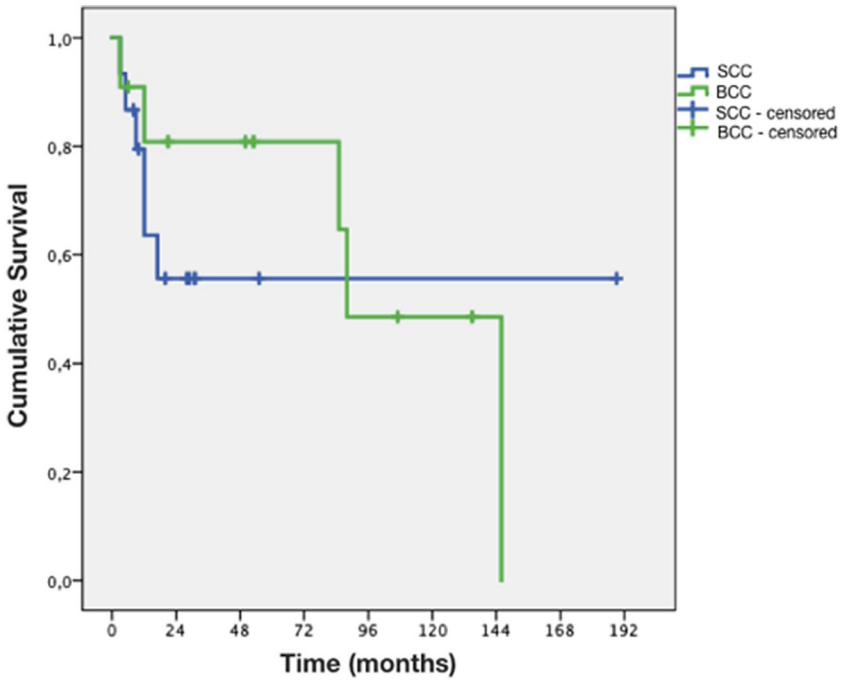

Fig. 4 Kaplan–Meier survival analysis of the overall population according to histology subgroups suggesting a trend towards worse prognosis with squamous cell carcinoma (SCC) comparing to basal cell carcinoma (BCC). Censored refers to people still alive at last the follow-up visit; the Y-axis represents cumulative survival and the X-axis refers to the time (in months)

Isolated or combined tobacco and alcohol abuse are well-known risk factors for head and neck malignancies; EAC carcinoma is not an exception [21, 22]. Although we only found 18.5% of patients being active smokers and 22.2% of them having significant alcoholic habits, these proportions are probably underestimated considering the high median age of our population and their possible past consumptions during adolescence and adulthood. Other established risk factors for SCC of the temporal bone include chronic otitis media (COM) and previous radiotherapy [10, 23, 24]. The chronic inflammatory process leading to metaplastic or neoplastic changes in the temporal bone lining may have a role in the often diagnosed COM (both suppurative and cholesteatomatous) in patients with EAC carcinoma [10], although we didn't find any association in our population, with only one case of previous COM reported. Radiation-associated tumours of the temporal bone may develop after a long period of latency (from 5 to 30 years) after head and neck irradiation both for benign entities such as acoustic neuroma or vascular malformations or malignant entities such as nasopharyngeal carcinoma [23, 24]. Our population included three patients (11.1%) that had previously been submitted to radiotherapy due to other malignancies, highlighting the relevance of past medical history in EAC

carcinoma and the common role for some risk factors in head and neck cancer field.

Tumours originating from the temporal bone often involve the parotid gland [25, 26]. Two main mechanisms are recognized: (1) direct invasion through natural orifices with anatomical weakness, namely the Santorini fissures and the foramen of Huschke; and (2) lymphatic spread from the EAC into intraparotid nodes via the natural drainage pathways. Regarding the first mechanism, Santorini fissures—located at the anterior part of the cartilaginous EAC—are a well-known potential outlet to the parotid gland, allowing for tumour spread even in early stages without bony structure invasion [27]. On the other hand, the foramen of Huschke (also known as foramen tympanicum)—located at the floor of the bony EAC—may also be a direct route for parotid invasion, although it is an embryonically determined anatomical variation that is normally closed in adults [28]. Considering this, the parotid tissue often corresponds to the anterior resection margin of the tumour. The second mechanism considered does not refers to an anatomically determined barrier but relates with normal EAC lymphatic drainage pathways. The parotid gland represents a lymphatic station profusely supplied by nearby lymph nodes draining from the face and scalp, where the EAC skin is also included [29]. Even though, some studies show that pinna skin carcinomas most frequently show parotid node involvement then EAC malignancies of the same nature, possibly due to less developed lymphatic network of the former, which mostly invades these echelon nodes in advanced stages [26, 30]. Our study found that 42.9% of patients submitted to any kind of parotidectomy showed evidence of gland invasion by the tumour when the specimens were examined, representing 22.2% of the population included in the research. These results are consistent with previous studies [25–30]. We did not identify any case of parotid gland specimen involvement in patients without preoperative suspicion of invasion, suggesting that clinical and radiographic examination of the gland is of value when investigating these patients, although our findings could be limited by our sample size. We also find that all the individuals with compromised facial nerve function showed pathologic evidence of parotid invasion, supporting the literature recommendation for parotidectomy in patients with advanced stage EAC carcinomas (III/IV) besides those with obvious clinical and/or radiographic involvement [25]. Although superficial parotidectomy may be adequate for patients with early stage disease with preserved facial nerve function, total parotidectomy may be considered for patients with advanced stage disease with compromised facial nerve function [25, 26].

Surgical management of the neck in EAC carcinoma remains controversial [31, 32]. Neck dissection not only allows for nodal metastases removal, but may also allow accurate staging and provide access to the major vessels for safe tumour resection or for free flap reconstruction purposes. Nodal metastases are uncommon in early stage disease, but may be clinically evident in more advanced stage patients [8]. Although node-positive necks are associated with a poor prognosis and upstages the disease regardless of the T status, most studies were not able to demonstrate survival improvement with neck dissection [8, 10, 33]. In our series, we reported two cN+ necks but actually ten patients were submitted to neck dissection; of those, only one case showed evidence of node metastases during specimen analysis, corresponding to 3.7% of all sample. The referred patient was diagnosed with a very aggressive advanced SCC staged as pT4aN2b. In accordance to previous studies, we didn't find any survival improvement with neck dissection.

The modified Pittsburgh staging classification is the most consensual system available to standardize comparison of outcomes between groups of patients with EAC carcinoma. It is based on clinical, pathological and radiologic evidence and was conceived by Arriaga in accordance with the American Joint Cancer Committee's TNM classification system, being updated later to consider facial nerve involvement as a prognostic indicator [1, 13, 14]. Since the updating, irrespective of the anatomical area of involvement or local extension, partial or complete facial nerve palsy would be classified as T4. We found a similar distribution of early stage (51.9%) and advanced stage (48.1%) tumours in our population, with most patients classified as stage I (40.7%) and only a few as stage IV (18.5%). Regarding the last group, three out of five stage IV patients had any kind of facial nerve involvement upgrading its staging irrespective of the local extension of the tumour, corroborating previous studies [1, 13, 14].

At present, there is no definitive consensus strategy for operative management of EAC carcinoma. As previously stated, extended tumour resection with postoperative radiotherapy appears to be the most effective treatment [10, 11]. Both en-bloc and piecemeal resection techniques are available approaches for local tumour control, although some recent studies suggest that most favourable survival rates may be achieved with the former [8, 10, 11, 33]. Notwithstanding the above, piecemeal dissection is often demanded by the nature of temporal bone tumours, as it is required due to tissue weakness ensuing fragmentation, for diagnostic purposes during mastoid exploration and/or to achieve tumour-free resection margins. In our department, we aim to achieve complete resection of EAC carcinomas, when anatomically feasible, regardless of the technique used; however, considering the high level of expertise in otologic microsurgery as a referral centre, to preserve vital functions such as hearing, balance and facial nerve function, piecemeal techniques are routinely performed when there is a need for dissection in the medial limits of the temporal bone. Lateral or subtotal petrosectomy were performed in 92.6% of the patients studied, although in some

old charts, the distinction between these two procedures and their nomenclature were not always clear, leading us to analyse them as a whole group.

The literature supports a beneficial effect of adjunctive radiotherapy on EAC carcinoma survival [8, 10, 11, 33, 34]. More than half (67%) of our cohort was submitted to postoperative radiotherapy, imposed by the presence of at least one adverse prognostic factor as supported by the literature: advanced stage disease (III/IV), margin positivity, nodal disease, extracapsular invasion or lymphovascular/perineural invasion [8, 10, 11, 33, 34]. Surprisingly, we did not find any statistically significant improvement in the overall survival with radiotherapy, possibly due to our sample size. The most frequent complication was related with flap necrosis, although we believe radiotherapy was not involved considering we only started adjunctive treatment 6–8 weeks after surgical procedure to maximize flap viability [35].

Individuals aged < 60 years and tumours with lymphovascular invasion were associated with higher recurrence rates in our cohort. Due to its aggressive behaviour, recurrent EAC carcinomas demanded very difficult management and ended up being fatal. These results are in accordance with those reported by other authors [6, 9, 22, 36].

Our study estimated similar 2-year and 5-year overall survival rates (66%), leading us to hypothesize that the first two years of follow-up were the most determinant in the survival function of our population and that they allowed to predict its outcome at 60 months. We also found that patients with early stage tumours survived more than those with advanced stage tumours: 5-year overall survival rate for these subgroups were, respectively, 91% and 37%, matching those reported by Yin, Moore, Gidley, Bacciu and Masterson [8, 10, 11, 33, 37]. This difference is more significant during the first 5 years of follow-up, probably because after this time point, other factors and diseases not directly related with the tumour are determining death in both groups. These results validate literature data reporting advanced T stage and advanced overall stage as risk factors linked to poor prognosis [1] and point out that contemporary surgery with adjuvant radiotherapy alone are insufficient for achieving acceptable survival rates for advanced stage patients, demanding the need to investigate other forms of management such as induction or concurrent chemotherapy [38]. Other risk factor associated with poor prognosis was the impairment of facial nerve function, as previously stated. Our data suggest that SCC histology determine worse prognosis than BCC lesions, results that also correspond well with that of previous studies in the temporal bone and in the head and neck in general [8, 10, 33]. Other risk factors associated with poor prognosis reported in the literature are dural invasion, parotid involvement, node-positive status, poor histological differentiation, perineural invasion and positive margins, although these results did not reach statistical significance in this study, likely due to the limited sample size [1, 8–11, 33].

As a strong point, the authors would like to emphasize that, according to our knowledge, this is the first Portuguese cohort of its kind regarding this rare entity. Considering that our department depicts a highly differentiated tertiary center in the treatment of this pathology, receiving a significant portion of the nation-wide cases, this study probably reliable reflects our country's picture in the diagnosis and treatment of EAC carcinoma. In addition, although limited to reach statistical significance in some subgroup analysis, our sample size still represents one of the largest single-institution studies in this field, with a negligible lost to follow-up. We included a survival analysis stratified by tumour staging, which allowed the identification of prognostic factors. We covered a long period of 15 years not only because of its low incidence (implying smaller sample sizes), but also to consider our institutional learning curve regarding the multidisciplinary management. We recognize that different phases of scientific and technologic knowledge are included, and that the experience improve the outcome and affect the surgical approach, although all the different surgeons belong to the same team, respecting the same oncologic principles and practicing the same techniques. The retrospective observational nature of the present study is a limitation, without any treatment randomization, although still essential when researching a rare entity such as EAC carcinoma. Given this fact, the origin of very advanced tumours may not be clear and it was not possible to know the cause of death, being only possible to calculate the overall survival.

Conclusion

Based on the available evidence in this review, individuals aged < 60 years, facial nerve impairment, advanced stage lesions, presence of lymphovascular invasion and SCC histology are all associated with a poor outcome and may be considered when discussing optimal treatment strategies. At present, as a tertiary centre with multidisciplinary expertise in this condition, contemporary advanced lateral skull base microsurgical techniques permit effective surgical tumour resection with safe margins. Controlled prospective multi-institutional cooperative studies should still be carried out in the future to expand our knowledge regarding management of EAC carcinomas.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Approved by the Portuguese Institute of Oncology—Lisbon Bioethics Committee; all procedures were in accordance with the ethical standards of the 1964 Helsinki Declaration.

Consent to participate and for publication No formal informed consent was required for this retrospective study.

Data transparency Patient medical records were identified and analysed anonymously.

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