Carcinomas of the external auditory canal: Management and results: A multicenter REFCOR propensity score matching study

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Original research

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Esteban Brenet [a], Sarah Atallah [b,c], Joanne Guerlain [d], Antoine Moya-Plana [d], Benjamin Verillaud [e], Romain Kania [e], David Bakhos [f], Pierre Philouze [g], Christian-Adrien Righini [h], Alexis Bozorg [i], Jean-Claude Mérol [a], Marc Labrousse [a], Sébastien Vergez [j], Nicolas Fakhry [k], Patrice Gallet [l], Dorian Cullié [m], Olivier Malard [n], Olivier Mauvais [o], Léa Fath [p], Philippe Schultz [p], Xavier Dufour [q], Nicolas Saroul [r], Diane Evrard [s], Maria Lesnik [t], Caroline Even [u], Valérie Costes [v], Juliette Thariat [w], Ludovic Le Taillandier de Gabory [x], Marc Makeieff [a], Xavier Dubernard [a], Bertrand Baujat [b,*]

[a] Department of ENT-Head and Neck Surgery, Robert Debré University Hospital, 51100 Reims, France
[b] Department of ENT-Head and Neck Surgery, Tenon University Hospital, APHP, Sorbonne Universite, 75020 Paris, France
[c] Doctoral School of Public Health, CESP, University of Paris Sud, 94807 Villejuif, France
[d] Department of ENT-Head and Neck Surgery, Gustave Roussy Cancer Campus, 94800 Villejuif, France
[e] Department of ENT-Head and Neck Surgery, Lariboisière University Hospital, APHP, 75010 Paris, France
[f] Department of ENT-Head and Neck Surgery, Bretonneau University Hospital, 37000 Tours, France
[g] Department of ENT-Head and Neck Surgery, La Croix Rousse University Hospital, HCL, 6900 Lyon, France
[h] Department of ENT-Head and Neck Surgery, Grenoble Alpes University Hospital, 38043 Grenoble, France
[i] Department of ENT-Head and Neck Surgery, François Mitterrand University Hospital, 21000 Dijon, France
[j] Department of ENT-Head and Neck Surgery, University Cancer Institute, 31100 Toulouse, France
[k] Department of ENT-Head and Neck Surgery, University Hospital of Marseille, APHM, 13915 Marseille, France
[l] Department of ENT-Head and Neck Surgery, University Hospital of Nancy, 54000 Nancy, France
[m] Department of ENT-Head and Neck Surgery, Lacassagne Cancer Institute, 06100 Nice, France
[n] Department of ENT-Head and Neck Surgery, University Hospital of Nantes, 44093 Nantes, France
[o] Department of ENT-Head and Neck Surgery, University Hospital of Besançon, 25000 Besançon, France
[p] Department of ENT-Head and Neck Surgery, University Hospital of Hautepierre, HUS, 67200 Strasbourg, France
[q] Department of ENT-Head and Neck Surgery, University Hospital of Poitiers, 86021 Poitiers, France
[r] Department of ENT-Head and Neck Surgery, University Hospital of Clermont-Ferrand, 63000, France
[s] Department of ENT-Head and Neck Surgery, Bichat University Hospital, APHP, 75018 Paris, France
[t] Department of ENT-Head and Neck Surgery, Curie Cancer Institute, APHP, 75005 Paris, France
[u] Department of Oncology, Gustave Roussy Cancer Campus, 94800 Villejuif, France
[v] Department of Pathologic Anatomy and onco-biology, University Hospital of Montpellier, France
[w] Department of Radiation Oncology, Cancer center Baclesse, 14076 Caen, France
[x] Department of ENT-Head and neck surgery, University Hospital of Bordeaux, France

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ABSTRACT

Objectives: To analyse prognostic factors and survival outcomes of malignant tumors of the external auditory canal, to investigate the role of regional surgery, and adjuvant radiotherapy in early stages and to investigate the role of surgery in operable T4 stage.
Setting: A retrospective analysis was conducted on all patients prospectively included in the national database of the French Expertize Network for Rare ENT Cancers (REFCOR) from January 2000 to December 2016.
Participants: 103 patients from 19 reference centers were included. A propensity score matching analysis was applied to enable comparisons between treatments.
Main outcomes and measures: Event-free survival, overall survival and factors of poor prognosis of the cohort were described. The interest of local and regional surgery and postoperative radiotherapy were evaluated.

* Correspondence to: Department of ENT-Head and neck surgery, Tenon University Hospital, APHP, 4 rue de la Chine, 75020 Paris, France.
E-mail address: bertrand.baujat@aphp.fr (B. Baujat).

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Results: The factors of poor prognosis on event-free survival were immunosuppression (p = 0.002), Karnofsky status less than 90% (p = 0.02), body mass index less than 19 Kg / m2 (p = 0.0009), peripheric facial palsy (p = 0.0016), and positive margin (p = 0.0006). In early stages, locoregional surgery was associated with an increase in event-free survival (p = 0.003, HR = 0.21) versus local surgery alone, while postoperative radiotherapy was not associated with an increase in event-free survival (p = 0.86, HR = 0.91) or overall (p = 0.86, HR = 0.91). In locally advanced stages, locoregional surgery followed by radiotherapy was associated with an increase in event-free survival (p = 0.03, HR = 0.39) and overall (p = 0.02, HR = 0.34) versus chemoradiotherapy alone.
Conclusion and relevance: Regional surgery is recommended for early stages of cancers of the external auditory canal. In operable cases, locoregional surgery followed by radiotherapy is recommended.

1. Introduction

Carcinomas of the external auditory canal (CEAC) account for only 0.2% of the head and neck tumors [1,2]. Because of their rarity, few epidemiological data are available and no consensus on management has emerged [3]. Treatment remains a challenge due to the lack of reliable prognostic factors and the multiple treatment modalities [4–6].

Since the early 2000 s, the modified Pittsburgh classification [2,7] has become widely used and has demonstrated to be reliable and reproducible [2,8].

Treatment options include wide surgical resection, radiotherapy, chemotherapy, or combinations of these modalities. The standard treatment for CEAC is surgery [9–11] which is often mutilating and can provide severe postoperative morbidity. In operable cases, surgical approaches seek to achieve “enbloc resection” or “piecemeal resection” of the temporal bone using lateral temporal bone resection (LTBR), subtotal temporal bone resection (STBR) or Total Bone Resection (TBR) [12], any of which can be combined with neck dissection and/or parotidectomy followed by postoperative radiotherapy [11,13–15]. Despite improvements in their management, advanced tumors (stages III–IV) are associated with a poor prognosis [16].

In early stages, the association of neck dissection and parotidectomy to the tumor resection is debated, as well as postoperative radiotherapy. In operable advanced local stages (T4a and T4b), the interest of surgery followed by radiotherapy versus radiochemotherapy is also controversial.

The main objective of our study was to analyse prognostic factors and survival outcomes in a series of patients presenting with CEAC.

The secondary objectives were to investigate 3 therapeutic options: 1) Regional surgery (parotidectomy and neck dissection) in early stages (T1 and T2). 2) Upfront surgery in operable advanced stages (T4). 3) Adjuvant radiotherapy in early stages.

2. Material and methods

We studied all patients prospectively included in the Réseau d’Expertise Français des Cancers ORL Rares (REFCOR) national database from January 2000 to December 2016.

Data collection for each patient was carried out at each hospital site by the patient’s physician. Data was anonymized and informed consent was requested from all patients in accordance with French law. REFCOR database has obtained the authorization of the ethical committee (CCTIRS n ° 11 337) and the authorization of the national control for databases (CNIL DR 2012–070) as well as the favorable opinion of the Committee of Protection of the People of 09/06/2011. Database and consent form were updated in 2020 to conform with the new RGPD law.

With the agreement of the REFCOR committee, the study manager checked and updated all files.

Inclusion criteria were:

- Patients enrolled in the database for a Carcinoma of the External Auditory Canal (CEAC). - Age $\geq$ 18 years.

- Informed written consent available.

Exclusion criteria were cancers of the middle ear and all skin cancers of the auricle and patients managed in a palliative manner since the beginning.

A total of 103 patients were included by 19 centers.

2.1. Patients’ characteristics and care

The diagnostic and therapeutic management of all patients was carried out according to the REFCOR guidelines for cancers of the external auditory canal. All patients underwent radiological assessment with injected cervicothoracic CT, cervicofacial MRI and 18-FDG PET-CT. The classification used by REFCOR is the modified Pittsburgh classification proposed by the Belgium Consensus Conference in March 2002. Lavieille et al. proposed a staging system for T4 tumors, taking into account the direction of the spread of the tumor.

-T4a involvement of the lateral cutaneous tissues (concha, retroauricular skin) and the parotid structures, the Temporo-Mandibular Joint or the infratemporal fossa.

-T4 b involvement of the inner ear and petrous apex.

-T4c dural and intradural involvement.

All patients were managed for curative purposes. Operated patients with T1 or T2 stage received LTBR with more or less superficial parotidectomy and neck dissection depending on the centers. Patients with a T3 or T4 stage underwent STBR or TBR, depending on the extent of the disease, combined with a total parotidectomy and neck dissection.

For the N0 necks, if a neck dissection was performed, the areas IIa, IIb, III and retro-mastoidian were removed. In case of N1 or N2 neck, a complete neck dissection was performed.

In T1N0 or T2N0 patients, adjuvant radiotherapy was performed in all cases except in selected cases based on clinical and histological criteria: exophytic tumor, well-differentiated carcinoma or low-grade histology, absence of angioinvasion, healthy margins.

All T3, T4 or N + patients had postoperative radiotherapy. In this case, a dose of 50 to 66 Gy was performed without chemotherapy. Patients who were managed with radiochemotherapy at the outset received a dose of 70 Gy (2 Gy/session, 1 session/day, 5 days a week). Chemosensitization was performed for SCC tumors if the patient’s condition allowed it.

2.2. Statistical analysis

2.2.1. Main criteria

Event-free survival (EFS) was defined as the time between diagnosis and local or distant recurrence, or death due to anycause, or the date of last follow-up for censored patients.

2.2.2. Secondary criteria

Overall survival (OS) was defined as the time between diagnosis and death, or the date of last follow-up for censored patients.

Categorical variables were described by their proportion and compared using the Pearson Chi 2 test or Fisher’s exact test. Distributions of continuous variables were described by their mean or median, minimum and maximum values and compared using the bilateral Student’s T-test or, in case of non-normality, bilateral Mann-Whitney test. A p-value less than 0.05 was considered statistically significant. EFS, OS and the influence of prognostic factors were analysed using the Kaplan-

Meier method and a Cox model.

To account for selection biases and potential confounders between groups in outcome comparisons, a propensity score matching analysis (PSM) was performed: for each patient, a score was calculated as the expected probability of receiving the treatment considered, from a multivariate logistics regression adjusting survival curves for the main confounders: age at diagnosis, immunosuppression, tobacco, and pain. These criteria were chosen after a consultative meeting between clinicians and statisticians' experts because of their clinical relevance. Only criteria available at the time of the indication of treatment could be eligible.

Each patient was weighted by the inverse probability of being part of the group of patients with treatment compared to the untreated group, in order to balance the observable characteristics. The concordance tolerance (caliper) of the score was set at 0.01.

Due to the presence of Adenoid Cystic Carcinoma (ACC), the study protocol scheduled a sensitivity analysis excluding ACC from analyses aiming to answer to the question of regional surgery, as these tumors are less prone to nodal invasion and have a better prognosis than other carcinomas.

Statistical analyses were performed using the R software (R version 3.6.0 (2019–04-26)).

3. Results

3.1. Patients' characteristics

The epidemiological, clinical and radiological characteristics of patients, histology and treatment modalities are detailed in Table 1.

3.2. Survival

The median follow-up was 25 months (range: 2 - 156). EFS and OS curves are shown in Fig. 1.

The 5-years OS was 49% (95% CI (0.38–0.64)); median 60 months (95% CI (36-na)).

The 5-years EFS was 37% (95% CI (0.28–0.50)); median 21 months (95% CI (15-na)). During the period of follow-up, 42 patients died, 50 patients presented with a loco-regional recurrence and 10 patients presented with a metastatic evolution.

3.3. Prognostic factors on EFS

1) Univariate analysis (Table 2):
   The factors significantly associated with a poor prognosis on EFS were immunosuppression (diabetes, immunosuppressive therapy, HIV infection) (p = 0.004, HR = 2.26; 95% CI (1.28- 4.01)), Karnofsky status less than 90% (p = 0.004, HR = 2,17; 95% CI (0.27 – 2.82)), BMI less than 19 Kg/m^2 (p = 0.0002, HR = 10.14; 95% CI (2.31 – 44.6)), facial palsy (p = 0.042, HR = 2.61; 95% CI (1.03 – 6.6)), poorly or undifferentiated tumor (p = 0.04, HR = 1.72; 95% CI (1.02 – 2.94)) and positive margin (p = 0.01; HR = 1.96; 95% CI (1.16 – 3.33)).
2) Multivariate analysis:

Factors significantly associated with a poor EFS were denutrition (HR = 14; 95% CI (2.9- 67.08); p = 0.0009), immunosuppression (diabetes, immunosuppressive therapy, HIV infection) (HR = 2.61; 95% CI (1.41 – 4.84); p = 0.002), Karnofsky statut less than 90% (HR = 2; 95% CI (1.45 – 11.2); p = 0.02), facial palsy (HR = 4.85; 95%CI (1.8 – 12,95); p = 0,0016) and positive margin (HR = 2.6; 95% CI (1.5 – 4.51); p = 0,0006).

Table 1
Patients characteristics and care.

Epidemiological and clinical characteristics	Value
Age, years, median (min-max)	69 (39-93)
Sex Ratio H/F	49/54
Body Mass Index (BMI), kg/m2, median (min-max)	24.2 (12.9-74)
Daily alcohol, n (%)	19 (18)
Daily smoking, n (%)	34 (33)
Immunosuppression* , n (%)	22 (21)
History of radiotherapy, n (%)	10 (10)
Karnofsky index, n (%)	
> ou = 90%	59 (57)
< 90%	44 (43)
Clinical presentation	
External otitis, n (%)	57 (55)
Otorrhea, n (%)	63 (61)
Pain, n (%)	76 (74)
Hearing loss, (%)	60 (58)
Vertigo, n (%)	3 (3)
Peripheric facial palsy, n (%)	5 (5)
Visible mass, n (%)	97 (94)
Side Right/Left	56/47
Diagnostic delay	
< or = 5 months, n (%)	54 (52)
> 5 months, n (%)	45 (48)
Radiological characteristics	
Computed Tomography (CT)scan, n (%)	103 (100)
T1	28 (27)
T2	14 (14)
T3	19 (18)
T4	42 (41)
T4a	29 (28)
T4b	8 (8)
T4c	5 (5)
T1/T2	42 (41)
T3/T4	61 (59)
N0	97 (94)
N +	6 (6)
M0	103 (100)
Magnetic Resonance imaging (MRI), n (%)	61 (59)
Middle ear extension	30 (29)
Intra dural extension	5 (5)
Therapeutic Characteristics	
Surgery, n (%)	83 (81)
LTBR* *, n (% of surgeries)	47 (56)
STBR* ** , n (% of surgeries)	33 (40)
TBR* ** *, n (% of surgeries)	3 (4)
Parotidectomy, n (% of surgeries)	46 (55)
Ipsilateral cervical dissection, n (% or surgeries)	46 (55)
Histology, n (%)	
Squamous cell carcinomas	82 (80)
Adenoid Cystic Carcinomas	13 (12)
Others	8 (8)
Sarcomas	1 (1)
Melanomas	2 (2)
Papillary Carcinomas	2 (2)
Neuroendocrine Carcinomas	2 (2)
Verrucous Carcinomas	1 (1)
Epidermoid carcinomas' degree of differenciation, n (%)	
Poor or not	30 (37)
Moderate or well	52 (63)
R Status, n (%)	
R0	48 (58)
R1	33 (40)
R2	2 (2)
Chemotherapy, n (%)	26 (25)
Induction, n (% of chemotherapies)	5 (20)
Concurrent, n (% of chemotherapies)	21 (80)
Adjuvant, n (% of chemotherapies)	0 (0)
Radiotherapy, n (%)	63 (63)
IMRT* ** **	63 (100)

*Diabetes, immunosuppressive therapy, HIV infection; * *LTBR = lateral temporal bone resection; * **STBR = subtotal temporal bone resection; * ** *TBR = temporal bone resection; * ** **Intensity modulated radiotherapy

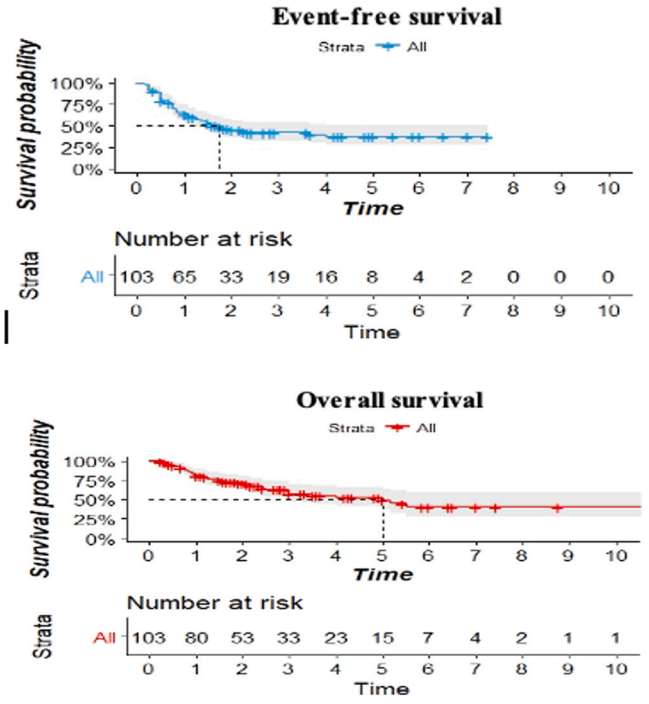

Fig. 1. Survival curves all stages combined. Time is expressed in years.

3.4. Prognostic factors on OS

1) Univariate analysis:
   The factors significantly associated with a poor prognosis on OS were immunosuppression (diabetes, immunosuppressive therapy, HIV infection) (p = 0.001, HR = 2.81 95% CI (1.46 - 5.39)), Karnofsky statut less than 90% (p = 0.003, HR = 2.49 95% CI (1.33 - 4.64)), BMI less than 19 Kg/m^2 (p = 0.0002, HR = 11.27 95% CI (2.54 - 49.96)), advanced tumor status (T3 or T4) (p = 0.002, HR = 2.49 95% CI (1.15 - 5.38)) and poorly or undifferentiated tumor (p = 0.0004, HR = 3.10 95% CI (1.60 - 5.99)).
2) Multivariate analysis:

Factors significantly associated with a poor OS were age over 65 (p = 0.04, HR = 2.08 95% CI (1.01 - 4.2)), immunosuppression (p = 0.0003, HR = 3.87 95% CI (1.88 - 8.01)) and initial pain (p = 0.03, HR = 11.27 95% CI (1.13 - 7.82)).

Sensitivity analysis excluding ACC and other histologies (Supplementary data Table 3) and excluding other histologies alone (Supplementary data Table 4) showed same prognostic factors associated with EFS.

3.5. Therapeutic strategies

1) ***Regional surgery (superficial parotidectomy and neck dissection) in early stages (T1 and T2).***

Our series included 42 operated patients (20 women / 22 men, mean age 67) with T1 or T2 tumors. In this group of patients, no parotid or cervical nodes were positive on postoperative histological analysis. The characteristics of the patient's groups (regional surgery or not) are presented in supplementary data (Table 5). Both groups were comparable for most characteristics except radiotherapy and chemotherapy. PSM generated 2 matched groups (9 pairs, n = 18 patients) with no significant difference of clinical and therapeutic characteristics.

3.5.1. EFS of 42 operated patients with T1 or T2 tumors (Fig. 2):

After PSM, the 2-year and 5-year EFS of patients who had regional surgery was 78% (95% CI [0.55 - 1.00]) for both, versus 33% (95% CI [0.13 - 0.84]) and 17% (95% CI [0.03 - 0.88]) respectively in patients who did not have regional surgery (HR = 0.21, 95% CI [0.04 - 0.95], p = 0.03).

3.5.2. OS of 42 operated patients with T1 or T2 tumors

After PSM, the 2-year and 5-year OS of patients who had regional surgery was 78% (95% CI [0.55 - 1.00]) for both, versus 100% and 27% respectively (CI 95% [0.05 - 1.00]) in patients who did not have regional surgery (HR = 0.80, 95% CI [0.14 - 4.48], p = 0.80).

PSM did not significantly change the results (Fig. 2).

A sensitivity analysis excluding ACCs was performed for the EFS. After PSM, we still observed a tendency towards a better EFS in the group with regional surgery versus without regional surgery (p = 0.25) *but no significant difference were seen and therefore no conclusion could be drawn* (supplementary data, figure 5).

2) ***Surgery in advanced stages (T4a and T4b).***

Our series included 37 patients (21 women and 16 men, mean age 67) with T4a and T4b tumors. In this subgroup, 26 patients were operated while 11 were not.

The characteristics of the two groups of patients (surgery or not) are presented in supplementary data (Table 6). There was no difference for most characteristics except for immunodepression, stage and chemotherapy. PSM generated 2 matched groups (8 pairs, n = 16 patients) with no significant difference of clinical and therapeutic characteristics.

3.5.3. EFS (T4a and T4b) (Fig. 3):

After PSM, the 2-year and 5-year EFS of T4a / T4b patients treated by surgery was 44% (95% CI [0.19 - 1.00]) for both, versus 18% (95% CI [0.03 - 0.98]) and 0% in patients not treated by surgery (HR = 0.39, 95% CI [0.16 - 0.94], p = 0.03).

3.5.4. OS (T4a and T4b)

After PSM, the 2-year and 5-year OS of T4a / T4b patients treated by surgery was 57% (95% CI [0.30 - 1.00]) for both, versus 42% (95% CI) [0.16 - 1.00]) and 0% in patients not treated by surgery (HR = 0.34, 95% CI [0.13 - 0.88], p = 0.02).

PSM did not significantly change the results (Fig. 3).

3) ***Interest of adjuvant radiotherapy in early stages (T1 and T2):***

Our series included 42 operated patients (20 women and 22 men, mean age 67 (range)) with T1 / T2 stages. In this subgroup, 17 patients received postoperative radiotherapy while 25 did not. The characteristics of the two groups of patients (radiotherapy or not) are presented in supplementary data (Table 7). Both patient groups were comparable for all characteristics. PSM generated 2 matched groups (13 pairs, n = 26 patients) with no significant differences of clinical and therapeutic characteristics.

3.5.5. EFS of 42 operated patients with T1 or T2 tumors (Fig. 4):

After PSM, the 2-year and 5-year EFS of patients treated with postoperative radiotherapy was 54% (95% CI [0.32 - 0.89]) for both, versus respectively 54% (95% CI [0.33 - 0.89]) and 43% (95% CI [0.22 - 0.84]) in patients not treated with radiotherapy (HR = 0.91, 95% CI [0.33 - 2.52], p = 0.86).

3.5.6. OS of 42 operated patients with T1 or T2 tumors

After PSM, OS at 2 years and 5 years of patients treated with

Table 2
Pronostic factors analysis on EFS:.

					Univariate analysis			Multivariate analysis (stepwise)		
	Modality	Effective	Events	Median	HR	IC 95%	p (log rank test)	HR	IC 95%	p
Age (years)	**< 65**	38	19	28						
	> ou = 65	65	38	18	1.45	0.83-2.52	0.2	na	na	na
Gender	**Female**	54	27	24						
	Male	49	30	18	1.46	0.87-2.47	0.1	na	na	na
Body Mass Index (kg/m2)	**Normal**	87	45	22						
	Malnutrition < 19	2	2	4.5	10.14	2.31-44.6	**0.0002**	**14**	**2.9-67.08**	**0.0009**
	Obesity > 30	14	10	9	1.92	0.97-3.82	0.13	na	na	na
Alcohol	**No**	84	46	21						
	Yes	19	11	18	1.16	0.60-2.24	0.7	na	na	na
Tobacco	**No**	69	42	18						
	Yes	34	15	na	0.63	0.35-1.14	0.1	na	na	na
Immunosuppression	**No**	81	40	27						
	Yes	22	17	9.5	2,26	1.28-4.01	**0.004**	**2.61**	**1.41-4.84**	**0.002**
History of radiotherapy	**No**	93	52	19						
	Yes	10	5	22	0.86	0.34-2.15	0.7	na	na	na
Karnofsky index (%)	**> 90**	59	28	28						
	<or = 90	44	29	9	2.17	0.27-2.82	**0.004**	**2**	**1.45-11.2**	**0.02**
Time diagnostic-symptoms (months)	**< or= 5**	54	32	19						
	> 5	49	25	24	0.77	0.46-1.31	0.3	na	na	na
Pain	**No**	27	10	na						
	Yes	76	47	19	1.78	0.9-3.52	0.09	na	na	na
Peripheric Facial Palsy	**No**	98	52	22						
	Yes	5	5	9	2.61	1.03-6.6	**0.042**	**4.85**	**1.8-12.95**	**0.0016**
Stage T	**T1-T2**	57	29	27						
	T3-T4	46	28	21	1.19	0.71-2.01	0.51	na	na	na
Stage N	**N0**	93	53	53						
	N+	10	4	4	1.46	0.53-4.02	0.5	na	na	na
Histology	**ACC***	13	5	na						
	SCC* *	82	47	19	0.57	0.23-1.45	0.5	na	na	na
Degree of differenciation	**Moderate/well**	66	31	44						
	poor / not	37	26	15	1.72	1.02-2.94	**0.04**	na	na	na
R Status	**0**	56	24	48						
	1	47	33	13	1.96	1.16-3.33	**0.01**	**2.6**	**1.5-4.51**	**0.0006**

*ACC = adenoid cystic carcinoma; * * SCC = Squamous Cell Carcinomas

postoperative radiotherapy was 83% (95% CI [0.65 - 1.00]) for both, versus 92% (95% CI) % [0.79 - 1.00]) and 60% (95% CI [0.35 - 1.00]) in patients not treated with radiotherapy (HR = 0.7, 95% CI [0.13 - 3.6], p = 0.66).

PSM did not significantly change the results (Fig. 4).

4. Discussion

To our knowledge, this is one of the larger cohort studies on CEAC currently reported in the literature.

The majority of tumors studied in our series were diagnosed at a late stage (59% of T3 and T4). This is consistent with the literature in which the proportion of locally advanced stages varies from 38% to 71% [17]. This high rate of late discovery has a direct impact on survival [17]. In our series, 5-year OS was less than 50%, and 5-year RFS was 41%. CEAC are known to be particularly aggressive, with a 5-year OS varying among studies from 33% to 66% [17,18].

We identified several prognostic factors for EFS and OS. Immunosuppression is a factor of poor prognosis in our study, wich is consistent with existing literature [19]. The degree of differentiation stands out as a strong prognostic value. [8,20–22].

Zanoletti et al proposed a prognostic score based on clinico-radiological criteria (T status, dural invasion if T4 and non-anterior extension if T4) and histological criteria (grade) [23]. This score makes it possible to determine a patient population at high risk of recurrence requiring more aggressive treatment and increased surveillance. Our series found the same prognostic factors as T status (locally advanced tumor) and and poorly or undifferentiated tumor, in univariate analysis, but not in mutltivariate analysis, probably due to a lack of power.

Our series included 80% SCC, which is consistent with the literature [17,24,25]. The survival of patients with SCC was significantly lower than the survival of patients with ACC. ACC is indeed associated with better survival, due to a frequently indolent evolution and relapses much more delayed than in SCC [26].

Lymph nodes invasion has been described as a strong prognostic factor for poorer EFS [4,27]. In our series, this factor did not appear to be significant, probably due to a lack of power. Nodal invasion occurred only in 6% of our cases and was always unilateral. These findings were in accordance with other series (6–13%) [4,25].

The presence of facial palsy was a rare event in our series (5%). It appears as a prognostic factor for poorer EFS without being significant in OS, suggesting that it is mainly a factor of recurrence rather than influencing OS. These results are consistent with the literature as it is known as a strong prognostic factor for poorer EFS since it defines T3 stage in the Pittsburgh's classification [21,22,28,29].

Positive margins were also a prognostic factor for poorer EFS, without any significant effect on OS, which highlights the consistency of the cohort.

Finally, time to diagnosis was not retained in our study as a significant prognostic factor, unlike in other series [30–32].

4.1. Role of surgery in the management of malignant tumors of EAC

4.1.1. Local surgery

The standard of care for the oncologic management of TBSCC is surgery [33]. Only one study suggests better local control with exclusive radiotherapy in the management of T1 tumors [34]. However, the role of definitive RT for early tumors has yet to be fully elucidate. Ogawa et al saw an improved 5-year DFS rate for T1 and reduced DFS rate for T2 in the definitive radiotherapy group [35]. However, other studies support improved OS with surgery vs definitive RT. Indeed, Morita et al

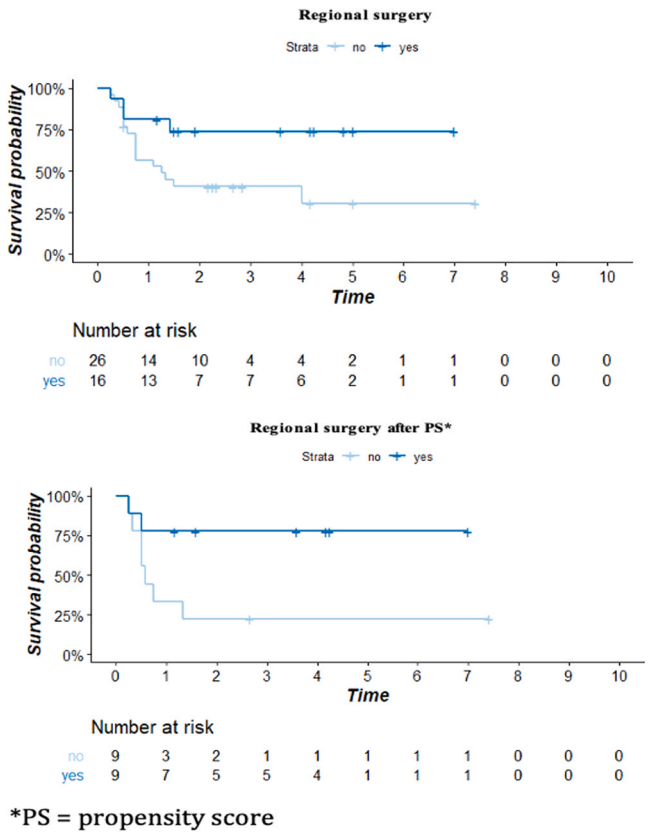

Fig. 2. Event-free survival curves of T1 and T2 patients with (yes) or without (no) regional surgery before and after propensity score matching. Time is expressed in years.

examined T1/T2 EAC SCC patients, and reported improved OS with surgery and adjuvant vs definitive radiotherapy [36].

While most authors consider that tumors classified T4c by involvement of the dura mater are inoperable [1,33], the management of T4a and T4b tumors is debated. Many authors propose a conservative attitude. For these authors, surgery, i.e. sub-total or total resection of the temporal bone, is considered too aggressive given the low survival rate of these patients [33].

On the contrary, our study suggests that upfront surgery in patients with T4a and T4b tumors is associated with a significant increase in OS and EFS.

4.1.2. *Regional surgery*

Our study suggests that regional control by neck dissection and parotidectomy in the surgical management of early-stage tumors is associated with an increase in EFS even if this has no significant influence on OS. These results are in line with the recommendations of the REFCOR and are consistent with the results of other series [15]. We therefore advocate maintaining the indication of this regional surgery in the early stages.

However, the parotid gland is also still a point of controversy when it comes to treating patients with glands not directly affected by their TBSCC. The parotid gland may be involved either by a direct extension of the TBSCC or via nodal dissemination of the disease because the gland contains first-line draining nodes. Preformed pathways around the EAC such as the cartilaginous fissures of Santorini, the petro-squamous suture line, and the bony foramen of Huschke are suspected of facilitating the tumor's anterior dissemination [37].

For some authors, there is no need to perform a superficial parotidectomy in T1/T2 N0 stages because of the low rate of parotid lymph node metastasis (0% to 5%) [38]. On the other hand, some authors

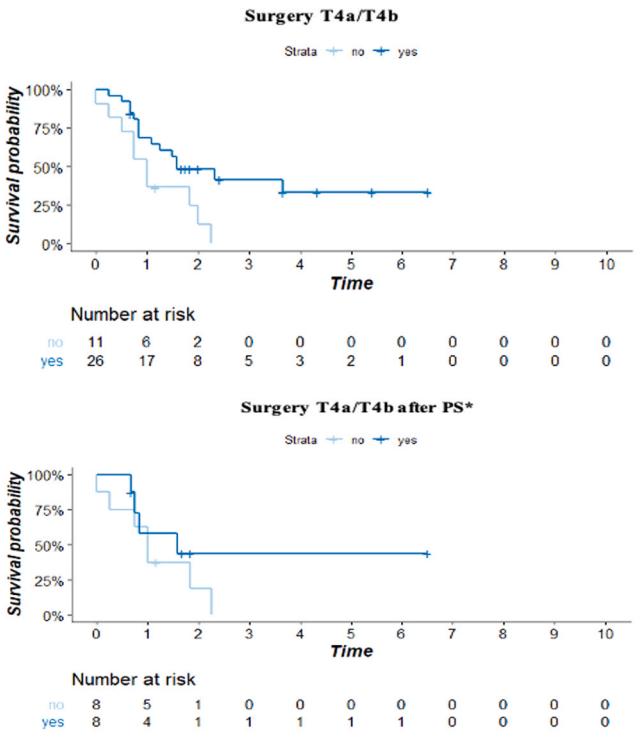

Fig. 3. Event-free survival curves of T4a and T4b patients with (yes) or without (no) surgery before and after propensity score matching. Time is expressed in years.

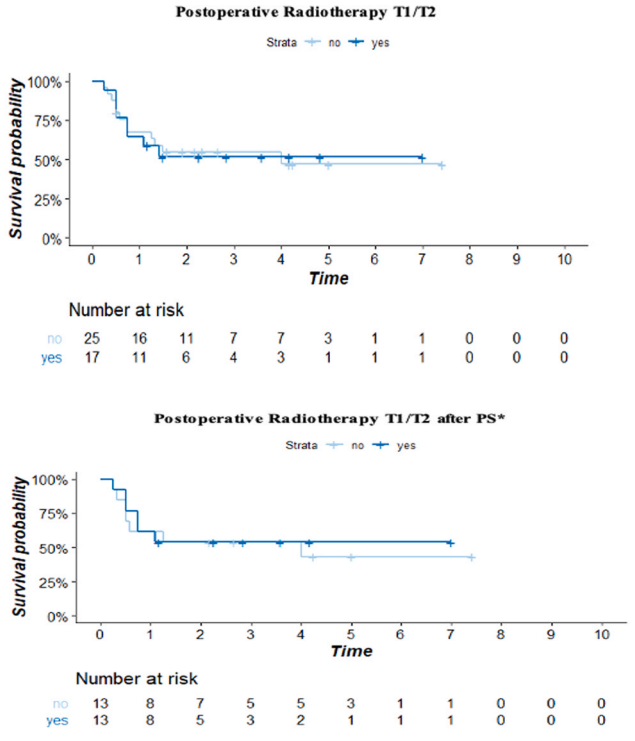

Fig. 4. Event-free survival curves of T1 and T2 patients with (yes) or without (no) postoperative radiotherapy before and after propensity score matching. Time is expressed in years.

disagree and recommend performing prophylactic superficial parotidectomy due to a high rate of parotid lymph node metastasis (17% to 62%) [39].

In the same way, neck dissection in clinically negative neck is still a matter of debate.

The EAC and middle ear are drained by the parotid and peri-parotid, pre- and post-auricular, sub-mandibular, upper deep cervical and retropharyngeal lymph nodes [37]. The incidence of lymph node involvement in TBSCC is relatively low (10–23%) [40], and levels I and II are the most commonly involved [41].

Some authors do not recommend elective neck dissection [42], while others perform it routinely [29]. Elective neck dissection has been recommended in all patients with locally-advanced TBSCC [43], in which case a selective neck dissection (SND) [I–III] is preferred by most authors [16]. Gidley and colleagues [44] suggested SND [II–III] for T1 and T2 patients as well to appropriately stage and select those requiring adjuvant radiotherapy.

However, we also observe that this might not apply to all histological types: our series included more than 80% of SCC vs 12% of ACC. Due to the natural history of ACC, it is likely that regional surgery is not required in cN0 patients. The need for neck dissection in case of ACC is widely debated [34–36] and our study is lacking power to contribute to this debate.

4.2. Radiotherapy

REFCOR recommendations, as well as numerous authors [13,16, 45–47], propose adjuvant irradiation after surgery for any tumor stage, except for some very selected cases of T1 tumors strictly confined to the posterior wall of the EAC and presenting no histological pejorative factor. Our study did not show any significant improvement in OS or EFS when adjuvant radiotherapy was performed in patients with T1 and T2 tumors. No conclusion can therefore be proposed. This modality of treatment remains to be evaluated, either by a study of higher power, or by a prospective evaluation.

Chemotherapy has not been evaluated in the therapeutic strategy of CEAC. A single meta-analysis found a significant increase in survival of patients receiving neo-adjuvant chemotherapy in locally advanced stages before surgery [48]. In our study, we could not evaluate the benefit of chemotherapy, as it was administered to a small minority of patients.

5. Conclusion

This study suggests that denutrition, immunosuppression, Karnofsky statut less than 90, facial palsy and positive margin are pejorative prognostic factors for EFS.

Our study suggests to perform systematically neck dissection and homolateral parotidectomy in T1/T2 SCC and that a surgical resection is worth proposing in advanced stages (T4a and T4b).

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Cullié Dorian: Writing – review & editing, Visualization, Validation, Data curation. **Gallet Patrice:** Writing – review & editing, Visualization, Validation, Data curation. **Moya-Plana Antoine:** Writing – review & editing, Visualization, Validation, Data curation. **Guerlain Joanne:** Writing – review & editing, Visualization, Validation, Data curation. **Schultz Philippe:** Writing – review & editing, Visualization, Validation, Data curation. **Fath Léa:** Writing – review & editing, Visualization, Validation, Data curation. **Mauvais Olivier:** Writing – review & editing, Visualization, Validation, Data curation. **Malard Olivier:** Writing – review & editing, Visualization, Validation, Data curation. **Lesnik Maria:** Writing – review & editing, Visualization, Validation, Data curation. **Atallah Sarah:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis. **Evrard Diane:** Writing – review & editing, Visualization, Validation, Data curation. **Brenet Esteban:** Writing – original draft, Validation, Supervision, Resources, Project administration, Investigation, Data curation, Conceptualization. **Saroul Nicolas:** Writing – review & editing, Visualization, Validation, Data curation. **Dufour Xavier:** Writing – review & editing, Visualization, Validation, Data curation. **Verillaud Benjamin:** Writing – review & editing, Visualization, Validation, Resources, Data curation. **Le Taillandier de Gabory Ludovic:** Writing – review & editing, Visualization, Validation, Resources, Data curation. **Thariat Juliette:** Writing – review & editing, Visualization, Validation, Data curation. **Costes Valérie:** Writing – review & editing, Visualization, Validation, Data curation. **Even Caroline:** Writing – review & editing, Visualization, Validation, Data curation. **Fakhry Nicolas:** Writing – review & editing, Visualization, Validation, Data curation. **Baujat Bertrand:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Dubernard Xavier:** Writing – review & editing, Visualization, Validation, Resources, Data curation. **Makeieff Marc:** Writing – review & editing, Visualization, Validation. **Righini Christian-Adrien:** Writing – review & editing, Visualization, Validation, Data curation. **Philouze Pierre:** Writing – review & editing, Visualization, Validation, Data curation. **Bakhos David:** Writing – review & editing, Visualization, Validation, Data curation. **Kania Romain:** Writing – review & editing, Visualization, Validation, Resources, Data curation. **Vergez Sébastien:** Writing – review & editing, Visualization, Validation, Resources, Data curation. **Labrousse Marc:** Writing – review & editing, Visualization, Validation, Data curation. **Mérol Jean-Claude:** Writing – review & editing, Visualization, Validation, Data curation. **Bozorg-Grayeli Alexis:** Writing – review & editing, Visualization, Validation, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113922.

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