European Journal of Cancer xxx (xxxx) xxx

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

A prospective multicentre REFCOR study of 470 cases of head and neck Adenoid cystic carcinoma: epidemiology and prognostic factors

Sarah Atallah [a,b], Odile Casiraghi [c], Nicolas Fakhry [d], Michel Wassef [e], Emmanuelle Uro-Coste [f], Florent Espitalier [g], Anne Sudaka [h], Marie Christine Kaminsky [i], Stéphanie Dakpe [j], Laurence Digue [k], Olivier Bouchain [l], Sylvain Morinière [m], Muriel Hourseau [n], Chloé Bertolus [o], Franck Jegoux [p], Juliette Thariat [q], Valentin Calugaru [r], Philippe Schultz [s], Pierre Philouze [t], Olivier Mauvais [u], Christian A. Righini [v], Cécile Badoual [w], Nicolas Saroul [x], Jean Michel Goujon [y], Jean Paul Marie [z], Rabah Taouachi [aa], Esteban Brenet [ab], Anne Aupérin [ac], Bertrand Baujat [a,*]

[a] *Sorbonne University, APHP, Department of ENT-Head and Neck Surgery, Tenon Hospital, 4 Rue de La Chine, 75020, Paris, France*
[b] *Doctoral School of Public Health, CESP, University of Paris Sud, 16 Avenue Paul Vaillant Couturier, 94807, Villejuif, France*
[c] *Department of Biopathology, Gustave Roussy Cancer Campus, 114, Rue Edouard Vaillant, 94805, Villejuif, France*
[d] *Department of ENT-Head and Neck Surgery, University Hospital of Marseille, APHM, 13915, Marseille, France*
[e] *Department of Pathology, Lariboisière University Hospital, Paris Diderot University, APHP, 75010, Paris, France*
[f] *Department of Pathology and Cytopathology, University Cancer Institute Toulouse, Toulouse University Hospital, 1 Avenue Irène Joliot-Curie, 31400, Toulouse, France*
[g] *Department of ENT-Head and Neck Surgery, Nantes University Hospital, 1 Place Alexis-Ricordeau, 44000, Nantes, France*
[h] *Department of Pathology, Centre Antoine-Lacassagne, 31 avenue de Valombrose, 06189, Nice, France*
[i] *Department of Medical Oncology, Oncology Institute of Lorraine, Vandoeuvre-Lès-Nancy, 54035, Nancy, France*
[j] *Department of Maxillofacial Surgery, University Hospital of Amiens-Picardy, Avenue René Laennec, 80000, Amiens, France*
[k] *Department of Medical Oncology, Radiotherapy, Dermatology and Palliative Care, University Hospital of Saint André, 1 Rue Jean Burguet, 33075, Bordeaux, France*
[l] *Department of ENT-Head and Neck Surgery, University Hospital of Liège, Belgium*
[m] *Department of ENT-Head and Neck Surgery, Tours Bretonneau University Hospital, 2 Boulevard Tonnellé, 37000, Tours, France*
[n] *Department of Pathology, Hospital Bichat, APHP, 75018, Paris, France*
[o] *Department of Oral and Maxillofacial Surgery, Sorbonne University, Pitié-Salpêtrière Hospital, APHP, 75013, Paris, France*
[p] *Department of ENT-Head and Neck Surgery, Rennes University Hospital, 2 Rue Henri Le Guilloux, 35000, Rennes, France*
[q] *Department of Radiotherapy, François Baclesse Centre, 3 Rue Du Général Harris, 14000, Caen, France*
[r] *Department of Oncology Radiotherapy, Curie Institute, 26 Rue D'Ulm, 75005, Paris, France*
[s] *Department of ENT-Head and Neck Surgery, University Hospital of Strasbourg, 67000, Strasbourg, France*

* *Corresponding author*:
E-mail address: bertrand.baujat@tnn.aphp.fr (B. Baujat).

https://doi.org/10.1016/j.ejca.2020.01.023
0959-8049/© 2020 Elsevier Ltd. All rights reserved.

Please cite this article as: Atallah S et al., A prospective multicentre REFCOR study of 470 cases of head and neck Adenoid cystic carcinoma: epidemiology and prognostic factors, European Journal of Cancer, https://doi.org/10.1016/j.ejca.2020.01.023

[t] Department of ENT-Head and Neck Surgery, Hospices Civils de Lyon, Lyon-Nord University Hospital, 103 Grande Rue de La Croix Rousse, 69000, Lyon, France
[u] Department of ENT-Head and Neck Surgery, University Hospital of Besançon, France, 25000, Besançon, France
[v] Department of ENT-Head and Neck Surgery, Grenoble Alpes University Hospital, CS 10217, 38043, Grenoble, France
[w] Department of Pathology, European Georges Pompidou University Hospital, Assistance Publique-Hôpitaux de Paris, Paris Descartes University, Paris University, PARCC INSERM U970, Paris, France
[x] Department of Radiotherapy, Jean Perrin Centre, University Clermont Auvergne, 63100, Clermont-Ferrand, France
[y] Department of Pathology, University Hospital of Poitiers, 2 Rue de La Milétrie, CS 90577, 86021, POITIERS, France
[z] Department of ENT-Head and Neck Surgery, Rouen University Hospital, 1 Rue de Germont, 76031, Rouen, France
[aa] Department of ENT-Head and Neck Surgery, Curie Institute, René Huguenin Hospital, Saint-Cloud, France
[ab] Department of ENT-Head and Neck Surgery, Robert Debré University Hospital, 51100, Reims, France
[ac] INSERM U1018, CESP, Université Paris-Sud, Université Paris-Saclay, 16 Avenue Paul Vaillant Couturier, 94807, Villejuif, France

Received 29 September 2019; received in revised form 14 January 2020; accepted 28 January 2020
Available online ■ ■ ■

KEYWORDS
Adenoid cystic carcinoma;
Prognostic factors;
Event-free survival;
REFCOR

Abstract ***Background:*** Adenoid cystic carcinoma (ACC) accounts for 1% of malignant head and neck tumours [1] and 10% of salivary glands malignant tumours. The main objective of our study is to investigate the prognostic factors influencing the event-free survival (EFS) of patients with ACC.
Patients and methods: A multicentre prospective study was conducted from 2009 to 2018. All 470 patients with ACC whose survival data appear in the REFCOR database were included in the study. The main judgement criterion was EFS. Both a bivariate survival analysis using log-rank test and a multivariate using Cox model were performed using the *R* software.
Results: Average age was 55 years. Females accounted for 59.4% of the cohort. The body mass index (BMI) was normal in 86% of cases. Tumours were located in minor salivary glands in 60% of cases. T3/T4 stages represented 58%; 89% of patients were cN0. histological grade III was observed on 21% of patients. The EFS and overall 5-year survival rates were 50% and 85%, respectively. After adjustment, the most significant pejorative prognostic factors were age $\geq$65 years (hazard ratio [HR] = 1.67), BMI<16.5 (HR = 2.62), and lymph node invasion cN (HR = 2.08).
Conclusion: Age, BMI and N stage are the three main clinical prognostic factors determining EFS identified in this prospective series of patients with ACC. Such findings open new research perspectives on the influence of these components on initial patient care.
© 2020 Elsevier Ltd. All rights reserved.

1. Background

The annual incidence of malignant tumours of the salivary glands represents 0.4 to 2 cases per 100,000 [2]. Adenoid cystic carcinoma (ACC) accounts for 1% of malignant head and neck tumours [1] and 10% of salivary glands malignant tumours [3].

Initially indolent, it behaves like a low-grade tumour but leads to multiple and late local and distant recurrences [4]. Its imprecise limits and its extensive and infiltrating power via the perineural sheaths make it a deadly prognosis tumour [5].

Its natural history is poorly known, and no risk factor has presently been identified [6].

Three types of tumour architecture have been described: cribriform, tubular, or solid. This classification was adopted by the *World Health Organization* and revised in 2017 [7].

The results of prognostic studies on ACC are inconsistent, particularly those concerning vascular embolisms and perineural invasion [8,9].

This can be explained because they are mainly retrospective series and include small populations [10−12]. The five main series of the literature (>1000 patients) collect only a limited number of variables [3,13−16].

A multicentre prognostic analysis was carried out in 2012 by the *French National Network on rare head and neck cancers* (REFCOR) [17]. Carried out two years after the network's creation, this series included 95 patients [18]. Since then, the network's growth has enabled a greater number of cases to be recorded.

Please cite this article as: Atallah S et al., A prospective multicentre REFCOR study of 470 cases of head and neck Adenoid cystic carcinoma: epidemiology and prognostic factors, European Journal of Cancer, https://doi.org/10.1016/j.ejca.2020.01.023

The main objective of our study is to investigate prognostic factors in terms of event-free survival (EFS) of patients with ACC. The secondary objective is to describe the natural history of this population.

2. Patients and methods

This study is a descriptive, prognostic, prospective, multicentric analysis. The inclusion of patients in the database was carried out by each centre of the REFCOR, using a standardised questionnaire. The data were anonymised, and an informed consent was signed by the patients in accordance with French law.

The inclusion period ran from January 2009 to February 2018. All patients followed in one of the REFCOR centres, with a M 8200/3 ICD O diagnosis code corresponding to ACC (N = 670 in 44 centres), were included. Patients for whom no EFS data was available (N = 183) or for whom the diagnosis was rectified after first review of the records (N = 17), were excluded. Overall, 470 patients were included, of a population of 5982 rare head and neck cancers.

Data quality control was ensured by two file reviews. An update of the database was requested from the referring physicians. A review of the histological reports available (surgical specimen or biopsy) was then performed, allowing additional verification of the variable of interest. All the samples were analysed by pathologists of the REFCOR and 7% (32/470) histological reports were analysed in first instance by a pathologist who considered that a second pathologic opinion by the REFCOR national experts was necessary. Of them, 15 cases were initially mislabelled and were corrected as ACC [19].

The characteristics of the 183 patients excluded for missing survival data were compared with those of patients with complete data to eliminate selection bias. No significant difference was found (data not shown).

The primary criterion for the prognostic analysis was EFS, events being defined as local recurrence or progression, metastasis or death.

Therapeutic data were excluded from the search for prognostic factors. They are the subject of a further study.

Follow-up durations were comprised between the date of histological diagnosis and the date of last consultation or of first event.

The secondary judgement criteria were overall survival (OS), locoregional recurrence-free survival (RFS), and metastasis-free survival (MFS).

Patients survival was studied in accordance with the following criteria: sex; age at diagnosis (<65 versus ≥65-year-old); BMI: undernutrition (<16.5) versus normal BMI versus obesity (≥30); occupation (exposed versus unexposed)[1]; tobacco consumption; alcohol consumption; immunodeficiency (diabetes, HIV, immunosuppressive treatment and other unspecified); tumour size: T1-T2 versus T3-T4; cN status: cN0 versus cN+; Stage I−II versus Stage III−IV (in accordance with AJCC/UICC 2008 classification) Tumour site: major salivary gland (MaSG) versus minor salivary glands (MiSG) (i.e. other sites); surgical margins: ("free" versus "close" or "positive"); histological grade: I−II versus III (i.e. solid component ≥30%); pN status: pN0 versus pN+; perineural invasion; vascular embolisms; necrosis.

A bivariate analysis with EFS as a function of these covariates was performed using log-rank test. The multivariate analysis was performed using a Cox model and the stepwise method. Schoenfeld residuals were measured to validate the model. Graphical representations were made using the Kaplan-Meier method. All statistical analyses were conducted using the *R* software (version 3.6.0; 2019-04-26).

3. Results

Characteristics of the patients are summarized in Table 1. Among the 470 patients, mean age at diagnosis was 54 years (median 55, range [18−90]), sex was predominantly female (sex ratio: 1.5), mean BMI was 25 kg/m^2 (median: 25, range: [16−46]), median Karnofsky index was 90% (mean: 91%, range: [40%−100%]).

Diagnosis dates ranged from 1992 to 2017. All patients were included after 2008.

MiSGs were more frequently affected than MaSGs (60%/40%). The four main affected sites were: sinus cavities (25%), parotid gland (21%), oral cavity (18%) and submandibular gland (13%).

The majority of patients had advanced stages: 20% T3, 38% T4 and 7% metastatic at the time of the diagnosis. Sinus tumours were classified as T3-T4 in 86% of cases, whereas MaSGs were classified as T1-T2 in 58% of cases. However, 89% of patients were cN0.

Patients had primary surgery in 86% of cases.

A neck dissection was performed on 51% of patients. A total of 18% of patients were pN+ (regardless of

[1] The Socio-Professional Category was collected according to the codification established by the *National Institute of Statistics and Economic Studies* (INSEE): 1/Farmers; 2/Craftsmen, shopkeepers, company operators; 3/Managers, higher intellectual professions; 4/Intermediate professions; 5/Employees; 6/Workers; 7/Formerly employed but inactive workers; 8/Others without professional activity. They have been recoded into two categories: "exposed" and "unexposed". "Exposed" included manual occupations and occupations at risk of toxic exposure: farmers, craftsmen, foremen, supervisors, supervisors and workers.

Please cite this article as: Atallah S et al., A prospective multicentre REFCOR study of 470 cases of head and neck Adenoid cystic carcinoma: epidemiology and prognostic factors, European Journal of Cancer, https://doi.org/10.1016/j.ejca.2020.01.023

Table 1
Characteristics of the 470 patients with ACC (na = data not available).

Variable	Modality	N	%
		470	100%
Sex	Female	279	59%
	Male	191	41%
Age	<65	352	75%
	≥65	118	25%
BMI	<16.5	5	1%
	Normal	342	86%
	≥30	52	13%
	na	71	
Occupation	Unexposed	241	77%
	Exposed	73	23%
	na	156	
Alcohol consumption	No	374	86%
	Yes	59	14%
	na	37	
Tobacco consumption	No	318	72%
	Yes	122	28%
	na	30	
Immunodeficiency[a]	No	437	93%
	Yes	33	7%
	na	0	
Variable	**Modality**	**Proportion**	**%**
		470	100%
Tumour site	**MiSG**	**281**	**60%**
	Oral cavity	83	18%
	Nasal ethmoidal cavity	62	13%
	Maxillary sinus	57	12%
	Oropharynx	34	7%
	External ear canal	14	3%
	Nasopharynx	13	3%
	Larynx infra glottic	7	1%
	Larynx glottic	5	1%
	Orbit	4	1%
	Larynx supra glottic	2	0%
	MaSG	**186**	**40%**
	Parotid	98	21%
	Submandibular	62	13%
	Sublingual	6	1%
	Unspecified	20	4%
	na	3	
T Status	T1	80	19%
	T2	97	23%
	T3	86	20%
	T4	164	38%
	na	43	
cN Status	cN0	385	89%
	cN1	27	6%
	cN2	20	5%
	cN3	1	0%
	na	37	
M Status	M0	403	93%
	M1	31	7%
	na	36	
TNM	Stage 1	74	18%
	Stage 2	81	19%
	Stage 3	74	18%
	Stage 4	187	45%
	na	54	
Surgery	No	67	14%
	Yes	399	86%
	na	4	
Surgical Margins	Free	126	38%
	Close	72	21%
	Positive	137	41%
	na	64	
Lymph node invasion (pN)	pN0	133	82%
	pN+	30	18%
	na	19	
Node capsular effraction	No	139	89%
	Yes	18	11%
	na	25	
Chemotherapy	No	363	82%
	Yes	80	18%
	na	27	
Radiotherapy	No	119	26%
	Yes	332	74%
	na	19	
Histological grade	I	163	60%
	II	51	19%
	III	58	21%
	na	198	
Necrosis	No	21	57%
	Yes	16	43%
	Na	433	
Vascular embolisms	No	99	67%
	Yes	49	33%
	na	322	
Perineural invasion	No	72	30%
	Yes	169	70%
	na	229	

MaSG, major salivary gland; MiSG, minor salivary gland.
ACC, adenoid cystic carcinoma; BMI, body mass index.
[a] Diabetes 70% (23/33); HIV (0/33); Immunosuppressive treatment 15% (5/33) and unspecified 15% (5/33).

initial cN status). Neck dissection rates varied based on the tumour sites: few neck dissections were performed for sinus tumours (17%), compared with MaSGs (67%) or oral cavity (84%).

Within the 470 cases, 334 histological reports from 29 centres were reviewed (71%).

Histological grade III was found in 21% of tumours; 33% had vascular embolisms and 70% had perineural invasion.

Patients received radiotherapy in 74% of cases, whether exclusive (15%) or postoperative (85%). Irradiated patients had T3-T4 stages at diagnosis in 65% of cases. Chemotherapy was performed on 18% of patients, 77% of whom received it concomitantly with radiotherapy. Induction chemotherapy was only performed on 6 patients with stage T4.

The average follow-up was 39 months with a first quartile at 13 months, a median at 25 months and a third quartile at 52 months (extreme values: 1−282). During follow-up, 213 events occurred; 45% of patients experienced at least one of these events.

The median EFS was 59 months (95% confidence interval [CI]: [54−73]). The 5-year and 10-year EFS rates

Please cite this article as: Atallah S et al., A prospective multicentre REFCOR study of 470 cases of head and neck Adenoid cystic carcinoma: epidemiology and prognostic factors, European Journal of Cancer, https://doi.org/10.1016/j.ejca.2020.01.023

were 50% (95% CI: [0.44−0.56]) and 20% (95% CI: [0.14−0.28]), respectively.

The rates of OS, MFS and RFS at 5 years were 85% (95% CI: [0.81−0.89]), 62% (95% CI: [0.57−0.69]) and 64% (95% CI: [0.58−0.7]), respectively. The 10-year rates of OS, MFS and RFS were 67% (95% CI: [0.60−0.77]), 46% (95% CI: [0.38−0.54]) and 30% (95% CI: [0.23−0.4]), respectively (Fig. 1)After bivariate analysis, 9 variables were identified as having a negative impact on EFS: among them, 2 epidemiological (age, BMI), 3 clinical (T stage, cN Stage, Stage III-IV) and 4 histological characteristics (capsular effraction, pN Stage, histological grade, perineural invasion).

After multivariate analysis, 3 factors having a negative impact on EFS were identified: Age ≥65 years; BMI<16.5 and cN + stage (Table 2 and Fig. 2).

4. Discussion

REFCOR has made it possible to structure the management of rare head and neck tumours nationally and to centralise the collection of research data. The REFCOR database has collected 25 epidemiological, clinical and histological variables. To our knowledge, it is the study with the largest number of variables taken into account simultaneously, and the largest French series of patients with ACC to date [6,18].

The mean diagnosis age was 55 years, in line with other studies [14,15]. Gender was predominantly female, with a sex ratio of 1.5, which corresponds to that of the other series [9,14].

Tumours were located in the MaSGs in 40% of cases. This figure varies from 29% to 47% depending on the study [8,9]. The most affected was parotid gland with a rate of 21% in our series. Similar proportions are found in the literature, ranging from 22% to 32% [20,21].

The MiSGs were mainly affected, with a predominance for the sinus site (25%). The frequency of such a location varies from 8% to 19% depending on the series [10,22]. The third most frequent location in our series was the oral cavity with a rate of 18%. This rate varies in the literature from 17% to 58% [9,20]. This variability can be explained by the classification ambiguity of these tumours. Being located on the hard palate, they can be categorized either as a tumour of the oral cavity or a tumour of the nasal cavities, especially in the case of large tumours.

In our series, 19% of tumours were classified as T1, comparable with the rates in the literature, ranging from 22% to 29% [9,15].

Of all tumours, 38% were classified as T4 at diagnosis. This rate is higher than in the literature (from 9% to 28%) [8,15]. As a possible explanation, we found a higher proportion of sinus tumours in our series, 86% of which were classified as T4. The high proportion of T4 among sinus tumours has already been reported [23]. In addition, this over-representation may be due to centre effects because some REFCOR centres are specialised in the management of sinus tumours.

Nodal invasion at diagnosis was rare with 11% of patients classified as cN+. This proportion varies in the literature from 9.2% to 15% [8,9]. This can be explained by the low propensity of sinus and parotid locations to lymph node invasion, particularly because of their natural history of extension via the perineural sheaths [24,25].

The percentage of metastases at diagnosis was low (7%), comparable with the literature (2.4%−4%) [10,15].

In our study, histological grade III was present in 21% of patients, in accordance with a previous study (27%) [26]. Perineural invasion was present in 70% of patients, in line with the literature (31%−70%) [8,26]. In

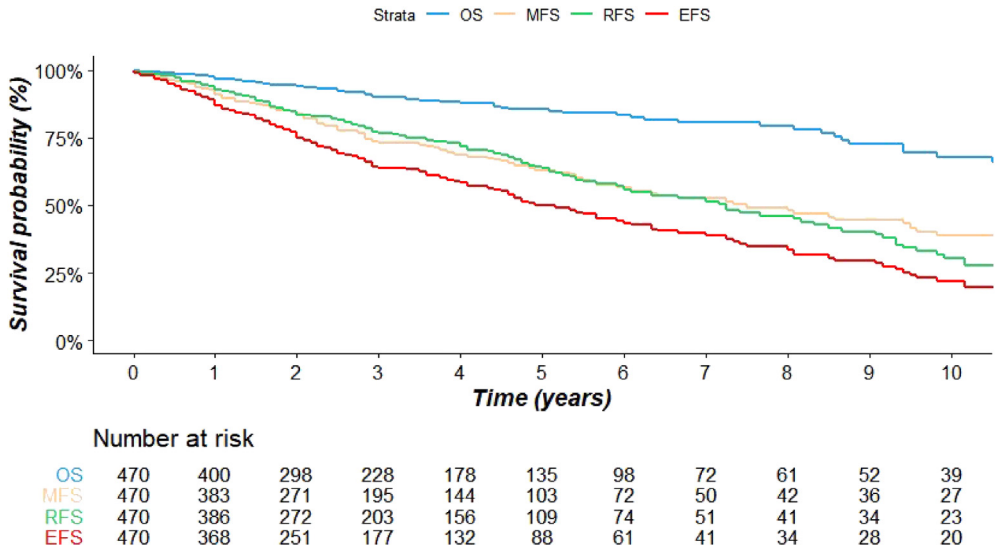

Fig. 1. Overall survival (OS), metastasis-free survival (MFS), local Recurrence-free survival (RFS) and event-free survival (EFS) curves. French. REFCOR patients diagnosed with adenoid cystic carcinoma in 2009−2018.

Please cite this article as: Atallah S et al., A prospective multicentre REFCOR study of 470 cases of head and neck Adenoid cystic carcinoma: epidemiology and prognostic factors, European Journal of Cancer, https://doi.org/10.1016/j.ejca.2020.01.023

Table 2
Event-free survival (median) by age, sex, occupation, BMI, alcohol, tobacco, immunodeficiency, tumour site, T status, cN status, stage TNM, surgical margin, pN status, capsular effraction, perineural invasion and vascular embolisms (na = data not available).

Variable	Modality		Event	EFS	Univariate analysis			Multivariate analysis (stepwise)		
					HR	CI 95%	P value	HR	CI 95%	P value
			(median)				(log-rank test)			(log-rank test)
Age	<65 year-old	352	161	68						
	≥65 year-old	118	52	43	1.76	[1.27−2.42]	<0.001*	1.67	[1,21-2,32]	0.002*
Sex	Female	279	121	59						
	Male	191	92	59	1.06	[0.80−1.39]	0.69	na	na	na
Occupation	Unexposed	241	104	59						
	Exposed	73	34	68	0.95	[0.64−1.40]	0.79	na	na	na
BMI	Normal	342	153	66						
	<16.5	5	4	35	3.17	[1.17−8.60]		2.62	[1.06-6.46]	
	≥30	52	24	57	1.31	[0.85−2.02]	0.03*	1.47	[0.99−2.17]	0.04*
Alcohol	No	374	170	62						
	Yes	59	27	73	1.16	[0.77−1.74]	0.48	na	na	na
Tobacco	No	318	147	64						
	Yes	122	53	52	1.18	[0.86−1.63]	0.3	na	na	na
Immuno	No	437	197	62						
deficiency	Yes	33	16	34	1.6	[0.95−2.66]	0.07	na	na	na
Site	MiSG	281	123	66						
	MaSG	186	89	55	1.09	[0.83−1.43]	0.56	na	na	na
T	T1-T2	177	64	77						
	T3-T4	250	123	52	1.37	[1.01-1.86]	0.042*	1.28	[0.96−1.70]	0.1
cN	cN0	385	153	68						
	cN+	48	35	27	2.69	[1.89−4.01]	<0.001*	2.08	[1.49−2.94]	<0.001*
Stage	Stage 1 Stage 2	155	53	80						
	Stage 3 Stage 4	261	130	54	1.46	[1.06−2.02]	0.02*	na	na	na
Surgical margin	free	126	43	87						
	positive	209	89	59	1.31	[0.91−1.89]	0.15	na	na	na
pN	pN0	133	50	80						
	pN+	30	20	27	2.78	[1.62−4.77]	<0.001*	na	na	na
Node Capsular	No	139	52	80						
effraction	Yes	18	14	18	3.89	[2.01−7.21]	<0.001*	na	na	na
Histological	Grade I-II	214	80	71						
grade	Grade III	58	31	46	1.56	[1,04-2,4]	0.03*	na	na	na
PNI	No	72	20	110						
	Yes	169	75	56	1.79	[1.09−2.93]	0.02*	na	na	na
VE	No	99	27	97						
	Yes	49	27	48	1.65	[0.96−2.83]	0.07	na	na	na

EFS, event-free survival; BMI, body mass index; MaSG, major salivary gland; MiSG, minor salivary gland; HR, hazard ratio.

our series, the notion of perineural invasion was specified in only 51% of histological reports. The histological description seems to be operator dependent, and there is no standard report regarding ACC, which would be worth considering.

Positive margins were observed in 41% of surgical specimens. This proportion varies widely from one study to another, ranging from 9% to 42% [8,11]. In our series, the high proportion of advanced stage (T4) operated on the technical difficulty of *in sano* resection for large tumours may explain this rate.

The OS, RFS, MFS and EFS rates at 5 years and 10 years are described in Table 3. They are comparable with those of the literature.

The bivariate analysis shows age, undernutrition, T3-T4 stage, cN + status, III-IV stage, pN+, capsular effraction, histological grade III and perineural invasion as having a negative impact on EFS. After adjustment, age >65 years, undernutrition and cN + status keep on independently and negatively influencing EFS.

Age is, as expected, found to be a prognostic factor for EFS in our study, as in most other series [9,12,15].

BMI less than 16.5 kg/m^2 is a negative prognostic factor, not specific to ACC. It is probably correlated with the tumour stage and age of the patient. *However only 5 patients had a BMI less than 16.5* kg/m^2 *so stating that undernutrition is correlated with a lower EFS should be considered with caution.*

In bivariate analysis, tumour size is a factor of negative prognosis. This factor does not resist adjustment in the multivariate model. This finding is consistent with the divergence of results found in the literature, where tumour size is considered prognostic for some [9,14,15]; but not for others [12,33].

Tumour sites do not influence the prognosis in our study. In the literature, however, sinus location is

Please cite this article as: Atallah S et al., A prospective multicentre REFCOR study of 470 cases of head and neck Adenoid cystic carcinoma: epidemiology and prognostic factors, European Journal of Cancer, https://doi.org/10.1016/j.ejca.2020.01.023

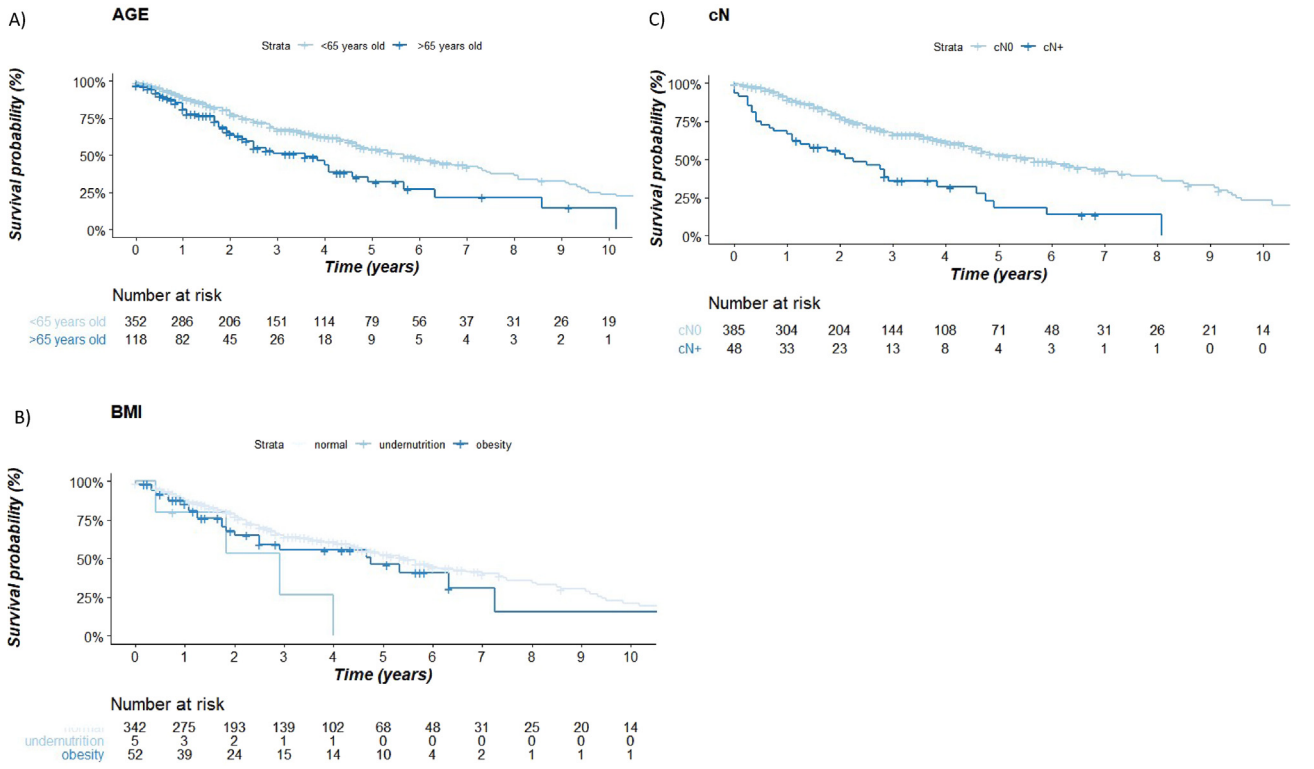

Fig. 2. Event-free survival curves based on prognostic factors: age (A), BMI (B) and cN status (C). BMI, body mass index.

described as a negative prognosis [3,12]. Sinus tumours are supposedly diagnosed at later stages owing to their more asymptomatic nature [3]. The tumour site may therefore only be a source of confusion because the data in these series do not include tumour size.

In our series, the rate of lymph node invasion is low at diagnosis (cN+ = 11%). Lymph node invasion is an unfavourable and independent prognostic factor. These results are supported by several studies, which have also shown a positive correlation between cervical lymph node invasion and metastases development [1,33].

In the bivariate analysis, capsular effraction and pN + are negative prognostic factors for EFS. They are correlated with cN+, which emerges independently in multivariate analyses. The absence of pN+ and capsular effraction in our multivariate model may be explained by the larger amount of missing data compared with cN+. Histological grade III has a negative impact on EFS in bivariate analysis. VanWeert [26] and Matsuba [34] find the same result, whereas Spiro contradicts them [35].

Table 3
Survival rates in comparison with the literature.

	5 years		10 years		
	REFCOR	Others	REFCOR	Others	References
OS	85%	76–90%	67%	52–65%	[3,10,11,26]
RFS	64%	55–90%	30%	37–86%	[27]
MFS	62%	40–70%	46%	30–50%	[28–30]
EFS	50%	56–89%	20%	20–40%	[31,32]

EFS, event-free survival; OS, overall survival; RFS, recurrence-free survival; MFS, metastasis-free survival.

The bivariate analysis shows perineural invasion as a negative prognostic factor, in accordance with the literature [9,10]. Vascular embolisms are not correlated with survival in our study. Few series consider this criterion. One only depicts such a prognostic influence [33].

We did not find that surgical margins influence EFS. However, Lloyd finds that this factor does not influence OS but has an effect on EFS [15].

The choice of EFS was dictated by several reasons. The aim was to focus on ACC at a locally advanced stage in order to optimize their initial management. EFS allows more events to be observed over a shorter follow-up period, with patients' vital prognosis generally being engaged long after the onset of metastatic evolution. It is precisely to avoid local and metastatic recurrences that our treatment process must be improved. The quality of our data allowed this choice, which most authors of the other published series did not have. This study is the first step in an analysis of therapeutic strategies to be carried out on REFCOR database. Treatment phases have therefore been deliberately excluded from prognostic analyses, to avoid Simpson's paradox: treatment is an extrinsic factor to the disease, which both influences and is influenced by the prognosis [36].

However, this study has limitations: 30% of the data were missing. The primary criterion (EFS) was missing for 183 patients who could not be included. Comparison

Please cite this article as: Atallah S et al., A prospective multicentre REFCOR study of 470 cases of head and neck Adenoid cystic carcinoma: epidemiology and prognostic factors, European Journal of Cancer, https://doi.org/10.1016/j.ejca.2020.01.023

of the variables for these patients versus the others did not reveal any difference, allowing them to be excluded without risk of selection bias. The effect of centre size on prognosis could not be investigated, as too much centres were involved, and the proportion of tumour stages varied from one centre to another. However, most of the patients were treated in the reference centres of the network, suggesting that they were treated as per the best standard of practice. We would still recommend that these malignant rare tumours be treated in centres treating high volume of head and neck cancers.

Currently, many biomarkers are emerging as prognostic and predictive factors, determining targeted therapies: ckit, VEGF, Notch 1 are described as prognostic influencing and Myb can help the diagnosis. They pave the way for targeted therapies [37,38].

We were unable to study biomarkers in our study because their notification in histological reports was extremely disparate and missing in a high proportion of cases.

5. Conclusion

This prospective series of 470 patients with ACC suggests that age and N stage are the two main clinical prognostic factors influencing EFS. Low BMI, tumour size T3-T4, presence of perineural invasion and the presence of histological grade III also have a negative influence on prognosis.

This study will be extended by the study of therapeutic strategies at the locally advanced stage.

Role of the funding source

Adenoid Cystic Carcinoma Research foundation had no role in data collection, interpretation and writing of the report.

Conflict of interest statement

The authors have declared no conflict of interest.

Acknowledgements

This work was supported by the Adenoid Cystic Carcinoma Research foundation.

The authors thank French National Institute INCa for funding the REFCOR.

The following are the REFCOR members: S. Albert, G. Andry, E. Babin, C. Bach, C. Badoual, A.C. Baglin, A. Banal, B. Barry, V. Bastit, E. Baudin, B. Baujat, R.J. Bensadoun, C. Bertolus, J.P. Bessède, D. Blanchard, N. Bonmardion, C. Borel, A. Bozorg-Grayeli, R. Breheret, E. Brenet, P. Breton, I. Broyard, L. Brugel, G. Calais, V. Calugaru, O. Casiraghi, E. Cassagnau, L. Castillo, P. Ceruse, F. Chabolle, D. Chevalier, J.C. Chobaut, O. Choussy, A. Cosmidis, A. Coste, V. Costes, L. Crampette, S. Dakpe, V. Darrouzet, H. De Kermadec, P. Dessi, B. Devauchelle, L. Digue, G. Dolivet, F. Dubrulle, S. Duo, X. Dufour, C. Even, S. Faivre, N. Fakhry, F. R. Ferrand, C. Ferron, F. Floret, L. de Gabory, R. Garrel, L. Geoffrois, L. Gilain, A. Giovanni, A. Girod, B. Guerrier, S. Hans, P. Herman, P. Hofman, M. Housset, R. Jankowski, F. Janot, F. Jegoux, M. Juliéron, M.-C. Kaminsky, F. Kolb, J. Lacau Saint Guily, L. Laccoureye, B. Lallemant, P. Lang, E. Lartigau, J.P. Lavieille, M. Lefevre, X. Leroy, M. Lesnik, O. Malard, F. Massip, O. Mauvais, J.-C. Merol, J. Michel, H. Mirghani, T. Mom, S. Morinière, E. de Monès, G. Moulin, A Moya-Plana, G. Noel, G. Poissonnet, J.-M.Prades, D. de Raucourt, E. Reyt, C. Righini, Y. Marie Robin, F. Rolland, B. Ruhin, N. Saroul, P. Schultz, E. Serrano, O. Sterkers, V. Strunski, A. Sudaka, M. Tassart, S. Testelin, J.Thariat, A. Timochenko, R. Touati, B. Toussaint, E. Uro Coste, T. Van den Abbeele, A. Varoquaux, F. Veillon, S. Vergez, B. Verillaud, I. Wagner, M. Wassef.

The authors thank Dr Pierre Demez at CHU Liège, Belgium, before his untimely demise.

The authors thank the patients and Alexis Baujat for editing the manuscript.

References

[1] Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma of salivary origin. A clinicopathologic study of 242 cases. Am J Surg 1974;128:512–20.

[2] Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, Kohler B, et al. Cancer Incidence in Five Continents: inclusion criteria, highlights from Volume X and the global status of cancer registration. Int J Canc 2015;137:2060–71. https://doi.org/10.1002/ijc.29670.

[3] Ciccolallo L, Licitra L, Cantú G, Gatta G, EUROCARE Working Group. Survival from salivary glands adenoid cystic carcinoma in European populations. Oral Oncol 2009;45:669–74. https://doi.org/10.1016/j.oraloncology.2008.10.010.

[4] Bradley PJ. Adenoid cystic carcinoma of the head and neck: a review. Curr Opin Otolaryngol Head Neck Surg 2004;12:127–32.

[5] Dantas AN, Morais EF de, Macedo RA de P, Tinôco JM de L, Morais M de LS de A. Clinicopathological characteristics and perineural invasion in adenoid cystic carcinoma: a systematic review. Braz J Otorhinolaryngol 2015;81:329–35. https://doi.org/10.1016/j.bjorl.2014.07.016.

[6] Coca-Pelaz A, Rodrigo JP, Bradley PJ, Vander Poorten V, Triantafyllou A, Hunt JL, et al. Adenoid cystic carcinoma of the head and neck-An update. Oral Oncol 2015;51:652–61. https://doi.org/10.1016/j.oraloncology.2015.04.005.

[7] Seethala RR, Stenman G. Update from the 4th edition of the World Health organization classification of head and neck tumours: tumours of the salivary gland. Head Neck Pathol 2017;11:55–67. https://doi.org/10.1007/s12105-017-0795-0.

[8] Ouyang DQ, Liang LZ, Zheng GS, Ke ZF, Weng D-S, Yang WF, et al. Risk factors and prognosis for salivary gland adenoid cystic carcinoma in southern China: a 25-year retrospective study. Medicine (Baltim) 2017;96:5964–74. https://doi.org/10.1097/MD.0000000000005964.

[9] Ganly I, Amit M, Kou L, Palmer FL, Migliacci J, Katabi N, et al. Nomograms for predicting survival and recurrence in patients

with adenoid cystic carcinoma. An international collaborative study. Eur J Cancer Oxf Engl 1990 2015;51:2768–76. https://doi.org/10.1016/j.ejca.2015.09.004.

[10] Amit M, Binenbaum Y, Sharma K, Ramer N, Ramer I, Agbetoba A, et al. Analysis of failure in patients with adenoid cystic carcinoma of the head and neck. An international collaborative study. Head Neck 2014;36:998–1004. https://doi.org/10.1002/hed.23405.

[11] Cao C, Ge M, Chen X, Xu J, Chen C. Clinical outcomes and prognostic factors of salivary gland adenoid cystic carcinomas: a case control study. Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:531–5. https://doi.org/10.1016/j.oooo.2016.11.015.

[12] Bonaparte JP, Hart R, Trites J, Taylor MS. Incidence of adenoid cystic carcinoma in nova scotia: 30-year population-based epidemiologic study. J Otolaryngol - Head Neck Surg J Oto-Rhino-Laryngol Chir Cervico-Faciale 2008;37:642–8.

[13] Shen W, Sakamoto N, Yang L. Model to predict cause-specific mortality in patients with head and neck adenoid cystic carcinoma: a competing risk analysis. Ann Surg Oncol 2017;24:2129–36. https://doi.org/10.1245/s10434-017-5861-z.

[14] Ellington CL, Goodman M, Kono SA, Grist W, Wadsworth T, Chen AY, et al. Adenoid cystic carcinoma of the head and neck: incidence and survival trends based on 1973-2007 Surveillance, Epidemiology, and End Results data. Cancer 2012;118:4444–51. https://doi.org/10.1002/cncr.27408.

[15] Lloyd S, Yu JB, Wilson LD, Decker RH. Determinants and patterns of survival in adenoid cystic carcinoma of the head and neck, including an analysis of adjuvant radiation therapy. Am J Clin Oncol 2011;34:76–81. https://doi.org/10.1097/COC.0b013e3181d26d45.

[16] Li N, Xu L, Zhao H, El-Naggar AK, Sturgis EM. A comparison of the demographics, clinical features, and survival of patients with adenoid cystic carcinoma of major and minor salivary glands versus less common sites within the Surveillance, Epidemiology, and End Results registry. Cancer 2012;118:3945–53. https://doi.org/10.1002/cncr.26740.

[17] Baujat B, Thariat J, Baglin AC, Costes V, Testelin S, Reyt E, et al. Rare tumorus of the head and neck; on behalf of the REFCOR, the French Network of rare head and neck tumorus. Bull Cancer (Paris) 2014;101:411–23. https://doi.org/10.1684/bdc.2014.1956.

[18] Meyers M, Granger B, Herman P, Janot F, Garrel R, Fakhry N, et al. Head and neck adenoid cystic carcinoma: a prospective multicenter REFCOR study of 95 cases. Eur Ann Otorhinolaryngol Head Neck Dis 2016;133:13–7. https://doi.org/10.1016/j.anorl.2015.09.009.

[19] Badoual C, Baglin A-C, Wassef M, Thariat J, Reyt E, Janot F, et al. Pathologists and the French network of expertise on rare cancers ENT: the REFCORpath. Ann Pathol 2014;34:64–9. https://doi.org/10.1016/j.annpat.2014.01.006.

[20] Marcinow A, Ozer E, Teknos T, Wei L, Hurtuk A, Old M, et al. Clinicopathologic predictors of recurrence and overall survival in adenoid cystic carcinoma of the head and neck: a single institutional experience at a tertiary care center. Head Neck 2014;36:1705–11. https://doi.org/10.1002/hed.23523.

[21] Bjørndal K, Krogdahl A, Therkildsen MH, Charabi B, Kristensen CA, Andersen E, et al. Salivary adenoid cystic carcinoma in Denmark 1990-2005: outcome and independent prognostic factors including the benefit of radiotherapy. Results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncol 2015;51:1138–42. https://doi.org/10.1016/j.oraloncology.2015.10.002.

[22] Balamucki CJ, Amdur RJ, Werning JW, Vaysberg M, Morris CG, Kirwan JM, et al. Adenoid cystic carcinoma of the head and neck. Am J Otolaryngol 2012;33:510–8. https://doi.org/10.1016/j.amjoto.2011.11.006.

[23] Michel J, Fakhry N, Santini L, Mancini J, Giovanni A, Dessi P. Sinonasal adenoid cystic carcinomas: clinical outcomes and predictive factors. Int J Oral Maxillofac Surg 2013;42:153–7. https://doi.org/10.1016/j.ijom.2012.11.007.

[24] International head and neck scientific group. Cervical lymph node metastasis in adenoid cystic carcinoma of the major salivary glands. J Laryngol Otol 2017;131:96–105. https://doi.org/10.1017/S0022215116009749.

[25] International head and neck scientific group. Cervical lymph node metastasis in adenoid cystic carcinoma of the sinonasal tract, nasopharynx, lacrimal glands and external auditory canal: a collective international review. J Laryngol Otol 2016;130:1093–7. https://doi.org/10.1017/S0022215116009373.

[26] Van Weert S, Bloemena E, Van der Waal I, De Bree R, Rietveld DHF, Kuik JD, et al. Adenoid cystic carcinoma of the head and neck: a single-center analysis of 105 consecutive cases over a 30-year period. Oral Oncol 2013;49:824–9. https://doi.org/10.1016/j.oraloncology.2013.05.004.

[27] Kokemueller H, Eckardt A, Brachvogel P, Hausamen J-E. Adenoid cystic carcinoma of the head and neck-a 20 year's experience. Int J Oral Maxillofac Surg 2004;33:25–31. https://doi.org/10.1054/ijom.2003.0448.

[28] Chen AM, Bucci MK, Weinberg V, Garcia J, Quivey JM, Schechter NR, et al. Adenoid cystic carcinoma of the head and neck treated by surgery with or without postoperative radiation therapy: prognostic features of recurrence. Int J Radiat Oncol Biol Phys 2006;66:152–9. https://doi.org/10.1016/j.ijrobp.2006.04.014.

[29] Khan AJ, DiGiovanna MP, Ross DA, Sasaki CT, Carter D, Son YH, et al. Adenoid cystic carcinoma: a retrospective clinical review. Int J Canc 2001;96:149–58.

[30] Miglianico L, Eschwege F, Marandas P, Wibault P. Cervico-facial adenoid cystic carcinoma: study of 102 cases. Influence of radiation therapy. Int J Radiat Oncol Biol Phys 1987;13:673–8.

[31] Gomez DR, Hoppe BS, Wolden SL, Zhung JE, Patel SG, Kraus DH, et al. Outcomes and prognostic variables in adenoid cystic carcinoma of the head and neck: a recent experience. Int J Radiat Oncol Biol Phys 2008;70:1365–72. https://doi.org/10.1016/j.ijrobp.2007.08.008.

[32] Fordice J, Kershaw C, El-Naggar A, Goepfert H. Adenoid cystic carcinoma of the head and neck: predictors of morbidity and mortality. Arch Otolaryngol Head Neck Surg 1999;125:149–52.

[33] Oplatek A, Ozer E, Agrawal A, Bapna S, Schuller DE. Patterns of recurrence and survival of head and neck adenoid cystic carcinoma after definitive resection. Laryngoscope 2010;120:65–70. https://doi.org/10.1002/lary.20684.

[34] Matsuba HM, Spector GJ, Thawley SE, Simpson JR, Mauney M, Pikul FJ. Adenoid cystic salivary gland carcinoma. A histopathologic review of treatment failure patterns. Cancer 1986;57:519–24.

[35] Spiro RH, Huvos AG. Stage means more than grade in adenoid cystic carcinoma. Am J Surg 1992;164:623–8. https://doi.org/10.1016/s0002-9610(05)80721-4.

[36] Hernán MA, Clayton D, Keiding N. The Simpson's paradox unraveled. Int J Epidemiol 2011;40:780–5. https://doi.org/10.1093/ije/dyr041.

[37] Sajed DP, Faquin WC, Carey C, Severson EA, Afrogheh HA, Johnson AC, et al. Diffuse staining for activated NOTCH1 correlates with NOTCH1 mutation status and is associated with worse outcome in adenoid cystic carcinoma. Am J Surg Pathol 2017;41:1473–82. https://doi.org/10.1097/PAS.0000000000000945.

[38] Mitani Y, Li J, Rao PH, Zhao Y-J, Bell D, Lippman SM, et al. Comprehensive analysis of the MYB-NFIB gene fusion in salivary adenoid cystic carcinoma: incidence, variability, and clinicopathologic significance. Clin Cancer Res Off J Am Assoc Cancer Res 2010;16:4722–31. https://doi.org/10.1158/1078-0432.CCR-10-0463.

Please cite this article as: Atallah S et al., A prospective multicentre REFCOR study of 470 cases of head and neck Adenoid cystic carcinoma: epidemiology and prognostic factors, European Journal of Cancer, https://doi.org/10.1016/j.ejca.2020.01.023