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

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# 1 A prospective multicentre REFCOR study of 470 cases of 2 head and neck Adenoid Cystic Carcinoma: epidemiology 3 and prognostic factors 4

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67

68 [Abstract](#)

69 [Background](#)

70 Adenoid cystic carcinoma (ACC) accounts for 1% of malignant head and neck tumours [1] and  
71 10% of salivary glands malignant tumours. The main objective of our study is to investigate the  
72 prognostic factors influencing the event-free survival of patients with adenoid cystic carcinoma (ACC).

73

74 [Patients and methods](#)

75 A multicentre prospective study was conducted from 2009 to 2018.

76 All 470 patients with ACC whose survival data appear in the REFCOR database were included  
77 in the study. The main judgement criterion was event free survival (EFS).

78 Both a bivariate survival analysis by log Rank test and a multivariate by Cox model were  
79 performed using the *R* software.

80

81 [Results](#)

82 Average age was 55 years. Females accounted for 59.4% of the cohort. The body mass index  
83 (BMI) was normal in 86% of cases. Tumours were located in minor salivary glands in 60% of cases.  
84 T3/T4 stages represented 58%; 89% of patients were cN0. histological grade 3 was observed on 21%  
85 of patients.

86 The EFS and overall 5-year survival rates were 50% and 85%, respectively.

87 After adjustment, the most significant pejorative prognostic factors were age  $\geq$  65 years (HR =  
88 1.67), BMI $<$ 16.5 (HR = 2.62), and lymph node invasion cN (HR = 2.08).

89

90 [Conclusion](#)

91 Age, BMI and N stage are the three main clinical prognostic factors determining EFS identified  
92 in this prospective series of patients with ACC. Such findings open new research perspectives on the  
93 influence of these components on initial patient care.

94

95 [Key words](#)

96 Adenoid cystic carcinoma; prognostic factors; Event free survival; REFCOR.

97 Background

98 The annual incidence of malignant tumours of the salivary glands represents 0.4 to 2 cases per  
99 100,000 [2]. Adenoid cystic carcinoma (ACC) accounts for 1% of malignant head and neck tumours [1]  
100 and 10% of salivary glands malignant tumours [3].

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

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

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

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

109 This can be explained because they are mainly retrospective series and include small populations  
110 [10–12]. The five main series of the literature (> 1,000 patients) collect only a limited number of  
111 variables [3,13–16].

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

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

118

119 Patients and methods

120

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

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

130 Data quality control was ensured by two file reviews. An update of the database was requested from  
131 the referring physicians. A review of the histological reports available (surgical specimen or biopsy)  
132 was then performed, allowing additional verification of the variable of interest. All the samples were  
133 analysed by pathologists of the REFCOR and 7 % (32/470) histological reports were analysed in  
134 first instance by a pathologist who considered that a second pathologic opinion by the  
135 REFCOR national experts was necessary. Out of them, 15 cases were initially mislabeled and  
136 were corrected as adenoid cystic carcinoma.

137 . [19]

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

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

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

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

147 The secondary judgment criteria were overall survival (OS), locoregional recurrence free survival  
148 (RFS), and metastasis free survival (MFS).

149 Patients survival was studied according to the following criteria: sex; age at diagnosis ( <65  
150 versus ≥65 year-old); Body Mass Index (BMI): undernutrition (<16.5) versus normal BMI versus obesity

151 ( $\geq 30$ ); occupation (exposed versus unexposed)<sup>1</sup>; Tobacco consumption; Alcohol consumption;  
152 immunodeficiency (diabetes, HIV, immunosuppressive treatment and other unspecified); Tumour size:  
153 T1-T2 versus T3-T4; cN status : cN0 versus cN+; Stage 1-2 versus Stage 3-4 (according to AJCC/UICC  
154 2008 classification) Tumour site: major (MaSG) versus minor salivary glands (MiSG) (i.e. other sites);  
155 surgical margins: ("free" versus "close" or "positive"); histological grade: 1-2 versus 3 (i.e. Solid  
156 component  $\geq 30\%$ ); pN status: pN0 versus pN+; perineural invasion; vascular embols; necrosis.

157 A bivariate analysis with EFS as a function of these covariates was performed by log Rank test.  
158 The multivariate analysis was performed using a Cox model and the stepwise method. Schoenfeld  
159 residuals were measured to validate the model. Graphical representations were made using the  
160 Kaplan-Meier method. All statistical analyses were conducted using the *R* software (v.3.6.0; 2019-04-  
161 26).  
162  
163

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<sup>1</sup> 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.

164 **Results**

165 Characteristics of the patients are summarized in *table 1*. Among the 470 patients, mean age at  
166 diagnosis was 54 years (median 55, range [18-90]), sex was predominantly female (sex ratio 1.5), mean  
167 BMI was 25 kg/m<sup>2</sup> (median 25, range [16-46]), median Karnofsky index was 90% (mean 91%, range  
168 [40%-100%]).

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

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

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

175 Patients had primary surgery in 86% of cases.

176 A neck dissection was performed on 51% of patients. A total of 18% of patients were pN+  
177 (regardless of initial cN status). Neck dissection rates varied according to the tumour sites: few neck  
178 dissections were performed for sinus tumours (17%), compared to MaSGs (67%) or oral cavity (84%).

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

180 Histological grade 3 was found in 21% of tumours; 33% had vascular embols and 70% had  
181 perineural invasion.

182 Patients received radiotherapy in 74% of cases, whether exclusive (15%) or postoperative (85%).  
183 Irradiated patients had T3-T4 stages at diagnosis in 65% of cases. Chemotherapy was performed on  
184 18% of patients, 77% of whom received it concomitantly with radiotherapy. Induction chemotherapy  
185 was only performed on 6 patients with stage T4.

186



<b>Variable</b>	<b>Modality</b>	<b>N</b>	<b>%</b>
		<b>470</b>	<b>100%</b>
<b>Sex</b>	Female	279	59%
	Male	191	41%
<b>Age</b>	< 65	352	75%
	≥ 65	118	25%
<b>BMI</b>	<16.5	5	1%
	Normal	342	86%
	≥ 30	52	13%
	na	71	
<b>Occupation</b>	Unexposed	241	77%
	Exposed	73	23%
	na	156	
<b>Alcohol consumption</b>	No	374	86%
	Yes	59	14%
	na	37	
<b>Tobacco consumption</b>	No	318	72%
	Yes	122	28%
	na	30	
<b>Immunodeficiency*</b>	No	437	93%
	Yes	33	7%
	na	0	

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

188 *\*Diabetes 70% (23/33) ; HIV (0/33) ; Immunosuppressive treatment 15% (5/33) and unspecified 15% (5/33).*

189

190

<b>Variable</b>	<b>Modality</b>	<b>Proportion</b>	<b>%</b>
		<b>470</b>	<b>100%</b>
<b>Tumour site</b>	<b>MiSG</b>	<b>281</b>	<b>60%</b>
	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%
	<b>MaSG</b>	<b>186</b>	<b>40%</b>
	Parotid	98	21%
	Submandibular	62	13%
	Sublingual	6	1%
	Unspecified	20	4%
	na	3	
<b>T Status</b>	T1	80	19%
	T2	97	23%
	T3	86	20%
	T4	164	38%
	na	43	
<b>cN Status</b>	cN0	385	89%
	cN1	27	6%
	cN2	20	5%
	cN3	1	0%
	na	37	
<b>M Status</b>	M0	403	93%
	M1	31	7%
	na	36	

191 *Table 1 (continuation). Characteristics of the 470 patients with ACC (na= date not available).*

192

193

<b>TNM</b>	Stage 1	74	18%
	Stage 2	81	19%
	Stage 3	74	18%
	Stage 4	187	45%
	na	54	
<b>Surgery</b>	No	67	14%
	Yes	399	86%
	na	4	
<b>Surgical Margins</b>	Free	126	38%
	Close	72	21%
	Positive	137	41%
	na	64	
<b>Lymph node invasion (pN)</b>	pN0	133	82%
	pN+	30	18%
	na	19	
<b>Node Capsular effraction</b>	no	139	89%
	yes	18	11%
	na	25	
<b>Chemotherapy</b>	no	363	82%
	yes	80	18%
	na	27	
<b>Radiotherapy</b>	no	119	26%
	yes	332	74%
	na	19	
<b>Histological grade</b>	I	163	60%
	II	51	19%
	III	58	21%
	na	198	
<b>Necrosis</b>	no	21	57%
	yes	16	43%
	na	433	
<b>Vascular embols</b>	no	99	67%
	yes	49	33%
	na	322	
<b>Perineural invasion</b>	no	72	30%

yes	169	70%
na	229	

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

195

196

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

200 The median EFS was 59 months (95%CI [54-73]). The 5-year and 10-year EFS rates were 50%  
 201 (95%CI [0.44-0.56]) and 20% (95% CI [0.14-0.28]), respectively.

202 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  
 203 64% (95%CI [0.58-0.7]), respectively. The 10-year rates of OS, MFS, and RFS were 67% (95% CI [0.60-  
 204 0.77]), 46% (95% CI [0.38-0.54]) and 30% (95%CI [0.23-0.4]), respectively (*Figure 1*)After bivariate  
 205 analysis, 9 variables were identified as having a negative impact on EFS: among them, 2 epidemiological  
 206 (Age, BMI), 3 clinical (T stage, cN Stage, Stage III-IV) and 4 histological characteristics (Capsular  
 207 effraction, pN Stage, Histological grade, perineural invasion).

208 After multivariate analysis, 3 factors having a negative impact on EFS were identified: Age  $\geq$  65  
 209 years; BMI<16.5 and cN+ stage (*Table 2 and Figure 2*).

## 210 Discussion

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

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

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

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

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

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

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

238 The percentage of metastases at diagnosis was low (7%), comparable to the literature (2.4% to  
239 4%) [10,15].

240 In our study, histological grade 3 was present in 21% of patients, in accordance with a previous  
 241 study (27%) [26]. Perineural invasion was present in 70% of patients, in line with the literature (31% to  
 242 70%) [8,26]. In our series, the notion of perineural invasion was specified in only 51% of histological  
 243 reports. The histological description seems to be operator dependent and there is no standard report  
 244 regarding ACC, which would be worth considering.

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

249 The OS, RFS, MFS, and EFS rates at 5 years and 10 years are described in table 3. They are  
 250 comparable to those of the literature.

251

	5 years		10 years		References
	REFCOR	Others	REFCOR	Others	
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]

252 *Table 3. Survival rates in comparison with the literature.*

253

254 The bivariate analysis shows age, undernutrition, T3-T4 stage, cN+ status, III-IV stage, pN+,  
 255 capsular effraction, histological grade 3, and perineural invasion as having a negative impact on EFS.  
 256 After adjustment, age >65 years, undernutrition, and cN+ status keep on independently and negatively  
 257 influencing EFS.

258 Age is, as expected, found to be a prognostic factor for EFS in our study, as in most other series  
 259 [9,12,15].

260 BMI less than 16.5 kg/m<sup>2</sup> is a negative prognostic factor, not specific to ACC. It is probably  
 261 correlated with the tumour stage and age of the patient. *However only 5 patients had a BMI less than*  
 262 *16.5 kg/m<sup>2</sup> so stating that undernutrition is correlated with a lower EFS should be considered with*  
 263 *caution*

264 In bivariate analysis, tumour size is a factor of negative prognosis. This factor does not resist  
265 adjustment in the multivariate model. This finding is consistent with the divergence of results found in  
266 the literature, where tumour size is considered prognostic for some [9,14,15] ; but not for others  
267 [12,33].

268 Tumour sites do not influence the prognosis in our study. In the literature, however, sinus  
269 location is described as a negative prognosis [3,12]. Sinus tumours are supposedly diagnosed at later  
270 stages due to their more asymptomatic nature [3]. The tumour site may therefore only be a source of  
271 confusion, since the data in these series do not include tumour size.

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

276 In the bivariate analysis, capsular effraction and pN+ are negative prognostic factors for EFS.  
277 They are correlated with cN+, which emerges independently in multivariate analyses. The absence of  
278 pN+ and capsular effraction in our multivariate model may be explained by the larger amount of  
279 missing data compared to cN+. Histological grade 3 has a negative impact on EFS in bivariate analysis.  
280 VanWeert and Matsuba find the same result [26,34] while Spiro contradicts them [35].

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

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

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

295        However, this study has limitations: 30% of the data were missing. The primary criterion (EFS) was  
296 missing for 183 patients who could not be included. Comparison of the variables for these patients  
297 versus the others did not reveal any difference, allowing them to be excluded without risk of selection  
298 bias. The effect of center size on prognosis could not be investigated, as too much centers were  
299 involved, and the proportion of tumour stages varied from one centre to another. However, most of  
300 the patients were treated in the reference centers of the network, suggesting that they were treated  
301 according to the best standard of practice. We would still recommend that these malignant rare  
302 tumours be treated in centers treating high volume of head and neck cancers.

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

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



308 **Conclusion**

309 This prospective series of 470 patients with ACC suggests that age and N stage are the two main  
310 clinical prognostic factors influencing EFS. Low BMI, tumour size T3-T4, presence of perineural  
311 invasion, and the presence of histological grade 3 also have a negative influence on prognosis.

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

313

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337 **Conflict of interest statement**

338

339 The authors have declared no conflict of interest.

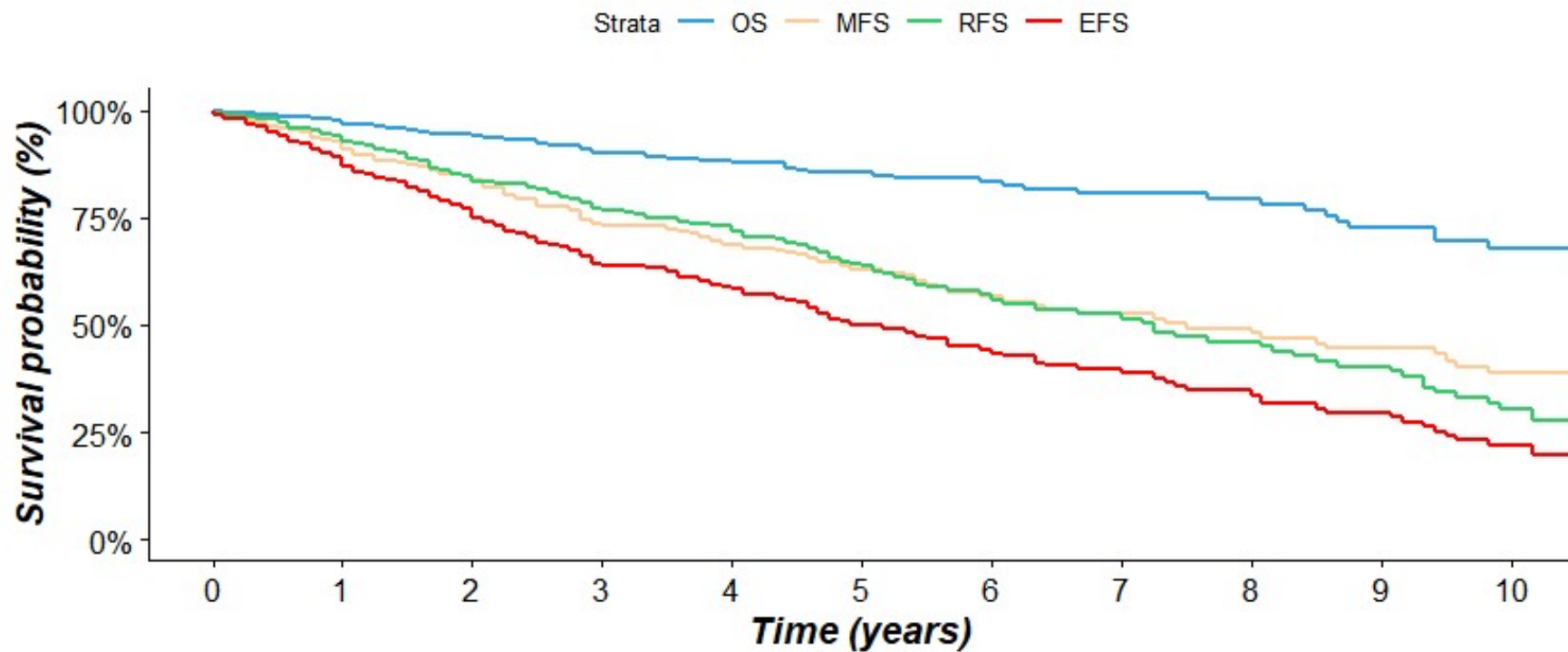
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- 457



**Number at risk**

OS	470	400	298	228	178	135	98	72	61	52	39
MFS	470	383	271	195	144	103	72	50	42	36	27
RFS	470	386	272	203	156	109	74	51	41	34	23
EFS	470	368	251	177	132	88	61	41	34	28	20

Figure 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.

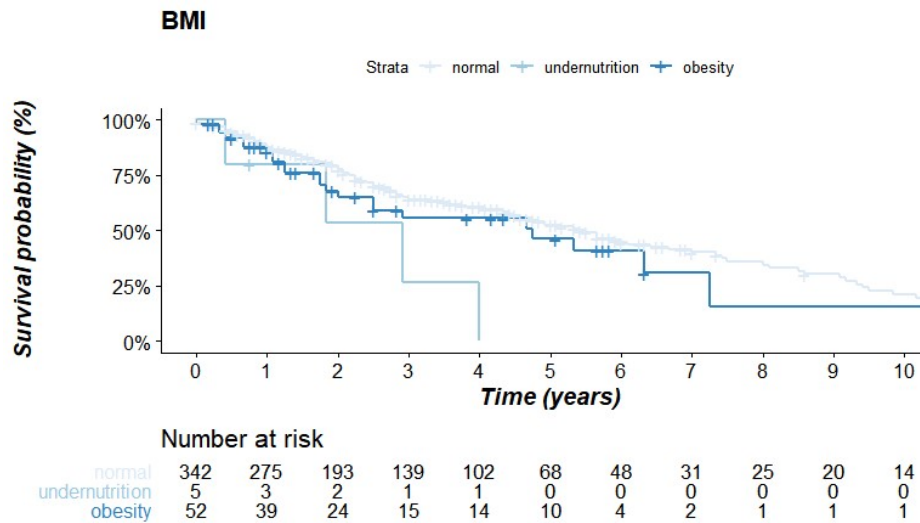
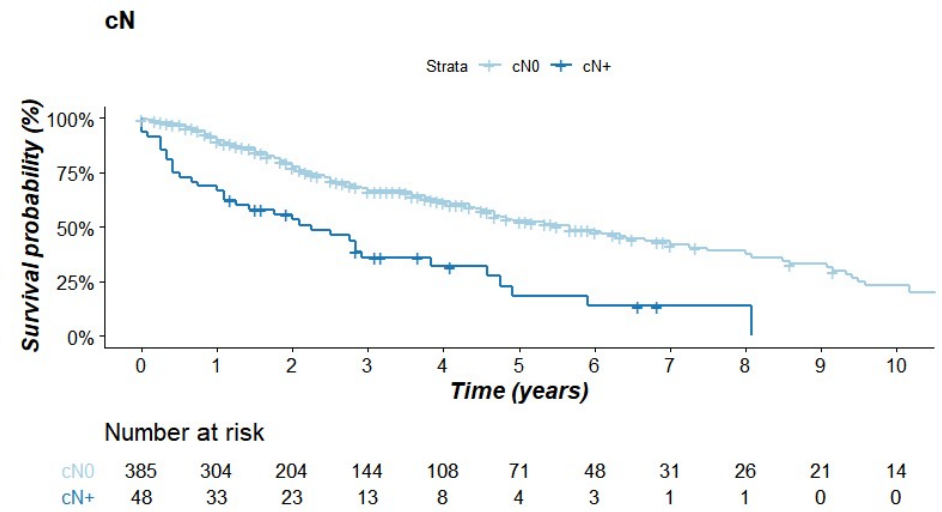
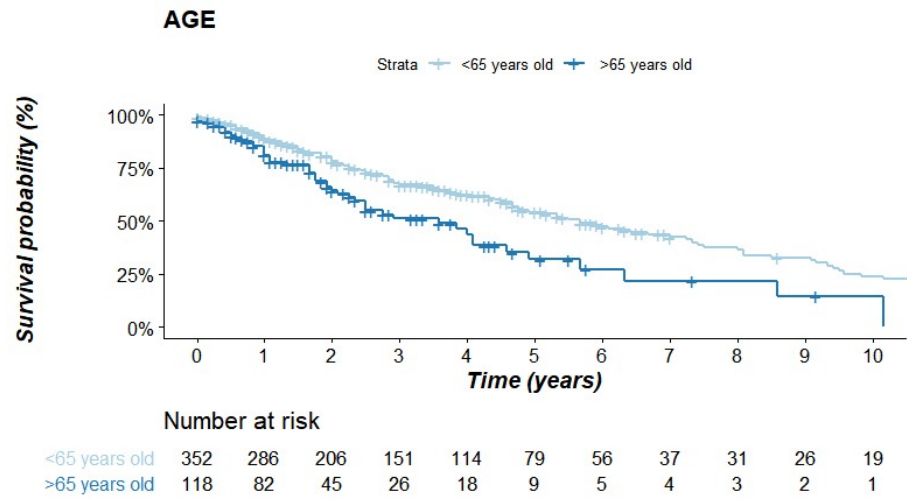


Figure 2. Event-ree survival curves ased on prognostic actors age ( ), M ( ) and c status (C).

Variable	Modality	Event (median)	EFS	Univariate analysis			Multivariate analysis (stepwise)			
				HR	CI 95%	P value (log rank test)	HR	CI 95%	P value (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

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 embols (na= data not available).

Variable	Modality	Event	EFS (median)	Univariate Analysis			Multivariate analysis (stepwise)			
				HR	CI 95%	P value (log rank test)	HR	CI 95%	P value (log rank test)	
Immuno deficiency	No	437	197	62						
	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

Table 2 (continuation). Event Free Survival (median) by age, sexe, occupation, BMI, alcohol, tobacco, immunodeficiency, tumour site, T status, cN status, stage TNM, surgical margin, pN status, capsular effraction, perineural invasion and vascular embols (na= data not available).



Variable	Modality	Events	EFS (median)	Univariate Analysis			Multivariate Analysis (stepwise)			
				HR	CI 95%	P value (log rank test)	HR	CI 95%	P value (log rank test)	
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 effraction	No	139	52	80						
	Yes	18	14	18	3,89	[2,01-7,21]	<0,001*	na	na	na
Histological grade	Grade I-II	214	80	71						
	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

Table 2 (continuation). 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 embols (na= data not available).