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## Original Research

# Should a neck dissection be performed on patients with cN0 adenoid cystic carcinoma? A REFCOR propensity score matching study

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## KEYWORDS

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**Abstract Background:** Patterns of nodal involvement in adenoid cystic carcinoma (ACC) of the head and neck have not been sufficiently assessed to guide a decision of prophylactic neck dissection (ND). The objective of this study is to analyse the influence of ND on event-free survival (EFS) for patients with cN0 ACC.

**Patients and methods:** A multicentre prospective study was conducted between 2009 and 2018. Patients presenting cN0 non-metastatic ACC on any site, and who received surgery on the tumour, were included. EFS was the main judgement criterion. A comparative survival analysis between the groups that received a ND versus those that did not was performed, using a propensity score. Analyses were carried out using the R software.

**Results:** Between 2009 and 2018, 322 patients with cN0 ACC were included, out of which 58% were female. The average age was 53 years. Tumours were in minor salivary glands in 58% of cases, and 52% had T3/T4 stages.

ND was performed on 46% of patients. Out of them, seven had histological lymph node invasion, out of which six had tumour infiltration in the mucosa of oral cavity.

After propensity score, the median EFS for N0 patients with ND was 72 months (95% Confidence Interval (CI) [48–81]), compared to 73 months (95% CI [52–85]) for patients without ND (HR = 1.33; 95% CI [0.82–2.16];  $p = 0.2$ ).

**Conclusion:** ND of cN0 patients does not provide any benefit on EFS, which suggests that its application on such patients is not necessary.

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## 1. Background

Adenoid Cystic Carcinoma (ACC) accounts for 1% of head and neck cancers and 10% of salivary gland cancers [1].

It is characterised by slow evolution, rare lymph node invasion and high rate of local and distant recurrences, which make it a deadly tumour [2].

The therapeutic strategy remains unconsensual, with the exception of surgical management at the localised and resectable stage [3]. Guidelines are based on mostly retrospective series [4,5].

ACC is often described as having relatively infrequent lymphophilic extension. Lymph node metastases (LNM) rates vary from 4% to 33% depending on the tumour sites [6–8]. LNM is a factor of negative prognosis [9–12].

The frequency of occult LNM (cN0pN+) is low (14%, according to Ning et al.) [13].

The need for prophylactic neck dissection (ND) on cN0 patients is therefore questionable: the few studies carried out so far have not shown any benefit in terms of overall survival (OS) when ND was performed [14].

The main objective of our study is to evaluate the impact on EFS of ND for cN0 ACC patients. The secondary objectives are to study this impact on local recurrence-free survival (RFS), metastasis-free survival (MFS) and OS.

## 2. Patients and methods

### 2.1. Population and database

A multicentre prospective inclusion of incident cases was conducted from January 2009 to February 2018. Data collection was carried out using a standardised questionnaire. Data were integrated into the REFCOR (French National Network on rare head and neck cancers) database. The comparative study protocol was elaborated in 2018. Analyses were performed after updating and quality control of the database.

Missing and inconsistent data were corrected after reviewing the files. A second data quality control was carried out by a checking of the histological reports. Records of patients that were found to be pN+ after dissection were reviewed.

Any patient managed in a REFCOR centre with a confirmed ACC was included in the series.

Only patients without clinical LNM at the diagnostic stage (cN0) who were surgically treated at the primary tumour site were included.

Exclusion criteria were metastatic patients at the diagnostic stage, unknown treatment status and under-age patients <18 years (Fig. 1).

In order to take into account the type of post-operative radiotherapy (PORT) and to verify the absence of influence of this treatment on survival in the compared groups, a survey was conducted among the network's radiotherapists.

### 2.2. Propensity score matching

A propensity score analysis was conducted to minimise the selection bias and potential confounding factors between groups.

This score was calculated for each patient as the expected probability of receiving ND, based on a multivariate logistic regression that included the main confounding factors associated with survival: age, body mass index (BMI), tumour site and T stage. These criteria were chosen following a meeting between expert clinicians because of their clinical relevance. In the series, BMI and age were identified as significantly influencing patient prognosis and included *de facto*. Only variables known at the time of the surgery were eligible [15]. Each patient was weighted by the inverse probability of being part of the group of patients with ND (ND+) versus the group without ND (ND-), in order

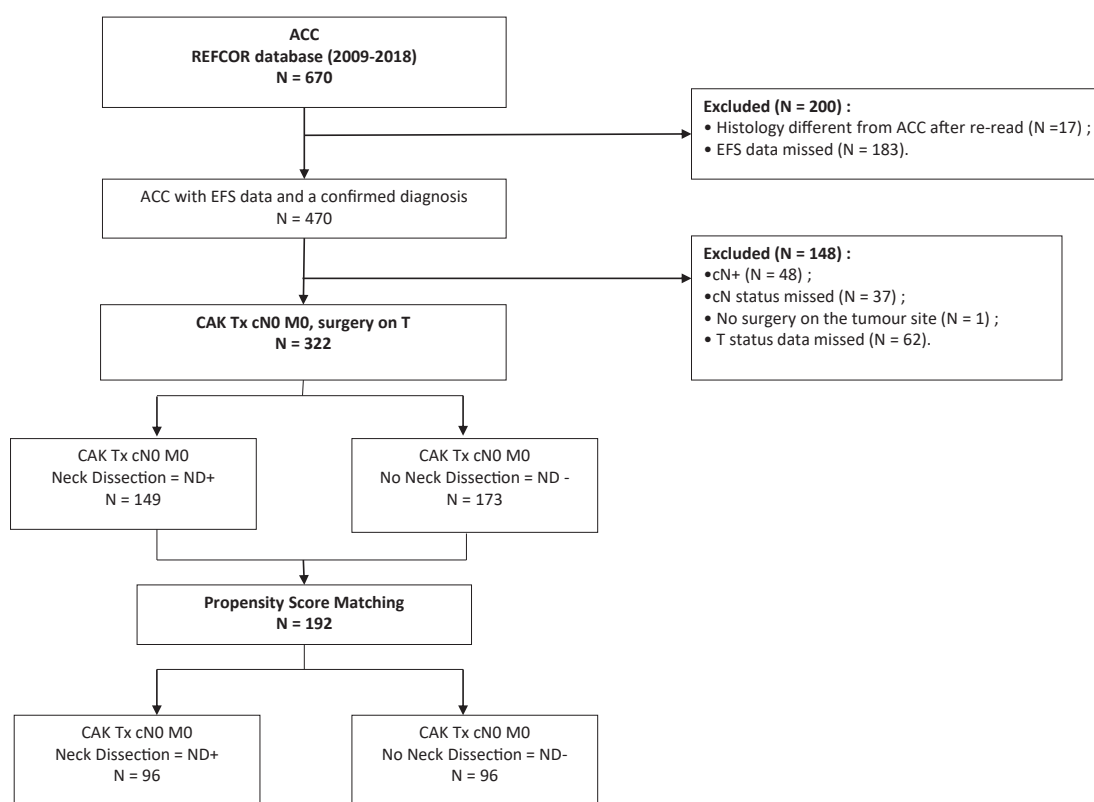


Fig. 1. Flow chart.

to balance observable characteristics. The concordance tolerance (*caliper*) was set at 0.02.

Given the presence of missing data, multiple imputation was used using the MICE method (R software). The results obtained on the series before and after imputation were compared in order to validate them. Sensitivity analyses had been scheduled *a priori*: exclusion of sinus tumours (where ND is only rarely recommended) and exclusion of BMI (12% of missing data).

### 2.3. Evaluation criteria

EFS was defined as the time between diagnosis and local or distant recurrence, death or the date of last follow-up for censored patients.

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

MFS was defined as the time between diagnosis and distant recurrence, death or the date of last follow-up for censored patients.

RFS was defined as the time between diagnosis and local recurrence, death or the date of last follow-up for censored patients.

### 2.4. Statistical analysis

The categorical variables were characterised by their proportion and compared using Pearson's chi-squared test or Fisher's exact test.

Continuous variables were described by their mean or median and their range. They were then compared using Student's t-test or Mann–Whitney test.

All statistical tests were two-sided. A *p* value less than 0.05 was considered statistically significant.

The Kaplan–Meier method and a Cox model were used to analyse EFS, OS, MFS and RFS.

Statistical analyses and survival curves were performed using the R software (v.3.6.0 (2019-04-26)).

## 3. Results

### 3.1. Patient characteristics

Our sample included 322 patients from 33 centres with cN0 ACC, a majority of which were female (58%; sex ratio 1:4).

The mean age at diagnosis was 53 years (median 54 [18–90]). The average BMI at diagnosis was 25 kg/m<sup>2</sup> (median 25 [16–46]).

Smoking and alcohol consumption were associated with 31% and 14% of patients, respectively. Patients had immunosuppression (diabetes or immunosuppressive therapy) in 6% of cases.

Minor salivary glands were mainly affected (58%). The parotid gland (27%), sinus cavities (25%), oral

cavity (20%) and submandibular gland (15%) were the four main tumour sites.

The proportion of patients treated for sinus tumours varied among centres, depending on their degree of specialisation in sinus surgery. Half of the patients had advanced T-stages at diagnosis: 20% of T3 and 32% of T4.

All the 322 patients underwent surgery of the tumour site: 46% of them ND+, 149 patients, versus 173 ND–.

Tumour resection margins were positive in 40% of patients and close in 22% of patients.

The presence of a solid component representing >30% of the tumour (histological grade 3), perineural invasion and vascular embols was found in 20%, 68% and 28% of patients, respectively.

Among the 149 patients who had a ND, histological reports of 85 of them could be reviewed. Among those, the results of 5 bilateral ND and 77 unilateral ND could be analysed. The average number of nodes was 22, median was 18 and range was [3–76].

PORT was performed on 75% of patients. Information regarding the type of radiotherapy and the irradiated site (on the tumour bed and/or lymph node bed) was missing in 70% of cases.

For ND– cN0 ACC patients, 85% of our surveyed radiotherapists performed prophylactic irradiation (50–60 Gy). In the case of ND+, 57% of them performed prophylactic irradiation even if pN0.

In addition, 13% of patients received chemotherapy along with PORT.

The characteristics of the two patient groups are presented in Table 1. They were comparable for the majority of characteristics, with the exception of BMI and tumour site.

Two groups matched by propensity score were generated (96 pairs, *n* = 194 patients). Matching erased clinical differences between groups (Table 1).

### 3.2. Characteristics of pN+ patients

Seven cN0 patients were found to be pN+, which implies an occult LNM rate of 5%. Four of them had capsular effraction Table 2.

The tumour sites were oral cavity (4 patients), maxillary sinus (1 patient), parotid gland (1 patient) and submandibular gland (1 patient). Histological grade 1 was predominant.

The pN+ involvement in the patient whose tumour site was parotid was a lymph node invasion by tumour contiguity.

For two patients, tumour invasion was localised on a boundary zone between two anatomical entities. The tumour of the first patient was located between the maxillary sinus and the oral cavity. It infiltrated the palatal mucosa. The second patient's tumour was located between the submandibular gland and the oral cavity. It infiltrated the mouth floor mucosa.

Table 1

Characteristics of patients according to “Neck Dissection”/“No Neck Dissection” group before and after propensity score matching ( $*p \leq 0.05$ ) (NA = data not available).

		Before Matching			After Matching		
		ND–	ND+	<i>p</i> value	ND–	ND+	<i>p</i> value
Age	Total	173	149		96	96	
	<65	131	114	0.87	75	71	0.5
	≥65	42	35		21	25	
BMI	NA		0				
	<16.5	2	2	0.05*	1	2	0.84
	Normal	138	105		76	75	
	≥30	13	24		19	19	
Sex	NA		38				
	Female	100	88	0.82	60	55	0.46
	Male	73	61		36	41	
Tobacco	NA		0				
	No	112	95	0.56	58	63	0.45
	Yes	48	47		38	33	
Alcohol	NA		20				
	No	132	123	0.44	70	77	0.23
	Yes	25	18		26	19	
Immunodeficiency	NA		24				
	No	162	141	0.71	87	90	0.42
	Yes	11	8		9	6	
Tumour site	NA		0				
	Parotid	36	50	0.003*	34	36	0.9
	Oral cavity	36	27		24	23	
	Sinus	67	14		13	14	
	Submandibular	15	33		15	13	
	Pharynx	12	14		7	7	
	Larynx	1	8		1	1	
	Ear	5	3		2	2	
T Stage	NA		1				
	T1	40	31	0.34	28	25	0.88
	T2	37	45		22	21	
	T3	34	29		20	19	
	T4	59	43		26	31	
Radiotherapy	NA		4				
	No	45	32	0.26	31	21	0.1
	Yes	118	113		65	75	
Chemotherapy	NA		14				
	No	137	125	0.63	83	85	0.66
	Yes	22	17		13	11	
	NA		21				

All in all, 6 of the 7 pN+ patients had an invasion of their oral cavity's mucosa.

### 3.3. Survival

The median follow-up was 25 months.

### 3.4. Main judgement criteria

Before the matching analysis, the median EFS of the ND+ group was 72 months (95% Confidence Interval (CI) [55–112]) versus 76 months (95% CI [59–114]) for the ND-group. The 5-year EFS rate for ND+ patients

Table 2

Characteristics of pN+ patients. PNI = perineural invasion. Area refers to Robbins classification of nodes (NA = data not available).

Patient	Age	Sex	Tumour Site	Mucosa Infiltration	Localisation	T	Surgical margin	Number node analysed	Number N+	Capsular effraction	Area pN+	Histological Grade	PNI
N°1	56	M	SUB MANDIBULAR	Yes	Mouth floor	2	Close	48	5	yes	II, III	1	yes
N°2	60	M	MAXILLARY SINUS	Yes	Palate	4	Positive	3	1	0	NA	1	NA
N°3	66	M	ORAL CAVITY	Yes	Cheek	2	Positive	22	8	yes	NA	3	yes
N°4	73	F	ORAL CAVITY	Yes	Mouth floor	2	Positive	14	1	0	IIA	NA	yes
N°5	57	F	ORAL CAVITY	Yes	Palate	4	Positive	37	1	0	NA	1	yes
N°6	47	M	ORAL CAVITY	Yes	Palate	1	Positive	67	1	yes	IIB	1	yes
N°7	71	F	PAROTID	No	NA	2	Positive	35	1	yes	IIB	1	yes

was 51% (95% CI [0.41–0.65]) versus 58% (95% CI [0.47–0.69]) for ND-patients (HR = 1.24; 95% CI [0.86–1.8];  $p = 0.2$ ).

After matching by propensity score, the median EFS of the ND+ group was 72 months (95% CI [48–81]), compared to 73 months (95% CI [52–85]) for the ND-group. The 5-year EFS rate for the ND+ group was 50% (95% CI [0.38–0.67]) versus 58% (95% CI [0.45–0.72]) for the ND-group (HR = 1.33; 95% CI [0.82–2.16];  $p = 0.2$ ) (See Fig. 2).

### 3.5. Secondary judgment criteria (results expressed after propensity score)

The rates of 5-year survival in the ND+ group compared to the ND-group were:

- RFS: 60% (95% CI [0.47–0.77]) for ND+ group versus 73% (95% CI [0.6–0.87]) for the ND- group (HR = 1.4; 95% CI [0.79–2.4];  $p = 0.3$ );
- MFS: 63% (95% CI [0.42–0.77]) for the ND+ group versus 67% (95% CI [0.56–0.83]) for the ND- group (HR = 1.15; 95% CI [0.66–2];  $p = 0.6$ );
- OS: 85% (95% CI [0.73–0.94]) for the ND+ group versus 88% (95% CI [0.76–0.99]) for the ND- group (HR = 1.4; 95% CI [0.58–3.18];  $p = 0.5$ ) (See Fig. 3).

## 4. Discussion

Our study found a low rate of occult LNM and no difference in EFS after adjustment on biases between the two groups of patients treated with ND or not.

To our knowledge, our study is the first to assess the influence of ND on EFS. It differs from previous studies by analysing survival with a propensity score that allows for a better comparison, despite the lack of randomisation [16]. The relevance of the question is supported by the finding in our series that patient characteristics are balanced between the ND+ and ND- groups, suggesting that the decision to perform ND is not based on a standardised attitude.

In our series, the cN+ rate at the time of diagnosis is low (11%, 48 patients). In comparison, Ning's meta-analysis finds a high variability of results (4%–33%) depending on the series, with an average of 16% of cN+ [13].

For the main salivary glands, a literature review suggests a 18.6% rate of LNM. The prevalence of LNM for ACC is 14.5% for the parotid gland, 22.5% for the submandibular gland and 24.7% for the sublingual gland. In this study, cervical LNM occur more frequently in the T3–T4 stage and are mainly found in zones II and III [17].

Few studies present the occurrence rate of occult LNM among the cN0 after ND. It varies from 8% to 23%, with an average of 14% in Ning's meta-analysis [7,13,17,18].

The variability of this rate can be explained by the difference in the proportion of cN0 patients who received ND, the number of lymph nodes collected and the small size of the studied populations [19].

In our study, the occurrence of cN0pN+ among the ND+ patients is low (5%). This rate could be artificially lowered by the fact that our definition of ND does not include the number of lymph nodes sampled due to 45% of missing data. It could also be due to a possible reclassification *a posteriori* as cN+ by technicians of a few patients initially considered as cN0.

After reviewing the seven records of cN0pN+ patients, it is observed that six of the tumours shared a common characteristic: they invaded the mucosa of the oral cavity. The seventh case corresponded more to an invasion by contiguity. These results are in line with other series [8,20,21]. More unexpected is the high proportion of grade 1 (5/7) among these patients, as histological grade is supposed to predict the risk of node invasion. It is although difficult to make hypotheses out of such a small number of patients.

Current data on ACC were insufficient to determine whether prophylactic ND should be recommended for cN0 patients: studies are mainly retrospective. Several of them show the limited benefit in terms of survival of treating patients with ND [8,14,22].

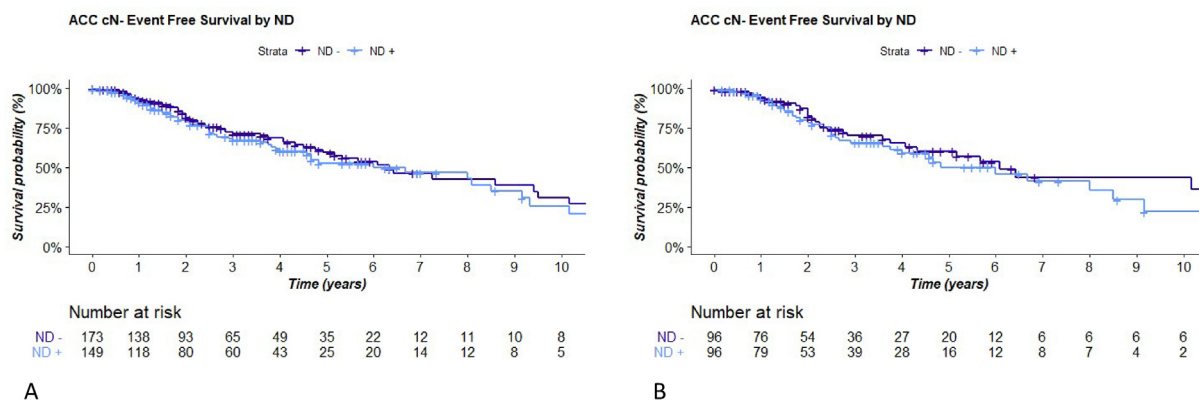


Fig. 2. Event-free survival curves of patients with cN- ACC by neck dissection before propensity score matching (A) and after propensity score matching (B).

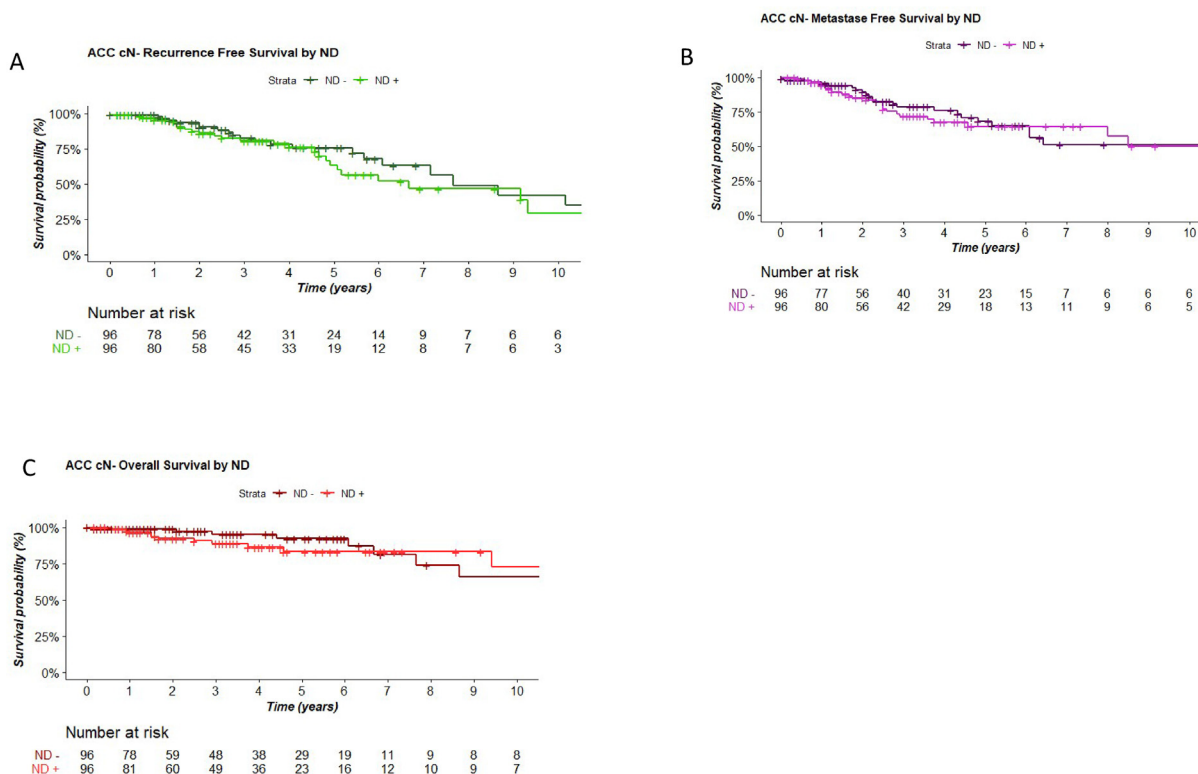


Fig. 3. ACC cN, recurrence-free survival (A), metastasis-free survival (B) and overall survival (C) curves by neck dissection (after propensity score matching).

Others use only the rate of LNM as a basis for recommendations: for the main salivary glands, the International Head/Neck Scientific Group recommends that ND be performed in N0 patients only at the T3–T4 stage [17], whereas for sinus, lacrimal gland and external auricular duct tumours with a low metastasis rate (5.3%), it recommends not performing a ND [23].

For ACC in the oral cavity and oropharynx, an international review recommends that, in the face of a higher occult metastases rate within these sites, ND should be performed when patients have negative prognostic factors and postoperative radiotherapy is not being considered [24]. Our study is in line with this conclusion: involvement of the oral mucosa is probably a risk factor of occult nodal involvement and should be considered in the decision process. For ACC in the larynx, an international review found only 12% LNM and recommends not to perform ND in cN0 patients [25].

Our results are in line with these studies, showing that ND does not bring any benefit in terms of survival for cN0 patients. The trend towards better survival in the ND-group is a strong argument to suggest that this negative result is not only due to a lack of power. The confidence interval of the matched HR (HR = 1.33; 95% CI [0.82–2.16]) leaves little space for a HR below 1, which would favour the ND.

PORT is often applied to patients with ACC, because of the frequency of negative histological prognosis

criteria. It has a positive impact on the survival rate of patients with advanced T-stage and positive margins [26].

In our series, the majority of patients received PORT. In addition, both groups of ND+ versus ND– patients had PORT in the same proportion.

A possible explanation for the lack of observed benefit in favour of ND could therefore be linked to PORT, which seems – according to our survey of the network’s radiotherapists – to be little influenced by the use of ND: radiotherapists tend to include at least the proximal nodes in their irradiation field, whether or not the cN0 patient has had a ND. This finding supports the absence of a potential bias induced by PORT.

Systematic ND can still be used to stage patients with the pN classification, which can theoretically guide the choice of post-operative treatment. However, it is an excessively invasive procedure for 95% of the cN0 patients in our series: Whether being functional or radical, ND remains a source of post-operative complications and morbidity in 35% of cases [27]. Functional disorders still occur frequently. They are often associated with damage to the spinal nerve, but shoulder morbidity can occur even if the nerve has been preserved [28,29].

However, the presence of LNM is a negative prognostic factor [9,10,12,30]. ND is therefore recommended if LNM are found during the initial assessment [4].

In order not to underestimate cN+ patients, we recommend carrying out a qualitative pre-operative assessment by imaging.

Positron emission tomography with 2-18-fluoro-2-deoxy-D-glucose coupled with a CT scan (PET-CT-FDG) plays a major role in the detection and staging of patients with head and neck cancer, but most studies focus on squamous cell carcinoma (SCC) [31]. However, ACC absorbs less FDG than SCC [32].

PET-CT-FDG could be an added value in the assessment of disseminated disease for patients with ACC, and therefore in determining treatment planning, but still needs to be evaluated [33].

Sentinel lymph node (SLN) technique was validated for the treatment of tumours of the oral cavity and oropharynx in 2005 by a consensus conference [34]. It enables to target the lymph node procedure and morbidity to be reduced. Our study suggests that it may be advisable to consider proposing the SLN technique for ACC involving the mucosa of the oral cavity, especially because they are the most suitable for this technique [29].

One of the limitations of our study is the number of missing data: it involved seven of the variables with an average of 6%. BMI variable had 12% missing data. Sensitivity analyses were performed by excluding this variable from our model. The results were not altered. Moreover, the analysis of missing data by individual and by variable showed a random distribution of these missing data suggesting the feasibility of multiple imputation [35].

## 5. Conclusion

The incidence of occult metastases in patients with cN0 ACC is low.

Patients not treated with ND do not show a difference in EFS compared to those treated with it, as long as post-operative radiotherapy is still considered.

Our results suggest that systematic ND should not be performed on cN0 patients with minor or major salivary gland ACC, except for infiltrating tumours of the oral cavity.

However, it is necessary to carry out a close pre-operative assessment of the intervention and quality imaging as well as early post-operative lymph node monitoring.

Evaluation of the SLN technique for patients with oral cavity ACC could be an alternative approach to ND.

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## Conflict of interest statement

The authors have declared no conflict of interest.

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