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Mucoepidermoid carcinoma of salivary glands: a French Network of Rare Head and Neck Tumors (REFCOR) prospective study of 292 cases.

Running title: Mucoepidermoid carcinoma of salivary glands

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Key-words: salivary glands, cancer, parotid gland, mucoepidermoid carcinoma

ABSTRACT

Background: To describe the characteristics of the largest European study of MEC of salivary glands and to determine the prognostic factors for overall and disease free survival.

Patients and methods: Patients with MEC were prospectively included in the Réseau d'Expertise Français sur les Cancers ORL Rares (REFCOR, French Network of Rare Head and Neck Tumors) database between 2009 and 2015.

Results: A total of 292 patients were included. Tumors were classified as low grade in 175 cases (60%), intermediate in 39 (13%) and high grade in 78 (27%). Median follow-up was 26 months. The 5-year OS and DFS rates were respectively 83% and 69%. In multivariate analysis, age ($p=0.004$), diabetes ($p=0.02$) and advanced stage ($p=0.03$) were found to have a significant negative impact on OS. Diabetes ($p=0.001$), alcohol consumption ($p=0.003$) and advanced stage ($p=0.001$) were found to have a significant negative impact on DFS. Compare to low grade, high grade tended to have a negative impact on OS ($p=0.05$) and had a significant effect on DFS ($p=0.002$) while intermediate grade had no significant influence on survival. The surgical treatment had a positive impact on both OS ($p=0.00005$) and DFS ($p=0.0005$). Postoperative radiotherapy had no impact in multivariate analysis.

Conclusion: Advanced clinical stage, high grade tumor, high age, the impossibility of carrying out a complete surgical resection, and diabetes are the main prognostic factors in this prospective series of patients with MEC. Such findings open new research perspectives on the influence of these components on initial patient care.

INTRODUCTION

Salivary gland carcinomas represent less than 5% of malignant tumors of head and neck.¹ Parotid is the most common localization of these tumors among the major salivary glands, and palate is the most frequent site for minor salivary glands tumors. The prevalence is higher among women aged between 50 to 60 years.

Mucoepidermoid carcinoma (MEC) is the most common histology and accounts for approximately 30% of salivary gland carcinomas.² MEC are composed of squamous cells (epidermoid cells), mucinous cells, and a variable proportion of intermediate cells. These tumors are classified into three histological grades, from low to high grade correlated with their aggressiveness, according to the World Health Organisation classification.³

Complete surgical resection is the gold standard for MEC. The protocols for adjuvant radiotherapy or chemotherapy are still matter of discussion. The therapeutic strategy as well as the prognosis of the intermediate grade are still not well defined.⁴ Several studies question the existence of the intermediate grades : the discovery of the MECT1-MAML2 translocation (mucoepidermoid carcinoma translocated1/ Mastermidlike gene family) in molecular biology could favor the use of two histological grades instead of three.⁵

Over the past ten years, the recent changes in clinical and histological classification criteria, the improvement of diagnostic imaging techniques and the advent of radiotherapy by IMRT have had an impact on the therapeutic strategy in MEC. The very low incidence of these cancers, makes it difficult to perform a randomized comparative trial.

The purpose of this article is to describe the clinical, histological and therapeutic features of the largest European study of MEC of salivary glands and to determine the prognostic factors for overall survival (OS) and disease free survival (DFS).

PATIENTS AND METHODS

This study is a descriptive, prognostic, prospective, multicentric analysis. The inclusion of patients in the database was carried out by 35 centers of the Réseau d'Expertise Français des Cancers ORL Rares (REFCOR, French Rare Head and Neck Cancer Expert Network), using a standardized questionnaire. The data were anonymized, and an informed consent was signed by the patients in accordance with French law. Data quality control was ensured by file reviews. An update of the database was requested from the referring physicians. The inclusion period ran from January 2009 to December 2015. Ten patients, initially diagnosed between 1994 and 2009 and who presented with an oncological event requiring a new management between 2009 and 2015 were also included. Overall, 292 patients treated for a salivary gland MEC were included.

The inclusion criteria were: age > 18 years, more than six months of follow-up and a defined histological grade. Sex, age of the patient at the time of diagnosis (in year), tobacco and alcohol consumption, longest time practiced profession according to the 24 categories established by the French official classification (INSEE⁶) and Karnofsky score were analyzed. Concerning therapeutic management, each case was discussed during the multidisciplinary tumor board of each center using REFCOR guidelines³² and the experience of medical and surgical team. The tumors were described by the following criteria: site, histological grade (low (LG), intermediate (IG) or high (HG)), tumor size, nodal stage and metastatic disease. Histological analysis was performed according to the World Health Organization criteria and patients were clinically staged according to the American Joint Committee on Cancer (AJCC) TNM staging system and UICC 7th edition 2009 classification.^{7 8}

The characteristics of the patients and the tumors were described by the mean, median, minimum and maximum values for continuous data, and by their number and percentage for categorical data.

Overall survival (OS), disease-free survival (DFS) were estimated using the Kaplan-Meier method. The log-rank test was used to compare the survival functions. The multivariate analysis was performed using the Cox regression model, with a p -value = 0.10 as threshold for entering variable. Hazards Ratio (HR) and its 95% confidence interval (95% CI) were estimated. The variables age, sex, clinical stage, histological grade and resection margins were systematically tested in the multivariate analysis because of their established relevance in this pathology. The tests were performed bilaterally and were considered statistically

significant when $p \leq 0.05$. All the statistical analyses were performed on R[®] software (version 3.1.0)

RESULTS

Demographics

A total of 292 patients were included in the study. Clinical and histological characteristics are presented in Table 1. The median age at diagnosis was 54 years (range 18-101 years). Our series included 124 men and 168 women (sex ratio, 0.74). The median follow-up was 26 months (range 6 - 60 months).

The most common tumor location was parotid (56.8%) followed by oral cavity (14%), oropharynx (9.5%), submandibular gland (6.8%), nasal mucosa (6.1%) and sublingual gland (1.3%).

In our study, 175 patients had a low grade (59.9%), 39 patients an intermediate grade (13.3%), 78 patients a high grade MEC (26.7%). Eighty-seven patients had stage I (29.7%), 64 patients had stage II (21.9%), and 93 patients had stage IV tumor (31.8%). Sixty-five patients (22.2%) had lymph node metastases and 7 patients (2.4%) had distant metastases at diagnosis.

Treatment

Two hundred and seventy-two patients (93.1%) underwent surgical resection of the tumor, among them 131 patients (44.8%) underwent neck dissection. One hundred and forty-nine patients (51%) were treated with surgery and radiotherapy, 29 patients (9.9%) with surgery and chemoradiotherapy, 14 patients with only radiotherapy (Table 2).

Adjuvant radiotherapy was proposed by each center according to the clinical staging, the quality of surgical margins after resection and the presence of positive lymph nodes.

Oncological outcomes

Fifty-seven patients (19.5%) had a recurrence and 26 (8.9%) died. The 5-year OS and 5-year DFS probabilities were 83% and 69%, respectively (Figure 1)

In univariate analysis, age ($p = 0.001$), male sex ($p = 0.03$), diabetes ($p = 0.01$), TNM Classification ($p = 0.0006$), stage ($p = 0.00002$), histological grade ($p = 0.0004$), positive surgical margins ($p = 0.0005$) and radiotherapy treatment ($p = 0.01$) or chemotherapy ($p < 0.0005$) were significantly associated with decreased OS (Table 3).

Alcohol consumption ($p = 0.001$), age ($p < 0.0001$), male sex ($p = 0.0002$), diabetes ($p = 0.003$), larger tumor size ($p < 0.0001$), histological grade ($p < 0.0001$), metastases ($p = 0.02$), no tumor resection ($p < 0.0005$), positive surgical margins ($p = 0.0005$) and positive lymph nodes on pathologic examination ($p = 0.0005$), were associated with a poorer DFS (Table 3). The high Karnofsky index (as continuous variable) was a good prognostic factor for OS ($p = 0.01$) and DFS ($p = 0.001$).

Tobacco consumption ($p = 0.2$), immunosuppression ($p = 0.1$), body mass index (BMI, as continuous variable) ($p = 0.4$), tumor site ($p = 0.7$) and extracapsular lymph node spread ($p = 0.8$) had no statistically significant impact on OS and DFS. No difference in survival was found between major and minor salivary glands tumors ($p = 0.4$).

Furthermore, HG patients had significantly lower OS and DFS than intermediate and LG patients ($p = 0.0001$ and $p = 0.001$) (Figure 2). 5 year-OS and DFS were 89% and 77% respectively, for patients with negative margins after resection (R0). OS and DFS were significantly lower for patients with positive margins (R1 and R2) than negative margins resection (R0) ($p = 0.006$ and $p = 0.0002$) (Figure 3)

In multivariate analysis, diabetes (OS: $p = 0.01$ and DFS: $p = 0.006$) and advanced clinical stage (OS : $p = 0.04$ et DFS : $p = 0.01$) were poor prognostic factors for both the OS and DFS. The increase of age had a negative impact on OS ($P = 0.002$). Compare to LG, HG tended to have a negative impact on OS ($p = 0.05$) and had a significant effect on DFS ($p = 0.002$), while IG had no significant impact (OS : $p = 0.60$ and DFS : $p = 0.84$). Surgical treatment had a positive impact on OS ($p < 0.00003$) and DFS ($p = 0.00085$). Chemotherapy was significantly associated with a decreased OS ($p = 0.05$). Radiotherapy treatment (OS : $p = 0.1$ and DFS $p = 0.8$) had no impact in multivariate analysis (Table 4).

DISCUSSION

In this study, 292 patients with MEC were analyzed from the REFCOR Database. This is the largest prospective European cohort of MEC salivary glands.

Most of the MEC occurred in patients during their fifth decade (median 54 years) in agreement with data from the literature where the average age was between 48 and 57 years.^{9–13}

In our series, women represented 57.5% of the MEC patients. This predominance of women was found in several studies ranging from 51% to 75% of MEC salivary glands.^{14–18} In a large American series of 2400 patients, Chen et al. also found a difference between men and women in terms of tumor aggressiveness with more high-grade MEC associated with men. Our results also showed, in univariate analysis, an association between male sex and decreased OS and DFS. This may be due to hormonal issues because the overexpression of several sex hormone receptors, in particular, estrogen receptor alpha, progesterone receptor, and androgen receptor, suggests their fundamental role in salivary gland tumor pathogenesis and progression.¹⁹

The tumor site of MEC was in two-thirds of the cases in the major salivary glands. In many studies, this localization represents the majority of the MEC (from 54.6% to 98.4% of patients) and the parotid gland, as in our cohort (56.8%), the main site.^{14–16} In a large series from UK, Bradley and McGurk have found that MEC occurred in major salivary glands in 79% (parotid gland was the main site with 58% of the tumors) and in minor salivary glands in 21% of cases.² In the literature, the distribution of grades is variable, LG generally being the most represented (21 to 78.5%).^{10,13,17,18} In our series (59.9%), as in the study of Serena et al.¹⁷ (63.6%), the majority of MEC were low grade.

The OS in our study was 83% , similar with the data from the literature (78% to 92%).^{13,17,20–22} In multivariate analysis: older age patients, diabetes, advanced clinical stage and HG were poor prognosis factors.

Older age was a negative prognostic factor for OS in many studies.^{16,18,23–25} Age-related comorbidities and confounding factors (tolerance of surgery and adjuvant treatments) have an impact on overall survival. We found no significant association between age and DFS as in

the study of Melonie et al.²⁴ In our study, alcohol consumption was significantly associated with a decrease of DFS in univariate analysis. Only the study of Lu ZH and al²⁶ found alcohol consumption as a factor of poor prognosis in univariate analysis

In our series, diabetes was a poor prognostic factor for both OS and DFS. To the best of our knowledge, our study is the first to find a significant association between diabetes and the survival of MEC. Indeed, in 2005 the study of Suba et al ²⁷ analyzing 438 patients suggested the existence of an epidemiological association between diabetes and the occurrence of tumors of the salivary glands, without any correlation with the malignancy rate. It has been suggested that diabetes may promote the progression of cancers, leading to poor outcomes, via pathways mediated by high levels of insulin and insulin-like growth factors.²⁸ Aviles-Jurado et al. have previously shown an association between high glycemic levels and poor disease-free survival in intermediate-advanced stage head and neck squamous cell carcinoma (HNSCC) suggesting ~~that suggest~~ that insulin resistance index might be a prognostic factor.²⁹

Park et al.³⁰ found a tendency for dose-dependent relationships between fasting serum glucose levels and risk of death among male patients with head and neck cancers. The biological rationale for these clinical associations might be explained by data that have demonstrated under aerobic conditions that the majority of the tested HNSCC cell lines rely on glucose metabolism for energy generation.³¹

In our database, we only had the information whether or not the patients had diabetes. We had no information about type of diabetes, blood glucose level and glycosylated hemoglobin. A more detailed analysis of our results may be interesting using these missing data.

Histological grade is reported to be a major prognostic factor influencing survival for both OS and DFS.^{11,23} MEC is classified in 3 histological groups: high, intermediate and low grade but there is still some discussion as to whether MEC should be classified in 3 grades including an intermediate grade or whether they should be classified only in low and high grades. There is particularly a debate regarding the prognosis of IG; some studies have indicated that IG behaves more like LG whereas others have suggested that prognosis in IG is more similar to that of HG.²¹

In a study analyzing 376 MEC of salivary glands, Liu et al²⁵ have shown that histological grade was an independent prognostic factor (odds ratio 5.865, $p < 0.001$). In the study of Chen et al²² OS in LG, IG, and HG were respectively 84%, 80% et 52% ($p = 0.008$). In our series, only HG was a factor significantly decreasing survival in multivariate

analysis. We found a significant difference for OS and DFS between LG and IG patients compared to HG patients but no difference was found between IG and LG. In the series of McHugh et Al.¹⁵, the OS for LG was 90% and IG 86%, similar to ours, and there was no significant difference in terms of survival between LG and IG. In addition, these results suggest that IG behave more like a LG. However, the retrospective nature of all MEC salivary glands studies induced a bias in the analysis of different histological groups. Indeed, the majority of low grades are treated by exclusive surgery while the intermediate grades benefit of post-operative adjuvant treatment like radiotherapy, with indeed a similar survival. However, the comparison of these two groups should be interpreted with caution given the difference in the treatment plan. Finally, in terms of grading, although the inclusion of patients in our database was carried out by regional REFCOR expert centers, no central revision of histopathological findings was done. This could have led to a misdiagnosis of the grading of MEC. The current grading systems vary in complexity with regard to the number of morphological parameters assessed. The systems can be broadly classified as descriptive or score-based. The original Healey system and its modifications represent the former.^{32,33} Score-based systems have been suggested by the Armed Forces Institute of Pathology (AFIP)³⁴, which is also endorsed by WHO³⁵; and Brandwein et al.³⁶ Inter- and intra-observer consistency varies; and the decision can be subjective and reflect experience/expertise. Improved histological grading could be achieved by combining particular strengths of different systems; combining histological grading with Ki67 index or molecular testing.³⁷

Stage had a significant impact on survival in our study: stages III and IV were strongly correlated with poor prognosis. In the study by Plambeck et al¹², the 5-year OS was 92% and stage was significantly associated with survival. More recently, Janet-Ofelia et al.³⁸ reported that stage was the best prognostic survival factor ($p = 0.063$ and OS = 78%). It represents a real decision-making factor on the therapeutic management of MEC. Unlike the histological grade, it is known in preoperative time and its major impact on prognosis allows to define a therapeutic management adapted to the aggressiveness of the MEC.^{21,22,25,39} It must have a major impact on the treatment of MEC in salivary glands. By leading the therapeutic strategy, it would allow therapeutic deflation for stages I and II and therapeutic intensification (systematic postoperative treatments) for stages III and IV.

Clear surgical margins had a positive impact on OS and DFS in our series, confirming that R0 resection is the reference treatment for MEC in the salivary glands.⁴⁰ In McHugh's study¹⁵, the DFS was significantly decreased for resection with positive margins (68% vs. 89%; $p = 0.04$). According to the recommendations of the REFCOR⁴¹, post-operative

radiotherapy is proposed for HG tumors, incomplete surgical resections, advanced stages and lymph node invasion. In our study, 93% of patients with high-grade MEC received radiotherapy. In the series of Emerick et al⁴², 99% of patients with high histological grade were treated with radiotherapy. In 2016, Holtzman et al⁴³ compared the long-term survival of patients after surgery with adjuvant radiotherapy compared with radiotherapy alone for salivary gland cancers. The 10-year OS for clinical stage IV was 30.3% versus 16.7% ($p = 0.09$). However, due to the retrospective design of these studies, the indication of adjuvant radiotherapy is based on low-grade level of evidence. In our study, the treatment plan also depended on the tumor grade. The role of radiotherapy according to the MEC grade can thus not be evaluated.

Chemotherapy associated with radiotherapy is increasingly being proposed for tumors with elevated risk of recurrence. A large American series on major salivary gland neoplasms recently showed that the addition of concomitant chemotherapy to radiotherapy in high-risk tumors did not provide any benefit on OS.⁴⁴ In a cohort of 2210 patients with salivary gland cancers, those treated with postoperative radio-chemotherapy had a lower OS than those receiving post-operative radiotherapy alone (HR 1.22; 95%CI = 1.03-1.44; $p = 0.02$). This was a retrospective analysis over a long period of time (18 years). Further studies are thus needed to evaluate this treatment: The Radiation Therapy Oncology Group (RTOG 1008, NCT01220583, phase II) and the Group d'Oncologie Radiothérapie Tête et Cou (SANTAL trial, GORTEC 2016-02, NCT02998385, phase III) are currently undertaking randomized trials to establish whether the administration of cisplatin together with postoperative radiotherapy improves outcome in patients with high-risk salivary gland tumors, including MEC.

The current problem is to be able to determine the best therapeutic strategy for tumors with very different progression profiles in order to obtain the best compromise between recovery and sequel: elements of aggressiveness (high grade, high TNM, positive margins after resection, peri-neural or vascular invasion) suggest therapeutic intensification (surgery and post-operative radiotherapy or adjuvant radio-chemotherapy), while other elements (low grade, low TNM, clear margins after surgery and no histological criteria aggressiveness) suggest therapeutic de-escalation (surgical resection of the tumor, no neck dissection or adjuvant treatment). However, the variability in the behavior of intermediate grade neoplasms makes difficult the choice of therapeutic strategy for these cases.

Molecular biology, including the determination of translocations of *MECT1-MAML2*⁴⁵ and *EGFR*⁴⁶ fusion gene for the determination of the aggressiveness of MEC, the high

expression of p53 and EGFR which are pejorative prognostic factors⁴⁷, could help to improve therapeutic decision-making.

CONCLUSION

The strengths of this study are that the REFCOR allowed us to analyze a large prospective series of patients, all coming from expert centers with a very low proportion of missing data. One weakness is that although the inclusion of patients in our database was carried out by REFCOR expert centers, no central revision of histopathological findings was done. This could have led to a misdiagnosis of the grading of MEC.

Advanced clinical stage, high grade tumor, high age, the impossibility of carrying out a complete surgical resection, and diabetes are the main prognostic factors both the OS and DFS in this prospective series of patients with MEC. Such findings open new research perspectives on the influence of these components on initial patient care. New advances in molecular biology, allowing precise characterization of "high risk" and intensification of therapeutic strategy in these patients, should contribute to optimal management in the future.

Conflict of interest: The authors have no conflicts of interest to disclose.

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Characteristic	No. (%) de Patients
Total no.	292
Sex	
Male	124 (42.4)
Female	168 (57.5)
Tobacco	
Yes	53 (18.2)
No	239 (81.8)
Alcohol	
Yes	37 (12.7)
No	255 (87.3%)
Diabetes	
Yes	14 (4.8%)
No	278 (95.2)
Immunosuppression	
Yes	18 (6.2%)
No	274 (93.8)
Tumor location	
Parotid	166 (56.8)
Submandibular gland	20 (6.8)
Sublingual gland	4 (1.3)
Oral Cavity	41 (14)
Oropharynx	28 (9.5)
Nasal	18 (6.1)
Other	15 (5.1)
Histological grade	
Low	175 (59.9)
Intermediate	39 (13.3)
High	78 (26.7)
Tumor classification	
T1	95 (32.5)
T2	84 (28.7)
T3	43 (14.7)
T4	60 (20.5)
NR	8 (2.7)
Nodal classification	
N0	223 (76.3)
N1	19 (6.5)

N2	46 (15.7)
NR	4 (1.3)
Metastatic disease	
M0	281 (96.2)
M1	7 (2.4)
NR	4 (1.3)
Clinical staging	
Stage I	87 (29.7)
Stage II	64 (21.9)
Stage III	41 (14)
Stage IV	93 (31.8)
NR	7 (2.4)
Surgical margins	
R0	224 (76.7%)
R1	29 (9.9%)
R2	19 (6.6%)
NR	20 (6.8%)
Lymph node dissection (n=131)	
pN0	91 (69)
pN+	39 (30)
NR	1 (1)
Extracapsular spread (39 pN+)	
Yes	18 (46)
No	21 (54)

NR : not reported.

Table 1. Clinical and Histopathologic Characteristics of the 292 patients included.

Treatment	Histological grade (%)		
	Low grade	Intermediate grade	High grade
Surgery	124 (42.4)	18 (6.1)	3 (1)
Surgery +RT	27 (9.2)	13 (4.4)	51 (17.4)
Surgery +CT	0	0	2(0.6)
Surgery+ RT+CT	9 (3)	4 (1.3)	16 (5.4)
RT	10 (3.4)	2 (0.6)	2(0.6)
RT+CT	1 (0.3)	0	4 (1.3)
CT	0	2 (0,6)	0
None	4 (1.3)	0	0
Total patient	175 (59.9)	39 (13.3)	78 (26.7)

Table 2. Repartition of the treatment modalities according to histological grade (RT= radiotherapy, CT= chemotherapy)

Table 3. Survival probabilities at 60 months, with their 95% confidence interval (CI), univariate analysis, all patients included (R0= negative margins, R1= margins close or microscopically invaded, R2= positive margins, RT= radiotherapy CT=chemotherapy).

Variables	OS			DFS		
	Survival Probability	95% CI	P	Survival Probability	95% CI	P
Sex						
Female	0.88	0.81-0.96	0.03	0.76	0.65-0.9	0.0002
Male	0.74	0.62-0.88		0.58	0.47-0.72	
TNM						
<i>Tumor classification</i>						
T1	0.94	0.87-1	0.0064	0.87	0.77-0.99	<0.0005
T2	0.88	0.79-0.99		0.79	0.69-0.9	
T3	0.72	0.54-0.95		0.48	0.26-0.9	
T4	0.68	0.52-0.88		0.54	0.41-0.72	
<i>Nodal classification</i>						
N0	0.90	0.84-0.96	0.00086	0.81	0.75-0.89	0
N1	0.31	0.07-1		0.55	0.31-0.95	
N2	0.67	0.5-0.9		0.37	0.23-0.61	
<i>Metastatic disease</i>						
M0	0.84	0.78-0.91	0.005	0.71	0.63-0.81	0.02
M1	0.27	0.05-1		0.25	0.05-1	
stage						
I and II	0.96	0.92-1	0.0012	0.87	0.78-0.96	<0.0001
III and IV	0.69	0.58-0.82		0.51	0.4-0.66	
<i>Tumor grade</i>						
LG	0.90	0.82-0.99	0.0004	0.81	0.72-0.91	<0.0001
IG	0.86	0.71-1		0.84	0.7-1	
HG	0.67	0.53-0.83		0.42	0.29-0.6	
<i>Surgical margins</i>						
R0	0.89	0.82-0.96	0.01	0.77	0.68-0.89	0.0005
R1	0.76	0.58-1		0.42	0.23-0.76	
R2	0.68	0.45-1		0.46	0.27-0.81	
<i>Histological nodal classification</i>						
pN0	0.83	0.72-0.96	0.3	0.79	0.69-0.9	0.001
pN+	0.84	0.72-0.99		0.41	0.23-0.71	
Treatments						
<i>Surgery</i>						
No	-	-	<0.0001	-	-	<0.0001
Yes	0.86	0.79-0.93		0.71	0.62-0.81	
RT						
No	0.92	0.86-0.98	0.01	0.82	0.73-0.93	<0.0001
Yes	0.74	0.63-0.87		0.57	0.46-0.7	
CT						
No	0.89	0.83-0.95	<0.0001	0.77	0.7-0.84	<0.0001
Yes	0.49	0.29-0.82		0.28	0.11-0.69	

Prognosis factors	OS			DFS		
	HR*	95%IC	p	HR*	95%IC	p
Age	1.05	1.02-1.08	0.002	1.02	1-1.03	0.08
Diabetes (yes vs no)	5.17	1.37-19.46	0.01	3.25	1.45-9.18	0.006
Stage (III-IV vs I-II)	4.11	1.04-16.29	0.04	2.81	1.25-6.32	0.01
Grade						
LG	1.00	Referent**		1.00	Referent**	
IG	1.47	0.34-6.3	0.60	0.89	0.29-2.75	0.84
HG	2.81	0.99-8.04	0.05	2.83	1.43-5.	0.002
Surgery (yes vs no)	0.13	0.05-0.33	<0.00003	0.27	0.13-0.58	0.0008
CT (yes vs no)	2.3	0.97-5.44	0.05	1.66	0.91-3.03	0.1

Tableau 4.
Prognosis factors in

multivariate analysis for the study population

* Adjusted by sex, RT, and alcohol, for DFS.

**HG and IG were evaluated using LG as a reference.

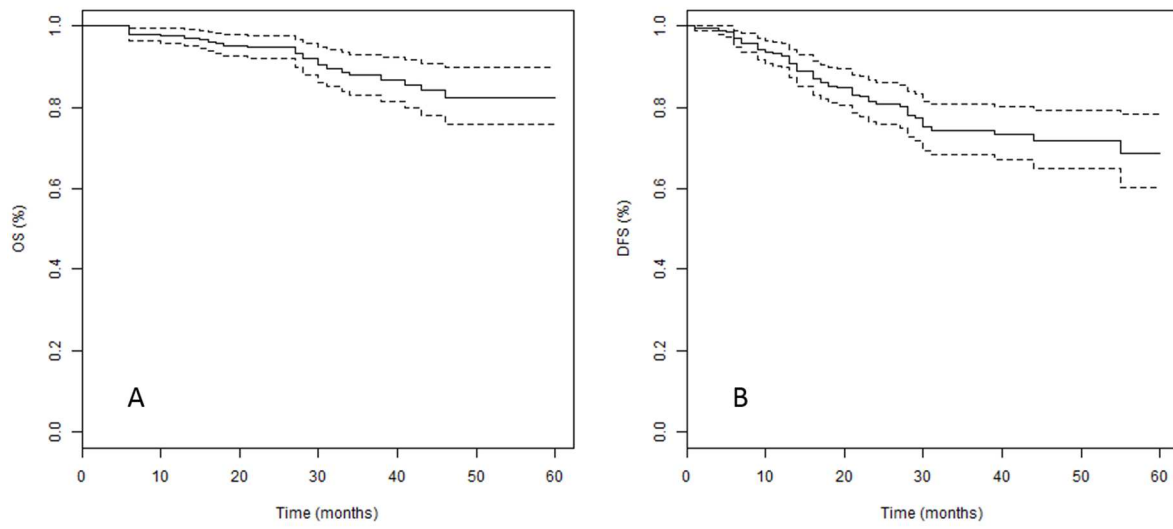


Figure 1. (A) Overall survival and (B) Disease free survival of all patients included

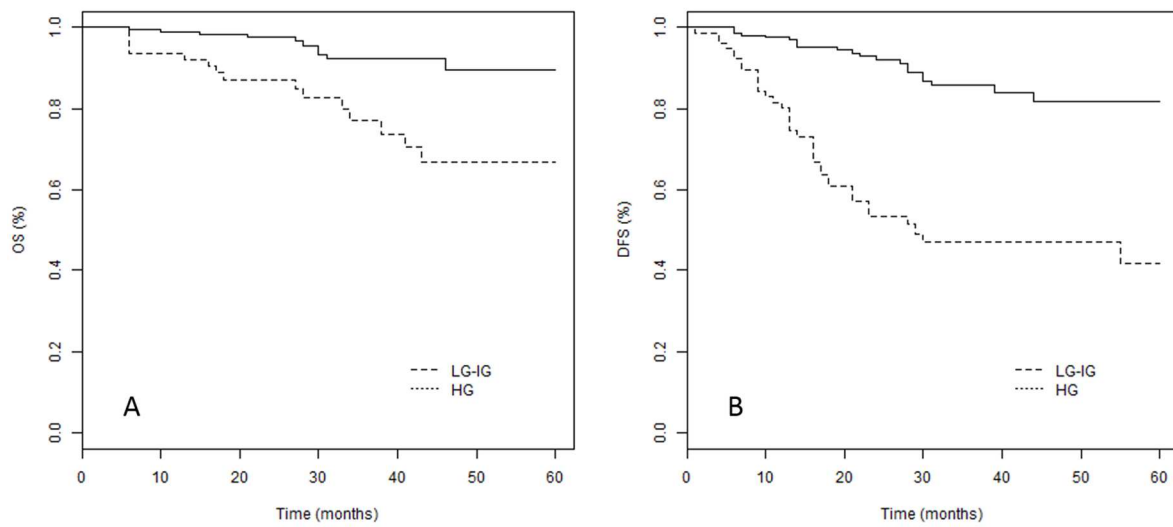


Figure 2. (A) Overall survival and (B) Disease free survival depending on histological grade in the study population.

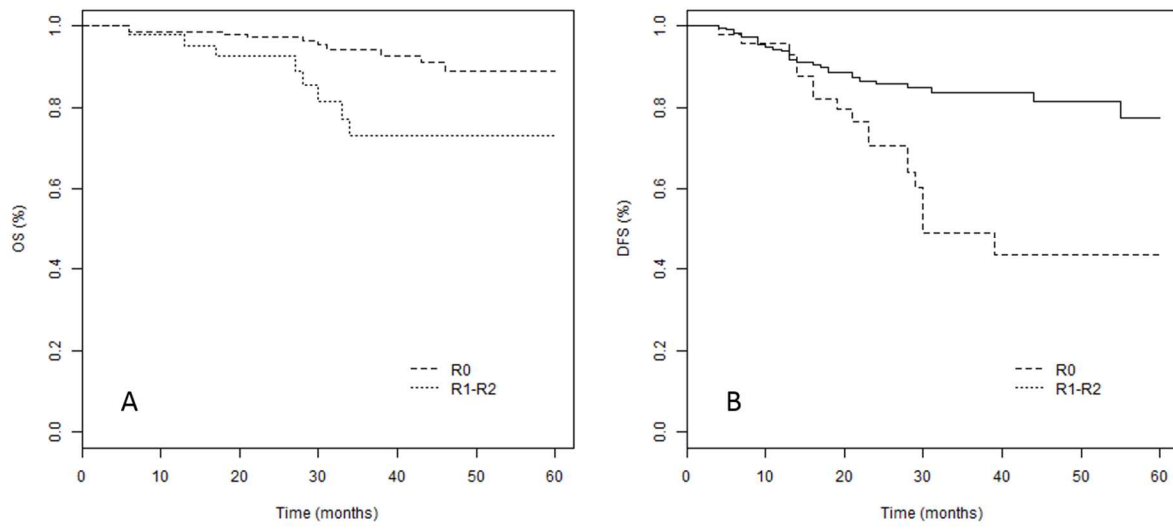


Figure 3. (A) Overall survival and (B) Disease free survival depending on surgical margins in the study population.