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Prognostic factors in head and neck mucoepidermoid carcinoma (MEC): a single-institution experience based on 64 consecutive patients and 28 years follow-up

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Abstract

Introduction. Mucoepidermoid carcinoma (MEC) is the most common malignancy of the salivary glands whose clinical behavior is largely unpredictable, ranging from indolent tumor growth to highly aggressive metastatic spread. The objective of this study was to determine the clinicopathologic predictors of recurrence and survival in patients with head and neck MEC.

Materials and Methods. The medical records of 64 patients who underwent surgical treatment for head and neck MEC between 1982 and 2010 were reviewed. Main outcome measures were disease-free survival (DFS) and overall survival (OS). Clinicopathologic parameters evaluated were age, gender, anatomic subsite, histological grade, tumor stage, tumor size, adjuvant therapy, nodal and margin status.

Results. Of the 64 patients, 33 parotid glands, 10 submandibular/sublingual, 21 minor salivary glands MEC (17 oral cavity and 4 maxillary sinus) primaries were identified and surgically treated. Twenty-one (32.8%) patient underwent postoperative radiotherapy. The 5-year DFS and OS for the entire cohort were 79.7%, and 67.2%, respectively. Histological grade, tumor stage and nodal status were a statistically significant predictor of DFS and OS. Furthermore, anatomical subsite and patient age were statistically significant predictors with respect to OS. There was no statistically significant difference in DFS or OS based on gender, adjuvant therapy, tumor size and margin status.

Conclusion. Advanced tumor stage, high histologic grade, submandibular/sublingual localization and positive nodal status were independent predictors of prognosis in patients with head and neck MEC. Further studies into the molecular biology of MEC are needed in order to provide new therapeutic strategies in patients with locally aggressive and highly metastatic carcinomas.

Introduction

Mucoepidermoid carcinoma (MEC) is the most common malignancy of the salivary glands, representing 30-40% of all major salivary gland malignancies and up to half of parotid gland malignancies.[1, 2] The clinical behavior of MEC is highly variable, ranging from indolent tumor growth to highly aggressive metastatic carcinomas. In order to clarify its largely unpredictable behavior, a different prognostic factors have been studied. Although inconsistently, conventional clinicopathologic parameters such as age, gender, tumor site, stage, TNM status, extracapsular spread (ECS), adjuvant therapy, and margin status have been shown to have predictive value with respect to survival.[3-5] However, it has been generally accepted that the most relevant prognosticators of survival are tumor grade and disease stage.[4, 6-7] The aim of this study was to describe head and neck MEC treated at a tertiary care hospital centre, as well as to determine the clinicopathologic predictors of recurrence and survival in this patient population.

Materials and methods

Using retrospective chart review, data collected included age, gender, tumor site, histological grade, stage, type of treatment modality, nodal status, histological status of surgical margins, disease status, and follow-up.

The study included 64 patients with head and neck MEC. Inclusion criteria were: histologically proven and surgically treated head and neck MEC. Patients with adverse histopathological features (high grade tumors, positive margin, perineural invasion, extracapsular spread (ECS), multiple positive lymph nodes, stage T3 or T4) underwent postoperative irradiation. MEC were staged according to TNM classification of malignant tumors of salivary glands.

In our institution MEC is graded into low grade (LG), intermediate grade (IMG) and high grade (HG) carcinomas according to WHO classification and includes following data: amount of cystic component, presence of neural invasion, necrosis, number of mitoses per 10 high power field (HPF) and presence or absence of anaplasia.[8] All of the listed data get their matching number of points, which all add together. The obtained point score responds to tumor grade, which in case of mucoepidermoid carcinoma can be low, intermediate and high grade. None of the patients was lost to follow-up.

Statistical analysis

To assess the association of clinicopathological parameters, a $\chi 2$-test or Fisher's exact test were performed. The primary endpoints were disease-free survival (DFS) and overall survival (OS). Follow-up intervals were calculated in months from the date of first date of surgical treatment to the date of last follow-up or death. A DFS event was defined as a pathologically confirmed recurrence; an OS event was defined as death from any cause; deaths from other causes were censored at the date of death. Patients with IMG-MEC were affiliated to LG-MEC due to small

sample size in IMG group and similar biological behavior between these two histological subtypes. DFS and OS curves were estimated by the Kaplan-Meier method while the log-rank test has been used to test differences between the actuarial curves. All statistics was done using Statistica, data analysis statistical software (StatSoft, Inc version 10, 2011). P values of <0.05 were considered statistically significant.

Results

There were 28 (43.7%) women and 36 (56.3%) men, with a mean age at diagnosis of 46.9 (range 9-80 years). Sixty (93.8%) previously untreated patients presented to our institution, while 4 patients (6.2%) were referred to our hospital due to recurrent tumors. Of previously untreated tumors, 44 patients had stage T1/T2, 15 had advanced disease (T3/T4) whereas 5 patients had unknown disease stage. The parotid gland was the most frequent primary tumor site. Clinicopathological characteristics of the study group are summarized in **Table 1**.

The 5-year OS for the entire cohort were 67.2%. The 5-year DFS was 79.7% with 13 (20.3%) patients developing recurrence. Univariate analysis showed that advanced histological grade and positive nodal status were a statistically significant predictor of DFS and OS (**Figure 1-4)**. Furthermore, anatomical subsite, tumor stage and patient age were statistically significant predictor with respect to OS. There was no statistically significant difference in DFS or OS based on gender, adjuvant therapy, and margin status.

Of 64 patients, 39 (60.9%) had low-grade (LG), 6 (9.4%) had intermediate-grade (IMG) and 19 (29.7%) had high grade (HG) MEC. The influence of histological grade on survival is shown in **Figure 1**, and their correlation on other clinicopathological parameters is summarized in **Table 2**. The 5-year DFS and OS was 97.4% and 82.1% in LG-MEC group compared to 83.3% and 50% in IMG-MEC group and 42.1% in HG-MEC group respectively. There was significant difference in survival when comparing LG/IMG-MEC compared to cohort with HG-MEC ($p=0.003$). In addition, higher histological grade statistically significant correlated with advanced tumor stage ($p=0.006$), positive nodal status ($p<0.001$) and submandibular/sublingual subsite of the tumor ($p=0.003$).

Twenty-one (32.8%) patient underwent postoperative radiation. Thirteen (20.3%) patients developed tumor recurrence following treatment in our institution. Four patients developed local recurrence, 5 regional and 4 distant metastases.

Twenty-one (32.8%) patients died during 5-year follow-up period. Seven (33.3%) of them died due to tumor recurrence and 14 (66.4%) died of other causes.

Follow-up information was available for all patients, range from 3 – 171 months.

Discussion

In this study we reported 28 year single-institution's experience on 64 patients with head and neck MEC. In our study, head and neck MEC occurred most often in the fifth decade of life and had a slight male predominance which is similar to prior reports.[9-10] The 5-year of the cohort OS was 67%, which is consistent with prior studies.[10-12]

On univariate analysis, features that correlated with significantly poorer survival were higher histological grade, advanced tumor stage, submandibular/sublingual localization and positive nodal status.

Tumor stage and histological grade appear to have significant impact on survival. We confirmed a significant decrease in survival for patients with T3/T4 tumors as well as presence of nodal disease. This is in accordance with previous findings in the literature.[6, 13]

Past reports indicated trend toward poorer survival when stratified according to grade status.[8, 14-15] LG-MEC characteristically shows better prognosis with lower recurrence and metastatic potential compared to HG-MEC. Due to less aggressive clinical course, LG-MEC is often treated with surgical excision with negative margins solely, while aggressive HG-MEC are treated in combination of surgery, neck dissection and post-operative adjuvant radiotherapy.[16] Three grading system was introduced raising major point about clinical behavior and prognosis of IMG-MEC.[17] Some studies have demonstrated that there is no significant difference in survival (DFS and OS) between LG and IMG-MEC group of patients, but significant difference between IMG and HG-MEC suggesting that IMG-MEC have similar clinical behavior to LG-MEC.[6, 18-19] Similarly, our analysis showed difference in survival when comparing LG/IMG tumors and HG-MEC. Tumor subsite appears to have significant impact on survival, showing that

submandibular/sublingual localization had the worst prognosis compared to parotid or other minor gland MEC regardless on tumor grade or extend of treatment. This finding is in accordance with prior studies.[13, 20-21] Also submandibular/sublingual MEC in our study tends to developed in older patients with larger size tumors comparing to other MEC patients.

In contrast to most solid human tumors, MEC is frequently characterized by chromosomal translocation. This includes t (11;19) (q21–22; p13) translocation resulting in a CRTC1-MAML2 gene fusion.[22-23]

The fusion positive cases show significantly higher survival rates compared to fusion-negative cases, representing prognostic marker in patients with MEC.[22, 24-26] Furthermore, preliminary studies using molecule inhibitors of the epidermal growth factor receptor (EGFR) or protein kinase pathways have shown inhibition proliferation of MEC cell lines in vitro, suggesting that targeting these pathways may offer a new treatment approach in CRTC1-MAML2 MECs positive patients.[27]

Although MEC is the most common salivary gland carcinoma, only few studies have addressed the role of systemic therapy in adjuvant and palliative settings. While addition of high-dose chemotherapy to radiation (concurrent chemoradiotherapy) in head and neck squamous cell carcinoma has led to significant survival improvement compared to radiation solely, the efficacy of chemotherapy seems to be limited in HG-MEC in both curative and palliative settings.

The retrospective type of the study represents the primary limitation of the study. In addition, this study includes time period from 1982 to 2015. During this time, treatment modalities have evolved. As such, the management of the study population is not homogeneous and may

influence final outcome and the results obtained from statistical analysis. Additionally, the study could not be strengthened by a meta-analysis due to the small sample size.

In conclusion, this study shows that advanced tumor stage, high histological grade, submandibular/sublingual localization and positive nodal status were unfavorable prognostic factors in patients with head and neck MEC. Further investigations are needed in order to provide new prognostic factors and therapeutic strategies in head and neck MEC.

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Table 1. Clinicopathological characteristics of mucoepidermoid carcinoma

Baseline Characteristic	Number of Patients (%)
Mean age (years)	46.9
Gender	
Male	36 (56.3)
Female	28 (43.7)
Tumor subsite	
Parotid gland	33 (51.6)
Submandibular/sublingual gland	10 (15.6)
Minor gland	21 (32.8)
Histological grade	
Low grade	39 (60.9)
Intermediate grade	6 (9.4)
High grade	19 (29.7)
Tumor stage	
T1/T2	44 (68.8)
T3/T4	15 (23.4)
Unknown	5 (7.8)
Nodal status	
Negative	50 (78.1)
Positive	14 (21.9)
Margin status	
Negative	56 (87.5)
Positive	7 (10.9)
Unknown	1 (1.6)
Radiation therapy	
No	43 (67.2)
Yes	21 (32.8)

Table 2. Histological grade and thier influence on other clinicopathological paremeters

Histological grade	Low (N=39)	Intermediate (N=6)	High (N=19)	p value
Mean age (years)	42.74	49.83	54.63	n.s.[1]
Gender				
Male	19 (48.7%)	4 (66.7%)	13 (68.4%)	n.s.[2]
Female	20 (51.3%)	2 (33.3%)	6 (31.6%)	
Tumor stage				
T1/T2	33 (84.6%)	4 (66.7%)	7 (36.8%)	0.006[2]
T3/T4	4 (10.3%)	2 (33.3%)	9 (47.4%)	
Unknown	2 (5.1%)	0	3 (15.8%)	
Nodal status				
Negative	39 (100.0%)	3 (50.0%)	8 (42.1%)	<0,001[2]
Positive	0	3 (50.0%)	11 (57.9%)	
DFS	38 (97.4%)	5 (83.3%)	8 (42.1%)	<0,001[2]
OS	32 (82.1%)	3 (50.0%)	8 (42.1%)	0.006[2]

[1] Oneway analysis of variance, [2] χ^2 – test

Table 3. Tumor subsite and thier influence on other clinicopathological paremeters

Tumor subsite	Parotid gland MEC (N=33)	Submand/subling gland MEC (N=10)	Minor gland MEC (N=21)	p value
Mean age (years)	49.67	61.10	35.90	0.003[1]
Tumor size (mm)	27.03	35.50	21.68	n.s.[2]
Gender				
Male	16 (48.5%)	9 (90.0%)	11 (52.4%)	n.s.[3]
Female	17 (51.5%)	1 (10.0%)	10 (47.6%)	
Histological grade				
Low	17 (51.5%)	2 (20.0%)	20 (95.2%)	0.003[3]
Intermediate	4 (12.1%)	2 (20.0%)	0	
High	12 (36.4%)	6 (60.0%)	1 (4.8%)	
Tumor stage				
T1/T2	24 (72.7%)	4 (40.0%)	16 (76.2%)	n.s.[3]
T3/T4	6 (18.2%)	6 (60.0%)	3 (14.3%)	
Unknown	3 (9.1%)	0	2 (9.5%)	
Nodal status				
Negative	25 (75.8%)	4 (40.0%)	21 (100.0%)	0.001[3]
Positive	8 (24.2%)	6 (60.0%)	0	
DFS	23 (69.7%)	8 (80.0%)	20 (95.2%)	n.s.[3]
OS	21 (63.6%)	3 (30.0%)	19 (90.5%)	0.003[3]

[1] Oneway analysis of variance, [2] Kruskal-Wallis test, [3] χ^2 – test

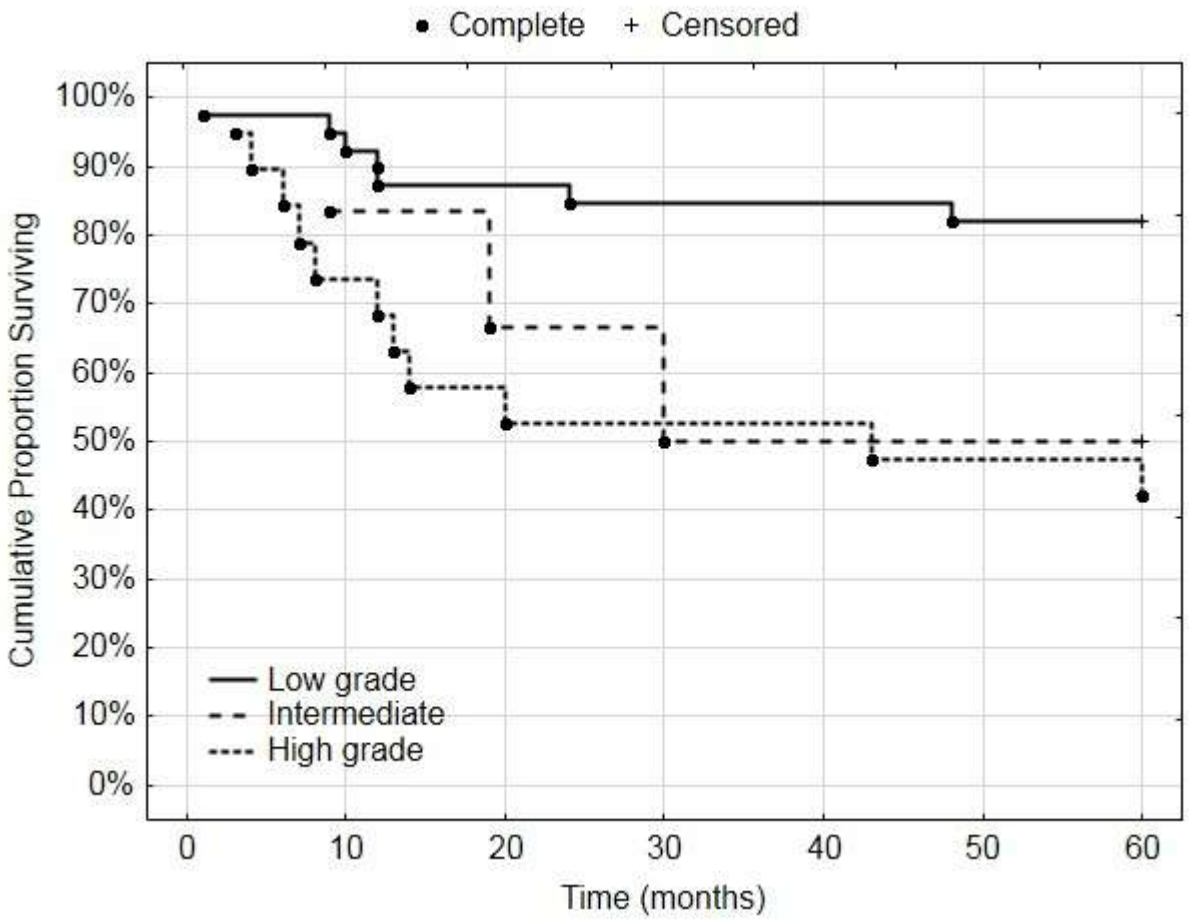

Fig. 1 Kaplan-Meier curve of 5-year OS comparing histological grade

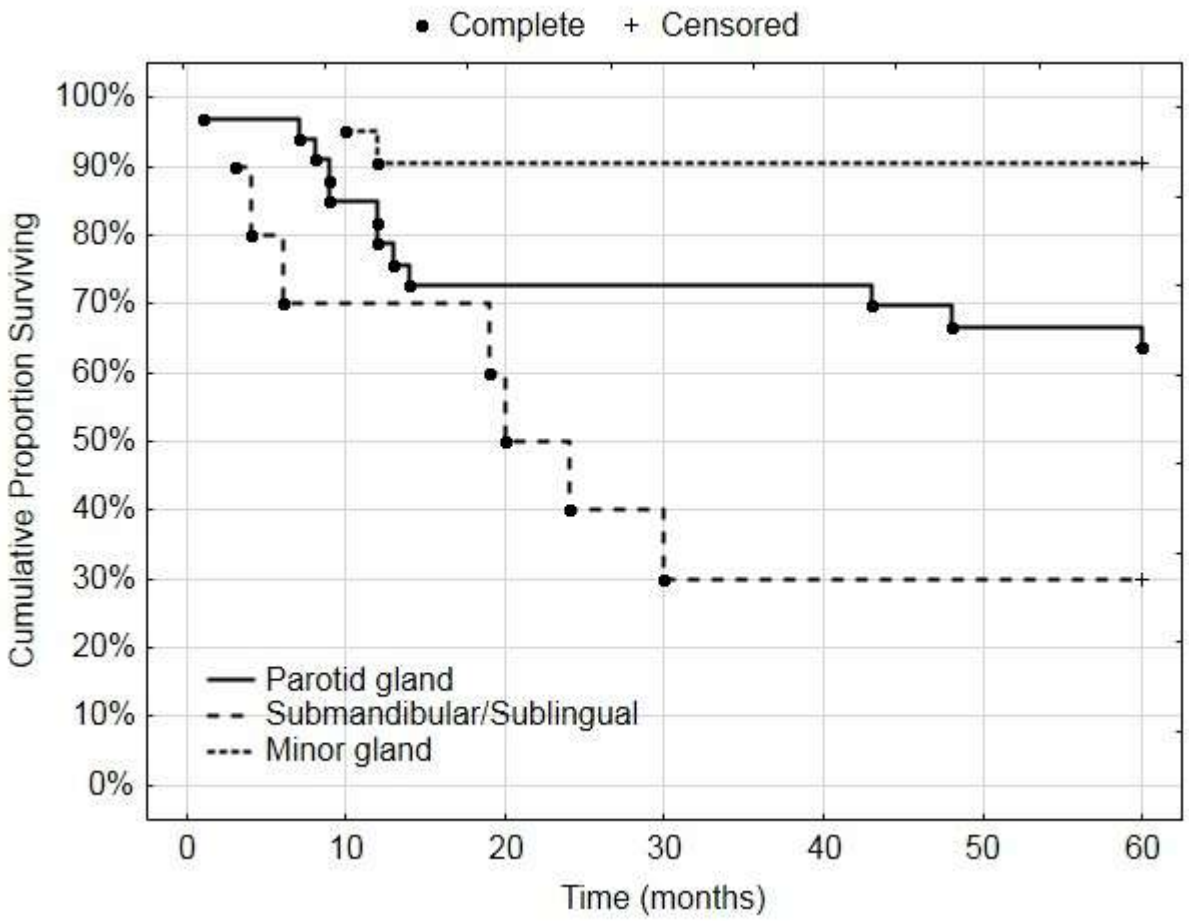

Fig. 2 Kaplan-Meier curve of 5-year OS comparing anatomical subsite

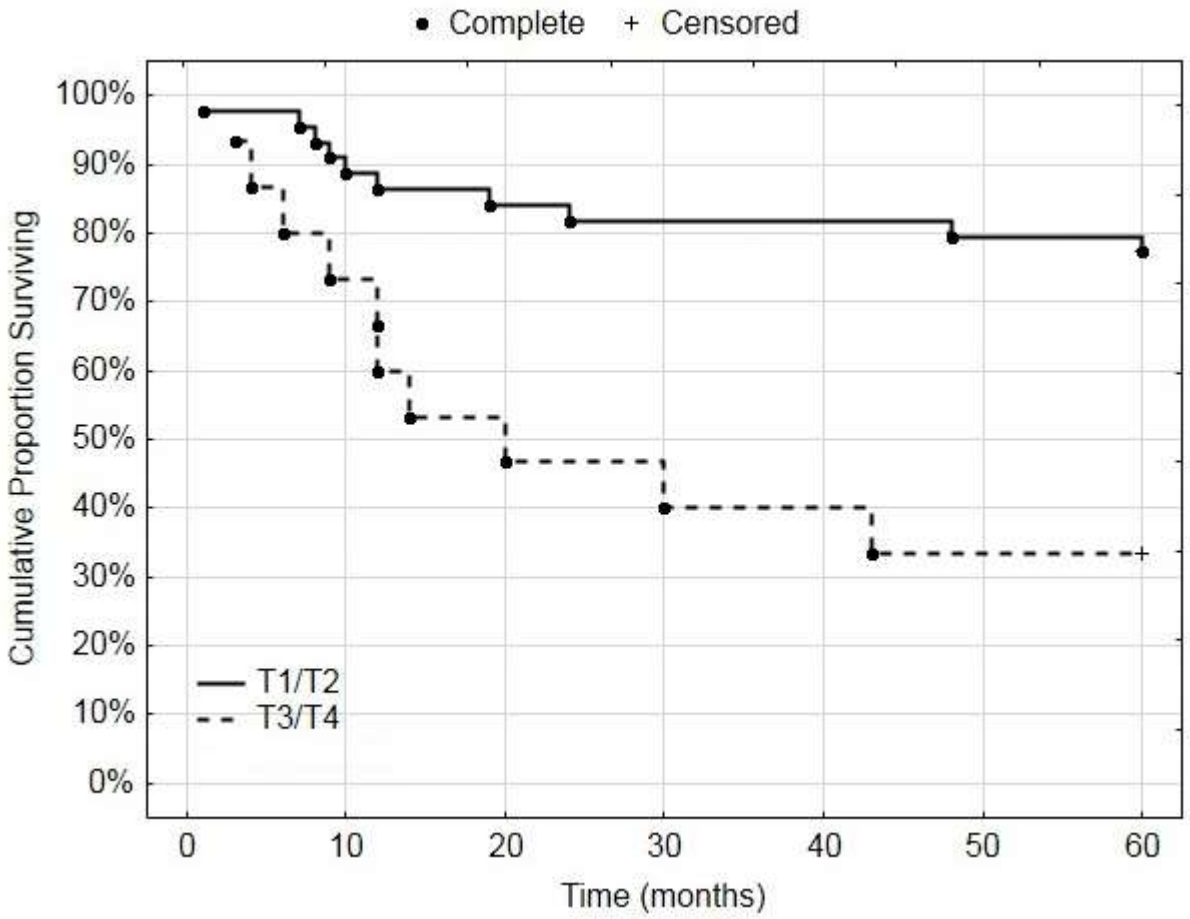

Fig. 3 Kaplan-Meier curve of 5-year OS comparing tumor stage

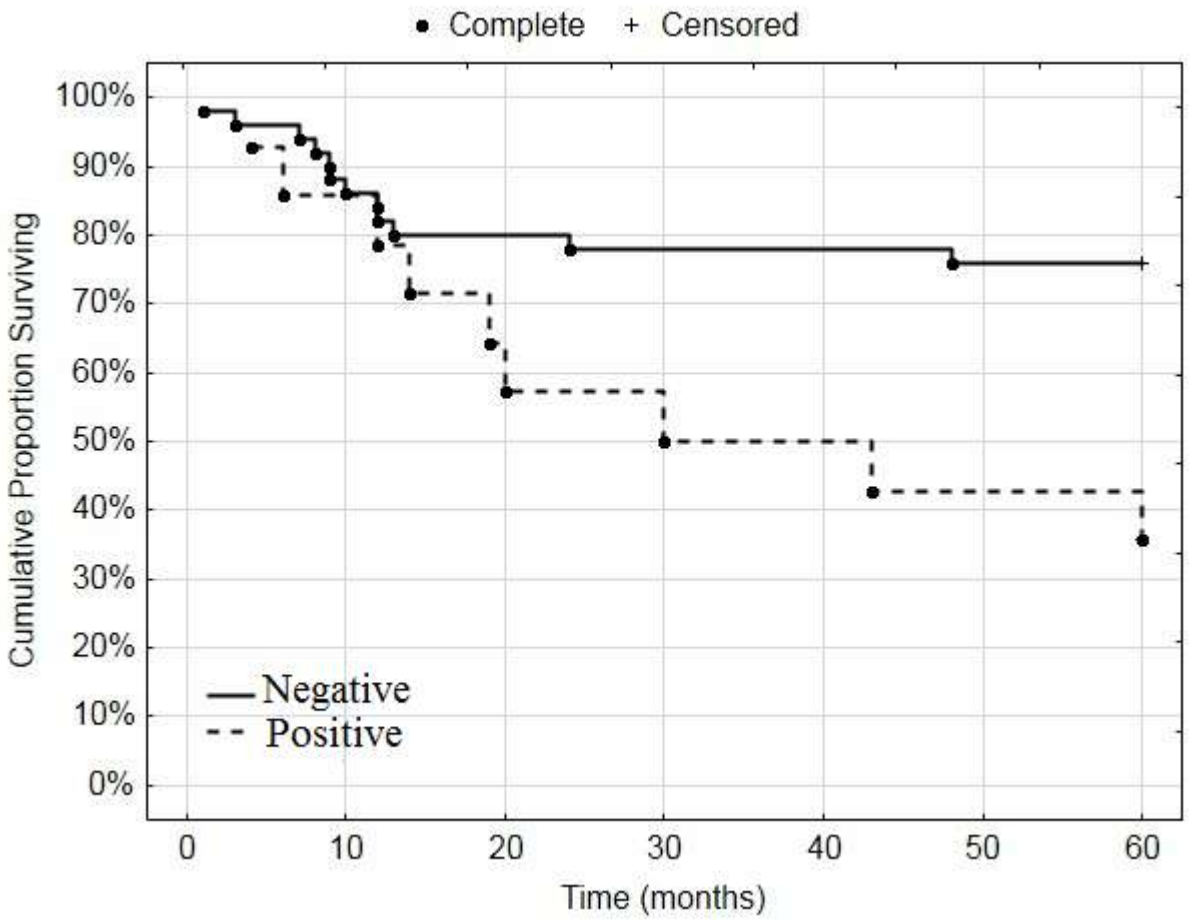

Fig. 4 Kaplan-Meier curve of 5-year OS comparing nodal status