



## Original Research

# Myoepithelial carcinoma of major salivary glands: Analysis of population-based clinicopathologic and prognostic features

Yunxiu Luo <sup>\*</sup>

Department of Radiotherapy Oncology, Hainan Cancer Hospital, Affiliated Cancer Hospital of Hainan Medical College, No. 9, Changbin West Fourth Street, Xiuying District, Haikou, Hainan 570100, China



## ARTICLE INFO

## Keywords:

Myoepithelial carcinoma  
Salivary gland  
Surveillance epidemiology and end results  
Population  
Radiotherapy  
Prognosis

## ABSTRACT

**Background:** This study aimed to investigate the effect of demographic characteristics and disease stage on the survival outcomes of patients with myoepithelial carcinoma (MECA) of the salivary glands, and to assess the role of radiotherapy in these patients.

**Methods:** The Epidemiology, Surveillance and End Results database was queried from 2000 to 2018 to identify patients with MECA. Data pertaining to the tumor stage, size, histological grade, and demographic characteristics were analyzed. The relationship between clinicopathological features and overall survival (OS) was assessed using statistical analyses.

**Results:** In total, 290 patients (137 men and 153 women) were identified. The parotid gland was the most common tumor location (76.6% patients). Approximately half of the patients had locally advanced tumors, and 14.5 and 6.6% had lymph node and distant organ involvement, respectively. The median OS was 142 months, while the survival rates at 120 months and 180 months were 53% and 39%, respectively. In the cohort, 160 patients (55.2%) underwent surgery alone, while 130 patients (44.8%) underwent surgery combined with radiotherapy. Multivariate Cox analysis revealed that histopathological grade, stage, T3 stage (hazard ratio [HR]: 2.47,  $P = 0.039$ ), T4 stage (HR: 3.33,  $P = 0.011$ ), N2 stage (HR: 6.59,  $P = 0.002$ ), and M1 stage (HR: 2.72, 95% confidence interval [CI]: 1.03–7.19;  $P = 0.044$ ) were associated with poor prognosis. Radiotherapy (HR: 0.58,  $P = 0.042$ ) was a favorable factor for OS, and it reduced the mortality risk by 42%.

**Conclusions:** Histological grade, stage, and radiotherapy are independent risk factors for OS. The decision to administer chemotherapy for MECA should be made with caution. Adjuvant radiotherapy is recommended in high-risk patients.

## List of abbreviations

MECA	myoepithelial carcinoma
OS	overall survival
SEER	surveillance epidemiology and end results
S	surgery
R	radiotherapy
AJCC	American joint committee on cancer
ICD-3	international classification of disease for oncology, third edition
CS	collaborative stage
EOD	extent of disease (EOD)
HR	hazard rate
CI	confidence interval

PSM	propensity score-matching
CCS	cancer-specific survival

## Introduction

Myoepithelial carcinoma (MECA) is a rare neoplasm of the head and neck. The most common site of occurrence of MECA is in the parotid gland, followed by the submandibular gland. The definition and diagnostic criteria for MECA have been reported in the literature since 1995 [1]. Histologically, MECA is a neoplasm that is exclusively or nearly exclusively composed of myoepithelial cells, and over 50% of MECA patients exhibits *PLAG1* fusion. The diagnostic signs of MECA may be easily overlooked, and they can be misclassified as a benign salivary gland neoplasms such as cellular or myoepithelial-rich pleomorphic

\* Corresponding author.

E-mail addresses: [ruoshuiluo@163.com](mailto:ruoshuiluo@163.com), [375237661@qq.com](mailto:375237661@qq.com).

adenoma (PA) [2]. CK and P63 expression in pulmonary MECA is regarded as a useful marker for the differential diagnosis [3]. Clinically, MECA can exhibit aggressive characteristics with a tendency for relapse and metastasize, even when it is intracapsular, or may show minimally invasive characteristics that are subclassified as de novo or ex-pleomorphic adenoma (PA) [2,4,5]. Most of the contemporary literature related to MECA comprises individual case reports or analysis of small case series; therefore, the condition is not well characterized and is under-recognized [5–8]. In two relatively large studies, a tumor size of >5 cm, a mitotic index of >10/10 in high-power field (HPF), lymph node involvement, and advanced stage were shown to be associated with shorter overall survival, and excision was found to be the optimal treatment for MECA [9,10]. One of these studies systematically reviewed all data of 691 patients and found that those with a positive margin may benefit from adjuvant radiotherapy [9]. In the present study, we comprehensively analyzed the demographic and clinicopathologic features, prognosis-related variables, and efficacy of treatments, especially radiotherapy, for MECA using the patient's data recorded in the Surveillance, Epidemiology, and End Results (SEER) database. Propensity score matching (PSM) was used to minimize the influence of confounding variables.

## Patients and methods

### Patient population

SEER-registered patients diagnosed with MECA with site codes C07.9-C08.9 and International Classification of Disease for Oncology, Third Edition (ICD-O-3) histological classification code 8982 from 2010 to 2018 were included in this study. Data on the diagnosis confirmation; derived American Joint Committee on Cancer (AJCC), 7th edition (2010–2015) stage; derived SEER combined stage (2016–2017); derived extent of disease (EOD) 2018 stage; primary tumor (T), nodal (N), and metastasis (M) stage; histological grade; collaborative stage (CS) tumor size; sequence of surgery and radiotherapy; chemotherapy; overall survival (OS) in months; survival status and cancer-specific survival (CSS) were obtained. The three staging systems were merged, and the outcomes were recorded as T, N, and M stages for analysis. Moreover, the baseline demographic variables, including age, sex, race, and year of diagnosis, were collected. Patients with unavailable survival data or survival status were excluded.

Patients who underwent surgery only (S group) were compared with those who underwent surgery combined with radiotherapy (S+R group). To identify the characteristics of patients who were most likely to benefit from adjuvant radiotherapy, we assessed the association between additional radiotherapy and survival outcomes was assessed after disaggregating patients by tumor histology, stage, sex, age, race, primary site, grade, and chemotherapy status. The covariates of interest included patient-related factors (age, sex, and race), disease-level factors (primary site, stage, grade, and CS tumor size), and treatment-related factors (radiotherapy, chemotherapy, and surgery). Patients included in the SEER database had previously consented to participate in any scientific research worldwide.

### Statistical analysis

Between-group differences were assessed using Fisher's exact probability and *t*-test (two tailed) for categorical and continuous variables, respectively, respectively. The Kaplan–Meier (KM) method was used to generate the survival curves, and a Cox proportional hazards regression model was used to determine the effects of variables on OS after adjusting for other significant prognostic factors using propensity score matching based on a 1:1 nearest neighbor algorithm. In the logistic regression model, the group (S or S+R) was used as a categorical variable, while the other variable (stage) was used as the matched variable. The factors that showed a significant association in the KM analysis were

included in the Cox hazard regression model. All analyses were performed using SPSS version 26.0 for Windows software (IBM Corporation, Chicago, IL) and EmpowerStats software 2.0, GraphPad Prism 7.0. A *P* value of <0.05 was considered significant.

## Results

### Patients' baseline characteristics

A total of 290 patients [153 (52.8%) women and 137 (47.2%) men] with MECA were identified in the SEER database (2010 to 2018). The median follow-up period was 79 months. Most patients (71.7%, 208/290) were aged  $\geq 55$  years at the time of diagnosis. Caucasians accounted for 74.8% (217/290) of all study patients. Most cases (76.6%, 222/290) showed parotid gland involvement. The mean tumor size was  $3.5 \pm 1.7$  cm. A total of 250 patients had available information on disease stage: 70 (24.3%), 67 (23.1%), 60 (20.7%), and 53 (18.3%) patients had stage I, II, III, and IV disease, respectively. Stage information was not available in 40 patients (13.8%). Meanwhile, 73 (25.2%), 70 (24.1%), 65 (22.5%), and 39 (13.4%) patients had T1, T2, T3, T4 disease stages, respectively; moreover, 43 patients (14.8%) had missing information on T stage. A total of 212 (73.1%) patients showed absence of lymph node invasion, while 36 (12.4%) patients had lymph node involvement; further, 42 patients (14.5%) had no information on lymph node involvement. In most patients (82.1%, 238/290), the disease had not spread to the distant organs, whereas 17 patients (5.9%) had developed distant metastasis; the metastasis status of 35 patients (12.10%) had not been recorded. In general, approximately half of the patients had locally advanced tumors (T3, T4, N+), the lymph node-positive rate was 14.5% (36/248), and 6.6% of patients (17/255) had distant metastasis. The distant organs that were invaded included the lung, liver, bone, and brain (in descending order of frequency). Most of the patients (262/290, 90.3%) did not receive chemotherapy. Chemotherapy was administered in 9.7% of patients (28/290), and most of them (20/26, 76.9%) had stage IV disease. A patient with stage I cancer who received chemotherapy had an undifferentiated tumor.

In general, 160 patients (55.2%) underwent surgery only (S group), while 130 patients (44.8%) underwent surgery combined with radiotherapy (S+R group) (Table 1). The mean CS tumor size in the S and S+R groups were  $3.3 \pm 1.6$  cm and  $3.8 \pm 1.0$  cm ( $P = 0.046$ ), respectively. Significantly more patients (82.3%, 107/130) in the S+R group developed MECA in the parotid gland than that in the S group (71.9%, 115/160) ( $P = 0.037$ ). However, the proportions of patients with adverse histological differentiation (poor and undifferentiated) in the S+R and S groups were 26.9% and 12.5% ( $P = 0.028$ ), respectively; a significantly greater proportion of patients in the S+R group (16.2% vs. 4.4%) received chemotherapy ( $P < 0.001$ ). More than half of the patients in the S group had an early-stage disease (I + II), compared with the <40% of patients in the S+R group ( $P = 0.03$ ). Similarly, more patients in the S+R group had advanced T stage (47.7% vs. 26.2%,  $P < 0.001$ ). Lymph node metastases occurred in 21.2% and 8.8% of patients in the S+R and S groups, respectively ( $P = 0.052$ ).

We filtered 105 pairs of patients for the post-PSM analysis (Table 1). After PSM, CS tumor size was found to be comparable in the S+R group ( $3.8 \pm 1.8$  cm) and the S group ( $3.4 \pm 1.7$  cm) ( $P = 0.17$ ). The baseline characteristics were similar between the S and S+R groups, except for chemotherapy ( $P < 0.001$ ).

### Prognostic value of the clinicopathological characteristics

The median OS for the 290 patients was 142 (95% confidence interval [CI]: 97–174) months, and the OS rates were 68.9% (95% CI: 63%–75.4%) at 60 months, 53% (95% CI: 45.7%–61.5%) at 120 months, and 38.1% (27.4%–52.8%) at 180 months (Fig. 1a). Stratified KM analysis was performed based on the clinicopathological features. The median OS times in the S and S+R groups were 144 months (95% CI:

**Table 1**  
Clinicopathologic features of patients with salivary gland myoepithelial carcinoma.

Number	Before matching		P-value	After matching		P-value
	S	S+R		S	S+R	
<b>CS Tumor size (mm)</b>	160	130		105	105	
<b>Follow-up (months)</b>	32.7 ± 16.0	38±10.3	<b>0.046</b>	34.13±16.6	38±18.1	0.17
<b>Status</b>	60.9 ± 52.0	64.0 ± 53.6	0.614	63.7 ± 46.82	62.4 ± 45.4	0.844
alive			0.986			0.662
dead	106 (66.2%)	86 (66.2%)		68 (64.8%)	71 (67.6%)	
<b>Age</b>	54 (33.8%)	44 (33.8%)	0.13	37 (35.2%)	34 (32.4%)	0.31
1–24	4 (2.5%)	3 (2.3%)		3 (2.9%)	3 (2.9%)	
25–39	15 (9.4%)	8 (6.2%)		11 (10.5%)	4 (3.8%)	
40–54	35 (21.9%)	17 (13.1%)		18 (17.1%)	15 (14.3%)	
55–69	49 (30.6%)	56 (43.1%)		35 (33.3%)	45 (42.9%)	
70–85	57 (35.6%)	46 (35.4%)		38 (36.2%)	38 (36.2%)	
<b>Sex</b>			0.541			0.49
Male	73 (45.6%)	64 (49.2%)		48 (45.7%)	53 (50.5%)	
female	87 (54.4%)	66 (50.8%)		57 (54.3%)	52 (49.5%)	
<b>Year of diagnosis</b>			0.299			0.66
2000–2009	55 (34.4%)	54 (41.5%)		38 (36.2%)	40 (38.1%)	
2010–2015	69 (43.1%)	43 (33.1%)		48 (45.7%)	42 (40.0%)	
2016–2018	36 (22.5%)	33 (25.4%)		19 (18.1%)	23 (21.9%)	
<b>Race</b>			0.365			0.344
White	115 (71.9%)	102 (78.5%)		74 (70.5%)	83 (79.1%)	
Black	24 (15.0%)	17 (13.1%)		17 (16.2%)	13 (12.4%)	
other	21 (13.1%)	11 (8.5%)		14 (13.3%)	9 (8.6%)	
<b>Site</b>			0.037			0.587
parotid	115 (71.9%)	107 (82.3%)		85 (80.9%)	88 (83.8%)	
Submandibular gland	45 (28.1%)	23 (17.7%)		20 (19.1%)	17 (16.2%)	
<b>Grade</b>			0.028			0.059
well	25 (15.6%)	12 (9.2%)		22 (20.9%)	10 (9.6%)	
moderately	35 (21.9%)	25 (19.2%)		21 (20.0%)	22 (20.9%)	
Poorly	11 (6.9%)	20 (15.4%)		6 (5.7%)	14 (13.3%)	
undifferentiated	9 (5.6%)	15 (11.5%)		7 (6.7%)	12 (11.5%)	
NA	80 (50.0%)	58 (44.6%)		49 (46.7%)	47 (44.7%)	
<b>Stage</b>			0.03			0.843
I	45 (28.1%)	25 (19.2%)		31 (29.5%)	26 (24.8%)	
II	41 (25.6%)	26 (20.0%)		27 (25.7%)	26 (24.8%)	
III	27 (16.9%)	33 (25.4%)		27 (25.7%)	31 (29.5%)	
IV	22 (13.8%)	31 (23.9%)		20 (19.1%)	22 (20.9%)	
NA	25 (15.6%)	15 (11.5%)				
<b>T stage</b>			0.003			0.426
T1	47 (29.4%)	26 (20.0%)		35 (33.3%)	26 (24.8%)	
T2	43 (26.9%)	27 (20.8%)		29 (27.6%)	27 (25.7%)	
T3	29 (18.1%)	36 (27.7%)		28 (26.7%)	34 (32.4%)	
T4	13 (8.1%)	26 (20.0%)		13 (12.4%)	18 (17.1%)	
NA	28 (17.5%)	15 (11.5%)				
<b>N stage</b>			0.052			0.22
N0	123 (76.9%)	89 (68.5%)		90 (85.7%)	85 (80.9%)	
N1	5 (3.1%)	12 (9.2%)		3 (2.9%)	10 (9.5%)	
N2	7 (4.4%)	10 (7.7%)		7 (6.8%)	7 (6.7%)	
N3	0 (0.0%)	2 (1.5%)		0	0	
NA	25 (15.6%)	17 (13.1%)		5 (4.6%)	3 (2.9%)	
<b>M stage</b>			0.535			0.506
M0	132 (82.5%)	106 (81.5%)		95 (90.5%)	96 (91.4%)	
M1	11 (6.9%)	6 (4.6%)		8 (7.6%)	5 (4.8%)	
NA	17 (10.6%)	18 (13.8%)		2 (1.9%)	4 (3.8%)	
<b>Chemotherapy</b>			<0.001			<0.001
no	153 (95.6%)	109 (83.8%)		102 (97.1%)	88 (83.8%)	
yes	7 (4.4%)	21 (16.2%)		3 (2.9%)	17 (16.2%)	

S, surgery; R, radiotherapy.

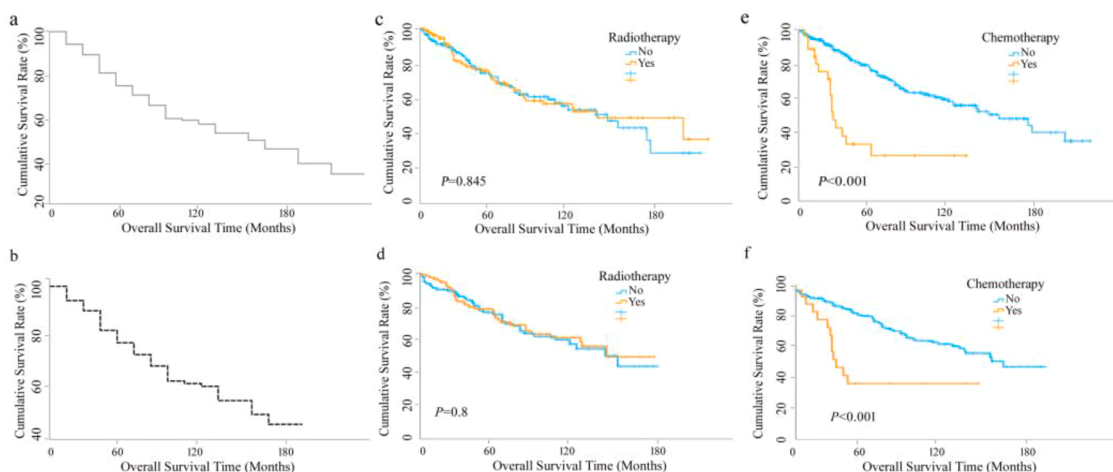
100–187) and 136 months (95% CI: 68–203), ( $P = 0.845$ ) (Fig. 1c). After PSM, the patients did not benefit from additional radiotherapy [135 months (95% CI: 83–170) vs. 136 months (95% CI: 95–171) months ( $P = 0.8$ )] (Fig. 1d). Patients did not appear to benefit from additional chemotherapy, as the median OS times of patients with and without chemotherapy were 26 months (95% CI: 21–30) and 152 months (95% CI: 102–200) months, respectively. In the PSM cohort, the median OS times of patients with and without chemotherapy were 28 months (95% CI: 17–38) and 136 months (95% CI: NA) months, respectively ( $P < 0.001$ ) (Fig. 1e and f).

When stratified by clinicopathological features, patients with younger age, low histological grade, early stage, early T stage, N0 stage,

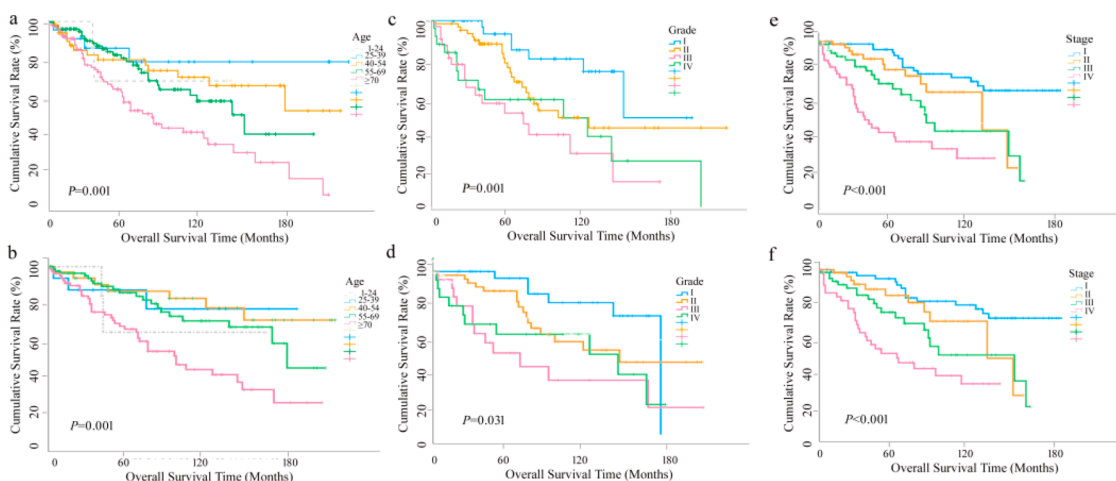
M0 stage, and chemotherapy had better OS than those with older age, high disease grade, late disease stage, advanced T stage, positive node, distant involvement, and no chemotherapy, both before and after PSM (Figs. 2 and 3). Unexpectedly, sex, year of diagnosis, primary site, and radiotherapy were not significantly association with the OS.

*Prognostic risk factors and the role of radiotherapy in MECA*

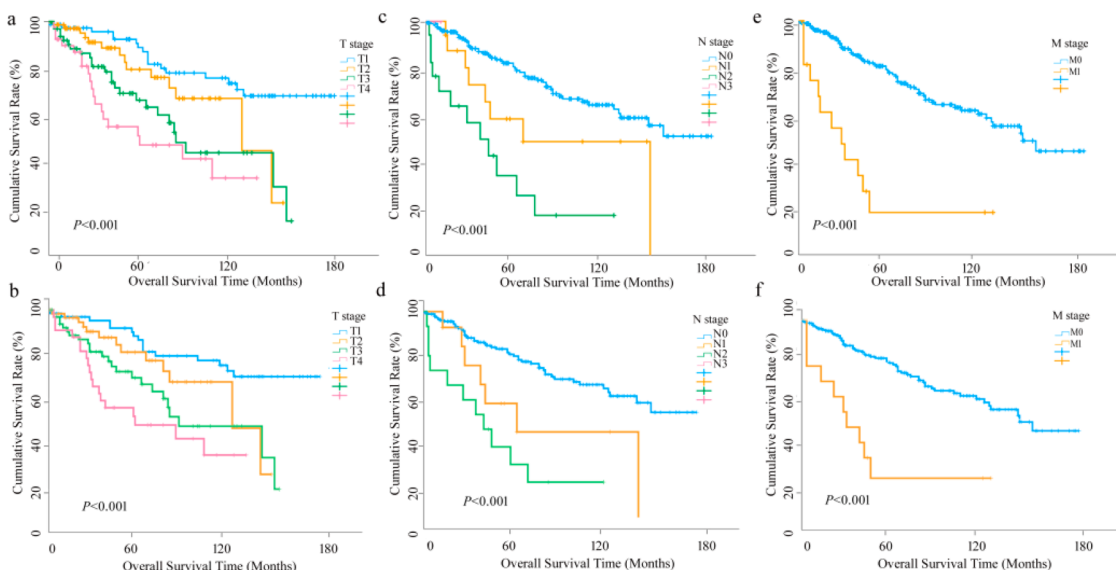
To investigate the clinical significance of radiotherapy, it was included in the Cox regression analysis. In the PSM cohort, patients with moderately differentiated (HR: 5.69, 95% CI: 1.69–19.16;  $P = 0.005$ ), poorly differentiated (HR: 4.31, 95% CI: 1.23–15.04,  $P = 0.022$ ), and



**Fig. 1.** Cumulative overall survival (OS) curves for patients with myoepithelial carcinoma (MECA) before (upper row) and after PSM (bottom row). (a and b) OS; (c and d) radiotherapy; (e and f), chemotherapy. PSM, propensity score matching.



**Fig. 2.** Stratified analysis of OS for patients with MECA before PSM (upper row) and after PSM (bottom row). (a and b) different age-groups; (c and d) grade; (e and f) stage. PSM, propensity score matching; MECA, myoepithelial carcinoma.



**Fig. 3.** Stratified analysis of OS for patients with MECA before PSM (upper row) and after PSM (bottom row). (a and b) T stage; (c and d) N stage; (e and f) M stage. MECA, myoepithelial carcinoma; T, tumor; N, lymph node; M, metastasis.

undifferentiated (HR: 5.57, 95% CI: 1.60–19.35,  $P = 0.006$ ) tumors exhibited a higher risk of death than those with well-differentiated tumors. Similarly, stage II (HR: 5.47, 95% CI: 3.55–17.44,  $P = 0.004$ ), stage III (HR: 3.66, 95% CI: 1.65–18.40,  $P = 0.016$ ), stage IV (HR: 8.74, 95% CI: 1.12–21.97,  $P = 0.038$ ), T3 stage (HR: 2.47, 95% CI: 1.04–5.84,  $P = 0.039$ ), T4 stage (HR: 3.33, 95% CI: 1.32–8.40,  $P = 0.011$ ), N2 stage (HR: 6.59, 95% CI: 1.95–22.27,  $P = 0.002$ ), and M1 stage (HR: 2.72, 95% CI: 1.03–7.19,  $P = 0.044$ ) were associated with adverse prognosis. Chemotherapy (HR: 2.34, 95% CI: 0.91–6.05;  $P = 0.079$ ) had no significant influence on patients' prognosis (Table 2). Radiotherapy (HR: 0.58, 95% CI: 0.33–0.98,  $P = 0.042$ ) was a favorable risk factor for OS, suggesting that it may benefit patients with MECA (Table 2).

*Analysis of cancer-specific survival (CSS)*

Lastly, the influence of clinicopathological features on cancer-specific survival (CSS) was analyzed, and only the CSS data of 286 patients were included as those of four cases were not available. Next, 103 matched pairs were next investigated after PSM, (Supplementary Table 1). Chemotherapy ( $P < 0.05$ ), grade ( $P < 0.05$ ), and stage (T, N, M,  $P < 0.05$ ) had a significant effect on CSS both before and after PSM (Figs. 4 and 5). Unexpectedly, radiotherapy ( $P > 0.05$ ) had no advantage in terms of CSS. In Cox regression analysis, T3 (HR: 5.61, 95% CI: 1.10–28.74,  $P = 0.039$ ), T4 (HR: 7.71, 95% CI: 1.66–35.81,  $P = 0.009$ ), and M1 (HR: 8.93, 95% CI: 2.32–34.37,  $P = 0.002$ ) were found to be independent risk factors for CSS (Supplementary Table 2).

**Discussion**

MECA is an uncommon neoplasm that most commonly arises in the salivary tissue and accounts for approximately 2% of all salivary neoplasms occurring in the salivary gland [2]. However, there are multiple classification systems for MECA, and there morphological and histological characteristics overlap with those of other entities. In addition, owing to its rarity, this tumor is under-recognized and can be misdiagnosed [2]. Indeed, histologically, MECA was shown to closely mimic PA; and the diagnosis of MECA was dependent on the expansile nodular lobulated pattern and zonal cellular distribution [2]; patients with this condition show a positive immunohistochemical staining for a AE1/AE3, CAM5.2, S100, calponin, SMA, CK7, P63, CK5/6, and IN1 in the salivary gland and other rare primary sites such as the larynx, lung, vulvar, shoulder, and soft tissues [2,3,11–14]. Immunohistochemical staining for 34BE12, CK20, GCDPF15, HHF35, HMB45, synaptophysin, chromogranin, and CD34 was negative in patients with shoulder MECA [11]. The reported molecular features were TGFBR3-PLAG1 fusion and SMARCB1-deficiency [12,15–17], and patients with clear cell MECA may present with other PLAG1 fusions including LIFR-PLAG1, CTNNB1-PLAG1, CHCHD7-PLAG1, EWSR1-ATF1, FGFR1-PLAG1, and CTNNB1-PLAG1 [17,18]. In our cohort, 55–57% of the patients were women, which is consistent with the report of other recent studies (52.8%) [2,10]. Our findings revealed that older adults are more susceptible to developing MECA, and the parotid glands are the most commonly affected site, followed by other major salivary glands [2,9,10]. Interestingly, most MECA tumors (72%) were <5 cm in size, and the median tumor size was 3.3–3.5 cm [2,9]. There is high consistency among previous studies in term of tumor diameter (mean: 3.5 cm), which indirectly reflects the low-grade malignant features of MECA. Approximately 35–40% of MECA patients have unfavorable differentiation [8,10], which may be a major factor for regional or distant metastasis. The reported incidence of metastatic involvement of the lymph nodes ranges from 8 to 41% [2,7,8,19,20]. Moreover, in patients with clear cell MECA of the parotid and submandibular glands and EWSR1 rearrangement, the incidence of lymph node involvement was reported to be up to 38% [21]; however, the incidence of lymph node involvement reported in the present study was 14.5%, which was similar to that reported by Xiao et al. [10]. Unexpectedly, the incidence of

**Table 2**

Univariate and multivariate analysis of patients with salivary gland myoepithelial carcinoma (OS).

	Before matching		After matching	
	Univariate HR (95% CI) P	Multivariate HR (95% CI) P	Univariate HR (95% CI) P	Multivariate HR (95% CI) P
<b>Age</b>				
1–24	1	1	1	
25–39	0.49 (0.09, 2.70) 0.414		0.48 (0.08, 2.90) 0.425	
40–54	0.75 (0.17, 3.34) 0.709		0.40 (0.08, 1.93) 0.251	
55–69	0.96 (0.23, 4.05) 0.957		0.59 (0.14, 2.53) 0.476	
70–85	1.88 (0.46, 7.72) 0.383		1.44 (0.35, 5.97) 0.618	
<b>Sex</b>				
male	1		1	
female	1.03 (0.69, 1.54) 0.873		1.23 (0.68, 2.20) 0.49	
<b>Race</b>				
white	1	1	1	
black	0.53 (0.28, 1.03) 0.060	0.92 (0.43, 1.97) 0.836	0.47 (0.17, 1.30) 0.147	
other	0.37 (0.15, 0.92) 0.031	0.41 (0.15, 1.14) 0.088	0.52 (0.17, 1.57) 0.246	
<b>Site</b>				
parotid	1	1	1	
submandibular gland	1.41 (0.90, 2.19) 0.132		1.14 (0.50, 2.59) 0.761	
<b>Grade</b>				
well	1	1	1	1
moderately	2.19 (0.93, 5.13) 0.071	3.70 (1.21, 11.29) 0.023	2.22 (0.87, 5.69) 0.095	5.69 (1.69, 19.16) 0.005
poorly	4.74 (1.96, 11.46) <0.001	7.90 (2.19, 28.53) 0.002	5.16 (1.93, 13.79) 0.001	4.31 (1.24, 15.04) 0.022
undifferentiated	3.83 (1.52, 9.60) 0.004	3.81 (1.16, 12.53) 0.027	3.57 (1.30, 9.83) 0.013	5.57 (1.60, 19.35) 0.006
<b>CS tumor Size</b>	1.03 (1.02, 1.04) <0.0001	1.03 (1.01, 1.05) 0.0007	1.03 (1.02, 1.04) <0.0001	1.00 (1.01, 1.04) 0.08
<b>Stage</b>				
I	1	1	1	1
II	3.73 (0.48, 29.12) 0.209	4.55 (0.38, 54.09) 0.230	1.83 (0.81, 4.13) 0.143	5.47 (3.55, 17.44) 0.004
III	5.87 (0.75, 45.91) 0.091	2.36 (0.26, 21.62) 0.447	2.97 (1.48, 5.98) 0.002	3.66 (1.65, 18.40) 0.016
IV	11.96 (1.57, 90.99) 0.016	13.14 (0.92, 187.02) 0.057	5.53 (2.81, 10.89) <0.001	8.74 (1.12, 21.97) 0.038
<b>T stage</b>				
T1	1	1	1	1
T2	1.62 (0.75, 3.49) 0.2194	2.22 (0.97, 5.09) 0.059	1.83 (0.86, 3.88) 0.116	2.33 (0.96, 5.62) 0.060
T3	2.93 (1.50, 5.73) 0.0017	2.56 (1.13, 5.78) 0.024	2.95 (1.54, 5.63) 0.001	2.47 (1.04, 5.84) 0.039
T4	5.64 (2.99, 10.65) <0.001	3.30 (1.34, 8.10) 0.009	4.53 (2.26, 9.11) <0.0001	3.33 (1.32, 8.40) 0.011
<b>N stage</b>				
N0	1	1	1	1
N1	2.14 (1.02, 4.50) 0.045	0.82 (0.21, 3.17) 0.778	2.61 (1.18, 5.80) 0.018	1.04 (0.36, 3.02) 0.942
N2	4.89 (2.60, 9.19) <0.001	6.48 (2.06, 20.37) 0.001	4.91 (2.53, 9.54) <0.0001	6.59 (1.95, 22.27) 0.002
<b>M stage</b>				
M0	1	1	1	1
M1	4.83 (2.59, 8.99) <0.001	4.88 (1.57, 15.22) 0.006	4.31 (2.19, 8.50) <0.0001	2.72 (1.03, 7.19) 0.044

(continued on next page)



Table 2 (continued)

	Before matching		After matching	
	Univariate HR (95% CI) P	Multivariate HR (95% CI) P	Univariate HR (95% CI) P	Multivariate HR (95% CI) P
<b>Chemotherapy</b>				
No	1	1	1	1
Yes	3.72 (2.15, 6.43) <0.0001	2.07 (0.89, 4.83) 0.092	3.36 (1.79, 6.31) 0.0002	2.34 (0.91, 6.05) 0.079
<b>Radiotherapy</b>				
No	1	1	1	1
Yes	0.96 (0.65, 1.43) 0.845	0.70 (0.43, 1.14) 0.146	0.94 (0.59, 1.50) 0.7994	0.58 (0.33, 0.98) 0.042

OS, overall survival.

distant metastasis was around 11–38% [2,7,8,19–22]. In the present study, the distant metastasis rate for parotid and submandibular MECA was 6.6%, and the most commonly affected organs were the lungs, liver, bones, and brain. In a study based on the National Cancer Database (NCDB) conducted in 2016, the metastasis rate was low (3.1%) [10]. The low rates of distant metastasis may be attributable to the differences in the histological sub-classification, genetic features, and inadequate imaging examinations. Positron emission tomography-computed tomography (PET-CT) may help improve the accuracy of distant metastasis detection [23].

The clinicopathologic features of MECA have been shown to be related to the patients' outcomes [2,8–10,22]. Age, high histological classification, mitotic index of >10/10 HPF, tumor size of >5 cm, and advanced stage were associated with an unfavorable factors for prognosis [9,10,24,25]. The certified histological grades assigned to the present cohort showed a robust association with OS in patients with MECA of the main salivary gland. Current research particularly demonstrates a link between advanced stage and poor outcomes. In another large cohort, a tumor size of >5 cm was found to be an alternative risk predictor to stage [9]. In fact, the cut-off diameters selected for T stage were 2 cm and 4 cm, whereas the current study indicated that the T3/T4 cut-off diameter should be >4 cm, and invasion of the facial nerve or other surrounding tissues (T4) was a prognostic risk factor.

Finally, prognosis was evaluated according to the treatment management provide to the patients. Maintaining a safe surgical margins decreases the incidence of recurrence and has a significant effect on the OS [6,9]. However, information related to resection status was not obtained. The role of chemotherapy in MECA is still under debate; some studies have shown that additional chemotherapy may not reduce the risk of tumor recurrence or metastasis [9]. However, chemo-agent interventions should be considered in the management of MECA patients with metastasis, and the use of cisplatin-based chemotherapy, or ifosfamide and etoposide, has been discussed several studies [2,6,24]. In the current study, only a few patients received chemotherapy, and most of them had stage IV disease. Therefore, it introduced a selection bias, and the decision to administer chemotherapy was based on the results of

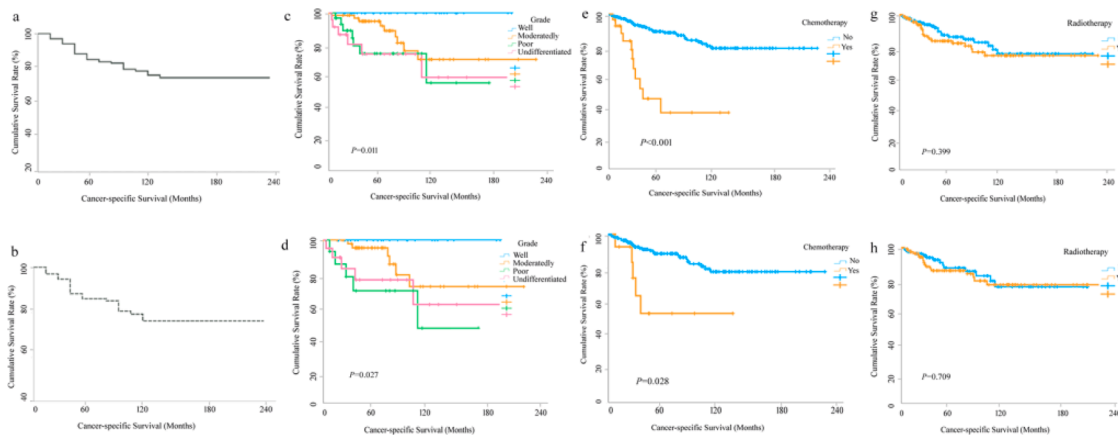


Fig. 4. Stratified analysis of Cancer-specific survival (CSS) for patients with MECA before PSM (upper row) and after PSM (bottom row). (a and b) overall CSS; (c and d) grade; (e and f) chemotherapy; (g and h) radiotherapy. MECA, myoepithelial carcinoma.

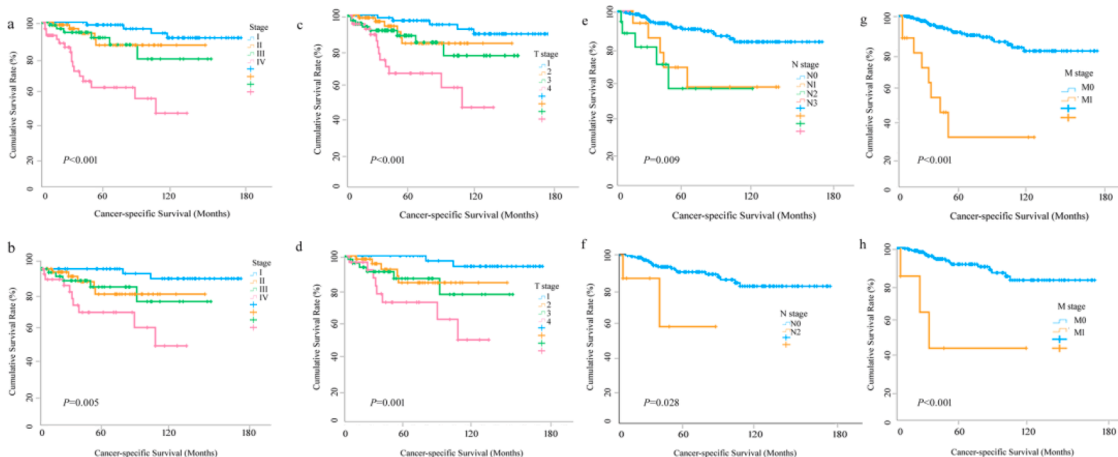


Fig. 5. Stratified Kaplan-Meier cancer-specific survival (CSS) curves for patients with MECA before PSM (upper row) and after PSM (bottom row). (a and b) stage; (c and d) T stage; (e and f) N stage; (g and h) M stage. MECA, myoepithelial carcinoma.

physicians' assessment and the characteristics of individual patients. As an important part of a comprehensive treatment, the value of radiotherapy in MECA requires further investigation. Approximately half of the patients in this study received adjuvant radiotherapy, and the analysis indicated that it had no OS advantage before PSM. However, there was an imbalance in the clinical baseline characteristics; the S+R group had more patients with advanced histological grade, stage, and T stage compared with the S group. Univariate analysis also indicated that radiotherapy did not have a significant effect on OS. Even so, radiotherapy was mandatorily included in the multivariate analysis, and the results indicated a beneficial effect of radiotherapy on the OS of patients with main salivary gland MECA after PSM. This finding seemed to affirm the significance of radiotherapy in managing MECA, although it did not improve the CSS. Notably, Giridhar et al. found that adjuvant radiotherapy decreased the risk of local relapse ( $P = 0.008$ ) but increased the risk of mortality ( $P = 0.04$ ) as shown in the univariate analysis [9]. However, radiotherapy had no significant effect on OS as observed in the multivariate analysis ( $P = 0.223$ ) or in the subgroup analysis of patients who underwent with R1 resection ( $P = 0.893$ ) [9]. The latter divergence may be attributable to the differences in other baseline features, such as the tumor size ( $P = 0.006$ ) and T/N/M stage [9]. MECA frequently causes local recurrence; hence, adjuvant radiotherapy (50–70 Gy) should be considered for patients with a high-risk of relapse, such as those with an extremely poor histological grade, positive margins, or perineural invasion [6,25]. The main limitations of the current study were as follows: some details regarding the therapeutic intervention including extent of resection or irradiation, especially neck lymph node dissection and surgical margins, irradiation dose, and chemotherapy regimen were not available. In addition, this was a retrospective analysis of data from a single database (SEER), which may have led to a selection bias. Currently, there is limited evidence of the efficacy of chemotherapy and radiotherapy in patients with MECA due to the lack of randomized clinical studies owing to the rarity of the condition, heterogeneous features, and the requirement for a long observation period.

## Conclusion

MECA is a rare type of tumor occurring in the parotid and submandibular glands. The 10-year OS rate in our cohort was 53%, and the histological grade, T/N/M stage, and radiotherapy were independent prognostic risk factors for OS. The decision to administer chemotherapy should be cautiously made in a selected subset of patients. In the PSM cohort, additional radiotherapy improved the OS of patients with MECA. High-risk patients with a positive surgical margin and potential risk of recurrence should be considered candidates for adjuvant radiotherapy. However, further studies are required to assess the value of radiotherapy in MECA.

## Funding

Not applicable.

## Ethics approval and consent to participate

Patients from the Surveillance, Epidemiology, and End Results (SEER) database had previously consented to participate in any scientific research worldwide.

## Consent for publication

All authors have read and agreed to the published version of the manuscript.

## Data availability statement for this work

Original data is available at Surveillance Epidemiology and End

Results (SEER) database (<https://seer.cancer.gov/data-software/documentation/seerstat/>).

## Supporting information

Supplementary table-r.xlsx

## CRediT authorship contribution statement

**Yunxiu Luo:** Conceptualization, Formal analysis, Writing – original draft, Visualization, Writing – review & editing, Funding acquisition.

## Declaration of Competing Interest

The authors declare no conflicts of interest

## Acknowledgments

We thank NIH for its dataset during the preparation of this manuscript.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.tranon.2022.101410](https://doi.org/10.1016/j.tranon.2022.101410).

## References

- [1] I. Dardick, Myoepithelioma: definitions and diagnostic criteria, *Ultrastruct. Pathol.* 19 (1995) 335–345, <https://doi.org/10.3109/01913129509021906>.
- [2] B. Xu, W. Mneimneh, D.E. Torrence, K. Higgins, D. Klimstra, R. Ghossein, N. Katabi, Misinterpreted myoepithelial carcinoma of salivary gland: a challenging and potentially significant pitfall, *Am. J. Surg. Pathol.* 43 (2019) 601–609, <https://doi.org/10.1097/PAS.0000000000001218>.
- [3] J. Wei, X. Yuan, Y. Yao, L. Sun, X. Yao, A. Sun, Primary myoepithelial carcinoma of the lung: a case report and review of literature, *Int. J. Clin. Exp. Pathol.* 8 (2015) 2111–2116.
- [4] D.L. Zhao, L.Z. Wang, H. Cao, J.Z. Sang, L. Gao, X.D. Cao, S. Cao, L. Chen, [Clinical characteristics and treatment of myoepithelial carcinoma of head and neck], *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 33 (2019) 1085–1088, <https://doi.org/10.13201/j.issn.1001-1781.2019.11.019>.
- [5] F. Wang, B. Li, Y. Wang, Y. Shen, H. Yang, Clinical and pathological analysis of 10 cases of salivary gland epithelial-myoeplithelial carcinoma, *Medicine* 99 (2020) e22671, <https://doi.org/10.1097/MD.00000000000022671>. Baltimore.
- [6] S. Vilar-González, K. Bradley, J. Rico-Pérez, P. Vogiatzis, D. Golka, A. Nigam, M. Sivaramalingam, S. Kazmi, Salivary gland myoepithelial carcinoma, *Clin. Transl. Oncol.* 17 (2015) 847–855, <https://doi.org/10.1007/s12094-015-1329-4>.
- [7] S. Yang, L. Li, M. Zeng, X. Zhu, J. Zhang, X. Chen, Myoepithelial carcinoma of intraoral minor salivary glands: a clinicopathological study of 7 cases and review of the literature, *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 110 (2010) 85–93, <https://doi.org/10.1016/j.tripleo.2010.02.023>.
- [8] M. Kong, E.N. Drill, L. Morris, L. West, D. Klimstra, M. Gonen, R. Ghossein, N. Katabi, Prognostic factors in myoepithelial carcinoma of salivary glands: a clinicopathologic study of 48 cases, *Am. J. Surg. Pathol.* 39 (2015) 931–938, <https://doi.org/10.1097/PAS.0000000000000452>.
- [9] P. Giridhar, P. Gupta, S. Mallick, A.D. Upadhyay, G.K. Rath, Impact of adjuvant therapy on survival in patients with myoepithelial carcinoma: a systematic review and individual patient data analysis of 691 patients, *Radiother. Oncol.* 140 (2019) 125–130, <https://doi.org/10.1016/j.radonc.2019.06.017>.
- [10] C.C. Xiao, A.B. Baker, S.J. White-Gilbertson, T.A. Day, Prognostic factors in myoepithelial carcinoma of the major salivary glands, *Otolaryngol. Head Neck Surg.* 154 (2016) 1047–1053, <https://doi.org/10.1177/0194599816637605>.
- [11] C. Yokose, J. Asai, S. Kan, T. Nomiya, H. Takenaka, E. Konishi, K. Goto, S.-I. Ansai, N. Katoh, Myoepithelial carcinoma on the right shoulder: case report with published work review, *J. Dermatol.* 43 (2016) 1083–1087, <https://doi.org/10.1111/1346-8138.13358>.
- [12] A. Agaimy, I. Naroditsky, O. Ben-Izhak, Primary high-grade myoepithelial carcinoma of the lung: a study of three cases illustrating frequent SMARCB1-deficiency and review of the literature, *Ann. Diagn. Pathol.* 53 (2021), 151759, <https://doi.org/10.1016/j.anndiagpath.2021.151759>.
- [13] G. Yu, G. Qu, L. Kong, X. Pan, W. Wang, J. Lv, Primary myoepithelial carcinoma of the larynx: case report and review of the literature, *Pathol. Res. Pract.* 207 (2011) 127–130, <https://doi.org/10.1016/j.prp.2010.10.006>.
- [14] M. Miyata, K. Hasegawa, K. Ishikawa, R. Kato, Y. Udagawa, M. Kuroda, Primary myoepithelial carcinoma of the vulva and review of the literature, *J. Obstet. Gynaecol. Res.* 37 (2011) 617–622, <https://doi.org/10.1111/j.1447-0756.2010.01392.x>.

- [15] M.G. Dalin, N. Katabi, M. Persson, K.-W. Lee, V. Makarov, A. Desrichard, L. A. Walsh, L. West, Z. Nadeem, D. Ramaswami, J.J. Havel, F. Kuo, K. Chadalavada, G.J. Nanjangud, I. Ganly, N. Riaz, A.L. Ho, C.R. Antonescu, R. Ghossein, G. Stenman, T.A. Chan, L.G.T. Morris, Multi-dimensional genomic analysis of myoepithelial carcinoma identifies prevalent oncogenic gene fusions, *Nat. Commun.* 8 (2017) 1197, <https://doi.org/10.1038/s41467-017-01178-z>.
- [16] S.C. Huang, L. Zhang, Y.S. Sung, C.L. Chen, Y.C. Kao, N.P. Agaram, C.R. Antonescu, Secondary EWSR1 gene abnormalities in SMARCB1-deficient tumors with 22q11-12 regional deletions: potential pitfalls in interpreting EWSR1 FISH results, *Genes Chromosom. Cancer* 55 (2016) 767–776, <https://doi.org/10.1002/gcc.22376>.
- [17] A. Skálová, A. Agaimy, T. Vanecek, M. Baněčková, J. Laco, N. Ptáková, P. Šteiner, H. Majewska, W. Biernat, L. Corcione, V. Eis, O. Koshyk, J. Vondrák, M. Michal, I. Leivo, Molecular profiling of clear cell myoepithelial carcinoma of salivary glands with EWSR1 rearrangement identifies frequent PLAG1 gene fusions but no EWSR1 fusion transcripts, *Am. J. Surg. Pathol.* 45 (2021) 1–13, <https://doi.org/10.1097/PAS.0000000000001591>.
- [18] M. Baněčková, E. Uro-Coste, N. Ptáková, P. Šteiner, O. Stanowska, G. Benincasa, G. Colella, J. Vondrák, M. Michal, I. Leivo, A. Skálová, What is hiding behind S100 protein and SOX10 positive oncocytomas? Oncocytic pleomorphic adenoma and myoepithelioma with novel gene fusions in a subset of cases, *Hum. Pathol.* 103 (2020) 52–62, <https://doi.org/10.1016/j.humpath.2020.07.009>.
- [19] S.V. Kane, I.N. Bagwan, Myoepithelial carcinoma of the salivary glands: a clinicopathologic study of 51 cases in a tertiary cancer center, *Arch. Otolaryngol. Head Neck Surg.* 136 (2010) 702–712, <https://doi.org/10.1001/archoto.2010.104>.
- [20] A.T. Saveria, A. Sloman, A.G. Huvos, D.S. Klimstra, Myoepithelial carcinoma of the salivary glands: a clinicopathologic study of 25 patients, *Am. J. Surg. Pathol.* 24 (2000) 761–774, <https://doi.org/10.1097/0000478-200006000-00001>.
- [21] A. Skálová, I. Weinreb, M. Hycza, R.H.W. Simpson, J. Laco, A. Agaimy, M. Vazmitel, H. Majewska, T. Vanecek, P. Talarčík, S. Manajlovic, S.N. Losito, P. Šteiner, A. Klimkova, M. Michal, Clear cell myoepithelial carcinoma of salivary glands showing EWSR1 rearrangement: molecular analysis of 94 salivary gland carcinomas with prominent clear cell component, *Am. J. Surg. Pathol.* 39 (2015) 338–348, <https://doi.org/10.1097/PAS.0000000000000364>.
- [22] C. Wang, Z. Zhang, Y. Ge, Z. Liu, J. Sun, Z. Gao, L. Li, Myoepithelial carcinoma of the salivary glands: a clinicopathologic study of 29 patients, *J. Oral Maxillofac. Surg.* 73 (2015) 1938–1945, <https://doi.org/10.1016/j.joms.2015.03.054>.
- [23] C. Li, Y. Tian, Y. Shen, B. Wen, Y. He, 18F-FDG PET/CT findings in a rare myoepithelial carcinoma arising in the parapharyngeal space, *Clin. Nucl. Med.* 45 (2020) 894–895, <https://doi.org/10.1097/RLU.00000000000003242>.
- [24] V.Y. Jo, Myoepithelial tumors: an update, *Surg. Pathol. Clin.* 8 (2015) 445–466, <https://doi.org/10.1016/j.path.2015.05.005>.
- [25] Y.-X. Su, D.B. Roberts, E.Y. Hanna, A. El-Naggar, G. Saylam, S.J. Frank, R. S. Weber, M.E. Kupferman, Risk factors and prognosis for myoepithelial carcinoma of the major salivary glands, *Ann. Surg. Oncol.* 22 (2015) 3701–3707, <https://doi.org/10.1245/s10434-015-4389-3>.