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Clinicopathological Characteristics of Salivary Gland Mucoepidermoid Carcinoma in Dr Hasan Sadikin Central Hospital (RSHS) Bandung: A 10-Year review

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ABSTRACT

Background
Primary salivary gland malignancy is rare and has limited reports. Mucoepidermoid carcinoma (MEC) is the most common malignant tumor of the salivary glands. However, epidemiological reports on salivary gland MEC are still limited, particularly in Indonesia. This study aimed to report the clinicopathological characteristics of salivary gland MEC in Dr Hasan Sadikin Central Hospital (RSHS) from January 2013 to December 2022.

Method
This study is a descriptive study with a cross-sectional method. Total cases of salivary gland MEC that were histopathologically diagnosed and recorded in the RSHS Hospital Information System (SIRS) medical records from 2013 to 2022 were collected. It included demographic, clinical, and histopathological data.

Result
A total of 86 MEC cases were diagnosed histopathologically between 2013 and 2022. The cases involved 44 (51.2%) females and 42 (48.8%) males. The mean age is 46.4 years old. The most common site affected is a parotid gland (37.2%). According to histopathological grade, 51.2% were high grade, 25.6% were intermediate grade, and 23.3% were low grade. The result of clinical stage is Stage III, which has the highest percentage (n=32, 37.2%). The majority of patients receive surgical combined with radiotherapy treatment (n=53, 61.6%).

Conclusion
There are 86 cases of salivary MEC in the RSHS period 2013-2022. MEC is common in females, with a mean age 46.4 years old. The parotid gland is the most common site. The most frequent histopathological grading and clinical staging are high grade and stage III.

Keyword: Mucoepidermoid carcinoma, salivary gland, clinicopathological, RSHS

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INTRODUCTION

The incidence of primary malignant tumors of the salivary glands is low, ranging from 3-6% of all malignant tumors in the head and neck area. This condition is due to the wide variety of histopathological diagnoses, the low number of cancer registration inputs, and several geographic variations. The most common histopathological subtype of salivary gland malignancy is mucoepidermoid carcinoma (MEC).[1-3] MEC is a salivary gland tumor with the highest incidence in Dr Hasan Sadikin Central Hospital (RSHS) Bandung Indonesia in 2009-2012.[4] MEC is composed of mucous cells, epidermoid cells, and intermediate cells. MEC architectural patterns can be cystic, tubular, and solid. The clinical behavior, outcomes, and treatment of MEC vary and are influenced by the histopathological grade of MEC and its clinical stage.[5] The clinicopathological reporting data on malignant tumors of the salivary gland is limited, especially in Indonesia. However, the morbidity and mortality of MEC cannot be ignored, especially high-grade MEC. Overall survival of high-grade MEC is significantly low (25%), and high-grade MEC requires multimodality treatment. The variability of demographic and clinical data can be found in many countries.[6] Therefore, this study aimed to report the clinicopathological characteristics of MEC of the salivary glands in RSHS in 2013-2022.

METHOD

This research is a descriptive study with a cross-sectional method. It collects secondary data in the form of demographic, clinical, and histopathological data of the MEC of the salivary glands from the RSHS Hospital Information System (SIRS) and the archives of the Department of Anatomic Pathology between January 2013 and December 2022. Demographic and clinical data included were gender, age, and tumor location. Histopathological grade evaluation according to the Armed Forces Institute of Pathology (AFIP) system recommended by the World Health Organization (WHO) 2017. The AFIP histopathological grading scoring system better shown in Table 1.[5,7] Clinical stage assessment based on the 8th edition of the American Joint Cancer Conference (AJCC) 2018. Patient's treatment history such as surgery, radiotherapy, and chemotherapy were also recorded. This study resulted in the average number calculation and the highest percentage.

Table 1. The AFIP system for grading salivary gland MEC

AFIP system	Point
Intracystic component <20%	2
Neural invasion	2
Necrosis	3
Four (4) or more mitosis per 10 HPF	3
Anaplasia	4
Grade	Total
Low	0-4
Intermediate	5-6
High	7-14

RESULTS

A total of 86 cases of MEC had been diagnosed histopathologically between 2013-2022. The frequency distribution of demographic data is showed in Table 2. A total of 44 (51.2%) samples were female and 42 samples were male (48.8%) with a ratio of 1.04:1. The age range is between 10-78 years old, with an average age of 46.4 years old. The most common age group in this study was 41-60 years old. Major salivary glands are in a more prominent location (n=49; 56.9%) than minor salivary glands (n=37; 43.1%). The parotid gland was the most common location for the major salivary glands (n=32; 65.3%).

The vast majority histopathological grade was high grade (p=44, 51.2%) followed by intermediate grade (p=22, 25.6%) and low grade (p=20, 23.3%). The histopathological picture based on MEC histopathological grade is shown in Figures 1 to 3. The clinical stage revealed that stage III had the greatest number of cases (n=32, 37.2%), followed by stage IV (n=29, 33.7%), stage II (n=17, 19.8%), and stage I (n=8, 9.3%). An overview of the distribution of TNM stages in the sample is shown in table 3. The majority of patients in this study had surgery combined with radiotherapy (n=53, 61.6%). A total of 26 samples (30.2%) received only surgery, while 7 samples (8.1%) received a combination of surgery, radiotherapy, and chemotherapy.

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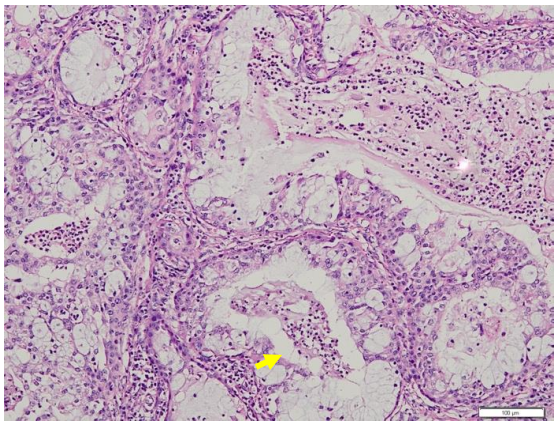

Figure 1. Low-grade MEC with a predominantly cystic architecture. Cystic component showed by yellow arrow (100 times Magnification).

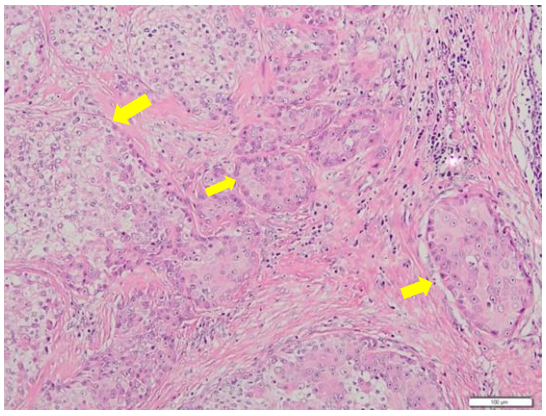

Figure 2. Intermediate grade of MEC with predominantly solid architecture with uniform nuclei. Solid component showed by yellow arrows (100 times Magnification).

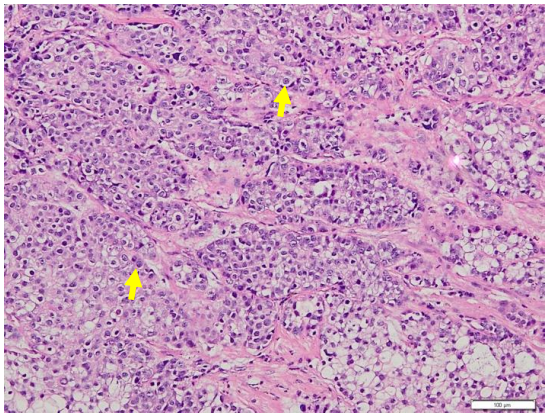

Figure 3. High grade MEC with solid dominant architecture with pleomorphic nuclei. Pleomorphism of nuclei showed by yellow arrows (100 times) Magnification).

Table 2. Clinicopathological characteristic of MEC in 2013-2022 period.

Patient Characteristics	n= 86(%)
Gender	
Male	42(48.8)
Female	44(51.2)
Age Range	
0-20 years old	8(9.3)
21-40 years old	19(22.1)
41-60 years old	41(47.7)
>60 years old	18 (20.9)
Salivary Gland Location	
Major	49(57)
Parotid Gland	32(65.3)
Submandibular	11(22.44)
Sublingual	6(12.24)
Minor	37(43)
Palate	11(29.7)
Sinonasal	11(29.7)
Oral cavity	11(29.7)
Tongue	4(10.8)
Histopathological Grade	
Low	20(23.3)
Intermediate	22(25.6)
High	44(51.2)
TNM Stage (AJCC 8th)	
I	8(9.3)
II	17(19.7)
III	32(37.2)
IV	29(33.7)
Therapy	
Surgery	26(30.2)
Surgery+Radiotherapy/Chemotherapy	53(61.6)
Surgery+Radiotherapy+Chemotherapy	7(8.1)

Table 3. TNM distribution in clinical stages of MEC according to the AJCC edition 8 of 2018.

Stadium (TNM)	n(%)
Stadium I (n=8, 9.3%)	
T1N0M0	8(100)
Stadium II (n=17, 19,7%)	
T2N0M0	17(100)
Stadium III (n=32, 37.2%)	
T3N0M0	24(75)
T1N1M0	2(6.2)
T2N1M0	2(6.2)
T3N1M0	4(12.5)
Stadium IV (n=29, 33.7%)	
Stadium IV A	27(92.8)
T1N2M0	1(3.8)
T2N2M0	3(11.5)
T3N2M0	10(34.6)
T4aN0M0	3(11.5)
T4aN1M0	4(15.3)
T4aN2M0	6(23)
Stadium IVB	1(3.6)
T3N3M0	1(100)
Stadium IVC	1(3.6)
T2N1M1	1(100)

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Table 4. Patients' demographic, clinical and therapy with histopathological grade crosstab.

Patient's Data	Histopathological Grade			Total n=86(%)
	Low n=20(%)	Intermediate n=22(%)	High n=44(%)	
Gender				
Male	9(21.4)	10(23.8)	23(54.8)	42(48.8)
Female	11(25)	12(27.3)	21(47.7)	44(51.2)
Age				
0-20 years old	3(37.5)	4(50)	1(12.5)	8(9.3)
21-40 years old	8(42.1)	3(15.8)	8(42.1)	19(22.1)
41-60 years old	5(12.2)	10(24.4)	26(63.4)	41(47.7)
>60 years old	4(22.2)	5(27.8)	9(20)	18(20.9)
Tumor location				
Major Salivary	10(20.4)	14(28.6)	25(51.0)	49(57)
Minor salivary	10(27)	8(21.6)	19(51.4)	37(43)
Therapy				
Surgical only	10(38.5)	7(26.9)	9(34.6)	26(30.2)
Surgical+radiotherapy/chemotherapy	9(17)	14(26.4)	30(56.6)	53(60.5)
Surgical+radiotherapy+chemotherapy	1(14.3)	1(14.3)	5(71.4)	7(8.1)

Table 5. Patients' demographic, clinical and histopathological grade with clinical stage crosstab.

Patient's Data	Clinical Stage				Total n(%)
	I n=8(%)	II n=17(%)	III n=33(%)	IV n=29(%)	
Gender					
Male	2(4.8)	9(21.4)	14(33.3)	17(40.5)	42(48.8)
Female	6(13.6)	8(18.2)	18(40.9)	12(27.3)	44(51.2)
Age					
0-20 years old	0(0)	0(0)	5(62.5)	3(37.5)	8(9.3)
21-40 years old	1(5.3)	6(31.6)	5(26.3)	7(36.8)	19(22.1)
41-60 years old	3(7.3)	8(19.5)	16(39)	14(34.1)	41(47.7)
>60 years old	4(22.2)	3(16.7)	6(33.3)	5(27.8)	18(20.9)
Tumor location					
Major Salivary	1(2)	4(8.2)	26(53.1)	18(36.7)	49(57)
Minor salivary	7(18.9)	13(35.1)	6(16.2)	11(29.7)	37(43)
Therapy					
Surgical only	4(15.5)	7(26.9)	9(34.6)	6(23.1)	26(31.4)
Surgical+radiotherapy/chemotherapy	3(5.7)	9(17)	23(43.4)	18(34)	53(60.5)
Surgical+radiotherapy+chemotherapy	1(14.3)	1(14.3)	0(0)	5(71.4)	7(8.1)
Histopathological grade					
Low	2(10)	10(50)	4(20)	4(20)	20(23.3)
Intermediate	3(13.6)	0(0)	14(63.6)	5(22.7)	22(25.6)
High	3(6.8)	7(15.9)	14(31.8)	20(45.5)	44(51.2)

DISCUSSION

In this study, there were slightly more female patients than males with a female-to-male ratio of 1,04:1. The average age of MEC cases was 46 years. The majority of tumors are located in major salivary glands, and the common site is the parotid gland. These results are in line with WHO and previous studies.[6,8,9] Stage III and Stage IV were the most frequent clinical stages in this study. Histopathological grading results show high-grade MEC is most prevalent. In contrast to the previous study, which revealed that early stage and low grade MEC were commonest.[9-12] In our study, there was a high incidence of advanced-stage patients due to RSHS status as a tertiary referral hospital that treats advanced cases of malignancy. Therefore, the largest number of MEC treatments in this study is surgery followed by radiotherapy or chemotherapy.

According to the results of the crosstab between demographic information, clinical and histopathological degree, there is no gender or age predisposition. The majority of female and male patients had high-grade MEC. High-grade MEC primarily affected people between the ages of 41 and 60 years old. There was one case of high-grade MEC in the age range of 0 and 20 years old. The patient's age was 20 years old. He was in stage IV with a 10 cm mass size and multiple ipsilateral nodal metastasis. He was treated with surgery and radiotherapy. Based on tumor location, high-grade histopathological grading is prevalent in both major and minor salivary glands. The majority of high-grade MEC receive surgical treatment followed by radiotherapy (56.6%), while low-grade MEC receive only surgical therapy (50%). There are 9 cases of low-grade MEC which receive surgical therapy accompanied by radiotherapy. These cases had indications for

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radiotherapy based on microscopic findings such as perineural invasion, surgical margin still contain tumor cells and lymphovascular invasion. In addition, there is one case of low grade and one of intermediate grade that received surgical, radiotherapy and chemotherapy. This condition is due to the clinical stage of patients being late stage (IV). There are 10 high-grade MEC cases that only receive surgical care. Therefore, these cases had indications for multimodality treatment. All of these cases are patients who were diagnosed before 2017. In this condition, we believe that the patient's medical and socioeconomic condition may possibly affect treatment decisions in Indonesia.[13-15]

Gender and age have no predisposing factors, according to crosstab data between demographic, clinical, and histopatological grade and clinical stage. Tumor location data suggest that late-stage MEC are often found in the major salivary gland, but early-stage MEC are mostly identified in the minor salivary gland. Tumors in the minor salivary glands can be diagnosed and treated earlier because patients are aware of the inconvenience and discomfort while masticating. Patients with stages III and IV mostly receive surgical therapy accompanied by radiotherapy or chemotherapy. However, there are 2 cases of early-stage patients receiving surgical therapy combined with radiotherapy and chemotherapy. Both cases are located in the oral cavity; one case has a low-grade and the other has an intermediate grade. Both cases have residual tumors and incomplete tumor resections, so they both received aggressive treatment. There were also 15 cases of stage III and IV patients receiving only surgical therapy. The cause of this situation is probably similar to the reason of high-grade patient not receiving further therapy.

TMN staging is composed of tumor (T), nodal (N), and metastasis (M) components. Tumors with T3N0M0 or any T stage with N2M0 are stage III. The T3N0M0 stage was the most frequent stage III (n=24; 75%). Stage T3 refers to a tumor size >4 cm and/or has extra parenchymal extension clinically or microscopically. Stage IV divides into IVA, IVB and IVC. Stage IVA had the majority proportion (n=27, 92.8%) among stage IV. Stage IVA with the T3N2M0 component had the highest proportion (n=10, 34,6%). N2 refers to the status of lymph nodes with ipsilateral tumor cell invasion more than 3 cm but less than 6 cm in size. N2 status could mean multiple ipsilateral tumor cell invasion but less than 6 cm in size, or bilateral or contralateral tumor cell invasion with less than 6 cm in size. There was no extranodal extension in N2.[16] TNM clinical staging is associated with overall survival (OS) and cause-specific survival (SCC), especially tumor size and lymph node invasion.[11] The histopathological grading of MEC is reported to be an independent factor related to patient outcome and prognosis.[7,11,17]

In our population study, the majority of high-grade MEC occur in stages III and IV. Meanwhile, low-grade MEC mostly occurs in stages I and II. Reny et al study shows there is a strong association between high-grade MEC and nodal metastasis.[18] Another previous study shows that there is a significant association between MEC histopathological grading with tumor size (T stage) and nodal metastastis.[7,18,19] In this study, there were 8 cases of low-grade MEC, which had stages III and IV. This condition due to the size of the patient's tumor which is more 4 cm and lymph node invasion. Low-grade MEC with stage IV involves multiple ipsilateral lymph node invasions less than 6 cm in size. In addition, there were also 10 cases where high-grade MEC had stages I and II. Patients who have high-grade and low-grade MEC cases have tumor size less than 4 cm and no lymph node invasion. The majority location in these cases is minor salivary glands. The priority in this case is aggressive treatment.

The main treatment for MEC is surgical therapy. Radiotherapy criteria according to the Perhimpunan Dokter Spesialis Bedah Onkologi Indonesia (PERABOI) and The National Comprehensive Cancer Network (NCCN's) therapeutic recommendations include for MEC patients include stage T3 or T4, surgical margin still contain tumor cells, locoregional metastases, adenoid cystic carcinoma, intermediate or high grade tumors, malignant tumors located in profunda lobe, perineural invasion, recurrent malignant tumors, and residual malignant tumors.[20,21] In prior studies, the treatment of intermediate-grade MEC is still under debate.[22] The behavior of intermediate-grade MEC tumors is more likely to resemble MEC with low histopathological grade. However, in our study intermediate-grade MEC behaviors resemble high-grade MEC and occur mostly in stages III and IV. Therefore, most intermediate-grade MECs are treated as high-grade MEC.

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CONCLUSION

In the RSHS period 2013–2022, there are 86 cases of salivary MEC. The most prevalent site for MEC is the parotid gland; females are slightly more dominant than males, with a mean age of 46.4 years. High grades and Stage III are the most common clinical staging and histological grading. Therefore, the most common therapy is surgery accompanied by radiotherapy or chemotherapy.

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