RESEARCH PAPER

Mucoepidermoid Carcinoma of the Salivary Glands: Survival and Prognostic Factors

Guevara-Canales Janet-Ofelia¹ · Morales-Vadillo Rafael¹ · Guzmán-Arias Guillermo¹ · Cava-Vergíu Carlos-Enrique¹ · Robello-Malatto José-Martín¹ · Guerra-Miller Henry² · Montes-Gil Jaime-Enrique²

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Abstract

Objective The aim of this study was to establish global survival rates and potential prognostic factors for mucoepidermoid carcinoma (MC) of the salivary glands in patients diagnosed at the Dr. Eduardo Cáceres Graziani National Institute for Neoplastic Diseases (INEN), Lima, Peru, between 2002 and 2012.

Materials and Methods This was an observational, analytical and longitudinal (information reconstructed in time) retrospective cohort study. Data were obtained from clinical records and used to determine the overall survival (OS) rate at 2 and 5 years, and the individual percentage survival for each prognostic factor using the actuarial technique. We also performed univariate analysis for each possible prognostic factor using log-rank analysis, and multivariate analysis using Cox's regression model. The study was approved by the institutional review board at Dr. Eduardo Cáceres Graziani INEN and conducted in accordance with the 1964 Declaration of Helsinki. For this type of study formal consent was not required.

Results The OS rate of the 51 patients enrolled in the study was 81 % at 2 years and 78 % at 5 years. In the multivariate analysis, the equation that best explained the survival result contained the variable, clinical stage ($p = 0.063$).

Conclusions The results revealed the importance of clinical stage regarding the survival of patients with a primary diagnosis of MC of the salivary glands.

Keywords Mucoepidermoid carcinoma · Survival · Salivary gland · Neoplasms

Introduction

Neoplasms in the major and minor salivary glands are a challenge to clinicians and histopathologists, because they occur infrequently and have a wide range of histological, clinical, epidemiological and developmental characteristics [1]. In the salivary glands, the most frequently occurring benign tumor is pleomorphic adenoma, and the most frequent malignant tumor is mucoepidermoid carcinoma (MC) [2].

MC is defined as a malignant epithelial neoplasm of the salivary glands [3] that represents 30–40 % of all malignant neoplasms of the salivary glands [4]. About 50 % of them occur in major salivary glands, with 80 % in the parotid gland, 8–23 % in the submaxillary gland and 2–4 % in the sublingual gland [5]. MC is more frequent in females, with a female:male ratio of 2:1 [6, 7] or 3:2 [8, 9]. The onset of MC has been found in patients from the 2nd to the 8th decades of life, and is the most frequent malignant tumor in persons aged <20 years [7]. Between 70 and 80 % of neoplasms of the salivary glands are located in the parotid gland, while the palate is the most common site for neoplasms of minor salivary glands [2]. Treatment depends on location, clinical aspects and histopathological grade. Standard treatment for the main types of salivary gland cancer is surgical resection in combination with adjuvant radiotherapy to reduce failure rates [10–14]; even though the role of adjuvant chemotherapy has not been proven, it has been used to treat distant metastasis and non-excisable disease and to reduce the effects of local/regional recurrence [15].

✉ Guevara-Canales Janet-Ofelia
janetguevara7@hotmail.com

¹ Universidad de San Martín de Porres (USMP), Lima, Peru

² Instituto Nacional de Enfermedades Neoplásicas (INEN), Lima, Peru

Prognosis depends on clinical stage [16], anatomical location [17, 18], histological grade and treatment [16]. Regarding histological grade, it has been reported that at the same histopathological grade, tumors in the parotid gland have better prognosis than tumors in the submandibular gland [19]. Although low-grade lesions have better prognosis, so do high-grade lesions if they are at stage I or II [11, 20, 21]. The 5-year survival rate for MC is 50 %, increasing to 90–100 % in cases with low-grade malignancy, and 26 % in cases with high-grade malignancy [8]. Some factors that influence survival are histological grade, clinical stage, facial nerve paralysis, lymph node metastasis, location (a worse prognosis in the submaxillary gland) and other factors such as age and gender (a better prognosis in young people and females). The “4 cm” guideline is often used, although there is limited information regarding the management of cancer of the salivary glands. Tumors of <4 cm (T1 or T2) in size have a better prognosis, regardless of histological grade [20]. MCs with high-grade malignancy have a 50 % probability of metastasizing [8]. The possibility of recurrence depends on the differentiation grade (higher in high-grade tumors) and the involvement of the resection margins [22]. Even with complete resection, there is substantial risk of local recurrence (16–27 %) and distant metastasis (13–26 %) [23–25].

The aim of the present study was to elucidate the overall survival (OS) at 2 and 5 years, and the potential prognostic factors of MC of salivary glands in patients diagnosed at the Dr. Eduardo Cáceres Graziani National Institute for Neoplastic Diseases (INEN) from 2002 to 2012. These data could be extrapolated to the situations of patients in other regions in order to provide further information for decision-making, such as in therapeutic strategy.

Patients and Methods

This was an observational, analytical, longitudinal (information reconstructed in time) retrospective cohort (using clinical epidemiological data from clinical histories) study. It included subjects with a primary diagnosis of MC of the salivary glands seen at the Dr. Eduardo Cáceres Graziani INEN, Lima, Peru, from January 2002 to December 2012. Clinical records with incomplete data were excluded.

OS was determined and defined as the percentage of subjects who remained alive over the period extending from the diagnosis date to the last visit to the doctor's office, or date of death. The following prognostic factors were analyzed: age, gender, size of lesion, location, pain, TNM staging system, clinical stage, presence of metastasis, histological grade, treatment, follow-up condition, and follow-up time. Data from clinical records were used to determine the OS and analyzed using two statistical tests: (1) the actuarial technique (mortality tables) to

Fig. 1 Overall survival curve for patients with MC of the salivary glands seen at the Dr. Eduardo Cáceres Graziani INEN, Lima, Peru, from 2002 to December 2012

determine the OS rate at 2 and 5 years and the individual survival percentage for each potential prognostic factor; and (2) Kaplan–Meier's limit-product method to determine survival regarding each potential prognostic factor. Prognostic factors were analyzed in two ways: (1) univariate analysis using the log-rank test (Mantel–Cox) to determine the individual statistical significance of the survival differences of Kaplan–Meier's limit-product; and (2) multivariate analysis using Cox's regression model, in which the variables considered in the multivariate analysis were those whose values were lower than 0.5 in the univariate analysis. All values found through the different statistical tests were considered at a significance level of 0.05 ($p < 0.05$). The collected data were transferred to a Microsoft Excel program. The analysis, tables and figures were completed with the assistance of the statistical program SPSS (Statistical Package for Social Sciences) version 20.0 (SPSS, Chicago, IL, USA) for the Windows XP® Operating System (Microsoft Inc., Seattle, WA, USA).

The study was approved by the institutional review board at Dr. Eduardo Cáceres Graziani INEN (protocol: INEN 13:27) and conducted in accordance with the 1964 Declaration of Helsinki. For this type of retrospective study formal consent was not required.

Results

Fifty-one patients were examined and diagnosed with MC from January 2002 to December 2012 at the INEN. All cases were diagnosed by means of pathological anatomy studies. There were more female patients (28 [54.9 %]), while 33.3 % of the patients were <30 years of age. OS rates at 2 and 5 years were 81 and 78 %, respectively (Fig. 1). Table 1 shows the following: (a) The 2- and 5-year survival rates for

Table 1 Survival rate at 2 and 5 years evaluated for potential prognostic factors in subjects with MC of the salivary glands seen at the Dr. Eduardo Caceres Graziani INEN, Lima, Peru, from January 2002 to December 2012

Risk Factors	Survival at 2 years (%)	Survival at 5 years (%)	<i>p</i> value according to log rank (Univariate)	<i>p</i> value according to Cox (Multivariate)
<i>Age (years)</i>				
≤60	93	93	0.003*	0.051
>60	60	53		
<i>Gender</i>				
Female	85	85	0.121	0.491
Male	75	67		
<i>Size of lesion</i>				
≤4 cm			0.005*	0.168
>4 cm				
<i>Location</i>				
Parotid gland	89	85	0.000*	0.002*
Submaxillary gland	17	–		
Minor glands	00	00		
<i>Pain</i>				
No	90	90	0.036*	0.264
Yes	67	61		
<i>TNM (T) Tumour size</i>				
T1	100	100	0.006*	0.226
T2	90	90		
T3	65	65		
T4	54	32		
<i>TNM (N) Nodal involvement</i>				
N0	82	79	0.000*	0.251
N1	75	75		
N2A	100	100		
N2B	–	–		
<i>TNM (M)</i>				
M0	78	74	0.566	–
M1	86	86		
<i>Clinical stage</i>				
I	100	100	0.000*	0.063**
II	100	100		
III	52	52		
IV A	50	50		
IV B	33	–		
IV C	86	86		
<i>Metastasis</i>				
No	78	74	0.566	–
Yes	86	86		
<i>Histologic grade</i>				
Low grade	95	95	0.007*	0.067
Intermediate grade	90	90		
High grade	63	56		
<i>Treatment</i>				
Sg	68	59	0.059	0.528
Sg + Rt	86	86		

Table 1 continued

Risk Factors	Survival at 2 years (%)	Survival at 5 years (%)	<i>p</i> value according to log rank (Univariate)	<i>p</i> value according to Cox (Multivariate)
Sg + Rt + Cht	–	–		
Cht + Rt	89	89		
Rt	–	–		

*Statistically significant value

** Variable included in the equation

TNM staging system; tumor, lymph nodes, metastasis

Cht chemotherapy, *Rt* radiotherapy, *Sg* surgery

each different variable assessed as a potential prognostic factor, through the survival statistics involving the mortality table test. (b) Univariate analysis of the different variables studied as potential prognostic factors using the log-rank (or Mantel–Cox) statistics test, which indicated that the following values differed significantly: age ($p = 0.003$), size of lesion ($p = 0.005$), location ($p = 0.000$), pain ($p = 0.036$), *TNM* (T stage) ($p = 0.009$), *TNM* (N stage) ($p = 0.000$), clinical stage ($p = 0.000$), and histological grade ($p = 0.007$). (c) The multivariate analysis of the different variables studied as potential prognostic factors with Cox's regression test only found that location was a significant factor ($p = 0.002$). The regression equation that best explains survival only contained the variable, clinical stage ($p = 0.063$) (Fig. 2). Table 2 shows the accrued survival rate at ≤ 10 years. The model selected from the Cox test (hazard ratio) showed a noticeable increase in survival risk for MC of the salivary glands from clinical stage III; clinical stage IV B was the most harmful and reduced the chance of survival by a factor of >12 (Table 3).

Discussion

Descriptive Analysis

In this study of patients diagnosed with MC at the INEN, 51 cases were found over a period of 10 years. In other epidemiological studies with a follow-up term >20 years, a scattered number of cases was found, such as those reported by Tian et al. [26] in a Chinese population study: 673 cases with MC were found. In a retrospective study involving a Brazilian population, 67 MC cases [27] were found, and in a Japanese population study 8 MC cases were found [28].

Survival Analysis

The OS rate reported in other studies has been generally good, and is listed from highest to lowest as follows.

Boahene et al. [29] reported a 5-year survival rate of 98.8 % in a series of 128 cases from the Mayo Clinic. Védrine et al. [30] reported a 5-year survival rate of 93.7 % in 18 pediatric cases. Rapides et al. [8] reported a 5-year specific OS rate of 85 %. Liu et al. [31] reported a survival rate of 80.47 % in a retrospective study. McHugh et al. [32] reported a 5-year OS rate of 79.3 %. Byrd et al. [33] reported a 5-year OS rate of 79 % and 5-year disease-free survival rate of 76 %. Villavicencio-Ayala et al. [34] reported a 5-year OS rate of 78.3 % and 10-year OS rate of 69.3 %, with 5- and 10-year disease free survival rates of 73.9 % and 67.5 %, respectively. The values for OS at 5 years in these studies (93.7–78.3 %) are consistent with that in our study: 78 %.

Univariate Analysis

In a study of 5-year OS in 125 patients by McHugh et al. [32], univariate analysis regarding gender revealed a rate of 71.2 % for males and 86.2 % for females. No statistically significant difference in OS was found between patients with and without pain ($p = 0.098$). The OS rate was 93.5 % for patients with T1 or T2 disease; it was statistically significantly lower, at 41.9 % ($p < 0.05$), for patients with T3 or T4 disease. The OS rate was also significantly lower for patients with stages III and IV disease than with stages I and II disease ($p < 0.05$). The OS rate was 92.8 % for low-grade MC, 95.1 % for intermediate-grade MC and 51 % for high-grade MC. In our study, univariate analysis showed clinical stage to be a prognostic factor influencing survival, in agreement with other studies that found this and/or other variables having an influence on survival. For example, Villavicencio-Ayala et al. [34] reported the following factors as clinical variables, which are important to survival: tumor invasion of adjacent structures ($p = 0.001$); tumor size T4 ($p = 0.0008$); regional metastasis ($p = 0.000$); and clinical stages III and IV ($p = 0.000$). All of these factors were associated with adverse prognosis. Schwarz et al. [35] report that OS was associated with: age >60 years

Fig. 2 Mortality and Kaplan–Meier curves with multivariate significance determined by the log-rank test, clinical stage predictor, for subjects with MC of the salivary glands seen at the Dr. Eduardo Caceres Graziani INEN, Lima, Peru, from January 2002 to December 2012

Table 2 Cumulative survival factors associated with survival for subjects with MC of the salivary glands seen at the Dr. Eduardo Caceres Graziani INEN, Lima, Peru, from January 2002 to December 2012

Time (years)	No of patients			Cumulative proportions of survival
	At the beginning of the interval	Censored	Lost	
0–1	51	5	7	0.86
1–2	39	4	2	0.81
2–3	33	5	1	0.78
3–4	27	3	0	0.78
4–5	24	1	0	0.78
5–6	23	5	0	0.78
6–7	18	4	1	0.73
7–8	13	2	0	0.73
8–9	11	3	0	0.73
9–10	08	3	0	0.73

Table 3 Potential prognostic factors associated with survival for subjects with MC of the salivary glands seen at the Dr. Eduardo Caceres Graziani INEN, Lima, Peru, from January 2002 to December 2012, according to Cox analysis multivariate hazard ratio

Variable analyzed	Hazard ratio	Confidence interval 95 %	p value according to Cox (multivariate)
<i>Clinical stage</i>			
Stage I	1.0		0.063*
Stage II	0.171	0.000–6.584E+116	
Stage III	10.830	0.000–4.088E+105	
Stage IV-A	10.663	0.000–3.479E+105	
Stage IV-B	12.221	0.000–1.642E+106	
Stage IV-C	9.603	0.000–1.199E+105	

* Variable included in the equation

($p = 0.001$); clinical stage II, III and IV versus stage I ($p = 0.031$); and intermediate and high histological grade versus low grade ($p = 0.001$). A point also mentioned by the authors was that histological grade was an independent prognostic factor that affected survival, as reported in a study by Liu et al. [31] and the study by Byrd et al. [33] with $p = 0.04$; this finding coincides with our study that also found a significant difference. The high histological grade negatively influenced the survival of these patients.

Multivariate Analysis

Multivariate statistical analysis in the study by Rapides et al. [8] on 18 cases indicated that the primary factor with significant influence on survival was the histological grade of the tumors (log rank test, $p = 0.013$; $\chi^2 = 8.59$). Liu et al. [31] consider that the only factor with significant multivariate influence at 5 years on the prognosis of patients with MC in salivary glands is histological grade. Similarly Nance et al. [36] concluded in their multivariate analysis that histological grade is one of the survival predictor factors, and according to the literature, there is a positive correlation between advanced histological grade and poor prognosis [32, 36]. This was shown, for example

in the study by Spiro [37] conducted at the Memorial Sloan Kettering Cancer Center in 2001 that clinical stage, particularly tumor size (T), rather than histological grade was the critical factor in the outcome of patients with cancer of the salivary glands. Our study arrived at the same conclusion, with patients with clinical stages I and II having a 10 times higher probability of surviving than patients with other clinical stages of the disease. Clinical stage as a predictor of survival was also reported in a study by Plambeck et al. [38], where the OS rate at 5 years was 92 %; however, all patients who died had stage III or IV disease at the time of diagnosis.

Conclusion

Our results regarding primary MC tumors of the salivary glands demonstrated the influence of clinical stage on the survival of patients with a primary diagnosis of this disease.

Funding This study was self-funded.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at Dr. Eduardo Caceres Graziani INEN (protocol: INEN 13:27) and conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent For this type of study formal consent is not required to be retrospective.

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