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Original Article

Squamous cell carcinoma at maxillary sinus: clinicopathologic data in a single Brazilian institution with review of literature

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Abstract: Squamous cell carcinoma arising at maxillary sinus is a rare neoplasm, characterized by aggressive growth pattern and glooming prognosis. There are no studies describing specifically its epidemiology in the South America. The aim of the current paper is to characterize a Brazilian maxillary sinus squamous cell carcinoma sample and to compare such data with others worldwide relevant series. The records of the Brazilian National Cancer Institute (1997-2006) were gathered and plotted. Additionally, an extensive literature review was carry out using electronic database (PUBMED/MEDLINE and LILACS) over a period of 54 years. A descriptive statistics and univariate survival test (log rank) were employed. Maxillary sinus squamous cell carcinoma was the commonest malignancy of sinonasal epithelium found. It affected mainly mid-age white men and most of them were diagnosed at advanced stage. Surgery combined with radiotherapy was the most therapeutic modalities given. The overall mortality rate in our sample was of 65.5%. Overall 1-, 2- and 5-year survival rate was 57.9%, 44.8%, and 17.7%, respectively. Maxillary sinus squamous cell carcinoma is an aggressive tumor normally diagnosed at the advanced stage and most patients present an unfavorable prognosis and reduced survival rate.

Keywords: Maxillary sinus, squamous cell carcinoma, paranasal carcinoma, treatment, prognosis, epidemiology

Introduction

Nasal cavity and paranasal sinuses carcinomas account for 0.2-0.8% of all human malignant neoplasms. Among them, sinonasal squamous cell carcinoma is one of the rarest epithelial neoplasms and represents about 3% of all malignancies of the head and neck region. It predominantly occurs within the maxillary sinus (60-70%) and less frequently in the nasal cavity (12-25%), ethmoid (10-15%) and sphenoid/frontal sinuses (1%) [1].

In respect to squamous cell carcinoma (SCC) from maxillary sinus (MxSSCC), it affects mainly mid-aged men (55-65 years old) from Eastern countries and has as the major risk factors some chemicals and virus [1-4]. It presents the highest incidence among the tumors developing within the sinonasal compartment and one of the worst outcomes in comparison with other head and neck tumors. One reason for this is the large number of patients who are diagnosed in advanced stage at the presentation [1, 3, 4]. Lymph node metastasis, stage, modality and sequence of treatment seem to be pivotal in determining the MxSSCC-affected patient prognosis [1, 2]. However, as most reports have included in their series other entities, like adenocarcinomas and sarcomas, the understanding of its behavior and prognosis is still uncertain [3, 4]. These facts have enshrouded the meaning of the results for this group of malignancy, especially in terms of clinicopathological data. Furthermore, there are few reports in the literature describing precisely these findings. Thus, studies with strictly inclusion and exclusion criteria of patients are warranted to permit

Table 1. Sociodemographics of the present sample

Variable	
Age	Mean: 58.7 years
	Median: 59 years
	Range: 19-89 years
Gender	Male: 35 (60.4%)
	Female: 23 (39.6%)
Skin color	White: 38 (65.5%)
	Non-white: 20 (34.5%)
Tabacco use	Current: 27 (46.5%)
	Formely: 12 (20.7%)
	Never: 19 (32.8%)
Alcohol use	Current: 20 (34.5%)
	Formely: 7 (12.1%)
	Never: 31 (53.4%)

Table 2. Clinic-pathological and treatmet data of the present sample

Variable	
Evolution time	Mean: 5.92 months
	Range: 1-44 months
Signs and symptoms	Swelling: 51 (87.9%)
	Pain: 35 (60.4%)
Staging	Stage I or II: 5 (8.6%)
	Stage III or IV: 53 (91.4%)
Histological grade	Low grade: 4 (6.9%)
	Moderate grade: 45 (77.7%)
	High grade: 9 (15.5%)
Surgical margins	Free: 20 (60.6%)
	Comitted: 13 (39.4%)
Regional metastasis	Present: 10 (17.2%)
	Absent: 48 (82.8%)
Distant metastasis	Present: 5 (8.6%)
	Absent: 53 (91.4%)
Local recurrence	Present: 10 (20.4%)
	Absent: 39 (79.6%)
Treatment modalities	No: 9 (15.5%)
	RxT + ST: 22 (37.9%)
	RxT: 13 (22.4%)
	ST: 9 (15.5%)
	RxT + ChT: 3 (5.2%)
	ST + RxT + ChT: 2 (3.4%)
Follow up	Mean: 18.1 months
	Range: 1-108 months
Outcomes	NED: 6 (10.3%)
	AWD: 14 (24.2%)
	DOD: 38 (65.5%)

AWD: alive with disease; ChT: chemotherapy; DOD: Died of disease; NED: no evidence of disease; RxT: radiotherapy; ST: surgical treatment.

accurately making out the MxSSCC clinicopathological features.

The aim of this study is to describe a recent experience of the Brazilian National Cancer Institute (INCA) on MxSSCC detailing the major socio-demographic and clinicopathologic data of a convenient sample and compare these findings with other relevant studies. Additionally, an extensive review of the literature on this subject is presented.

Patients and methods

This study was authorized to be conducted by the Institutional Review Board of the INCA (CEP # 080/08). The files of all MxSSCC-affected patients between 1997 and 2006 were gathered, reviewed and assessed according to the most recently WHO classification [1]. It was considered eligible to be employed in this study patients whose the medical files had assessable information about tumor localization (specifically within the maxillary sinus) and histopathological data. All MxSSCC-affected patients with less than two years of follow-up and/or not treated at the INCA were excluded of our samples. Demographic (age, gender, skin color, and lifestyle) and clinicopathological data (time of evolution, signs and symptoms, TNM staging, histological grading, and invasion to neighboring structures), treatment modality and outcome (tumor recurrence, clinical condition at last appointment, and follow-up time) were retrieved from each patient's medical file.

Moreover, a review of the English literature about MxSSCC was performed by using electronic database (PUBMED/MEDLINE and LILACS) since 1960 (covering a period of 54 years). For this, the following terms were used: "maxillary sinus" and "squamous cell carcinoma". A complementary search was also made by using the references from the retrieved manuscripts. MxSSCC case-report manuscripts were also included [5-49]. However, studies either describing other maxillary sinus malignancies or focusing on only in treatment modality were discarded, as also those reports lacking clinic-pathological data [31-40]. Studies that came from either the same group or Institution, it was used that report presenting the highest number of cases [41-48]. For each selected study, it was collected information about year of publication, covered period, number of cases, incidence, male/female ratio,

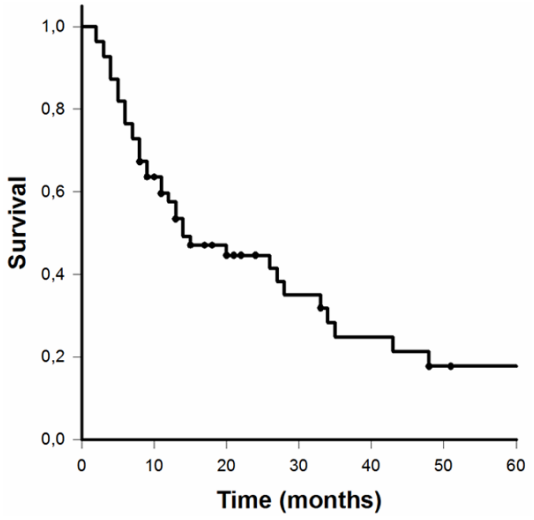

Figure 1. Overall survival for the present cohort of maxillary sinus squamous cell carcinoma.

age, TNM, treatment, recurrence, surgical margin status, and overall survival data.

Statistics

The chi-square test and logistic regression analysis were used to verify the association between the clinic-pathological data. All tests were developed by using SPSS for Windows, version 15 (SPSS Inc, Chicago, IL, USA). Null hypothesis was rejected when *P* value was less than 0.05.

Results

Over a period of 10 years, 58 cases of MxSSCC were retrieved, which represented 54.2% of all epithelial malignancies and 41.2% of all ones that originated within the maxillary sinuses. **Tables 1** and **2** summarize the sample data obtained from each MxSSCC-harboring patient. Most cases were histologically categorized as well/moderate histological grade. However, no association between TMN stage and histopathological grade was found ($P > 0.05$).

A common clinical aspect observed in our samples was that all MxSSCC-affected patients reported some symptoms at the first appointment, which had lasted in average 7.1 ± 9.0 months, ranging from 1 to 44 months. Interestingly, a great majority of the patients reported during the anamnesis that face (62.1%) and mouth (56.7%) were the main locations where the symptoms had occurred for the first time, while nasal cavity was reported in 32.8% of them. In respect to staging, there was no patient diagnosed at stage I, and most of them were diagnosed in advanced stage (III e IV). Comparing staging and symptoms, it was observed that those early-stage-disease patients had lower lasted symptoms (3.2 ± 1.0 months) when compared with advanced-stage-disease patients (7.4 ± 9.4 months). In addition, loss of weight, facial paralysis, trismus, paresthesia and bleeding were observed only among advanced-stage-disease patients.

The main treatment modalities used in our samples were surgery combined with radiotherapy (n = 22, 45.0%), whereas either radiotherapy or surgery was given to treat only 13 (26.5%) and nine (18.4%) of them, respectively (**Table 2**). Nine patients (18.4%) did not receive any kind of treatment due to advanced stage of their diseases. From 40 patients who received radiation therapy, cobalt-60 external beam radiation was used in 19 patients (59.4%), with a mean dose of 45.9 ± 18.9 Gy, whereas the remaining patients (n = 13, 40.6%) were given linear particle accelerator-based radiation one, with a mean dose of 57.9 ± 10.5 Gy. However, there was no significant association between patient survival improvement and radiation modality ($P = 0.271$).

The overall mortality rate was of 65.5% (38/58), being the highest and the lowest mortality rates found in advanced-stage-disease (93.9%) and early-stage-disease patients (40.5%), respectively. All patients who developed regional and/or distant metastasis died between 11.3 and 23.3 months after diagnosing. The median survival time was of 14 months and the overall 1-, 2- and 5-year survival rate was of 57.9%, 44.8%, and 17.7%, respectively (**Figure 1**). A univariate analysis is shown in **Table 3**. No statistical significance among clinic-demographic (age, gender, tumor staging), histological grade, extension of tumor invasion, status of tumor margin, recurrence, metastasis, and treatment modality and survival was identified. The distribution of recurrences and metastases is detailed in **Figure 2**. As could be seen, only patients harboring advanced-stage disease developed metastases and recurrences. **Table 4** shows the clinic-pathological and treatment data collected from the retrieved manuscripts published in the literature since 1960.

Discussion

Paranasal sinus malignancies are rare neoplasms that present an ominous prognosis.

Table 3. Maxillary sinus squmous cell carcinoma: comparison of median survival based on demographics, tumor characteristics and therapy given

Variable[a]	Subgroup	Median survival rate (months)	*P* value[b]
Age	< 65 years (n = 37)	14	0.765
	≥ 65 years (n = 21)	26	
Gender	Male (n = 35)	13	0.673
	Female (n = 23)	28	
Staging	Stage I or II: (n = 5)	-	0.066
	Stage III or IV: (n = 53)	14	
Histological grade	Low grade: (n = 4)	15	0.824
	Moderate grade: (n = 45)	14	
	High grade: (n = 9)	9	
Surgical margins	Free: (n = 20)	13	0.154
	Comitted: (n = 13)	27	
Regional metastasis	Present (n = 10)	28	0.599
	Absent (n = 48)	14	
Distant metastasis	Present (n = 5)	14	0.505
	Absent (n = 53)	15	
Local recurrence	Present (n = 10)	27	0.365
	Absent (n = 39)	13	
Treatment	RxT + ST (n = 22)	26	0.138
	Other (n = 36)	9	
Orbital invasion[a]	Present (n = 22)	9	0.315
	Absent (n = 29)	26	
Intra-cranial invasion[a]	Present (n = 5)	9	0.110
	Absent (n = 46)	26	
Pterygoid invasion[a]	Present (n = 14)	20	0.901
	Absent (n = 37)	14	

[a]Only valid information; [b]Log-rank test.

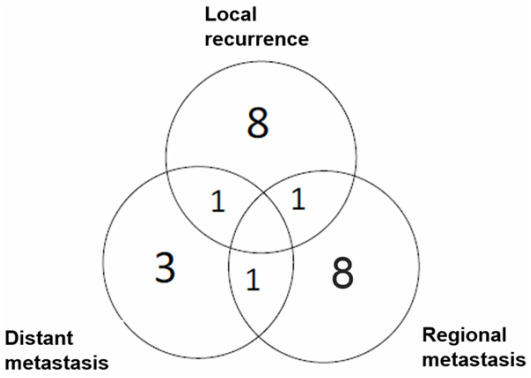

Figure 2. Distribution of metastases and relapses observed in the maxillary sinus squamous cell carcinoma sample studied.

They account for 0.2-0.8% of all human malignant neoplasms and most cases are SCC, representing approximately 70% of all cancer-developing paranasal sinuses [5-30]. Due to its low incidence, it is very difficult for any Institution accumulates significant information about these tumors [5-30]. In an attempt to overcome this limitation, a number of reports have been classifying maxillary sinus-originating tumors, including MxSSCC, within the major group of the paranasal neoplasms, which comprises tumors of different histological and behavioral aspects, enshrouding the real demographic and clinic-pathological features of this tumor. Therefore, other studies focusing on MxSSCC in a particular view should be done as a way to understand more precisely its clinical behavior and pathogenesis (**Table 4**). Thus, the present report aimed to describe the demographic and clinic-pathological data of 58 MxSSCC-affected patients, the 14th biggest casuistry, and summarize the main data of this tumor based on the pertinent literature.

In our study, MxSSCC samples corresponded to 43.5% of all malignancies that gave rise to within the maxillary sinus, which is supposed to be lower than seen in other series from the South American [49]. Despite representing one of the biggest casuistry worldwide, looking at the number of cases diagnosed per year, our study might be put at 8th position in terms of incidence. Although it was pointed out elsewhere that the frequency of maxillary sinus-developing SCC outnumbered adenocarcinomas originating from the same location, our series found a predominance of the latter [4]. MxSSCC commonly affects male patients (about two times more than women) in the sixth and seventh decade of life, but it is extremely rare in children and adolescents [5-30]. Our findings confirm these observations with no case being diagnosed in children and the male : female rate of 1.5:1.

Table 4. Clinic-pathological and treatment data of the retrieved manuscript

Author, year	Period	Country	Cases (n)	% of paranasal malignacies	M:F ratio	Median Age (Range)	T stage (%)		N+ (%)	M+ (%)	Prevalent treatment	Local recurrence	Surgical margins	Overall Survival 5-years
							T 1-2	T 3-4						
Marchetta FC, 1969 [5]	1935-1965	USA (Buffalo)	119	85.0%	1:0.61	-	22%	78%	10%	-	RT only (53.8%)	-	-	-
Pezner RD, 1979 [6]	1960-1976	USA (Washington)	63	-	1:0.43	63.0 (32-94)	7.9%	92.1%	20.6%	-	-	-	-	-
St-Pierre S, 1983 [7]	1964-1975	USA (Ann Arbor)	66	-	1:0.57	60.0 (25-89)	13.6	86.4%	10.6%*	12.0%	RT + Sx (48.5%)	-	-	27.3%
Kondo M, 1984/1985 [8, 9]	1967-1979	Japan (Tokyo)	97	-	1:0.45	57.3 (30-84)	3.1%	96.9%	12.4%	2.1%	RT + ChT + S (most)	48.5%	-	-
Okawa T, 1989 [10]	1969-1985	Japan (Tokyo)	76	-	1:0.55	61 (31-84)	12%	88%	18%*	-	RT + ChT + S (78%)	-	-	43.3%
Lavertu P, 1989 [11]	1977-1986	USA (Cleveland)	48	46.6%	1:0.8+	60.3 (23-80)+	25.0%	75.0%	14.6%*	4.2%*	RT + Sx (41.6%)	52.1%	18.75%	38.2%
Kudo K, 1992 [12]	1974-1988	Japan (Morioko)	30	-	1:0.43	56.9 (30-83)	6.6%	94.4%	26.6%	30%	-	36.6%	-	55.4%
Stern SJ, 1993 [13]	1971-1986	USA (Texas)	85	-	1:0.44	60.2 (14-91)	-	-	16.9%*	3.6%*	Sx+ RT (40.0)	-	-	-
Paulino AC, 1997 [14]	1971-1995	USA (Chigaco)	42	-	1:0.20	63.5 (42-77)	14.3%	85.7%	9.5%*	11.9%	Sx+ RT (73.8)	45.3%	-	-
Itami J, 1998 [15]	1973-1992	Japan (Tokyo)	37	-	1:0.61	63 (40-85)	18.9%	81.1%	18.9%	10.8%	Sx+ RT (86.5)	40.5%	-	-
Konno A, 1998 I [16]	1971-1982	Japan (Akita)	74	-	1:0.54	58.8 (-)	12.2%	87.8%	10.8%	16.2%	RT + ChT + S (100%)	5.4%	-	68.9%
Konno A, 1998 II [16]	1982-1987	Japan (Akita)	23	-	1:0.39	57.9 (-)	3.1%	96.9%	9.4%	9.4%	RT + ChT + S (100%)	6.3%	-	75.0%
Kim GE, 1999 [17]	1984-1993	Korea (Seoul)	116	-	1:0.31	55 (23-85)	6.0%	94.0%	10.3%*	1.8%	RT alone (80.2%)	49.1%	39.1%	30.5%
Passali D, 1999 [18]	-	Italy (Siena)	36	-	1: 0.24	65.5 (41-76)	0%	100%	8,30%	16%	RT alone (58.3%)	63%	-	17%
Tiwari R, 1999 [19]	1975-1994	Netherlands (Amsterdam)	43	73.0%	1:0.53	(32-90)	[16.2%]	[83.8%]	4.1%*	-	S + RT (60.5%)	-	-	-
Jeremic B, 2000 [20]	1987-1993	Yugoslavia (Kragujevac)	44	-	1:0.22	-	-	100%	-	9.1%	RT + Sx (100.0%)	29.5%	-	66%
Waldron J, 2000 [21]	1976-1993	Canada (Toronto)	110	61%	1:0.43	64 (38-89)	16%	84%	15%	10.9%	RT alone (75.5%)	57.3%	25%	30.0%
Hayashi T, 2001 [22]	1983-1997	Japan (Asahikawa)	74	-	1:0.42	66 (34-86)	12.2%	87.8%	10.8%*	1.4%*	RT + ChT + S (83.8%)	13.5%	3.4%	58.5%
Ogawa K, 2001 [23]	1979-1998	Japan (Nishihara-cho)	41	-	1:0.28	55 (37-79)	14.6%	85.4%	12.2%*	7.3%	S + RT (100.0%)	41%	65.8%	48%
Yoshimura R, 2002 [24]	1977-1996	Japan (Tokyo)	110	-	1:0.40	57 (26-84)	20.0%	80.0%	15.5%	-	RT + ChT + S (100%)	26.4%	-	63%
Isobe K, 2005 [25]	1983-2002	Japan (Chiba)	124	-	1:0.3	60.8 (30-82)	7.3%	92.7%	16.9%*	-	RT + ChT + S (100%)	-	-	56.6
Qureshi SS, 2006 [26]	1994-1999	India (Mumbai)	62	-	1:0.59	55 (15-70)	16.2%	83.8%	8%	1.6%	Sx+ RT (65.0)	45%	37.5%	35%
Nishimura G, 2009 [27]	1991-2007	Japan (Yokohama)	41	63.1%	1:0.1	59.5 (34-81)	2.5%	97.5%	10%	2.5%	S + ChT + RT (40.0%)	29.4%	-	59.2
Ashraf M, 2010 [28]	1979-2005	India (Kolkata)	379	-	1:0.38	47.2 (23-67)	7.4%	92.6%	16.6%	11.4%	Sx+ RT (59.4%)	49.3%	-	53%
Hinerman, 2011 [29]	1969-2006	USA (Florida)	54	-	1:0.6	62 (36-79)	3.7%	96.3%	33.3%	24%	RT alone (54%)	-	-	30%
Kreppel M, 2012 [30]	1980-2006	Germany (Cologne)	53	-	1:0.3	57.9 (18-78)	5.7%	94.3%	47.1%	-	RT + ChT + S (100%)	34.0%	-	35.0%
Present data	1997-2006	Brazil (Rio de Janeiro)	58	43.5%	1:0.40	58.7 (19-89)	8.6%	91.4%	17.2%	8.6%	RxT + ST (37.9%)	20.4%	39.4%	17.7%

%: percentage; *at first appointment; []: Stage; ChT: chemotherapy; F: female; M: male; n: number; N+: positive cervical nodes; M+: positive distant metastasis; RT: radiotherapy; S: surgery; T: tumor.

Reviewing the literature about geographical distribution of MxSSCC, it was identified that its incidence among oriental and occidental population are almost the same and ranged from 40% to 80% within the group of the paranasal malignancies [5-30]. In contrast, some reports from Japanese series have shown a higher MxSSCC incidence in Asiatic population than other regions of the Globe, which might be related to the extensive use of soft wood in the Japanese furniture industry, high prevalence of chronic sinusitis, and widespread use of cigarette smoking [49] (**Table 4**). However, other studies should be done to clarify this apparently geographical MxSSCC predilection.

The risk factors associated with MxSSCC development are enormous, but chronic exposure to nickel, chlorophenol, formaldehyde, textile dust, wood, cigarette smoking have been frequently reported [1-4]. In our study, 70% of the patients were either ex-smokers or smokers, indicating that this habit might be considered as an important risk factor associated with MxSSCC. Another risk that has been identified is the presence of sinonasal-inverted papilloma (IP), a lesion that may increase in 10% the chance of MxSSCC development. One explanation for that might be the presence of HPV, which might be found in both lesions [1, 50, 51]. In spite of knowing the aforementioned risk factors of its occurrence, there is no well-defined precancerous lesion of the maxillary sinus as it is observed in other sites of the head and neck region [1-4, 50, 51].

An interesting observation detected in the review was the great number of symptoms reported by MxSSCC-affected patients, which varied from nasal fullness, stuffiness, obstruction, epistaxis, rhinorrhea, pain, paresthesia to tooth mobility, tooth loss, proptosis, diplopia, and lacrimation [1-30]. In the current study, these symptoms were also reported by our patients, reflecting MxSSCC invasiveness to the surrounding structures like nasal cavity, palate, other paranasal sinuses, skin, mouth, orbit, and skull [1-30].

With regard to staging, T1/T2 tumors are uncommon and represent less than 20% of all MxSSCC [5-30]. In this study, T1/T2 tumors represented only 8.6% of all cases (5 cases), while 91.3% (53 cases) were T3/T4, as has been observed in other series [5-3]. These findings clearly show that MxSSCC is mainly diagnosed in advanced stage, which helps to explain the lowest survival rate when compared with other kind of tumors like oral SCC [5-30]. In part, these data might be explained by the maxillary sinus anatomy, which contents an air filled space that facilitates silently its growth with few or no signs and symptoms until achieving considerable size [1].

The percentage of loco-regional MxSSCC metastasis is approximately 15%, with about 10% of them presenting metastatic focus at the first appointment [5-30]. Moreover, lymph node metastasis has been considered as a significant prognostic marker [14]. Here, we found a similar incidence of cervical node metastasis when compared with other series [5-30]. However, some reports have found a higher incidence [6, 12, 29, 30]. In a retrospective study by Kim et al., 1999 [17], it was observed that the risk of neck metastases significantly increased when tumor invaded the oral cavity. In our current study, this association was not detected ($P < 0.95$). Distant metastases are less common and range from 10% to 30% of cases. A similar proportion was seen in the present study (8.6%).

Histologically, MxSSCC is identical to SCC originating in other head and neck regions and most tumors present a well/moderate differentiation [1]. As observed here, as well as in other series, histologic differentiation appears not to be significantly associated with prognosis [14, 17, 20, 22, 25].

Surgical treatment of MxSSCC aims to promote local control and preserve or restore facial contour and function, but in most advanced-stage patients, the treatment frequently fails to achieve these targets [30]. Unfortunately, there is no optimal treatment for MxSSCC, but surgery remains as the *gold-standard* approach to improve significantly the overall survival and loco-regional control for all patients. On the other hand, radiotherapy associated or not with chemotherapy has rarely achieved the best results [5-30]. Furthermore, these patients normally suffer from several complications such as visual impairment, carotid blow-out, cerebrovascular accident, and superficial necrosis [29, 30]. Our review evidenced that those patients who were treated by trimodal therapy achieved the highest survival rate [16, 22, 24, 25, 27]. In contrast, a published series by *Jeremic et al., 2000* [20] showed a higher survival ratio in

patients treated with both surgery and radiotherapy. In our samples, surgery and radiotherapy were used in most patients, but no impact in the survival rate was observed. So, multicentric studies are warranted to discovery the best way to treat these patients needed to be done. Regardless of the treatment employed, recurrence remains the major cause of failure. In our retrospective review, this was found in more than one-third of the cases, and similar findings were detected in the present study. Surgical margins are difficult to ascertain in MxSSCC as is practically impossible to carry out en bloc resection due to its extensive size [11]. The literature reveals positive margins in approximately 33% of cases, more than those observed in our samples [5-30]. As stated by *Hayashi et al., 2001* [22], incomplete surgical resection may have impact on prognosis. A new craniofacial surgical approach to remove large tumors has been used and it is possible to speculate that over the next decades, the survival rate will enhance even with increasingly risk of other surgical-related complications [52-54]. About lymph node resection, a recent international review on this subject suggested that regional nodes should be treated in these patients electively, especially in T3 and T4 patients [55].

MxSSCC prognosis is ominous and most patients dying in two years' time [7, 56]. Moreover, 5-year overall survival rate improvement has remained unaltered over the last decades, ranging from 17% to 75% [5-30]. In our review, the highest survival rate was found in all retrospective series from Japanese Institutions, which might be associated with reduced patients' local recurrences and aggressively treatment modalities carried out in their patients (**Table 4**) [5-30]. In contrast, our samples showed one of the lower overall survival rates, which might reflect the higher number of advanced-stage patients at the presentation and positive margins at the surgery when compared with other series [5-30]. Because of this, we also failed to find a significant association among gender, staging, treatment modality, orbital and intracranial invasion with prognosis (**Table 3**), as has been observed in the literature [14, 17, 20-22]. More studies with a large number of patients (multicentric studies) should be done to confirm these clinicpathological data as being of importance in predicting prognosis.

In summary, our study confirmed the findings about MxSSCC in terms of unfavorable prognosis, reduced survival rate and advanced stage of the disease at presentation, in special the second, as it has not been improving over the last decades. For this reason, multicentric randomized studies are essential and must be done to underlie the biology and best treatment options for this tumor.

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Disclosure of conflict of interest

None.

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