RESEARCH COMMUNICATION

Prognostic Factors in Patients with Malignant Salivary Gland Neoplasms in a Brazilian Population

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Abstract

Due to the difficulty of follow-up for long periods, information about the survival rates of malignant salivary gland tumors is deficient in the global scientific literature. This study was aimed at investigating the epidemiological profile and prognostic factors that might affect survival in patients with primary malignant salivary gland tumors in Brazil. Patients were investigated regarding histopathological subtypes, age, gender, anatomic localization, smoking and alcohol intake, tumor size, clinical stage, histological grade, recurrence, metastasis, and treatment on clinicopathological outcomes. Survival curves were generated using the Kaplan-Meier method, and both univariate and multivariate analyses were performed using the log rank test and Cox regression, respectively. A total of 63 cases were analyzed, females beingslightly predominant (50.8%), with ages ranging from 13 to 87 years. The most common diagnosis was adenoid cystic carcinoma and the most affected anatomical location was the parotid. Tumors were predominantly classified as stage I and high-grade at the diagnosis. The 5- and 10-year overall survival rates were 84.6% and 74.7%, respectively. Disease-free survival (DFS) rates were 71.6% (5 years) and 56.6% (10 years). Univariate analysis showed significant effects of tumor size and clinical stage on the DFS (P < 0.0001 for both), and Cox regression analysis confirmed clinical stage as an independent prognostic factor (P = 0.035). Our results highlight the relevance of clinical stage as an independent prognostic parameter for malignant salivary gland tumors.

Keywords: Salivary gland neoplasms - disease-free survival - prognostic factors

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Introduction

Primary malignant salivary gland tumors are relatively uncommon head and neck neoplasms. These malignancies are heterogeneous, with several different incidence patterns and clinicoepidemiological and histopathological features. They represent less than 3% of head and neck cancers and 10-15% of all glandular tumors (Tullio et al, 2001; Ansari, 2007). The annual estimated global average incidence rate is 0.9 (ranging from 0.4 to 13.5) per 100,000 persons (Ansari, 2007; Tian et al, 2010) and varies widely according to geographic area and ethnic group (Speight and Barrett, 2002; Drivas et al, 2007). The most affected sites are usually the parotid, submandibular, and minor salivary glands, and the most common histopathological diagnosis is mucoepidermoid carcinoma (Ansari, 2007; Speight and Barrett, 2002).

Due to its rarity and diverse histology, prognostic factors for malignant salivary gland tumors have been very difficult to elucidate. These tumors usually follow an uncertain clinical course with pronounced locoregional failure because they are relatively radioresistant (Bell et al, 2005). In addition, they are associated with high morbidity, mainly due to their interference with the ingestion of food and/or association with facial deformation (Ochicha et al, 2009).

Epidemiological investigations on the malignant salivary gland neoplasms are uncommon in Latin America, and the informations about the survival rates of these tumors are deficient in global scientific literature, generally due to the difficulty of follow-up for long periods. Thus, this study aims to document the epidemiological pattern of malignant salivary gland neoplasms diagnosed in a teaching hospital in Brazil, as well as to establish possible clinicopathological factors associated with prognosis through a survival analysis of the affected patients.

Materials and Methods

This retrospective study was conducted in a teaching hospital in Brazil. Throughout the 20-year period between 1990 and 2009, the medical files of patients diagnosed with malignant salivary gland neoplasms were analyzed to collect information concerning patient age, gender, smoking and alcohol intake history, tumor size, primary anatomic localization, clinical stage, histological grade,

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histopathological subtype, treatment, tumoral recurrences, metastases, disease-free survival (DFS) and overall survival (OS). After this analysis, we applied the following inclusion criteria: 1) sufficient clinicopathological data with sufficient follow-up (at least 6 months); 2) no previous history of head and neck cancer; 3) no initial or distant metastasis; 4) no prior oncologic therapy; and 5) histologically proven as a malignant salivary gland neoplasm according to the histological classification of the World Health Organization (WHO) (Barnes et al, 2005). All cases were carefully reviewed by two oral pathologists (LRO and DFS) and were staged according to the TNM classification (Wittekind et al, 2005). The study protocol was carried out with the approval of the local Human Research Ethics Committee.

Patients were classified as "current consumers" or "never consumers" of tobacco or alcohol for statistical analysis. Former consumers who had discontinued tobacco and/or alcohol consumption more than five years before diagnosis were included in the "never consumers" group (Lindhe et al, 2008). Individuals who used a cigarette, pipe, and/or cigar, or drank wine, beer, and/or other distilled drinks on a daily basis were considered to be "current consumers" (Oliveira et al, 2008). Similarly, patients were divided into age groups of ≤ 60 or > 60 years according to WHO criteria (Sarini et al, 2001).

Patients' features were summarized through descriptive statistics (mean and range for continuous variables and frequency and percentage for categorical variables). The recurrence and metastasis rates were analyzed relative to the investigated clinicopathological variables through cross tables using Fisher's (two variables) or $\chi 2$ (three or more variables) tests. The DFS was defined as the time from diagnosis until the occurrence of local recurrence or metastasis, and the OS was outlined as the interval between the diagnosis and the date of death (for uncensored observations) or the last date for which information was available (for censored observations). Univariate analyses were performed using the Kaplan-Meier method and log rank test to estimate and compare cumulative survival rates. Multivariate Cox proportional hazard regression was used to build models containing subsets of candidate risk factors with independent prognostic properties. All tests were two tailed, and P values ≤ 0.05 were considered significant.

Results

A total of 63 surgically treated cases of malignant salivary gland neoplasm met the inclusion criteria for this survey during the specified period. Of these tumors, 32 (50.8%) were in female patients and 31 (49.2%) were in male patients, with ages at diagnosis ranging from 13 to 87 years (mean, 55.3 years). The peak incidence occurred in the 5th decade of life (tumors in this decade accounted for 25.4% [16/63] of all cases). Histopathological

Table 1. Histopathological Subtypes, Gender, Age, Primary Anatomical Localization and Size of the Investigated Malignant Salivary Gland Neoplasms

Tumors	Total	Gender N (%)		Age Range	Average	Anatomical Site (%)			Min. and Max. Average	
		Male	Female	(years)		Parotid	Sub	Minor	Diameter	(cm)
ACC	19 (30.1)	7 (36.8)	12 (63.2)	14-72	(51.3)	6 (19.3)	7 (46.6)	6 (37.5)	0.2 - 7.0	(3.1)
MC	16 (25.4)	11 (68.7)	5 (31.3)	13-82	(55.4)	9 (29.0)	3 (20.0)	3 (18.7)	0.5 - 4.0	(2.5)
A.(nos)	8 (12.7)	5 (62.5)	3 (37.5)	41-87	(56.8)	1 (3.2)	3 (20.0)	4 (25.0)	0.3 - 3.4	(2.1)
ACA	6 (9.5)	4 (66.6)	2 (33.3)	17-82	(47.6)	6 (19.3)	0	0	2.5 - 7.0	(4.2)
Cex.PA	5 (7.9)	2 (40)	3 (60)	50-85	(73.0)	4 (12.9)	1 (6.6)	0	2.0 - 2.5	(2.2)
BCA	5 (7.9)	0	5 (100)	48-68	(59.0)	2 (6.4)	1 (6.6)	2 (12.5)	0.3 - 4.5	(3.5)
SDC	3 (4.8)	2 (66.6)	1 (33.3)	45-70	(59.3)	3 (9.7)	0	0	0.8 - 3.3	(2.9)
MYC	1 (1.6)	0	1 (100)	40		0	0	1 (6.2)	2.5	(2.5)
Total	63 (100)	31 (49.2)	32 (50.8)	13-87 (55.3)		31 (100)	15 (100)	16 (100)	0.2-7.0	(2.9)

Sub, Submandibular; Minor, Minor Salivary Gland; ACC, adenoid cystic carcinoma; MC, mucoepidermoid carcinoma; A(nos), adenocarcinoma not otherwise specified; ACA, acinic cell carcinoma; CexPA, carcinoma ex pleomorphic adenoma; BCA, basal cell adenocarcinoma; SDC, salivary duct carcinoma; MYC, myoepithelial carcinoma

Table 2. Drinking and Smoking Habits, Recurrence, and Metastases According to Histopathological Subtype

Tumors	Smoke (%)		Alcohol (%)		Recurrence (%)		Metastasis (%)	
	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)
ACC	6 (42.8)	13 (26.5)	5 (41.7)	14 (27.4)	6 (42.8)	13 (26.5)	6 (40.0)	13 (27.1)
MC	2 (14.3)	14 (28.6)	2 (16.7)	14 (27.4)	3 (21.4)	13 (26.5)	5 (33.3)	11 (22.9)
A(nos)	2 (14.3)	6 (12.2)	1 (8.3)	7 (13.7)	2 (14.3)	6 (12.2)	0	8 (16.6)
ACA	0	6 (12.2)	0	6 (11.8)	1 (7.1)	5 (10.2)	1 (6.7)	5 (10.4)
CexPA	2 (14.3)	3 (6.1)	3 (25.0)	3 (5.9)	1 (7.1)	4 (8.2)	0	5 (10.4)
BCA	0	5 (10.2)	0	5 (9.8)	1 (7.1)	4 (8.2)	2 (13.3)	3 (6.3)
SDC	1 (7.1)	2 (4.1)	1 (8.3)	2 (3.9)	0	3 (6.1)	1 (6.7)	2 (4.2)
MYC	1 (7.1)	0	0	0	0	1 (2.1)	0	1 (2.1)
Total	14 (100)	49 (100)	12 (100)	51 (100)	14 (100)	49 (100)	15 (100)	48 (100)

CC, adenoid cystic carcinoma; MC, mucoepidermoid carcinoma; A(nos), adenocarcinoma not otherwise specified; ACA, acinic cell carcinoma; CexPA, carcinoma ex pleomorphic adenoma; BCA, basal cell adenocarcinoma; SDC, salivary duct carcinoma; MYC, myoepithelial carcinoma

diagnosis also varied according to gender. The adenoid cystic carcinoma (ACC) was the most common salivary gland malignancy (30.2%), particularly in females (12 out of 19; 63.2%). The second most prevalent tumor was the mucoepidermoid carcinoma (MC) (25.4%), which was especially common in males (11 out of 16; 68.8%). Notably, the youngest patient (female, 13 years) was diagnosed with MC.

Most of the malignant salivary gland tumors originated from the parotid gland (31 out of 63; 49.2%). Those arising from minor salivary glands occurred mainly in the palate (7 out of 16; 43.8%). The submandibular gland was the third most common site of involvement (15 out of 63; 23.8%) and only one case was found in the sublingual gland (1.6%). The parotid glands predominantly gave rise to MC neoplasms (9 out of 31; 29%), whereas the minor and submandibular glands generally gave rise to ACC (6 out of 16; 37.5%, and 7 out of 15; 46.7%, respectively). Most tumors initially presented as T1/T2 in size (41 out of 63; 65%). Table 1 shows the distribution of primary anatomical localizations and histopathological types, as well as the gender, age, and tumor size of all neoplasms in our investigation.

The majority of patients reported that they did not consume tobacco and alcohol (46 out of 63; 73%). Five (7.9%) reported tobacco consumption alone, three (4.8%) reported alcohol consumption alone, and nine patients reported concomitant tobacco and alcohol use (14.3%) (Table 2). Most tumors were diagnosed as high-grade (33 out of 63; 52.4%), whereas 19 (30.1%) and 11 (17.5%) presented as intermediate and low-grade malignant neoplasms, respectively. Surgical therapy was performed in all patients, 31 (49.2%) of whom received surgical therapy alone whereas the remaining patients (32; 50.8%) were given adjuvant radio- and/or chemotherapeutic treatments. The overall rates of recurrence, metastasis, and death were 22.2%, 23.8%, and 23.8%, respectively. Among the patients who developed metastases (15 out of 63; 23.8%), nine (60%) out of 15 had cervical metastasis and six (40%) were affected by distant metastases, which in turn occurred predominantly in the lungs and bones (two cases each). There were 23 patients (36.5%) with stage I, 18 (28.5%) with stage II, nine (14.3%) with stage III, and 13 (20.7%) with stage IV tumors.

Among all histopathological subtypes, the ACC tumors showed the highest rates of recurrence, metastasis, and death (42.8%, 40%, and 33.3%, respectively). However, there were no significant differences in recurrence and metastasis rate (P = 0.786 and P = 0.429, respectively) or length of survival (OS, P = 0.957; DFS, P = 0.939) according to histopathological subtype.

Furthermore, we did not identify any significant influence on tumoral recurrences for gender (P = 0.274), age (P = 0.102), primary anatomical localization (P = 0.641), tobacco and/or alcohol consumption (P = 0.793), histological grade (P = 0.891), tumor size (P = 0.201), or treatment type (P = 0.109). Similarly, metastasis was not correlated with gender (P = 0.108), age (P = 0.088), primary anatomical localization (P = 0.393), tobacco and/or alcohol consumption (P = 0.907), histological grade (P = 0.265), tumor size (P = 0.115), or treatment type (P = 0.432).

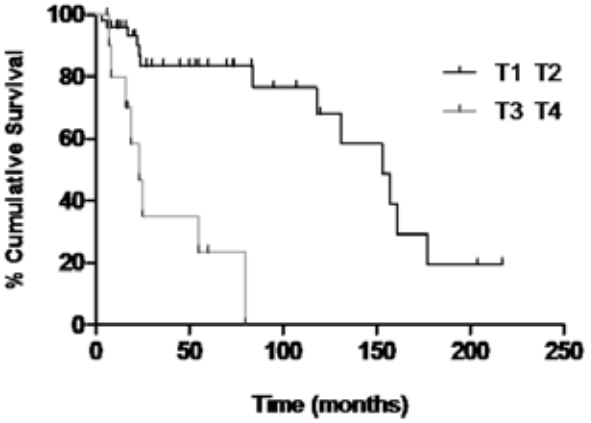

Figure 1. Kaplan-Meier Plots of Cumulative Disease Free Survival According to Grade

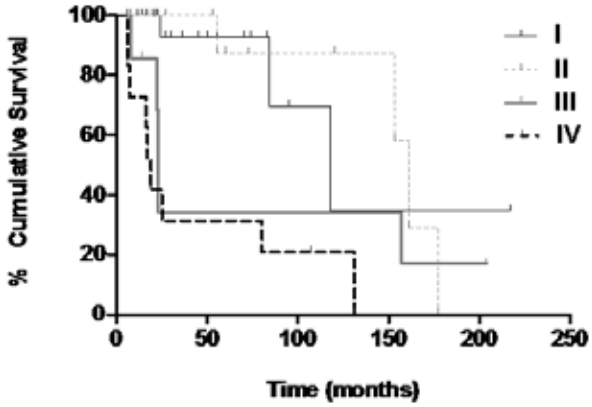

Figure 2. Kaplan-Meier Plots of Cumulative Disease Free Survival According to Stage

The follow-up times in this study ranged from six to 260 months. The median survival of this cohort was 179 months, and the 5- and 10-year OS were 84.6% (SE 5.6%) and 74.7% (SE 8.4%), respectively. The DFS rates were 71.6% (SE 6.9%) and 56.6% (SE 9.5%) for 5 and 10 years, respectively. Using the Kaplan-Meier survival analysis with the log rank test, we found that patients diagnosed with T3/T4 tumor, as well as those in stage IV, had a significantly poorer DFS than others with smaller or less advanced tumors (P < 0.0001 for both). These results are shown in Figures 1 and 2, respectively. However, no significant association was found between tumor size/stage and OS rate (tumor size, P = 0.132; clinical stage, P = 0.142).

The parotid gland was the anatomical site with the poorest rates of OS and DFS (5 year OS and DFS = 71.7% and 70%, respectively), but anatomic localizations proved not to be a statistically significant factor (OS, P = 0.765; DFS, P = 0.445), nor did the histopathological subtype of the tumor (OS, P = 0.958; DFS, P = 0.939). Similarly, none of the other clinicopathological variables investigated showed any statistically significant correlations in univariate survival analyses: age (OS, P = 0.459; DFS, P = 0.757), gender (OS, P = 0.716; DFS, P = 0.956), tobacco and/or alcohol consumption (OS, P = 0.219; DFS, P = 0.547), histological grade (OS, P = 0.424; DFS, P = 0.770), and treatment (OS, P = 0.929; DFS, P = 0.166).

Multivariate survival analysis via the Cox proportional

Table 3. Results of Cox Regression Analysis Regarding Clinical Stages in Salivary Gland Neoplasms

Clinical Stage	Cases n (%)	SE	HR	5-yr OS (%)	5-yr DFS (%)	P value
I	23 (36.5)	1.32	0.58	92.9	88.8	
II	18 (28.5)	1.62	2.58	87.5	84.2	0.035
III	9 (14.3)	2.69	8.51	75.0	34.3	
IV	13 (20.7)	1.46	8.62	62.8	31.2	

Tumors staged according to Wittekind et al (2005).

hazards model confirmed clinical stage as a unique independent prognostic factor. Stage IV tumors had a hazard ratio 8.6 times that of stage I, II, and III tumors (P = 0.035; HR 8.62; 95% confidence interval 0.21-35.85). Although tumor size had a significant effect according to log rank test, this effect was not supported by the Cox model. The multivariate analysis for clinical stages is shown in Table 3.

Discussion

The epidemiological distribution pattern of primary malignant salivary gland tumors differ between countries, in part due to their infrequency and histopathological diversity. Moreover, prognostic factors for these neoplasms are difficult to assess because they are one of the most heterogeneous groups of cancers, their clinical progression is usually slow and stealthy, and long-term follow-up is required to establish factors that influence clinical outcome.

There is little consensus in the literature regarding the gender prevalence of these tumors. Although most studies have shown some kind of difference in frequency between gender, i.e., the tumors were more predominant in males (Capote Moreno et al, 2005; Ito et al, 2005) or females (Vargas et al, 2002; Ochicha et al, 2009; Tilakaratne et al, 2009), several studies (Kokemueller et al, 2004; Lima et al, 2005; Ansari, 2007; Tian et al, 2010), including this one, have found no difference in prevalence between genders. Our finding that these cancers peak in incidence between the ages of 40 and 49 is in agreement with a majority of authors (Tilakaratne, 2009; Tian et al, 2010), and the mean age determined here is very close to that found by others (Tullio et al, 2001; Bell et al, 2005).

In previous studies performed in Brazil, the MC was the most frequently identified tumor (Vargas et al, 2002; Ito et al, 2005). In contrast, the most common tumor found in our investigation was the ACC. Nevertheless, our findings are consistent with research conducted in many different countries (Satko et al, 2000; Masanja et al, 2003; Kokemueller et al, 2004; Lima et al, 2005; Luukkaa et al, 2005; Subhashraj, 2008; Tian et al, 2010), and some of the discrepancies found may be due to revisions in diagnostic criteria of histopathological classification for salivary gland tumors that may have contributed to apparent changes in their prevalence (Barnes et al, 2005). This is a potential bias that could influence the identification of the most frequent histopathological subtype. According to Tilakaratne et al. (2009), some high-grade MCs may be diagnosed as squamous cell carcinomas or unspecified adenocarcinomas, reducing the apparent prevalence of MC.

Consistent with all large investigations of salivary gland tumors, the parotid gland was the most common primary anatomical location of malignant neoplasms, and the MC was the most frequent tumor type in this location (Subhashraj, 2008; Tian et al, 2010). The palate was the most frequently affected region among minor glands, again in agreement with previous studies (Vargas et al, 2002; Ito et al, 2005; Subhashraj, 2008; Ochicha et al, 2009; Tilakaratne et al, 2009). In addition, in contrast to other studies performed in Brazil (Vargas et al, 2002; Ito et al, 2005), we found one case of MC in the sublingual gland.

Malignant salivary gland lesions tend to exhibit an occult symptomatology, leading to late diagnosis at an advanced clinical stage (Rapidis et al, 2004). Although the average size of the primary tumors in our study was 2.9 cm, the wide variation found is in agreement with the results of Vargas et al (2002), and the predominant initial presentation of tumors as T1/T2 (65%) was different from other reports (Rapidis et al, 2004; Capote Moreno et al, 2005).

The evaluation of the smoking and drinking habits of patients in the present study was stimulated due to the lack of investigation into potential risk factors for malignant salivary gland tumors. A monograph published by the IARC (International Agency for Research on Cancer) could not classify tobacco as a salivary gland carcinogen because of insufficient data (Yach, 2005). Although a few investigations of smoking and heavy alcohol consumption have shown evidence for a positive association (Hayes et al, 1999; Horn-Ross et al, 2007), our findings just indicated a small proportion of patients exposed to smoking (22.2%) and alcohol consumption (19%) in malignant salivary gland tumors.

In agreement with the scientific literature, our findings showed that a surgical therapeutic approach was generally taken to treat malignant salivary gland tumors, with adjuvant radio- and/or chemotherapy regimens use to manage those patients with advanced neoplasms (Bell et al, 2005). The recurrence rate observed here (22.2%) was very close to that reported elsewhere (Bell et al, 2005; Capote Moreno et al, 2005; Lima et al, 2005). On the other hand, there is a lack of consensus in the literature regarding the true incidence of cervical lymph node metastasis, ranging from 14.6% to 53% (Stennert et al, 2003; Ansari, 2008). We found a low incidence of cervical metastasis (9 out of 63 patients; 14.3%), very close to the rate found by Ansari (2007) (14.6%). Similarly, the distant metastasis rate in this study (6 out of 63; 9.5%) was slightly smaller than that found by Bell et al. (2005) (12.9%).

The DFS (71.6% and 56.6% for 5 and 10 years, respectively) and OS (84.6% and 74.7% for 5 and 10 years, respectively) rates found here were higher than those reported elsewhere, likely due to the low metastasis rate in this study (Satko et al, 2000; Tullio et al, 2001; Capote Moreno et al, 2005; Lima et al, 2005; Subhashraj, 2008). Capote Moreno et al (2005) noted a relatively poorer prognosis, with DFS (51.8% and 43.2% for 5 and 10 years, respectively) and OS (74.9% and 63% for 5 and 10 years, respectively) rates lower than those found here. On the

other hand, the five year DFS rate reported by Bell et al. (2005) was higher (77%). Nevertheless, all these results must be interpreted with caution, because recurrence after a long period (more than 10 years), as well as late mortality, are characteristics of many malignant salivary gland tumors.

Although the ACC have demonstrated the highest recurrence and metastasis rates of all salivary gland tumors, there were no significant differences between the histopathological subtypes (P = 0.786 and P = 0.429, respectively). There is a disagreement in the literature concerning the prognostic significance of the different histopathological subtypes of malignant salivary gland tumors. In some studies it has been shown to be a strong prognostic indicator (Kokemueller et al, 2004; Lima et al, 2005). However, this could not be confirmed in our investigation (OS, P = 0.958; DFS, P = 0.939) which, in agreement with others, suggests that this factor does not seem to act as a major prognostic factor in these tumors (Spiro et al, 1991; Renehan et al, 1999; Hocwald et al, 2001; Speight and Barrett, 2009). In the same way, age, gender, smoking and alcohol consumption, primary tumor location, histological grade, and treatment did not significantly influence the prognosis of patients in terms of survival rate (DFS and OS) and the rate of recurrence and metastasis.

In agreement with several studies, we were able to recognize significant differences in clinical outcome based on tumor size (T) and clinical stage (TNM) of disease (Renehan et al, 1999; Hocwald et al, 2001; Kokemueller et al, 2004; Bell et al, 2005; Capote Moreno et al, 2005; Lima et al, 2005; Luukkaa et al, 2005; Speight and Barrett, 2009). These clinicopathological factors were significantly correlated with DFS rates in our evaluation (P < 0.0001 for both), with smaller tumors (T1/T2) and early clinical stages (I/II) showing better prognosis. To date, Hocwald et al. (2001) have presented similar findings with respect to tumor size features and DFS rates. Additionally, the clinical stage at diagnosis proved to be an independent prognostic factor as shown by multivariate analysis, confirming some previous studies (Bell et al, 2005; Lima et al, 2005).

Our findings showed that several clinicopathological features in malignant salivary gland tumors were comparable to those found in other geographical locations. However, few investigations have examined prognostic factors that could affect the behavior of these neoplasms through long-term survival analysis in scientific literature. The univariate analysis in our study confirmed that clinical characteristics such as tumor size and stage can be used to predict a poor outcome, but could not validate the prognostic utility of histopathological subtype or other clinicopathological variables. It has clearly been established that T1 and T2 tumors less than 4 cm in size commonly have a good prognosis regardless of any other features (Renehan et al, 1999; Speight and Barrett, 2009).

The presented results highlight the importance of clinical stage as an independent prognostic parameter for the prediction of tumor behavior and therapeutic choice according to initial presentation at diagnosis, to pursue a surgical conservative approach or then a more aggressive adjuvant treatment with wide tumoral resection plus radio- and chemotherapy.

The identification of clinicopathological factors associated with prognosis in this heterogeneous disease may provide additional data for comparison with other studies of patients from distinct geographical regions and ethnicities, helping to guide and standardize therapeutic procedures. Similar investigations or prospective multi-center clinical evaluations should be conducted to contribute to a more successful and efficient management of malignant salivary gland tumors.including the use of calcium with Vitamin D, calcitonin, testosterone in men, the SERMs in females, and most effectively by use of bisphosphonates (Heaney, 1989; Reid, Hughes et al., 2000). Most recently the efficacy, safety and superiority of humanized monoclonal antibody Denosumab for Prevention of Fractures in patients with Osteoporosis has been established (Cummings, Martin et al., 2009; Smith, Egerdie et al., 2009). Assessment of the bone density is ideally done by bone mineral density, however if used appropriately a CT can also be render clinically useful images and in appropriate setting such as, CT-based finite elements study , can accurately predict bone strength (Bessho, Ohnishi et al., 2007).

Compromised bone health has dramatic impact on general health, poses a significant burden on society and results in increasing cost of health care (Ethgen, Tellier et al., 2003). Unfortunately proper emphasis on the issue is not suggested effectively by the general guidelines in cancer treatment which suggest high dose steroid therapies (NCCNetwork, 2009). It has been assessed that in patients with bony metastasis who have fear of fracture are generally more concerned about their quality of life then their health care providers, who generally attempt to handle current symptoms (Harris, Chow et al., 2009).

It remains a challenge to make the bone health assessment of patients who present for cancer care an integral part of management so that an essentially preventable and treatable condition like osteoporosis is dealt with before it causes a sequence of complications originating from poor bone health.

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