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Survival Probabilities Related to Histology, Grade and Stage in Patients With Salivary Gland Tumors

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Abstract. *Background: The diversity of malignant salivary gland tumors challenges the study of survival rates. The current study evaluated patient survival rates using Kaplan–Meier analysis and examined the relative effects of histology, grade and stage on survival. Materials and Methods: Using the Kaplan–Meier model, cancer-specific (CSS) and disease-free (DFS) survival probabilities were calculated as a function of time. Results: Of 101 patients, 79 survived and 22 died of their disease. The probability of CSS was 0.83, 0.73 and 0.61 at 5, 10 and 15 years, respectively; corresponding probability of DFS was 0.69, 0.59 and 0.54, respectively. Conclusion: CSS and the DFS probabilities in patients with salivary malignancies were quite high at 5 years, although these rates dropped over the long-term; the lethal effect of the malignancy is often delayed and prolonged. Tumor histology, grade and stage are well established factors in predicting prognosis. Although the subgroups of patients with MECA and SCC were too small to allow adequate statistical analysis, clear tendencies for devastating effects of poor differentiation in SCC and higher grade in MECA were shown. That is, 2/4 patients with high-grade MECA died from their disease, while only 1/15 with low-intermediate grade MECA died from their disease. Similarly, 2/4 patients with poorly differentiated SCC died from their disease, while only 1/5 with well-to-moderately-differentiated SCC died from their disease. Factors such as molecular markers should be further studied in an effort to improve prognosis prediction.*

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Key Words: Salivary tumors, survival, stage, grade, histology.

The diversity of malignant salivary gland tumors in their histopathology and in a variety of other characteristics challenges the study of survival rates and treatment outcomes. Many studies over the years have reported variable rates of overall (1-3) and disease-free (DFS) (4-6) survival for patients with malignant salivary gland tumors.

Assessment of prognostic factors in salivary gland cancer is difficult, since these tumors are characterized by a low incidence and an enormous morphological heterogeneity with different clinical courses. Subtypes such as acinic cell carcinomas or polymorphous low-grade adenocarcinomas present an excellent prognosis with a 5-year survival of about 75-100% (7). Rare subtypes such as salivary duct carcinomas or undifferentiated carcinomas are associated with low 5-year survival rates of about 20-50% (8).

However, in spite of the numerous studies published concerning the factors affecting the prognosis of patients with salivary tumors, including various molecular aberrations which have been suggested to compromise prognosis (9-15), the topic is still controversial and far from well established. Aside from histological type, often mentioned prognostic factors include: age, stage, grade, gender, pain level, skin and soft-tissue infiltration, facial nerve involvement, perineural growth, resection status and comorbidities (16-19). Prognosis of salivary gland cancer in children and adolescents is much more favorable than in adults. The 5-year overall survival rate for children after curative surgery is about 95% compared to 60% for adults (20, 21). This is probably due to moderate tumor growth with well-differentiated histology, absence of extension into adjacent tissues and lower frequency of neck node metastasis, although positive lymph nodes are reported in 10-30% (20, 21).

A review published by Jeannon *et al.* in 2009 showed the clear correlation among advanced tumor size, high-grade histopathology and poor prognosis (with only 35% overall

Table I. *Prevalence of tumor by type in patients who died from their disease and those who survived.*

Tumor type	Died (N=22), n (%)	Survived (N=79), n (%)	Total (N=101), n
All tumors (%)			
MECA (all grades)	6 (27.3)	22 (27.8)	28
ACC	8 (36.4)	17 (21.5)	25
SCC (all)	4 (18.3)	6 (7.6)	10
PLGA	1 (4.6)	8 (10.1)	9
Acinic cell carcinoma	1 (4.6)	6 (7.6)	7
Adenocarcinoma NOS	1 (4.6)	5 (6.3)	6
Basal cell adenocarcinoma	0	1 (1.3)	1
Cribriform cystic adenocarcinoma*	0	1 (1.3)	1
Salivary duct carcinoma	0	2 (2.5)	2
Carcinoma ex PA	1 (4.6)	4 (5.1)	5
PA[#]	0	4 (5.1)	4
Ep. myoepithelial carcinoma	0	1 (1.3)	1
Myoepithelial carcinoma	0	2 (2.5)	2
MECA			
Non specified	3 (13.6)	5 (6.3)	8
Low grade	0	6 (7.6)	6
Intermediate grade	1 (4.6)	8 (10.1)	9
High grade	2 (9.1)	2 (2.5)	4
Intra-osseous	0	1 (1.3)	1
SCC			
Non specified	1 (4.6)	0	1
Poorly differentiated	2 (9.1)	2 (2.5)	4
Moderately differentiated	0	1 (1.3)	1
Well differentiated	1 (4.6)	3 (3.4)	4

ACC: Adenoid cystic carcinoma; PA: pleomorphic adenoma; NOS: not otherwise specified; SCC: squamous cell carcinoma; MECA: mucoepidermoid carcinoma; PLGA: polymorphous low-grade adenocarcinoma; *low grade; [#]with squamous metaplasia.

survival rate) in patients with parotid malignant tumors (22). Spiro *et al*. showed in 2001 how the clinical stage in general and tumor size in particular highly influence prognosis and survival (23). Furthermore, tumor size was suggested by Speight *et al*. to be a critical predictive factor, more important than histopathological grade (24). Speight's group introduced their '4 cm rule' to the professional world – claiming that stage III and IV tumors which are larger than 4 cm in diameter will always have a worse prognosis, regardless of their histopathological type and regardless of the existence of neck metastasis (24). They maintained that malignant tumors larger than 4 cm in diameter are considered an absolute indication for administration of postoperative adjuvant radiotherapy, and also that the tumor size (specifically T3 and T4 tumors) is considered an independent prognostic factor with negative impact on survival (25-27). According to the results published in 2011 by the Danish Head and Neck Cancer Group, disease-specific survival rate decreases dramatically for patients diagnosed with T3 and T4 tumors, and recurrence rates are significantly increased in these patients (28).

The purpose of the current study was to evaluate the survival rates of patients with different salivary malignancies using Kaplan–Meier analysis and to examine the relative effect that histology, grade and stage have on survival.

Materials and Methods

In the current study, we analyzed data for all 101 consecutive patients who received definitive therapy for malignant salivary gland tumors at Rambam Medical Center in Haifa, Israel. We did not exclude any patient who was diagnosed with malignant salivary gland cancer. This study was a retrospective one involving patient records. Since the patients were not directly involved and it would not be possible to identify any from the data in this article, approval from the Institutional Ethics Committee and informed-consent forms were not necessary

Statistical evaluation and Kaplan–Meier survival analysis. The statistical analysis was performed using STATA 12.0 software (Stata Corp LLC, TX, USA).

The various categorical variables, numbers and percentages were calculated. The distributions for the categorical variables between the two study groups (the surviving patients as compared to the patients who died due to their disease), were compared and analyzed by the chi-square test (a parametric test) or by Fisher–Irwin exact test (a non-parametric test for small numbers). The Kaplan–Meier model was used to calculate the probability of cancer-specific survival (CSS) and the probability of DFS as a function of time. The differences between the Kaplan–Meier survival curves were tested for significance by the log-rank test.

All statistical tests were analyzed to a significance level of 0.05.

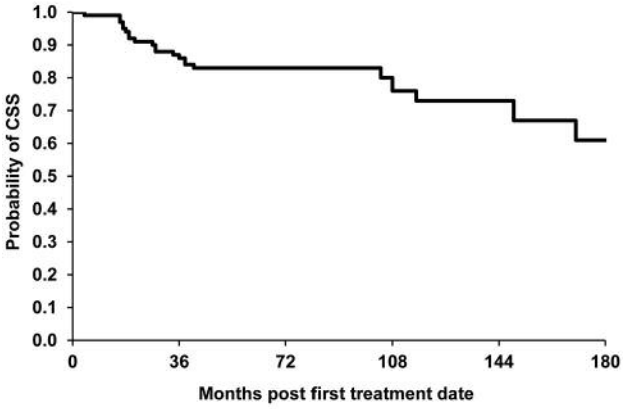

Figure 1. *Probability of cancer-specific survival (CSS) of all study patients with primary salivary tumor. Median survival was 206 months.*

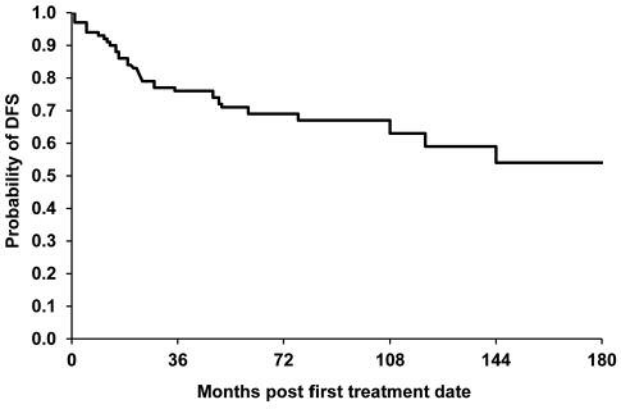

Figure 2. *Probability of disease-free survival (DFS) of all study patients with primary salivary tumors. Median survival not calculable.*

Results

Patients, prevalence of tumors, grade and stage. In the current study, we analyzed data for 101 patients who received definitive therapy for malignant salivary gland tumors at Rambam Medical Center in Haifa, Israel. Of the 101, 79 survived and 22 died due to their disease (Table I). These patients were followed-up for up to 15 years post therapy whenever possible.

The most prevalent group was mucoepidermoid carcinoma (MECA) with 28 patients, followed by adenoid cystic carcinoma, squamous cell carcinoma (SCC), polymorphous low-grade adenocarcinoma, acinic cell carcinoma and adenocarcinoma groups. These six groups of salivary malignancies were responsible for 85 of the patients. The other 16 patients belonged to one of the other seven tumor categories (including 1-5 patients in each group), as shown in Table I. Of these smaller groups, the carcinoma ex pleomorphic group was the most prevalent one, with five patients, while other groups such as basal cell adenocarcinoma and cribriform cystic adenocarcinoma were rather rare, with only one patient each (Table I).

Two of the most prevalent tumor groups, the MECA and the SCC groups were further divided into subgroups according to the histological grade or level of differentiation (Table I).

Further division of each histological group into patients who survived the disease following adequate therapy and those who died of their disease revealed no statistical difference in the distribution as related to the specific tumor type involved. For example, 27.3% of patients who died from their disease had MECA and an almost identical percentage, 27.8%, of those who survived also had MECA (Table I). Of note is the observation that the distribution of major malignant salivary gland tumors in the current study was similar to and typical of other previously published reports (29, 30).

The probability of CSS of all patients with salivary malignant tumors. The probability of CSS at 5 years was 0.83 [95% confidence intervaI (CI)=0.73-0.89]), at 10 years it was 0.73 (95% CI=0.57-0.83) and at 15 years it was 0.61 (95% CI=0.41-0.77) (Figure 1).

The probability of DFS of patients with malignant salivary gland tumors. The probability of DFS at 5 years was 0.69 (95% CI=0.58-0.78), at 10 years it was 0.59 (95% CI=0.44-0.71), and at 15 years it was 0.54 (95% CI=0.37-0.68) (Figure 2).

The probability of CSS of patients with MECA. The probability of CSS at 5 years was 0.81 (95% CI=0.56-0.93), at 10 years it was 0.68 (95% CI=0.32-0.87) and at 15 years it was 0.68 (95% CI=0.32-0.87) (Figure 3).

The probability of CSS of patients with adenoid cystic carcinoma. The probability of CSS at 5 years was 0.67 (95% CI=0.42-0.83), at 10 years it was 0.67 (95% CI=0.42-0.83) and at 15 years it was 0.45 (95% CI=0.10-0.76) (Figure 4).

The probability of CSS of patients with SCC. There were 10 patients with SCC who lived 3 months to 12.4 years. The probability of CSS at 5 years was 0.63 (95% CI=0.24-0.87), at 10 years it was 0.63 (95% CI=0.24-0.87) and at 15 years it was 0 (Figure 5).

The probability of CSS of patients with polymorphous low-grade adenocarcinoma (PLGA). There were nine patients with PLGA tumor type who lived 59 to 178 months. The

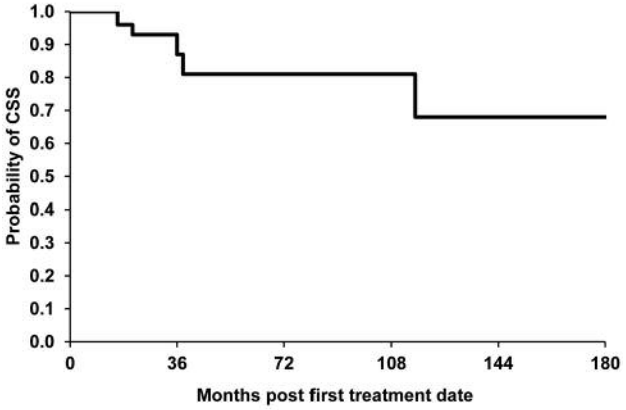

Figure 3. *Probability of cancer-specific survival (CSS) of patients with mucoepidermoid adenocarcinoma. Median survival not calculable.*

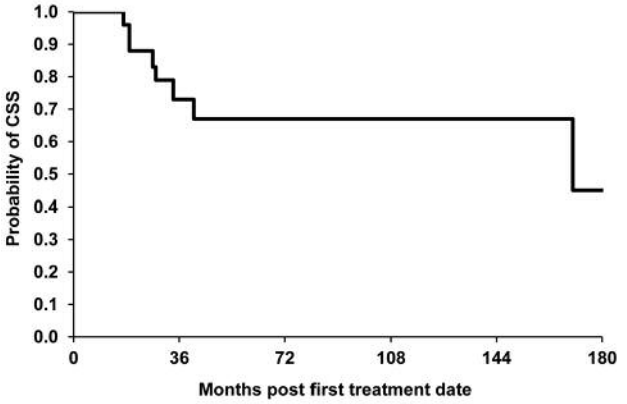

Figure 4. *Probability of cancer-specific survival (CSS) of patients with adenoid cystic carcinoma. Median survival was 170 months.*

probability of CSS at 5 years was 1.00, at 10 years it was 0.83 (95% CI=0.27-0.97) and at 15 years it was 0.83 (95% CI=0.27-0.97) (Figure 6).

Although the subgroups of patients with MECA and SCC were too small to allow adequate statistical analysis, clear tendencies for devastating effects of poor differentiation in SCC and higher grade in MECA were shown. That is, 2/4 patients with high-grade MECA died from their disease, while only 1/15 with low-intermediate grade MECA died from the disease. Similarly, 2/4 patients with poorly differentiated SCC died from their disease, while only 1/5 with well-to moderately differentiated SCC died from the disease (Table I).

Discussion

The overall rates for DFS and CSS rates that we report here are quite in agreement with previous reports, *i.e.* at 60 months they were 0.69% and 0.83% respectively and at 180 months they were 0.54% and 0.61% respectively:

Bell *et al.* showed disease-free survival rates and locoregional control rate at 5 years of 77% and 86%, respectively. Stage, grade, cervical lymph node metastasis and age were found to make a statistically significant contribution to outcome. They showed that neither site, presence of positive margins nor perineural invasion had a significant impact on survival. Bell *et al.* concluded that the treatment of salivary gland malignancies remains primarily surgical, although adjunctive radiotherapy may play an important role in patients with advanced-stage disease (31).

The role of chemotherapy in the management of patients with salivary gland cancer is evolving. Various chemotherapeutic regimens are currently used for palliation of advanced-stage tumors. Yet there is no demonstrated benefit in the

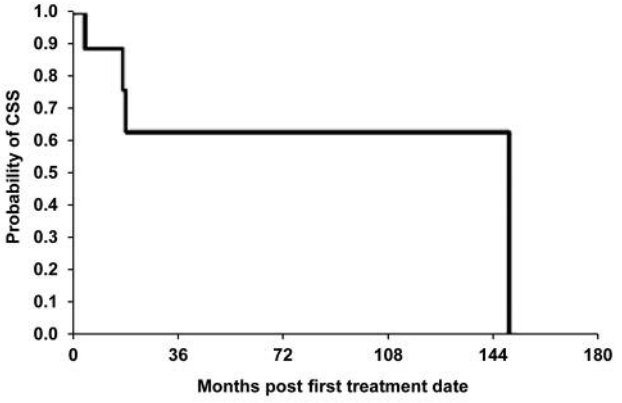

Figure 5. *Probability of cancer-specific survival (CSS) of patients with squamous cell carcinoma. Median survival was 149 months.*

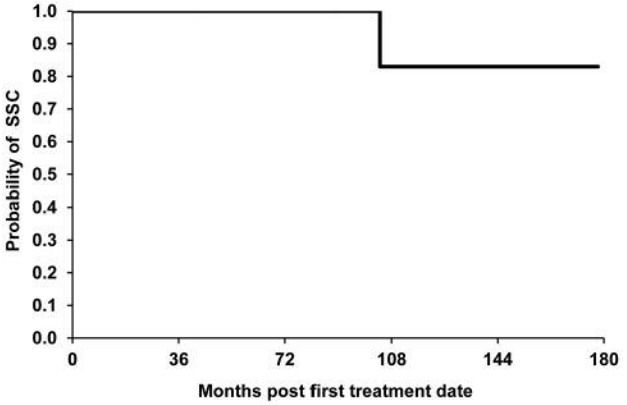

Figure 6. *Probability of squamous cell carcinoma (SCC) patients with polymorphous low-grade adenocarcinoma. Median survival not calculable.*

Table II. *Overall survival probabilities*.

	CSS at						
	5 Years		10 Years		15 Years		
Overall	Survival probability	95% CI	Survival probability	95% CI	Survival probability	95% CI	*p*-Value*
MECA	0.81	0.56-0.93	0.68	0.32-0.87	0.68	0.32-0.87	
ACC	0.67	0.42-0.83	0.67	0.42-0.83	0.45	0.10-0.76	0.5046[a]
SCC	0.63	0.24-0.87	0.63	0.24-0.87	0		0.0831[a]
							0.2420[b]
PLGA	1.00		0.83	0.27-0.97	0.83	0.27-0.97	0.3529[a]
							0.0917[b]
							0.0215[c]

ACC: Adenoid cystic carcinoma; MECA: mucoepidermoid carcinoma; SCC: squamous cell carcinoma; PLGA: polymorphous low-grade adenocarcinoma; CI: confidence interval. *Log-rank test (between survival graphs): *vs*. [a]MEGA, [b]ACC, [c]SCC.

induction or adjuvant setting. The response rates associated with combination therapy, most commonly cyclophosphamide, doxorubicin and cisplatin, are higher than those with a single agent (32).

Management of the N0 neck in patients with malignant salivary gland tumors is still controversial. There is a lack of consensus on the rate of cervical metastasis, which can reach 53% (33), and that of occult metastasis has been reported to be from 8% to 19% (33-36). In 2013, Herman *et al*. found that patients with cN0 high-grade salivary gland carcinomas who were to undergo surgery and postoperative RT likely do not benefit from a planned neck dissection (37).

The long-term survival rate of patients with minor salivary gland malignant tumors is high. Evaluating the prognostic factors and the efficacy of treatment is more complex: Li *et al*. evaluated the treatment outcome of 103 patients with minor salivary gland carcinomas of the hard palate treated with surgery alone or with combined surgery and postoperative radiotherapy. The most common histological types were adenoid cystic carcinoma and MECA. Overall survival rates at 5 and 10 years were 77.9% and 65.7%, respectively, with recurrence-free survival and CSS of 77.9%. There was no significant difference in overall survival, recurrence-free survival and CSS between patients who underwent surgery alone and those who underwent surgery plus post-operative radiotherapy (38). Surgery is the primary treatment for minor salivary gland carcinoma of the hard palate. Sufficient surgical excision with adequate margins is essential for a favorable outcome. In the current study, we also noted a tendency for diversity in CSS probabilities among the different types of malignancies, especially in the long-term where patients with adenoid cystic carcinoma fared more poorly and those with PLGA fared better. This difference in CSS probabilities between these two groups of patients was highly significant. These rates at 5 years for patients with MECA, adenoid cystic carcinoma, SCC and PLGA were 0.81, 0.67, 0.63 and 1.00, respectively, while at 15 years they dropped to 0.68, 0.45, 0.63 and 0.83, respectively (Table II). This tendency is reflected in the mortality rates as given in Table I where among the patients who died, 36.4% were diagnosed with adenoid cystic carcinoma, while only 21.5% of the surviving patients were diagnosed with this malignancy. This pattern was reversed in the case of PLGA, for which only 4.6% of patients who died had this diagnosis as compared to 10.1% of the surviving patients.

In summary, one can conclude from the currently presented data that the CSS and the DFS probabilities in salivary malignancies were quite high at 5 years (0.69-0.83), higher than, for example, in oral cancer (39). However, these rates dropped over the long-term and at 15 years they reached 0.54-0.61; this shows that in salivary gland cancer, the lethal effect of malignancy is often delayed and prolonged. Tumor histology, grade and stage certainly play a role in predicting prognosis; however, other factors such as molecular markers should be further studied for their role in an effort to improve prognosis prediction.

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