Journal of Cancer Research and Clinical Oncology (2019) 145:2123–2130
https://doi.org/10.1007/s00432-019-02953-9

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Kaplan–Meier analysis of salivary gland tumors: prognosis and long-term survival

Yair Israel[1] · Adi Rachmiel[1] · Konstantin Gourevich[2] · Rafael Nagler[1]

Received: 25 March 2019 / Accepted: 7 June 2019 / Published online: 11 June 2019

Abstract

Purpose We evaluated the impact of various tumor related parameters on survival probability in a cohort of patients with malignant salivary tumors, using the Kaplan–Meier analysis.

Methods We measured patients up to 15 years following therapy, looking at T N M stage, grade perineural invasion and extra-parenchymal spread.

Results Of 101 patients diagnosed with various salivary malignant tumors in our medical center, 79 patients survived while 22 died with disease (DWD). The impact of distant metastasis (M+) was devastating (survival probability at 60 months and at 180 months dropped from 0.93 (M−) to 0.40 (M+) and from 0.67 to 0.40, respectively, $p=0.0001$), the impact of perineural invasion was severe (at 180 months the probability of survival dropped from 0.75 to 0.21, $p=0.002$). Higher stage tumor also decreased survival (from 0.82 to 0.53 at 180 months, $p=0.002$) as did poor histological grade (from 0.85 to 0.48 at 180 months, $p=0.019$). Neck metastasis (N+) impact was quite moderate (at 180 months the probability of survival dropped from 0.69 to 0.58, $p=0.044$) while neither tumor size (T) nor extra-parenchymal spread significantly affected survival.

Conclusions Salivary tumor location and its potential to infiltrate nerves and blood vessels and to metastasize is the most telling parameter. Systemic therapy aimed at halting distant metastatic spread is the most effective therapeutic goal. Dissection of N0 neck metastasis is not necessarily a valuable treatment.

Keywords Salivary tumors · Survival · Prognosis · Kaplan–Meier · Perineural · Extra-parenchymal

Introduction

Malignant salivary gland tumors are a heterogeneous and highly diverse group, widely studied and debated. They include many groups and subgroups of tumors found in major and minor salivary glands, and various sub-locations (Speight and Barrett 2009; Bjorndal et al. 2012; Li et al. 2012; Lobo et al. 2018). These tumors differ widely from each other in histology, clinical manifestation and responsiveness to various modes of therapy. Some are almost benign in their natural behavior while others are extremely aggressive (Guzzo et al. 2010; Seethala 2017; Carlson and Schlieve 2019). The treatment of choice is based on surgical removal of the tumor, sometimes supplemented with a form of adjuvant therapy including neck dissection for removal of neck metastasis. Radiotherapy may be aimed at the tumor site and or the neck, while chemotherapy is sometimes added (Renehan et al. 1999; Terhaard et al. 2004; Nakano et al. 2016).

The role and significance of neck involvement and extent of lymphatogenous metastatic spread from salivary gland malignancies is still controversial (Eppsteiner et al. 2017; Munhoz et al. 2019). Obviously, clinically positive lymph nodes should be removed by a neck dissection, together with the resection of the tumor. However, treatment of the neck may not be mandatory and especially not in all N0 cases (no evidence for neck metastasis) (Kopec et al. 2015). The frequency of nodal involvement and associated risk factors are

Yair Israel and Adi Rachmiel had contributed equally.

✉ Rafael Nagler
nagler@tx.technion.ac.il

[1] Department of Oral and Maxillofacial Surgery, Rambam Medical Center, Faculty of Medicine, Rappaport Family Institute for Research in the Medical Sciences, Technion-Israel Institute of Technology, 31096 Haifa, Israel

[2] Department of Nuclear Medicine, Rambam Medical Center, Faculty of Medicine, Rappaport Family Institute for Research in the Medical Sciences, Technion-Israel Institute of Technology, 31096 Haifa, Israel

constantly being studied and evaluated (Nobis et al. 2014; Kopec et al. 2015). Another parameter often discussed with respect to prognosis is perineural involvement, which is a well-recognized clinicopathologic entity found in salivary gland malignancies. Perineural invasion (PNI) and spread (PNS), also known as neurotopism, describes the growth of a tumor around or through a nerve. An important distinction has been made in the literature between PNI, a microscopic finding of tumor cells infiltrating or associated with small nerves (which cannot be radiologically imaged) and PNS, the presence of gross tumor spread along a nerve, at least in part distinct from the main tumor mass. For example: adenoid cystic carcinoma (ACC) has less of a tendency for PNI and more for PNS, whereas polymorphous adenocarcinoma (PAC) and salivary duct carcinoma (SDC) have a tendency for PNI rather than PNS (Witt 1999; Johnston et al. 2012). Another parameter considered important in its ability to affect patient outcome is extra-parenchymal extension. Clinical or macroscopic extra-parenchymal extension (invasion of soft tissue and nerve) upgrades the tumor size (T value) to T3 regardless of the tumor's maximal diameter or size Barnes et al. 2005; Walvekar et al. 2011). A Korean (Cho et al. 2016) study of 134 cases of low-grade salivary gland cancer found 45 to have presence of extra-parenchymal extension. The study showed how post-operative radiotherapy significantly reduces recurrence rates in cases with a pathologic feature such as extra parenchymal extension. A study from Stodulski et al. (2012) showed how histologically positive extra-parenchymal extension worsens prognosis by 4–5 times.

The purpose of the current study was to evaluate the impact of various tumor-related parameters on the survival probability of a representative cohort of patients with salivary malignant tumors, using the Kaplan–Meier analysis, considered the most powerful, non-parametric statistical tool for estimating the survival function from life-time data.

Methods

We collected available data for 101 patients diagnosed with a variety of malignant salivary tumors. These patients had been admitted to and treated at Rambam Medical Center in Haifa, Israel. Due to the retrospective nature of this study, Rambam Medical Center's Ethics Committee did not require board approval and patient consent was not necessary. We measured the surviving patients up to 15 years following therapy, examining T N M stage, grade, perineural invasion and extra-parenchymal spread. The aim of our research was to investigate the impact of the T N M stage, grade perineural invasion and extra-parenchymal spread on survival rates and patient prognosis. In the introduction section we detailed the role of surgical removal, neck dissection, radiation and chemotherapy in cases of salivary gland malignancies. In this section we describe the effect of neck dissection and radiotherapy on survival—a subject which is still controversial and under argument. The treatment options for salivary gland malignancy are very well studied and reported; therefore, our focus is presently on the influence of tumor-related parameters on patient survival.

Statistical evaluation and Kaplan–Meier survival analysis

The statistical analysis was performed using the STATA 12.0 software.

For the categorical variables, numbers and percentages were calculated. The distributions for the categorical variables between the two study groups 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 disease-free survival (DFS) as a function of time. The differences between the K&M curves were tested for significance by the log-rank test.

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

Results

Patients, prevalence of tumors, grade and stage

Of the 101 patients, 79 survived while 22 died with disease (DWD). The distribution of the various sorts of tumors was typical of previously published studies (Guzzo et al. 2010; Seethala 2017; Carlson and Schlieve 2019) and their specific prevalence in both the DWD patients and the surviving patients (the "Other" group) was not significantly different (data not shown). The most prevalent group of tumors was mucoepidermoid carcinoma (MECA), followed by adenoid cystic carcinoma (ACC), squamous cell carcinoma (SCC), polymorphous low-grade adeno-carcinoma, acinic cell carcinoma and adeno carcinoma groups. These six tumor groups were included in 85 of the 101 patients, with MECA and ACC most prevalent (28 and 25 patients, respectively). The other four tumor groups had 5–10 patients in each. Finally, the remaining 16 patients belonged to seven other tumor groups with 1–5 patients in each. Carcinoma ex pleomorphic was found in five patients while other cancers such as basal cell adeno carcinoma and cribriform cyst adeno carcinoma were found in only one patient.

Of the 101 patients, 17 had distant metastasis (M+) as depicted in Table 1a, b. Almost half of the patients (10/22)

Table 1 Summary of tumor parameters and metastasis by study group

(A) Tumor parameters	DWD *N* = 22 *n* (%)	Other *N* = 79 *n* (%)	*p* value
Distant metastasis (M+)			
Yes	10 (45.5)	7 (8.9)	┣0.0001**
No	12 (54.5)	72 (91.1)	
(B) Tumor parameters	DWD and M+ *N* = 10 *n* (%)	Other and M+ *N* = 7 *n* (%)	Total *N* = 17 *n* (%)
Tumor (%)			
Mucoepidermoid carcinoma	3 (30.0)		3 (17.6)
Adenoid cystic carcinoma	6 (60.0)	5 (71.4)	11 (64.7)
Squamous cell carcinoma	1 (10.0)		1 (5.9)
Polymorphous low-grade adeno carcinoma		1 (14.3)	1 (5.9)
Adeno carcinoma		1 (14.3)	1 (5.9)

p value by ┣Chi square test

p value by ┻Fisher exact test ($p = 0.2360$ NS)

who died due to the disease [(DWD) belonged to the M+ subgroup while only about 10% (7/79) of the patients who did not die due to the disease ("other" group, Table 1a, b] had distant metastasis (Table 1a). The relationship between distant metastasis and negative outcome is depicted in Table 1b according to tumor groups. While no statistically meaningful results may be drawn from the relatively small number of cases involved (no. = 17), it is noteworthy that all 3 cases of mucoepidermoid carcinoma with distant metastasis died from the disease, and the distribution of patients diagnosed with adenoid cystic carcinoma and had distant metastasis was almost equal. In other words, of 11 patients who had adenoid cystic carcinoma and distant metastasis (by far the largest group with M+), 6 died from the disease and 5 survived (Table 1b).

Cancer-specific survival (CSS) probabilities

The probability of cancer-specific survival (CSS) of patients with small tumor size (≤ 4 cm) at 60 months (5 years) was 0.86 [with 95% CI of (0.75–0.92)]. The probability of CSS of patients with large tumor size (> 4 cm) at 60 months was 0.64 [with 95% CI of (0.28–0.86)]. The probability of CSS of patients with small tumor size (≤ 4 cm) at 180 months was 0.70 [with 95% CI of (0.47–0.84)]. The probability of CSS of patients with large tumor size (> 4) at 180 months was 0.64 [with 95% CI of (0.28–0.86)]. The difference was not significant ($p = 0.1752$) (Fig. 1a), nor was the difference with respect to CSS among the T size subgroups divided to 4 [tumor size (≤ 2, 2 ≤ 4, 4 ≤ 6, > 6 cm)] (Table 2).

The analysis of the various subgroups of patients with salivary tumors by tumor size included the following:

1. Tumor size (≤ 2), 41 patients with small T size ≤ 2 cm. Tumor size (2 to ≤ 4), 36 patients with T size between 2 ≤ 4 cm.
2. Tumor size (4 to ≤ 6), 12 patients with T size between 4 ≤ 6 cm.
3. Tumor size (> 6), 4 patients with T size larger than 6 cm.

The probability of CSS of patients with neck metastasis (N+) at 60 months (5 years) was 0.58 [with 95% CI of (0.33–0.77)]. The probability of CSS with no neck metastasis (N−) at 60 months was 0.89 [with 95% CI of (0.78–0.95)].

The probability of CSS of patients with N+ at 180 months (15 years) was 0.58 [with 95% CI of (0.33–0.77)]. The probability of CSS with N− at 180 months was 0.69 [with 95% CI of (0.46–0.84)]. The difference is significant ($p = 0.0440$) (Fig. 1b).

The probability of CSS of patients with distant metastasis (M+) at 60 months (5 years) was 0.40 [with 95% CI of (0.17–0.62)]. The probability of CSS with M− at 60 months was 0.93 [with 95% CI of (0.84–0.97)]. The probability of CSS of patients with M+ at 180 months (15 years) was 0.40 [with 95% CI of (0.17–0.62)]. The probability of CSS with M− at 180 months was 0.67 [with 95% CI of (0.42–0.83)]. The difference was significant ($p = 0.0001$) (Fig. 1c).

The probability of CSS of patients with low stage (1 + 2) at 60 months (5 years) was 1.00. The probability of CSS with high stage (3 + 4) at 60 months was 0.69 [with 95% CI of (0.53–0.80)]. The probability of CSS of patients with low stage (1 + 2) at 180 months was 0.82 [with 95% CI of (0.42–0.96)]. The probability of CSS with

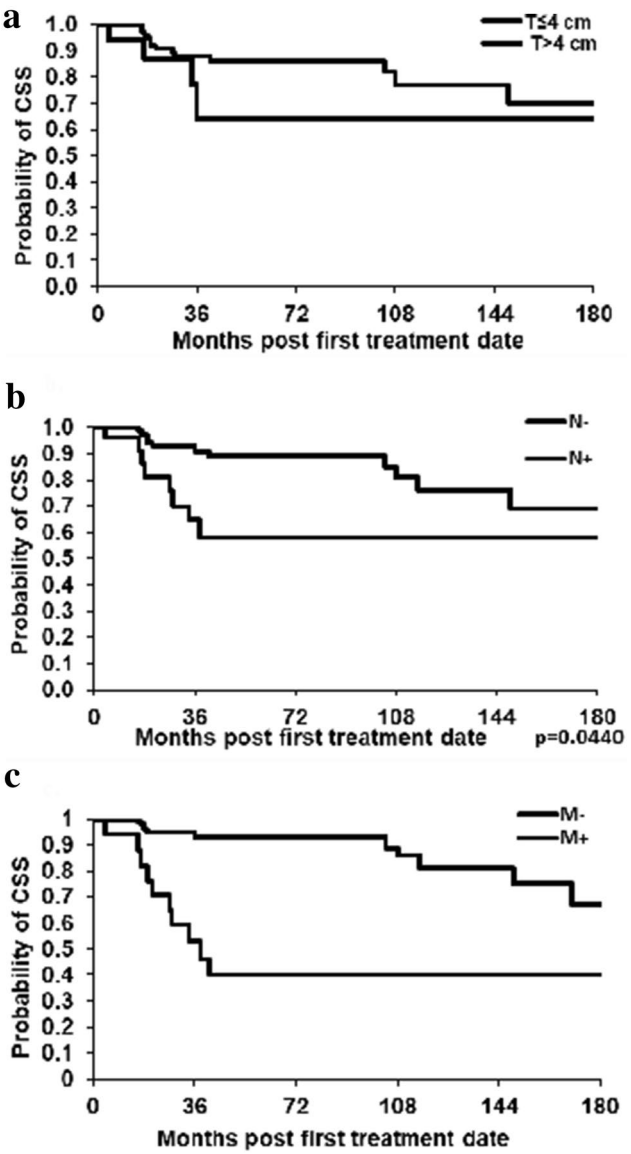

Fig. 1 Probability of cancer-specific survival (CSS) of patients with salivary tumors by **a** tumor size (T); **b** neck metastasis (N); and **c** distant metastasis (M)

high stage (3 + 4) at 180 months was 0.53 [with 95% CI of (0.30–0.72)]. The difference is significant ($p = 0.0020$) (Fig. 2).

The probability of CSS of patients with low grade at 60 months (5 years) was 1.00. The probability of CSS with high grade at 60 months was 0.73 [with 95% CI of (0.59–0.83)]. The probability of CSS of patients with low grade at 180 months was 0.85 [with 95% CI of (0.51–0.96)]. The probability of CSS with high grade at 180 months was 0.48 [with 95% CI of (0.23–0.70)]. The difference is significant ($p = 0.01910$) (Fig. 3).

Low grade—there were 23 patients with low-grade (level = 1) primary malignant disease.

High grade—there were 68 patients with high-grade (level = 3) primary malignant disease.

The probability of CSS of patients with perineural invasion at 60 months (5 years) was 0.69 [with 95% CI of (0.46–0.83)]. The probability of CSS with no perineural invasion at 60 months was 0.90 [with 95% CI of (0.78–0.95)].

The probability of CSS of patients with perineural invasion at 180 months (15 years) was 0.21 [with 95% CI of (0.01–0.56)]. The probability of CSS with no perineural invasion at 180 months was 0.75 [with 95% CI of (0.49–0.89)]. The difference was significant ($p = 0.0020$) (Fig. 4a). There were 29 patients with perineural invasion.

The probability of CSS of patients with extra-parenchymal invasion at 60 months (5 years) was 0.65 [with 95% CI of (0.42–0.80)]. The probability of CSS with no extra-parenchymal invasion at 60 months was 0.90 [with 95% CI of (0.79–0.95)]. The probability of CSS of patients with extra-parenchymal invasion at 180 months was 0.65 [with 95% CI of (0.42–0.80)]. The probability of CSS with no extra-parenchymal invasion at 180 months was 0.74 [with 95% CI of (0.50–0.88)]. The difference is not significant ($p = 0.1162$) (Fig. 4b).

Discussion

The Kaplan–Meier analysis enabled us to see the impact of seven different indices/parameters on the outcome of salivary cancer: T N M stage, grade, perineural invasion and extra-parenchymal spread. These numbers detailing the probability of survival up to a 15-year time point, followed the commonly administered therapy that is based on surgery, radiotherapy and, sometimes, adjuvant chemotherapy. A Kaplan–Meier curve enables one to be immediately impressed by both the severity and the dynamics of the analyzed effect on survival.

The impact of distant metastasis (M+) was devastating (the probability of survival at 60 months and at 180 months dropped from 0.93 to 0.40 and 0.67 to 0.40, respectively, $p = 0.0001$). The impact of perineural invasion was severe as well (the probability of survival dropped from 0.75 at 60 months to 0.21 at 180 months, $p = 0.002$). There were also significant decreases in survival probability in patients with higher stage (from 0.82 to 0.53 at 180 months, $p = 0.002$) and in patients with poorer histological grade (from 0.85 at 60 months to 0.48 at 180 months, $p = 0.019$). In contrast, the impact of neck metastasis (N+) was quite moderate (from 0.69 at 60 months to 0.58 at 180 months, $p = 0.044$), and there was no significant impact on survival probability due to either tumor size (T) or extra-parenchymal spread. However, larger tumors did show a limited tendency towards decreasing the probability of survival as did

Table 2 Cancer-specific survival of patients by tumor size and salivary tumors

Primary-cancer specific survival (CSS)				
Tumor size	1 (≤2)	2 (2≤4)	3 (4≤6)	4 (>6)
Patients	41	36	12	4
Event: died with disease (pts)	7	7	2	2
No event: died from other cause	1	1	2	
No event: censored	33	28	8	2
Range (months)	[3–222]	[12–196]	[10–180]	[4–43]
CSS at 12 months (1 year)	1.00	1.00	1.00	0.75 (95% CI [0.13–0.96])
CSS at 24 months (2 years)	0.95 (95% CI [0.81–0.99])	0.86 (95% CI [0.69–0.94])	0.90 (95% CI [0.47–0.99])	0.75 (95% CI [0.13–0.96])
CSS at 36 months (3 years)	0.92 (95% CI [0.78–0.97])	0.82 (95% CI [0.65–0.92])	0.77 (95% CI [0.34–0.94])	0.38 (95% CI [0.01–0.81])
CSS at 60 months (5 years)	0.89 (95% CI [0.73–0.96])	0.82 (95% CI [0.65–0.92])	0.77 (95% CI [0.34–0.94])	
CSS at 120 months (10 years)	0.80 (95% CI [0.52–0.93])	0.75 (95% CI [0.51–0.88])	0.77 (95% CI [0.34–0.94])	
CSS at 180 months (15 years)	0.64 (95% CI [0.26–0.86])	0.75 (95% CI [0.51–0.88])	0.77 (95% CI [0.34–0.94])	

$p = 0.1648$ (log rank test)

Comparing the probability of cancer-specific survival of patients with primary malignant disease by the four levels of tumor size (≤2, 2≤4, 4≤6, >6 cm). The difference is not significant ($p = 0.1648$)

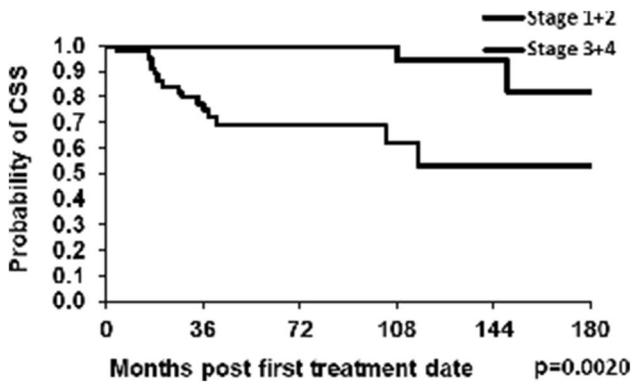

Fig. 2 Probability of cancer-specific survival (CSS) of patients with salivary tumors by stage

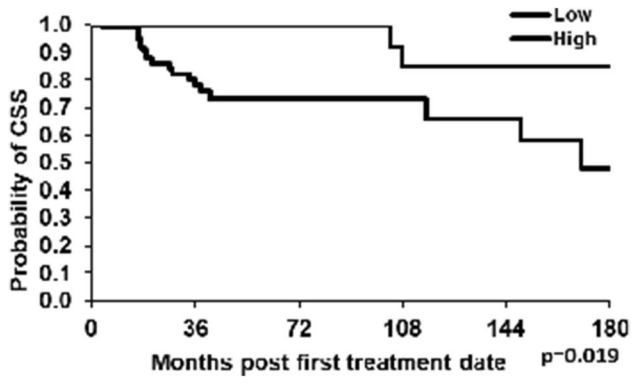

Fig. 3 Probability of cancer-specific survival (CSS) of patients with salivary tumors by grade

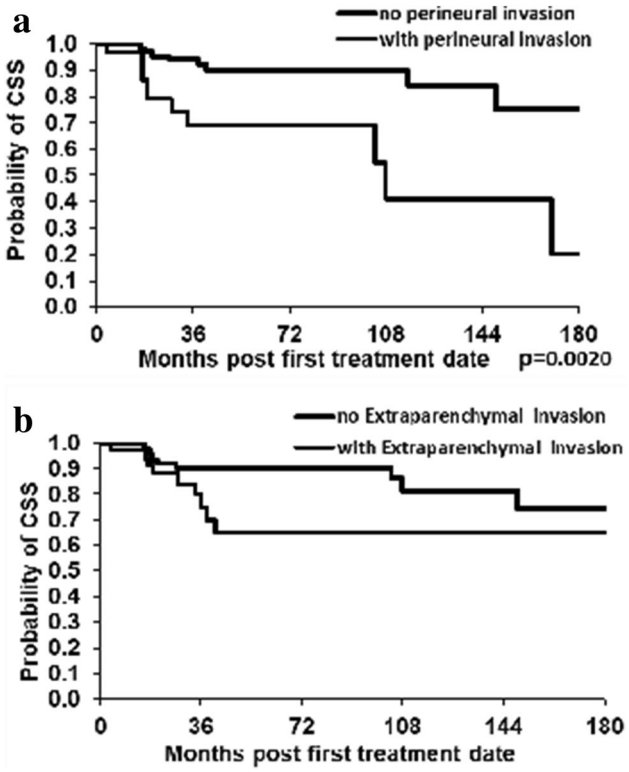

Fig. 4 Probability of cancer-specific survival (CSS) of patients with salivary tumors by **a** perineural invasion; **b** extra-parenchymal invasion

extra-parenchymal spread (both, as previously mentioned, not reaching statistical significance).

Perineural invasion and spread is an important characteristic feature of adenoid cystic carcinoma and it corresponds

to the common clinical finding of pain in these patients. Sometimes, the cells appear to have a swirling arrangement around nerve bundles. However, it is not pathognomonic only for adeno cystic carcinoma; this may also be seen in other salivary malignancies, especially polymorphous adenocarcinomas. Several studies have shown that microscopic identification of perineural invasion has little effect on prognosis (Neville 2008). However, most studies show that perineural involvement has implications on locoregional disease diagnosis and management (Frankenthaler et al. 1991; Inouye et al. 2017; D'heygere et al. 2018).

Because of the extensive neural pathway system, malignant tumors of the major salivary glands have many routes by which they can invade cranial nerves and intracranial structures. Perineural spread has a significant, negative impact on treatment and prognosis, because it requires more extensive surgical resection and adversely affects treatment outcome. Patients who have perineural spread often have tumor recurrence, so that long-term survival is jeopardized. Many treatment failures are related to unrecognized perineural tumor invasion (Frankenthaler et al. 1991). McHugh et al. (2012) studied the prognostic factors of mucoepidermoid carcinoma. They showed that perineural invasion together with positive lymph nodes, extracapsular lymph node spread and advanced stage were all found to be poor prognostic indicators. They demonstrated how high-grade mucoepidermoid carcinoma has a higher tendency to invade the nerves than do low- and intermediate-grade illness.

Johnston et al. (2012) reported a case of salivary duct carcinoma of the parotid gland that extended centrifugally along the inferior alveolar nerve through the mandibular foramen. Magnetic resonance imaging (MRI) is the most useful and reliable imaging for identifying neural involvement. Computed tomography (CT) can assist by evaluating bony erosion or enlargement of foramina and canals.

As for distant metastasis, the very devastating effect that distant metastasis had on survival probability in our patients may be explained by hematogenous rather than lymphogeneous spread of the metastasis to remote sites. This finding suggests the need to develop systemic therapeutic solutions to counter hematogenous metastatic spread, obviously in addition to the known established local/regional available tools. We feel that choosing to develop in this direction is further supported by the relatively low impact that neck metastasis had in our patients, which further ignites the debate surrounding the need to treat N0 necks (where no neck metastasis is found clinically or by imaging).

The management of N0 neck is still not under consensus as estimating the risk for neck occult disease is difficult. Kruse et al. (2010) advocated that the benefit of elective neck dissection for patient with low-grade malignant tumor is insignificant. However, some researchers believe that many patients should be advocated for elective neck dissection for any salivary gland malignancy (Kopec et al. 2015).

Spiro (2001) introduced the consensus that exists regarding the predictors for occult neck metastasis risk: unfavorable histology, pathologic grade, stage and size of the primary lesion. Stennert et al. (2003) showed high rates of cervical metastasis (in 53% of the malignant salivary gland tumors). Herman et al. (2013) studied the benefit of elective neck dissection prior to radiotherapy for patients with high-grade salivary gland cancer and cN0. Occult metastases were found in 18 (44%) of the 41 patients in the elective neck dissection group. This group had a 10% recurrence rate. It was concluded that patients with cN0 high-grade salivary gland carcinomas who are planned for surgery and postoperative RT are not likely to benefit from a planned neck dissection.

Therefore, it seems that neck metastasis is to be treated when positive (based on clinical and/or imaging) and in certain cases even when negative. Our results supported this approach as, neck metastasis certainly did worsen prognosis, but to a rather limited extent especially when compared to either distant metastasis or perineural invasion.

Our results relating to the reduced importance of both tumor size (the T indicator) and extra-parenchymal spread were unexpected, considering the traditional "respect" given by clinicians to tumor size (T value). For example, Spiro showed in 2001 that the clinical stage, particularly tumor size, highly influences prognosis and survival rate. In another study, T stage was a significantly more predictive factor than histological grade of the specific tumor (Speight and Barrett 2009). In some studies it was reported that stage III and IV tumors which are larger than 4 cm in size (with or without nodal involvement) have worse prognosis and outcomes, regardless of their histological type. Therefore, malignant tumors larger than 4 cm were considered an absolute indication for postoperative adjuvant radiotherapy (McGurk 2001; Slevin and Frankenthaler 2001); stage, specifically stages III and IV, is considered an independent prognostic factor with negative impact on survival. Disease-specific survival rates decrease dramatically in up to 40% and recurrence rate is significantly higher for T3 and T4 tumors (Bjorndal et al. 2012). Review by Jeannon et al. (2009) showed the clear relationship between advanced T stage, high-grade parotid malignant tumors and poor prognosis with 35% overall survival rates.

In our study both the T and the extra-parenchymal spread did not significantly decrease survival probability, probably due to the fact that specific location of the tumor is more important than its size. If the tumor is located near major deep blood vessels, as in the case of the parotid deep lobe, then its potential for metastasizing is greater, as is its lethality. Similarly, a tumor located in the parotid gland is in far more intimate contact with blood vasculature than one located within an encapsulated or palatal minor gland; thus

the former is expected to be more lethal. Another problem with the concept of extra-parenchymal spread is that the boundaries of the tumor are not always clear and the margins within a wide spread parenchymal gland such as the parotid are not well defined. Thus, this may affect the statistical significance of the results as the deviation of the results is quite significant. It is worthwhile to note that the proximity to the margins of the resected tumor and the clinical outcome are well associated. While often the type of the tumor is considered an important factor prediction prognosis, in the current study we found salivary SCC to be relatively more prevalent than usually reported in other series. In the current study we also included both low- and high-grade malignancies, which may be regarded as an issue of concern (Badlani et al. 2018; Radomski et al. 2018).

In summary, the results of the current study demonstrate clearly that the two most important factors related to prognosis of salivary malignant tumors are distant metastasis and perineural invasion. The effect of the first is rapid and the survival probability of the patients drops to its lowest within the first 3 years, while the effect of perineural invasion, though more prolonged, is also devastating. The dynamics of perineural invasion are much slower, so that its full effect is revealed only at a delayed time point of up to 15 years. Following these two parameters were tumor grade and stage which also negatively and significantly decreased survival probability and also demonstrated a gradual and prolonged dynamic. In contrast, neck metastasis had only a limited, albeit significant, negative impact on survival, while neither tumor size nor extra-parenchymal spread had a significant effect (apart from showing a rather limited negative tendency). We conclude that the location of the salivary tumor and its potential to infiltrate nerves and blood vessels and to metastasize are weightier parameters than its size and potential spread to the neck lymph nodes. Furthermore, tumor of minor salivary glands, especially in the sino-nasal tract and skull-base, typically fares worse than those of major salivary glands. Two other potentially important prognostic predictors should be examined in a future study: the proximity of the margins of resected tumors and immune-histochemical analysis for various markers (Schmitt et al. 2014; Ranjbar et al. 2019). Perhaps the topic of therapy should undergo rethinking, where mandatory treatment of N0 neck would be exchanged for systemic therapy aimed at distant metastatic spread.

Funding This study did not receive funding of any kind.

Compliance with ethical standards

Conflict of interest Yair Israel declares no conflict of interest, financial or otherwise, relating to this study. Adi Rachmiel declares no conflict of interest, financial or otherwise, relating to this study. Konstantin Gourevich declares no conflict of interest, financial or otherwise, relating to this study. Rafael Nagler declares no conflict of interest, financial or otherwise, relating to this study.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent forms were not necessary for this study, as the study had no effect on patient management or identification.

References

Badlani J, Gupta R, Balasubramanian D, Smith J, Luk P, Clark J (2018) Primary salivary gland malignancies: a review of clinicopathological evolution, molecular mechanisms and management. ANZ J Surg 88(3):152–157. https://doi.org/10.1111/ans.14201

Barnes L, Eveson JW, Reichart P (2005) World Health Organization classification of tumors: Pathology and genetics of head and neck tumors. IARC Press, Lyon

Bjorndal K, Krogdahl A, Therkildsen MH, Overgaard J, Johansen J, Kristensen CA, Homøe P, Sørensen CH, Andersen E, Bundgaard T et al (2012) Salivary gland carcinoma in Denmark 1990–2005: outcome and prognostic factors. Results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncol 48:179–185

Carlson ER, Schlieve T (2019) Salivary gland malignancies. Oral Maxillofac Surg Clin N Am 31:125–144

Cho JK, Lim BW, Kim EH, Ko YH, Oh D, Noh JM, Ahn YC, Baek KH, Jeong HS (2016) Low-grade salivary gland cancers: treatment outcomes, extent of surgery and indications for postoperative adjuvant radiation therapy. Ann Surg Oncol 23:4368–4375

D'heygere E, Meulemans J, Vander Poorten V (2018) Salivary duct carcinoma. Curr Opin Otolaryngol Head Neck Surg 26:142–151

Eppsteiner RW, Fowlkes JW, Anderson CM, Robinson RA, Pagedar NA (2017) Aggressive salivary malignancies at early stage: outcomes and implications for treatment. Ann Otol Rhinol Laryngol 126(7):525–529. https://doi.org/10.1177/0003489417702655

Frankenthaler RA, Luna MA, Lee SS, Ang KK, Byers RM, Guillamondegui OM, Wolf P, Goepfert H (1991) Prognostic variables in parotid gland cancer. Arch Otolaryngol Head Neck Surg 117:1251–1256

Guzzo M, Locati LD, Prott FJ, Gatta G, McGurk M, Licitra L (2010) Major and minor salivary gland tumors. Crit Rev Oncol Hematol 74:134–148

Herman MP, Werning JW, Morris CG, Kirwan JM, Amdur RJ, Mendenhall WM (2013) Elective neck management for high-grade salivary gland carcinoma. Am J Otolaryngol 34:205–208

Inouye CM, Anagnostou V, Li QK (2017) Primary parotid adenocarcinoma metastasis to the spleen with PIK3CA mutation: cytological findings and review of the literature. Int J Clin Exp Pathol 10:5999–6005

Jeannon JP, Calman F, Gleeson M, Tan IB, Keus RB, Hart AA (2009) Management of advanced parotid cancer. A systematic review. Eur J Surg Oncol. 35:908–915

Johnston M, Yu E, Kim J (2012) Perineural invasion and spread in head and neck cancer. Expert Rev Anticancer Ther 12:359–371

Kopec T, Mikaszewski B, Jackowska J, Waśniewska-Okupniak E, Szyfter W, Wierzbicka M (2015) Treatment of parotid malignancies—10 years of experience. J Oral Maxillofac Surg 73:1397–1402

Kruse AL, Gratz KW, Obwegeser JA, Lubbers HT (2010) Malignant minor salivary gland tumors: a retrospective study of 27 cases. Oral Maxillofac Surg 14:203–209

Li Q, Zhang X-R, Liu X-K, Liu Z-M, Liu W-W, Li H, Guo Z-M (2012) Long-term treatment outcome of minor salivary gland carcinoma of the hard palate. Oral Oncol 48:456–462

Lobo R, Hawk J, Srinivasan A (2018) A review of salivary gland malignancies: common histologic types, anatomic considerations, and imaging strategies. Neuroimaging Clin N Am 28:171–182

McGurk M (2001) Management of salivary gland cancer: clinically or pathologically based? Overview. In: McGurk M, Renehan A (eds) Controversies in the management of salivary gland disease. Oxford University Press, Oxford, pp 155–161

McHugh CH, Roberts DB, El-Naggar AK, Hanna EY, Garden AS, Kies MS, Weber RS, Kupferman ME (2012) Prognostic factors in mucoepidermoid carcinoma of the salivary glands. Cancer 118:3928–3936

Munhoz L, Ramos EADA, Im DC, Hisatomi M, Yanagi Y, Asaumi J, Arita ES (2019) Application of diffusion-weighted magnetic resonance imaging in the diagnosis of salivary gland diseases: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. https://doi.org/10.1016/j.oooo.2019.02.020

Nakano K, Sato Y, Sasaki T, Shimbashi W, Fukushima H, Yonekawa H, Mitani H, Kawabata K, Takahashi S (2016) Combination chemotherapy of carboplatin and paclitaxel for advanced/metastatic salivary gland carcinoma patients: differences in responses by different pathological diagnoses. Acta Otolaryngol 136:948–951

Neville BW (2008) Oral and maxillofacial pathology, 3rd edn. Saunders/Elsevier, St. Louis

Nobis CP, Rohleder NH, Wolff KD, Wagenpfeil S, Scherer EQ, Kesting MR (2014) Head and neck salivary gland carcinomas—elective neck dissection, yes or no? J Oral Maxillofac Surg 72:205–210

Radomski S, Dermody S, Harley EH Jr (2018) Clinical characteristics and outcomes of major salivary gland malignancies in children. Laryngoscope 128(5):1126–1132. https://doi.org/10.1002/lary.26946

Ranjbar MA, Ranjbar Z, Zahed M, Nikookar N (2019) CD73 a novel marker for the diagnosis of benign and malignant salivary gland tumors. J Clin Exp Dent 11(3):e213–e218. https://doi.org/10.4317/jced.54918

Renehan AG, Gleave EN, Slevin NJ, McGurk M (1999) Clinicopathological and treatment-related factors influencing survival in parotid cancer. Br J Cancer 80:1296–1300

Schmitt AC, McCormick R, Cohen C, Siddiqui MT (2014) DOG1, p63, and S100 protein: a novel immunohistochemical panel in the differential diagnosis of oncocytic salivary gland neoplasms in fine-needle aspiration cell blocks. J Am Soc Cytopathol 3(6):303–308

Seethala RR (2017) Salivary gland tumors: current concepts and controversies. Surg Pathol Clin 10(1):155–176

Slevin N, Frankenthaler R (2001) The role of radiotherapy in the management of salivary gland cancer. In: McGurk M, Renehan A (eds) Controversies in the management of salivary gland disease. Oxford University Press, Oxford, pp 163–172

Speight PM, Barrett AW (2009) Prognostic factors in malignant tumours of the salivary glands. Br J Oral Maxillofac Surg 47:587–593

Spiro RH (2001) Factors affecting survival in salivary gland cancers. In: McGurk M, Renehan A (eds) Controversies in the management of salivary gland disease. Oxford University Press, Oxford, pp 143–150

Stennert E, Kisner D, Jungehuelsing M, Guntinas-Lichius O, Schröder U, Eckel HE, Klussmann JP (2003) High incidence of lymph node metastasis in major salivary gland cancer. Arch Otolaryngol Head Neck Surg 129:720–723

Stodulski D, Mikaszewski B, Stankiewicz C (2012) Are all prognostic factors in parotid gland carcinoma well recognized? Eur Arch Otorhinolaryngol 269:1019–1025

Terhaard CH, Lubsen H, Van der Tweel I, Hilgers FJ, Eijkenboom WM, Marres HA, Tjho-Heslinga RE, de Jong JM, Roodenburg JL, Dutch Head and Neck Oncology Cooperative Group (2004) Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. Head Neck 26:681–692

Walvekar RR, Filho PAA, Seethala RR, Gooding WE, Heron DE, Johnson JT, Ferris RI (2011) Clinicopathologic features as stronger prognostic factors than histology or grade in risk stratification of primary parotid malignancies. Head Neck 33:225–231

Witt RL (1999) Facial nerve function after partial superficial parotidectomy. Otolaryngol Head Neck Surg 121:210–213