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ORIGINAL PAPER

# Mortality rates and prognostic factors in patients with malignant salivary tumors

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## Abstract

Malignancies of the salivary glands represent a multifarious disease. Evaluating the prognostic factors of these malignancies may help predict patient outcome and aid decision-making in choosing the most suitable therapy. We examined the role of various salivary tumorigenic, clinical and therapeutic features in a cohort of 101 patients diagnosed and treated for primary malignant salivary tumors. These include histo-pathological diagnosis, stage, grade and T, N, M values as well as the existence of perineural invasion and extra-parenchymal spread. We also identified the salivary gland involved, the sub-compartment specific location of the tumor and the therapy administered. All these were related to mortality. Of the 101 patients examined, 79 survived and 22 died due to the disease. Tumor staging, distant metastasis and perineural invasion were highly significant predictors of increased lethality. Histo-pathological grading was also a predictor but to a lesser degree. Neither neck metastasis nor tumor size or type had a significant impact on lethality. Performing neck dissections did not decrease lethality rate. Location of the tumor in the parotid gland and more so in its deep lobe adversely affected lethality; extra-parenchymal spread also had an adverse effect. Our results seem to indicate hematogenous rather than lymphogenous spread of metastasis from malignant salivary tumors. The highest therapeutic priority should be achieving full local control of the disease by safe removal of the primary salivary tumor, accompanied by regional control of perineural invasion and extra-parenchymal spread and appropriate systemic treatment aimed at eradicating distant metastasis.

**Keywords** Salivary tumors · Mortality · Stage · Distant metastasis · Grade · Adjuvant therapy

## Introduction

Malignancies of the salivary glands represent a multifarious disease. Evaluating the prognostic factors may help predict patient outcome and identify the most suitable therapy. Several factors are known to influence prognosis, outcome and overall survival rates. Spiro et al. [1] showed in 2001 how clinical stage, particularly tumor size (T value), highly influences prognosis and survival rate. Speight et al. suggested tumor size to be a critical predictive factor, more important than histo-pathological grade [2]. They introduced to the professional world their "4 cm rule"—claiming that stage III and IV tumors larger than 4 cm in diameter will always have a worse prognosis, regardless of histo-pathological type or whether neck metastasis exists. They maintained that malignant tumors larger than 4 cm in diameter are an absolute indication for administration of postoperative adjuvant radiotherapy, and that T value (specifically stage III and IV tumors) is an independent prognostic factor with negative impact on survival [3–5]. According to the results published in 2011 by the Danish Head and Neck Cancer Group (DAHANCA), disease specific survival rates decrease dramatically in up to 40% and recurrence rates are significantly increased in patients with T3 and T4 tumors [6]. Jeannon et al. in 2009 showed the clear correlation among advanced T value, high-grade histo-pathology and poor prognosis (with only 35% overall survival rates) in patients with parotid malignant tumors [7].

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The role and significance of neck involvement and extent of lymphogenous metastatic spread from salivary gland malignancies is still controversial. Therefore, treatment of the neck is not mandatory and especially not in N0 cases (no evidence for neck metastasis). Clinically positive lymph nodes should be removed by a neck dissection, together with the resection of the tumor. The frequency of nodal involvement and associated risk factors are constantly being studied and evaluated. [8, 9].

Extra-parenchymal extension, clinical or macroscopic evidence of soft tissue invasion by the malignant tumor into the surrounding soft tissue and nerves, upgrades the T stage to T3 regardless of the malignant tumor's maximal diameter and size [10–12], and is accepted as a poor prognostic indicator. Microscopic invasion alone does not constitute extra-parenchymal invasion [13]. A study from 2012 showed how extra-parenchymal significantly worsens prognosis by 5.4 times [10]. The presence of extra-parenchymal extension correlates with treatment outcomes. A Korean study [14] of 134 cases of low-grade salivary gland cancer included 45 cases with extra-parenchymal extension and showed that postoperative radiotherapy significantly reduced recurrence rates in patients with extra-parenchymal extension [14]. However, a consensus concerning the clinical significance of extra-parenchymal local invasion has yet to be determined, probably because the parotid gland, where many salivary malignancies are located, is not an encapsulated gland to begin with and, as a multi-globular gland, its boundaries are not always clear. Therefore, it is not easy to determine whether a parotid tumor is still confined within the gland, or has already invaded to its surroundings.

We wanted to examine the role of salivary tumorigenic, clinical and therapeutic features in patients diagnosed and treated for primary malignant salivary tumors, including histo-pathological diagnosis, stage, grade and T, N, M values, and perineural invasion and extra-parenchymal spread of the tumors. We also examined which salivary gland was involved, sub-compartment-specific location of the tumor, and therapy administered. These parameters were correlated with mortality rates.

## Methods

### Patients, study design and prevalence of tumors

In the current study, we analyzed 101 patients who received definite therapy for salivary glands malignant tumors in Rambam Medical Center in Haifa, Israel. For this retrospective study based on medical record data, approval of Rambam Medical Center's Ethics Committee was unnecessary, as was the signing of patient consent forms. Out the 101, 79 survived and 22 died due to the disease. The distribution of the salivary malignancies reflected the often-found situation where several tumor groups are much more prevalent than others. Thus, the most prevalent group was the mucoepidermoid carcinoma (MECA) followed by the adenoid cystic carcinoma, the squamous cell carcinoma (SCC) and, finally, the polymorphous low-grade adenocarcinoma. We then divided each group of tumors into two further groups: patients who were surviving and those who had died with the disease (DWD).

Data relating to tumor characteristics and therapy administered (type of surgery, radiotherapy, chemotherapy) were harvested from patient files. We documented other parameters: T, N, M, staging, grading, glandular location and sub-location of tumors, rate of perineural invasion and extra capsular spread. For all parameters, the data are divided into the surviving versus the DWD groups, and statistical analyses are shown whenever possible. The impact of each parameter on a patient's mortality is clearly presented.

### Statistical evaluation

Statistical analysis was performed using the STATA 12.0 software.

The various categorical variables, numbers and percentages were calculated. 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).

## Results

### Tumor distribution and glandular location and sub-location

There were no statistically significant differences in the distribution of tumor types between the surviving and the DWD groups. That is, no specific tumor was significantly more lethal than the others; otherwise, we could have perhaps identified a greater prevalence of a "killer" tumor in the DWD group as compared to the surviving group. Nor did we find relatively non-aggressive tumors with a higher prevalence in the surviving group as compared to the DWD group. For example, in the most prevalent tumor group, the MECA ($n=28$), there were 22 surviving patients (27.8% of all survivors) and 6 DWD patients (27.3% of all DWD patients). In the second-most prevalent tumor group, the adenoid cystic carcinoma tumors ($n=25$), these numbers were 36.4% and 21.5%, respectively; in the third most prevalent group, the SCC tumors ($n=10$), these numbers were 18.3% and 7.6%, respectively; and in the fourth most prevalent group, the polymorphous low-grade adenocarcinoma tumors ($n = 9$), the numbers were 4.6% and 10.1%, respectively.

In almost all patients (100/101 cases) the tumor appeared in a solitary salivary gland, either major or minor and there was no predilection for either the right or the left side (Table 1). Most of the tumors (59%) were found in the parotid gland followed by the minor salivary glands, the submandibular glands and the sublingual glands with prevalence rates of 29, 10 and 3%, respectively. In the parotid gland, the sub-location of the tumor was crucial; of 14/59 (23%) parotid tumor patients whose tumor was located in the parotid tail, three had died (21.4%). No fewer than 34/59 (57.6%) patients' parotid tumor was located in the superficial lobe, the most prevalent sub-location for parotid gland tumors. Of the 34, 10 patients (29.4%) belonged to the DWD group. Most interesting was the significance of the parotid deep lobe: although only 10/59 parotid tumors were located in the deep lobe, four (40%) of these patients died.

Concerning tumor location and sub location's relationship to mortality rates, there was significant importance to the specific gland involved. In the great majority of cases (27/29, $p = 0.03$) where the malignant tumor was diagnosed in the minor salivary glands, the patients survived. In contrast, there was a significant lethal tendency when the tumor was in the parotid gland, and while 77.3% of the DWD group were parotid tumor patients, only 53.1% of the surviving patients were parotid tumor patients ($p = 0.04$, Table 1). Furthermore, as mentioned earlier, the sub-location of the parotid gland tumor was crucial.

Among our patients, only three had sublingual tumors, of these two died due to the disease. Obviously, this number is too small for statistical analysis. In the submandibular group there was no significant difference between the DWD and the surviving groups. As for the specific location of minor salivary glands involved, although the hard palate minor salivary glands represented the largest group involved, no fewer than 14/29 patients in this group had salivary malignancies in minor salivary glands elsewhere, throughout the oral cavity. These included minor glands in

**Table 1** Salivary gland tumor location and sub-location in both DWD and surviving groups

| Tumor parameters | DWD $N = 22$ $n$ (%) | Other $N = 79$ $n$ (%) | $p$ Value |
|---|---|---|---|
| Side | | | |
| Right | 7 (31.8) | 37 (46.8) | $^{\perp}$0.3980 |
| Left | 15 (68.2) | 41 (51.9) | |
| Bilateral | | 1 (1.3) | |
| Location | | | |
| Parotid | 17 (77.3) | 42 (53.1) | $^{\vdash}$0.0420* |
| Submandibular | 1 (4.5) | 9 (11.4) | $^{\perp}$0.6860 |
| Sublingual | 2 (9.1) | 1 (1.3) | $^{\perp}$0.1290 |
| Minor | 2 (9.1) | 27 (34.2) | $^{\perp}$0.0310* |
| Sub-location | | | |
| Parotid | 17 | 42 | |
| Parotid tail | 3 (17.7) | 11 (26.2) | |
| Parotid superficial lobe | 10 (58.8) | 24 (57.1) | |
| Parotid deep lobe | 4 (23.5) | 6 (14.3) | |
| Parotid (sublocation unknown) | | 1 (2.4) | |
| Submandibular | 1 | 9 | |
| Sublingual | 2 | 1 | |
| Minor | 2 | 27 | |
| Minor salivary gland of hard palate | 1 (50.0) | 14 (51.9) | |
| Minor salivary gland of lip | | 1 (3.7) | |
| Maxillary sinus | 1 (50.0) | 3 (11.1) | |
| Minor salivary gland of soft palate | | 2 (7.4) | |
| Minor salivary gland of buccal mucosa | | 2 (7.4) | |
| Minor salivary gland of para pharyngeal space | | 3 (11.1) | |
| Tongue dorsum | | 1 (3.7) | |
| Mandible | | 1 (3.7) | |

$p$ Value by $^{\vdash}\chi^2$ test or $^{\perp}$Fisher exact test; *$p \le 0.05$ (Sig) the lip, maxillary sinus, soft palate, buccal mucosa, para pharyngeal space, dorsum of tongue and mandible.

## Tumor T, N and M and staging

In our examination, median values of tumor size in the surviving and DWD groups were similar (2.4 cm and 2.9 cm, respectively), so that tumor size was not found to significantly alter the fate of the patient. The distribution of the T values (1–4) was also similar in both the DWD and the surviving groups. 43% of the surviving patients and in 36.4% of the DWD patients had small size tumor (≤ 2 cm). Perhaps this is why tumor size was not found to be a significant lethality factor: the tumors were treated at a relatively early stage, and did not reach a point where vital proximal structures such as blood vessels or nerves were invaded by metastasis spread (Table 2).

Concerning neck metastasis, 36.4% of the DWD group had neck metastasis, as opposed to 20.2% of the surviving group. Yet this difference did not reach statistical

**Table 2** Tumor T, N and M and staging in the DWD and surviving groups

| Tumor parameters | DWD *N* = 22 *n* (%) | Survived *N* = 79 *n* (%) | *p* Value |
|---|---|---|---|
| T (cm) | | | |
| Median | 2.9 | 2.4 | ┤0.2484 |
| Mean ± SD | 3.4 ± 2.4 | 2.6 ± 1.5 | |
| Range | [1–10] | [0.3–6.5] | |
| Unknown (patients) | 4 | 4 | |
| T (cm) | | | |
| ≤ 2 cm, patients (%) | 8 (36.4) | 34 (43.0) | ┴0.3220 |
| ≤ 4 | 7 (31.8) | 29 (36.7) | |
| ≤ 6 | 2 (9.1) | 10 (12.7) | |
| > 6 | 1 (4.5) | 2 (2.5) | |
| Unknown | 4 (18.2) | 4 (5.1) | |
| N | | | |
| 0-No–no LN | 13 (59.1) | 60 (76.0) | ┴0.1960 |
| LN | 8 (36.4) | 16 (20.2) | |
| 1-N1: single LN ipsilateral < 3 mm | 1 | 6 | |
| 2-N2a: single LN ipsilateral 3–6 mm | 2 | 2 | |
| 3-N2b: Metastasis in multiple ipsilateral lymph nodes, none > 6 em in greatest dimension | 4 | 8 | |
| 4-N2c: Metastasis in bilateral or contralateral lymph | 1 | | |
| Unknown | 1 (4.5) | 3 (3.8) | |
| M | | | |
| Yes | 10 (45.5) | 7 (8.9) | ├0.0001** |
| No | 12 (54.5) | 72 (91.1) | |
| Staging | | | |
| I | 2 (9.1) | 17 (21.5) | ┴0.0001** |
| II | 1 (4.5) | 20 (25.3) | |
| III | 1 (4.5) | 17 (21.5) | |
| IV A | 5 (22.7) | 18 (22.8) | |
| IV B | 2 (9.1) | 4 (5.1) | |
| IV C | 10 (45.5) | 3 (3.8) | |
| Unknown | 1 (4.5) | | |
| Staging | 3 (13.6) | 37 (46.8) | ┴0.0001** |
| I + II | | | |
| III | 1 (4.5) | 17 (21.5) | |
| IV A + B+C | 17 (77.3) | 25 (31.7) | |
| Unknown | 1 (4.6) | | |

*p* Value by ├$\chi^2$ test or ┴Fisher exact test or *$p \leq 0.05$ (Sig). Died with disease (DWD), lymph node (LN), node (N), tumor (T), metastasis (M), standard deviation (STD), centimeter (CM) significance (p = 0.19) (Table 2). In stark contrast to the neck proximal metastasis, the effect of distant metastasis (mostly pulmonary but also skeletal), was devastating: 10/22 patients of the DWD group (45.5%) had distant metastasis while only 7/77 surviving patients (8.9%) did, a highly significant difference ($p = 0.0001$). Staging, which is based in part on the distant metastasis parameter, was similarly disparate, and patients with higher stages performed poorly and had much higher rates of mortality (Table 2).

## Tumor grading, perineural invasion and extra parenchymal spread

Histo-pathological grading was also found to be a significant predictor of mortality ($p = 0.02$) (Table 3). Patients with low-grade tumors upon diagnosis survived at a rate of three times those diagnosed with high grade disease. Only a minority of the patients (21/23, (9%)) with low-grade disease died due to the disease as compared with 20/68 (29%) of patients with high-grade disease. Similarly, perineural invasion was found to adversely affect the patient mortality rate; 54.5% of the patients in the DWD group versus 21.5% of the surviving patients exhibited this aggressive manifestation of the disease during treatment, a very highly significant difference ($p = 0.002$) (Table 3). Interestingly, however, was our finding that extra parenchymal spread of the tumor did not have a significantly adverse effect on survival rate, although extra parenchymal spread was about 50% higher in the DWD group than in the surviving group (45.5% vs. 31.7%, $p = 0.22$) (Table 3).

**Table 3** Tumor grading, perineural invasion and extra-parenchymal invasion in both DWD and surviving groups

| Tumor parameters | DWD $N = 22$ $n$ (%) | Other $N = 79$ $n$ (%) | $p$ Value |
|---|---|---|---|
| Grading | | | |
| Low grade | 2 (9.1) | 21 (26.6) | $^{\perp}$0.0240* |
| Intermediate grade | | 10 (12.7) | |
| High grade | 20 (90.9) | 48 (60.7) | |
| Perineural invasion | | | |
| Yes | 12 (54.5) | 17 (21.5) | $^{\vdash}$0.0020** |
| No | 10 (45.5) | 62 (78.5) | |
| Extra-parenchymal invasion | | | |
| Yes | 10 (45.5) | 25 (31.7) | $^{\vdash}$0.2290 |
| No | 12 (54.5) | 54 (68.3) | |

$p$ Value by $^{\vdash}\chi^2$ test or $^{\perp}$Fisher exact test or *$p \leq 0.05$ (Sig)

[a]2 of the 9 who received Chemo are not certain

[b]1 of the 7 who received Chemo are not certain

## Therapy modalities administered

In nearly 100% of the cases (except for one inoperable case) therapy was local surgical removal of the tumor using various procedures that often included neck dissection (on various levels). The surgical techniques used are depicted in Table 4, also showing that although neck dissections were performed in the DWD group more often than in the surviving group (45.5% vs. 34.2%), this difference did not reach statistical significance. Administration of adjuvant radiotherapy and/or chemotherapy was much more prevalent in the DWD group than in the surviving group; radiotherapy, chemotherapy and radio-chemotherapy were administrated in rates 2–6 times higher in the DWD group ($p = 0.0001$–$0.0006$). This difference was very highly significant.

# Discussion

The most important findings obtained in the current study are the higher mortality rates in patients with parotid gland malignancies, especially those located in the deep lobe of the parotid. In addition, important is the adverse effect of high grade histology, distant metastasis, perineural metastasis and extra-parenchymal spread. Conversely, tumor distribution was more or less the same between the surviving and the DWD groups, so the specific type did not significantly affect survival. Neither tumor size nor spread of proximal lymph node metastasis to the neck showed a significant adverse effect on patient survival. The lesser importance of neck metastasis in salivary malignancies we report is supported by the fact that neck dissections performed in our patients did not significantly improve their prognosis. However, adjuvant radiotherapy, chemotherapy or a combined treatment administered to patients following local tumor removal dramatically improved their outcome ($p = 0.0001$). This information seems to indicate the importance of systemic characteristics of the disease in its lethality, again supported by the dramatic negative effect of distant metastasis on patient survival. Over 90% of the distant metastases were in the lungs, indicating the crucial role of hematogenic metastasis spread in salivary malignancies in contrast to the relatively limited role of lymph metastasis spread. This finding is in full contrast to what we know from oral cancer, the other most prevalent malignancy in head and neck cancer [15–18], where lymph metastasis to the neck makes the difference and not hematogenic spread [16–18]. A clinician seldom sees a patient diagnosed for the first time with oral cancer who already has distant metastasis [19]. Neck metastasis in oral cancer is not only quite prevalent but also known to profoundly reduce patient survival rates [20]. It seems that salivary glands whose location facilitates their potential for

**Table 4** Therapy modalities administered to both DWD and surviving groups

| Tumor parameters | DWD<br>$N=22$<br>$n$ (%) | Survived<br>$N=79$<br>$n$ (%) | $p$ Value |
|---|---|---|---|
| Surgical technique | | | |
| Local excision | 1 (4.6) | 1 (1.3) | |
| Superficial/partial parotidectomy | 3 (13.6) | 22 (27.8) | |
| Total parotidectomy | 7 (31.8) | 17 (21.5) | |
| SMG sialo adenectomy | 1 (4.6) | 9 (11.4) | |
| Wide local excision | | 18 (22.8) | |
| Maxillextomy subtotal | 2 (9.1) | 8 (10.1) | |
| Partial glossectomy | | 1 (1.3) | |
| Mandibulectomy | | 1 (1.3) | |
| Mandibulectomy and total parotidectomy | | 1 (1.3) | |
| Sublingual sialadenectomy | | | |
| In operable | 2 (9.1) | | |
| | 6 (27.3) | 1 (1.3) | |
| Neck dissection | | | |
| Yes | 10 (45.5) | 27 (34.2) | ├0.3320 |
| No | 12 (54.5) | 52 (65.8) | |
| Levels of neck dissection | 10 (45.5) | 27 (34.2) | |
| 1–2 | | 1 | |
| 1–3 | 2 | 4 | |
| 1–4 | 3 | 5 | |
| 1–5 | 4 | 6 | |
| 2–3 | | 3 | |
| 2–4 | | 2 | |
| Unknown | 1 | 6 | |
| Chemo therapy | | | |
| Yes (%) | 9 (40.9) | 7 (8.9) | ├0.0001** |
| Radio therapy | | | |
| Yes (%) | 17 (77.3) | 35 (44.3) | ├0.0060** |
| Chemo and radio therapy | | | |
| Yes (%) | 8 (36.4) | 5 (6.3) | ├0.0001** |

$p$ Value by ├Chi square test or ┴Fisher exact test or $*p \leq 0.05$ (Sig)

hematogenic spread are likely to be more lethal, and thus our observation of higher mortality from parotid tumors, especially when located in the deeper lobe, supports this notion. The parotid parenchyma is in more intimate proximity with blood vessels as it is spread in multi lobules and acini on a relatively vast region, and not encapsulated and confined as are the submandibular and the minor salivary glands [21–23]. Similarly, the deep parotid lobes are much closer to major blood vessels than the superficial or the parotid tail lobes. The deep portion of the parotid gland accounts for approximately 20% of the entire parotid gland. The deep lobe usually hosts 0 to 9 lymph nodes, which can be found in approximately 75% of the specimens [21]. It lies beneath the facial nerve and over the deep parotid musculature: stylohyoid, stylopharyngeus and styloglossus muscles. The carotid sheath and the vast venous drainage lies posterior and medially to the deep lobe [22]. Locating a tumor mass in the deep portion can be challenging by clinical examination or imaging studies.

Deep lobe removal in a selective manner or as part of total parotidectomy is advocated by most surgeons in cases of primary malignant tumors of the deep portion, palpable or radiographic evidence of metastatic cancer to the deep lobe, or in cases of a direct extension from the parotid gland's superficial lobe malignant primary neoplasm [23]. Routine removal of the deep lobe is a point of debate—Thom et al. [24] showed in 2014 how removal of deep lobe improves local control. This study specifically showed the advantageous role of total parotidectomy for metastatic cutaneous squamous cell carcinoma and invading malignant melanoma. Wertz [25] showed the oncological benefit of deep lobe removal in cases of advanced stage melanoma that had metastasized to the parotid gland and underwent total parotidectomy compared to only superficial parotidectomy.

Metastasis from a non-primary malignancy that traveled to the intra-parotid nodes is a critical factor encouraging deep lobe removal.

In cases of primary parotid cancer: the risk of deep lobe and node involvement increases in cases of high-grade malignancies and cases with relatively superficial malignant tumors but with positive neck nodes.

Olsen et al. and Armstrong et al. demonstrated the invasion pattern of a high-grade cancer from the superficial to the deep lobe and the deep lymph nodes of the neck [26, 27]. Removal of the deep lobe seems to reduce recurrence risk compared to administration of radiation therapy and leaving the deep lobe intact.

Understanding the benefit of deep lobe removal is challenging from the pathologist's point of view since it is difficult to distinguish between the lobes in a removed specimen, as evidenced by the effects of both perineural and extra-parenchymal invasions by the tumors. The former's devastating effect was highly significant while the latter's effect was clear even though it did not reach statistical significance in our study (enhancing mortality rate by 50% as compared with tumors that did not present extra parenchymal spread). We feel that these results imply that each and every infiltrated neuron is in full contact with its supplying blood vessels, and that the extra-parenchymal spread is often found in surrounding tissues rich with blood vessels. This suggested crucial role of hematogenic metastasis spread in salivary malignancies may be supported by the fact that neither tumor size nor histological diagnosis affected patient outcome to a similar degree. Our results were initially rather surprising since the literature is rife with reports of certain salivary malignancies being more aggressive than others and that tumor size is a crucial parameter [28–32]. In our study, similar distribution between DWD and surviving groups of the same kind of tumor, supports our theory; as for the importance of tumor size, perhaps less attention was paid in the past to the specific sub location of the tumor, so that a tumor was considered more lethal simply because it was large rather than because it had also infiltrated into the deep lobe of the parotid and not only to the superficial lobe. Perhaps a tumor of the same size would not have yielded such a poor prognosis had it remained confined to the superficial lobe and not infiltrated the deep lobe. The two most prevalent tumor types we found were mucoepidermoid carcinoma and adenoid cystic carcinoma, followed by SCC, polymorphous low-grade adenocarcinoma and acinic cell carcinoma. Previous studies have often reported the same [33], thus adding credence to our observations. Earlier mention of the similar distribution of tumor types between DVD and surviving groups implies a rather minor role for the specific histo-pathology, at least in these common salivary tumors. However, although they are the most commonly treated by clinicians, these prevalent groups are not necessarily the most lethal salivary malignancies in salivary duct carcinoma [34, 35]. One exception is the adenoid cystic carcinoma, known for its long-term high mortality [36], and indeed, this was also true in our study though this did not reach statistical significance (36.4% in the DWD group vs. 21.5% in the surviving group had adenoid cystic carcinoma). The long-term lethality of adenoid carcinoma is well known and often attributed to perineural invasion [37]. We also show that perineural invasion is a most profound predictor for increased lethality ($p=0.0002$).

Perineural invasion occurring in salivary gland malignancies is known to have severe consequences. This type of invasion often remains obscure, and even in rare cases where it is diagnosed it is extremely difficult to achieve satisfying therapeutic results. Although perineural invasion is familiar and often discussed, its mechanistic aspects are enigmatic. It is not clear exactly how and why tumor metastasis spreads via the nerve sheets relatively easily and why this phenomenon is so intimately related to increased rates of recurrence. To date, the diagnostic modality of choice recommended for perineural invasion is MRI imaging. As for therapy, advanced radiotherapy is preferable (as intensity-modulated radiation therapy and image-guided radiation).

In the same vein as the perineural significance, we found that both distant metastasis (M) and staging are very strong predictors of increased mortality ($p=0.0001$), and to a lesser degree, histo-pathological grading was found to be a significant predictor ($p=0.02$). Our findings that neither T nor N values were significant prognostic indications were surprising to us and, we feel, of importance. These results were supported by therapeutic data in which systemic therapies such as radiotherapy and chemotherapy were administered much more often in the DWD group, while neck dissections were performed at similar rates in both the DWD and the surviving groups. In other words, neck dissections performed to prevent mortality due to neck metastasis (the effect of the "N"), did not have the desired effect (did not increase the number of the patients surviving the disease). Radiotherapy and chemotherapy for patients with distant metastasis, intended to prevent the lethal effect of such metastasis, were unable to fulfill their purpose and prevent death.

Our findings did not show impact of tumor size (no significant role for the "M") that previous studies had claimed (described in the "Introduction" section). Perhaps this is explained by our theory of the specific importance of tumor sub-location in the parotid deep lobe: the lethality of the large tumor is derived not from its size alone but from where its 'largeness' penetrates (the deeper lobe of the parotid). We suggest that the lethality of tumors located in deep lobes is due to immediate proximity to major blood vessels, facilitating hematogenous distant metastasis spread. Similarly, the relatively higher lethal potential of parotid gland tumors compared with either submandibular and minor salivary glands tumors, may result from the fact that the parotid parenchyma is spread in lobules in a vast region and thus is in intimate contact with an array of blood vessels. Our results show that the most pivotal and devastating factor in salivary malignant pathogenesis is the “M”, the existence or absence of distant metastasis that most often makes the difference between survival and death. The highest therapeutic priority should be achieving full local control of the disease by safe removal of the primary salivary tumor, accompanied by regional control of perineural invasion and extra-parenchymal spread and with appropriate systemic treatment aimed at eradicating distant metastasis.

## Limitations

This was a retrospective, single-institution study that is limited in its patient numbers, especially when subdividing into disease sites or tumor characteristics. A limitation such as this one is expected, since salivary gland malignancies are a relatively rare cancer. Our study is also limited in that survival-time data is not included, just whether patients are alive or dead-with-disease. However, we do plan to conduct a Kaplan–Meier analysis in a separate study of our patients.

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### Compliance with ethical standards

**Conflicts of interest** The authors declare no conflicts of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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