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Patterns of treatment failure in salivary gland cancers

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ABSTRACT

Aim: The purpose of the study was to publish our experience of salivary gland cancer treatment with large number of patients treated at a single institution.

Background: Salivary gland cancers are rare tumors of the head and neck representing about 5% of cancers in that region and about 0.5% of all malignancies. Due to the rarity of the disease, most of the studies regarding treatment outcome consist of low number of patients, thus making it difficult to draw conclusions.

Material and methods: 115 patients with primary salivary gland cancer were included in a retrospective study. The subsites of tumor were the parotid gland (58% patients), submandibular gland (19%) and minor salivary glands (23%). All patients underwent primary surgical resection. The following were collected: age, stage of the disease, T status, N status, grade of tumor, perineurial invasion, lymphovascular invasion, extracapsular spread, final histological margin status and postoperative treatment. Details of local, regional or distant recurrence, disease free survival and overall survival were included.

Results: The majority (65%) of patients presented in early stage, T1 and T2 tumors. 81% of patients were N0. Free surgical margins were achieved in 18% of patients, close in 28% patients and positive surgical margins in 54% (62) patients. Factors that significantly increased the risk of recurrence: T stage ($p = 0.0006$); N-positive status ($p < 0.0001$); advanced stage of the disease ($p < 0.0001$); high grade of tumor ($p = 0.0007$); PNI ($p = 0.0061$); LVI ($p = 0.0022$); ECS ($p = 0.0136$); positive surgical margins ($p = 0.0022$). On multivariate analysis, high grade of tumor and positive surgical margins remained significant independent adverse factors for recurrence formation.

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Conclusions: This report shows a single institution results of oncological treatment in patients with malignant salivary gland tumors, where positive surgical margins strongly correlate with patients' worse outcome. Whether to extend the procedure, which very often requires sacrificing the nerve is still a question of debate.

1. Background

Salivary gland cancers are rare tumors of the head and neck representing about 5% of cancers in that region and about 0.5% of all malignancies.[1] The WHO recognizes over 20 subtypes of the disease which can affect nearly any region of the head and neck, including major salivary gland, minor salivary glands within the oral cavity, oropharynx, sinonasal region and larynx.[2] Due to the histologic complexity, salivary gland tumors require a comprehensive treatment plan, nevertheless surgical treatment has become the treatment of choice for resectable disease.[3] Adjuvant radiotherapy (RT) applies to patients with adverse treatment factors, including advanced stage of the disease, nodal disease, close resection margin, perineural invasion (PNI) or lymphovascular invasion (LVI). Chemoradiation can be considered when clear margins are not achieved and extracapsular spread (ECS) is detected in the lymph nodes.[4] Due to the rarity of the disease, most of the studies regarding treatment outcome consist of low number of patients, thus making it difficult to draw conclusions. What is more, treatment recommendations for various histological grades and stages are controversial due to the discordance in literature.[5]

2. Aim

The purpose of the study was to compare our experience of salivary gland cancer treatment with large number of patients treated at a single institution with available published data and to highlight factors that significantly affected the outcome in our group of patients.

3. Material and methods

3.1. Patients

One hundred and fifteen patients with primary salivary gland cancer were included in a retrospective study, of which 71 (62%) were males and 54 (38%) were females. The mean age at time of presentation was 63.7 years (25–94 ± 15.8). The subsites of tumor were the parotid gland (67 patients – 58%), submandibular gland (22 patients – 19%) and minor salvary glands (26 patients – 23%). In terms of histology, the most common tumor subtype was adenoid cystic carcinoma (33 pts; 28.6%) followed by mucoepidermoid carcinoma (19 pts; 16.5%). All patients underwent primary surgical resection. The mean follow up was 25 months (range 3–110 ± 18.5 months).

For each patient, the following clinical parameters were collected: age at presentation, stage of the disease, T status, N status, grade (G) of tumor, perineurial invasion (PNI), lymphovascular invasion (LVI), extracapsular spread (ECS), final histological margin status and postoperative treatment. Details of local, regional or distant recurrence, as well as disease free survival (DFS) and overall survival (OS) were also included in analysis (Table 1).

Table 1 – Patient's demographics.

	Variable	Number (%)
Sex	Male	71 (62)
	Female	54 (38)
Median age	63.7	
Site of primary tumor	Parotid	67 (59)
	Submandibular	22 (19)
	Oral cavity	12 (10)
	Oropharynx	5 (4)
	Sinonasal region	9 (8)
Histologic type	Adenoid cystic carcinoma	33 (28.6)
	Mucoepidermoid carcinoma	19 (16.5)
	Carcinoma ductale	14 (12.1)
	Acinic cell carcinoma	12 (10.4)
	Adenocarcinoma	12 (10.4)
	Carcinoma ex pleomorphic adenoma	10 (8.7)
	Carcinoma myoepithelial	7 (6.1)
	Other	8 (6.9)

3.2. Treatment

All patients were reviewed by the institutional multidisciplinary team (MDT), and were qualified for primary surgical treatment. When indicated, patients were qualified for adjuvant treatment. The standard radiotherapy protocol was 60–66 Gy (2.0 Gy/fraction) daily, Monday–Friday, over 6–7 weeks. Factors that qualified the patient for adjuvant radiotherapy were: pT3/4 tumor, close surgical margins (1–5 mm), positive nodes, and evidence of perineural/vascular invasion. The chemotherapy protocol comprised concurrent single-agent cisplatin at 100 mg/m^2 every 3 weeks or 40 mg/m^2 every week, alternatively; indications were positive surgical margins or extra capsular spread. Potential side effects and benefit were explained to each patient prior to adjuvant chemotherapy. Of 62 patients with indications for concomitant chemotherapy 54 refused such treatment and decided to proceed with adjuvant radiotherapy only. Written informed consent has been obtained from each patient.

Study approval was obtained from the Research Ethics Board at Poznan University of Medical Sciences.

3.3. Statistical analysis

Statistical analysis was performed using Statistica software. Outcomes were evaluated as disease free survival calculated from the time of surgery until the time of recurrence or last follow up visit, and overall survival from the time of surgery until death or last follow up visit. Kaplan–Meier methods were used to estimate the above outcomes and the log-rank test was used to compare survival curves. The following factors were analyzed: age, sex, clinical stage, T stage, N stage, grade of tumor (G), final margin status, presence of perineural invasion, presence of lymphovascular invasion, presence of ECS, and adjuvant therapy. Chi-square test was used to evaluate the examined factors on loco-regional control and survival, $p < 0.05$ being statistically significant.

4. Results

4.1. Patients

The majority of patients presented in early stage, T1 and T2 tumors (28 patients (24%) and 47 patients (41%), respectively). In 93 (81%) patients, there was no evidence of metastases to regional lymph nodes (N0). Perineurial invasion (PNI) was present in 33 patients (29%), vascular invasion in 20 patients (17%), and extracapsular spread in 13 patients (11%). Free surgical margins (>5 mm) were achieved in 21 pts (18%), close (1–5 mm) in 32 pts (28%) and positive surgical margins in 62 pts (54%), respectively (margins < 1 mm were considered positive). All patients were followed for at least 12 months, unless death occurred earlier. Most patients (73–63%) received post-operative radiotherapy of whom 8 (7%) received additional chemotherapy (Table 1).

4.2. Outcome

Post-operative follow up revealed that in terms of relapse of the disease patients can be assorted into 3 different categories: (1) Recurrence developed locally (isolated local, locoregional and simultaneous local and distant) – 15 patients (13%); (2) Regional recurrence (isolated regional, locoregional and simultaneous regional and distant) in 8 patients (14%); (3) Distant metastasis (isolated distant, simultaneous local/regional and distant) was observed in 25 (21.7%) patients. The mean time from treatment to recurrence was 29.2 months (2–110 months; SD 26.2 months).

Univariate analysis was performed to determine the effect of histologic subtype, grade of tumor, stage of disease, T/N status, positive surgical margins, PNI, ECS, LVI and adjuvant treatment with regards to the incidence of recurrence (Table 1). Factors that significantly increased the risk of recurrence: T stage ($p = 0.0006$; HR 1.90, 95% CI 1.32–2.75), N-positive status ($p < 0.0001$; HR 4.12, 95% CI 2.08–8.13), stage of the disease ($p < 0.0001$; HR 2.04, 95% CI 1.45–2.86), high grade of tumor ($p = 0.0007$; HR 4.63, 95% CI 1.91–11.18), PNI ($p = 0.0061$; HR 2.45, 95% CI 1.29–4.66) LVI ($p = 0.0022$; HR 2.93, 95% CI 1.47–5.86), ECS ($p = 0.0136$; HR 2.70, 95% CI 1.27–5.95), and positive surgical margins ($p = 0.0022$; HR 3.39, 95% CI 1.55–7.43). On multivariate analysis high grade of tumor ($p = 0.0175$) and positive surgical margins ($p = 0.0312$) remained significant independent adverse factors for recurrence formation (Table 2).

As distant recurrence was the prevailing pattern of failure, univariate and multivariate analysis was performed for that group separately. Factors that significantly increased the risk of distant recurrence: T stage ($p = 0.0136$; HR 1.78, 95% CI 1.12–2.83), N-positive status ($p = 0.0003$; HR 5.65, 95% CI 2.23–14.32), Stage of the disease ($p = 0.0011$; HR 2.06, 95% CI 1.33–3.18), high grade of tumor ($p = 0.0003$; HR 8.08, 95% CI 2.59–25.17), PNI ($p = 0.0039$; HR 3.21, 95% CI 1.45–7.11), LVI ($p = 0.0043$; HR 3.50, 95% CI 1.48–8.28), ECS ($p = 0.0195$; HR 3.75, 95% CI 1.24–11.40), and positive surgical margins ($p = 0.0110$; HR 3.30, 95% CI 1.31–8.26). On multivariate analysis only positive surgical margins remained significant ($p = 0.0287$; HR 3.08, 95% CI 1.12–8.42).

5. Discussion

Malignant tumor of the salivary gland is a rare disease; therefore, the high evidence prospective studies with a large group of patients are lacking in the literature. Most available data is based on single institution, retrospective reports frequently involving small, heterogenous groups of patients. In our study, we analyzed 115 patients and all had been treated with surgery. Therefore, we believe that our group is homogenous enough to deliver some evidence. What is more, in our study we decided to exclude patients with squamous cell carcinoma as it mostly represents metastatic skin cancer rather than a primary salivary gland malignancy.[6] Distant recurrence was the most common pattern of failure in our study. Multiple reports revealed that it actually ranged from 11.1% to 52% of cases constituting the most likely reason for poor outcome.[7–10] Hence, we decided to perform an analysis of risk factors for all patterns of failure followed by separate analysis of the group involving only individuals with distant recurrence. Independent analysis revealed several factors associated with a higher recurrence risk. The grade of tumor, T stage, N-positive status, stage of the disease, PNI, LVI, ECS, and positive surgical margins significantly increased the risk for development of recurrence. On multivariate analysis only tumor grade ($p = 0.0175$) and positive surgical margins ($p = 0.0312$) remained significant independent adverse factors for recurrence formation. Regarding distant failure only positive surgical margins remained significant in multivariate analysis.

High grade of tumor has been described in many papers as one of the most compelling risk factors of failure. In a study by Haderlein et al. the authors stated that high tumor grade is the strongest risk factor of distant metastasis and shorter overall survival, irrespective of tumor subtype.[10] The authors managed to collect a homogenous group of patients with high-risk primary salivary gland cancer treated with surgery and post-operative (chemo)radiotherapy. Chen at al. studied a cohort of 2400 patients with mucoepidermoid carcinoma to find that high grade of tumor significantly alters prognosis.[11] There is another interesting study where authors divided their group of 126 patients into 2 subgroups: low-grade cancers and high-grade cancer and examined the recurrence free survival. In the first group age and LVI were significant factors for recurrence,

Table 2 – Univariate and multivariate analysis for recurrence.

Factor	Recurrence N = 38	No recurrence N = 77	Univariate analysis		Multivariate analysis	
			p	Hazard ratio 95% CI	*p*	Hazard ratio 95% CI
T						
T1	6/15.8%	22/28.6%				
T2	12/31.6%	35/45.5%	0.0006	1.9 1.31–2.74	0.7443	1.25 0.32–4.84
T3	10/26.3%	17/22.1%				
T4	10/26.3	3/3.9%				
N						
N0	24/25.8%	69/74.2%	<0.0001	4.11 2.08–8.13	0.1677	2.29 0.70–7.48
N1+N2+N3	14/63.6%	8/36.4%				
STAGE						
S1	5/13.2%	20/25.9%				
S2	8/21.0%	34/44.2%	<0.0001	2.04 1.45–2.86	0.2425	0.53 0.18–1.54
S3	7/18.4%	16/20.8%				
S4	18/47.4%	7/9.1%				
PNI						
No	20/52.6%	62/80.5%	0.0062	2.45 1.29–4.66	0.0567	2.32 0.98–5.52
Yes	18/47.4%	15/19.5%				
LVI						
No	26/68.4%	69/89.6%	0.0022	2.94 1.47–5.86	0.8976	0.93 0.32–2.68
Yes	12/31.6%	8/10.4%				
ECS						
No	30/78.9%	72/93.5%	0.0136	2.7 1.23–5.95	0.4489	1.78 0.42–7.4
Yes	8/21.1%	5/6.5%				
RT						
No	14/36.8%	28/36.4%	0.1669	0.62 0.32–1.22		
Yes	24/63.2%	49/63.6%				
CRT						
No	34/89.4%	73/97.8%	0.0941	2.44 0.32–1.22		
Yes	4/10.5%	4/5.2%				
Margins						
Free + close	8/21.1%	45/58.4%	0.0022	3.39 1.55–7.43	0.0312	2.51 1.49–8.42
Positive	30/78.9%	32/41.6%				
Grade						
High	22/64.7%	19/28.4%	0.0007	4.63 1.91–11.18	0.0175	2.89 1.08–5.84
Int + low	12/35.3%	48/71.6%				

whereas in the second group PNI was the only significant factor for failure.[12]

There are on the other hand studies which did not confirm any relation between tumor grading and treatment failure. In a study of Feinstein et al., the authors found that the only factor facilitating both risk of recurrence and death was the N-status. The authors gathered a fairly homogenous group consisting of high stage salivary gland cancer cases treated with surgery and post-op RT.[13] Another study examining lymph node metastasis and its impact on survival was published by Stenner et al. The authors selected patients with early stage (T1-T2) parotid gland cancer treated with parotidectomy and elective neck dissection. The incidence of occult metastasis was 17.2% and positive lymph node stage was significantly related to poor prognosis; therefore, the authors recommend elective neck dissection in early stage parotid gland cancers. It is worth mentioning that 32 out of 70 cases were high-grade tumors.[14] Another issue regarding lymph node status in salivary gland cancers was discussed in a study by Hong et al. Authors investigated 87 patients with primary salivary high-grade cancers treated with primary surgery and neck dissection with possible adjuvant therapy. Next to well established factors like the N status, pT status, perineural invasion or lymphovascular invasion, the authors also focused on lymph node density (LND), the number of metastasis-positive nodes divided by the total number of all excised lymph nodes. Following calculations, the cut-off point for LND was set at 4.0%. On univariate analysis, several factors, including the N-status, PNI, ECS and LND affected survival. By contrast, T stage and total number of excised nodes did not impair survival. In multivariate analysis, only LND affected overall survival, cancer-specific survival and disease free survival. The study by Hong shows how important is neck dissection in the management of salivary gland cancers and that LND is superior to classical TNM staging system in patients prognosis.[15]

In majority of studies, the tumor grade and the N status are considered to be important negative prognosticators in prognosis. However, in terms of positive surgical margins, the results are more equivocal. The occurrence of positive surgical margins in surgical specimens, mostly because of the proximity of facial nerve to the tumor, is much higher than in other subsites in the head and neck. Several studies have noted positive surgical margins between 32% and 64.7%.[3,4,8,16] In our study, it was 53.9%. Amit et al. published a study where the authors revealed the correct surgical margin of adenoid cystic carcinoma (ACC) of the head and neck. Five hundred and

seven pts with ACC were conducted in the study. The authors managed to achieve 50% of negative margins (>5 mm), 18% of close margins and 32% of positive margins. OS in this study was most strongly affected by positive surgical margins, as well as DSS. But, interestingly, there was no difference in OS and DSS in subgroups with close and negative surgical margins (excluding oral cavity ACC).[16] In a study by Liu, 37 patients with acinic cell carcinoma of the parotid gland were investigated and positive surgical margins in multivariate analysis significantly decreased overall survival but did not affect DFS. In contrast, patients with PNI, LVI and positive N status affected both OS and DFS.[17] Some studies, however, have revealed that positive surgical margins do not affect the outcome. Study by Pantvaidya et al. on the cohort of 116 patients showed that tumor grade, nodal status and adjuvant radiotherapy were significant predictors of DFS on multivariate analysis but did not compromise margins (36.9% of all pts in analysis). However, the authors considered only patients with sinonasal salivary gland tumors.[18] The question whether to expand the procedure and achieve negative surgical margins remains open as conclusions coming from various studies are self-excluding. This question is of utmost importance. Parotid gland tumors which require sacrificing the nerve, dramatically decrease the patient's quality of life. But what was strongly addressed by McHugh in her study, where positive surgical margins affected DFS and increased the rates of recurrence and distant disease, is that "complete oncological resection should not be compromised in favor of facial nerve preservation in tumors clearly involving the nerve." The author suggests to biopsy the suspicious part of the nerve for intraoperative examination and eventually extend the proceudre.[8]

Another controversial factor, in our study not statistically significant, is adjuvant radiotherapy in salivary gland cancers. In our study exactly the same percentage of patients (33%) had recurrence whether treated with adjuvant RT or not. Notably, of 33 patients with adenoid cystic carcinoma, 26 (78.7%) received adjuvant radiotherapy. Of those, 4 (15.3%) patients developed recurrence. Out of 7 patients who have not received adjuvant radiotherapy, 4 (57.1%) developed recurrence, but the number was too small to draw statistical conclusions. There are studies, like the above mentioned by Pantvaidya, where no adjuvant RT decreased DFS.[18] In another study by Lee et al., where the authors examined the effect of adjuvant RT in major salivary adenoid cystic carcinoma, the conclusion was that RT increases survival in subgroups with early stage local disease (pT1-T2), advanced disease (pT3-T4), nodal disease (pTanyN+) and for positive surgical margins. The only subgroup that did not gain from adjuvant RT was the one with negative surgical margins.[19] In recurrent disease, there are papers examining the effect of re-irradiation but it was not studied in our cohort.[20]

Our study has several limitations. First of all, it is a single institution retrospective study and, therefore, the strength of evidence is limited, especially, in salivary gland cancers where due to the rarity of the disease selection bias is at the greatest risk. Secondly, because some of the patients had only 12 months follow up, we could not draw 5-year outcome figures. Follow up time in salivary gland cancers is crucial due to late distant metastases that can occur throughout patient's life. And thirdly, to compare more patients, we decided to include in the analysis all head and neck salivary gland cancers making the group more heterogenous but, on the other hand, statistical analysis is thus more reliable.

6. Conclusions

This report shows a single institution results of oncological treatment in patients with malignant salivary gland tumors, where grade of tumor, N status and positive surgical margins strongly correlate with patient's worse outcome. In distant disease, only positive surgical margins played a significant role, but whether to extend the procedure that very often require sacrificing the nerve is still a question of debate. Nevertheless, to draw direct conclusions, prospective randomized trials are being awaited to help to build a successful treatment plan.

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Conflict of interest

None declared.

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