Malignant Salivary Gland Tumours - a single centre experience

Akshat Malik[1], Yadsan Devabalan[1], Jonathan Bernstein[2], Zaid Awad[3], Dorothy Gujral[2], Sarah Partridge[2], Gitta Madani[2], Peter Clarke[2], Justin Weir[2], and Alasdair Mace[4]

[1]Charing Cross Hospital
[2]Imperial College Healthcare NHS Trust
[3]Imperial College
[4]Royal Free Hospital

June 10, 2020

Abstract

Objectives: Salivary gland malignancies are an uncommon and heterogeneous group of cancers. We report our experience of clinicopathological variables that affect survival in patients treated by curative intent with surgery at a UK institution over a period of 15 years. Design: Retrospective cohort study Setting: Single centre study Participants We included 108 patients with malignant salivary gland tumours treated by curative intent with surgery from 2004 to 2019. Main outcome measures: The association between clinicopathological factors and their impact on overall survival (OS) and disease-free survival (DFS). Results: 77 (71.3%) presented with early pT classification and 81 (75%) of were node-negative. The parotid was the commonest site of malignancy (86, 79.6%). Perineural invasion (PNI) was present in 40 (37%) and lymphovascular invasion (LVI) was present in 20 (18.5%). 63 (58.3%) underwent adjuvant therapy. Median follow up was 36 months. Five-year OS and DFS were 81.7% and 71%. Age ?50, pT classification 3-4, high tumour grade, PNI, and advanced TNM stage were all associated with worse OS and DFS, and LVI with worse DFS. There was no survival difference between a close (1-<5 mm) or negative ([?]5 mm) resection margin. Conclusions: Age >50 years, advanced TNM stage, PNI and LVI are predictors of poor DFS. There was no difference in OS or DFS between patients with negative and close resection margins, indicating that close margins may be adequate for maintaining good oncologic outcomes in this group of patients.

Malignant Salivary Gland Tumours - a single centre experience

Abstract

Objectives

Salivary gland malignancies are an uncommon and heterogeneous group of cancers. We report our experience of clinicopathological variables that affect survival in patients treated by curative intent with surgery at a UK institution over a period of 15 years.

Design

Retrospective cohort study

Setting

Single centre study

Participants

We included 108 patients with malignant salivary gland tumours treated by curative intent with surgery from 2004 to 2019.

Main outcome measures

The association between clinicopathological factors and their impact on overall survival (OS) and disease-free survival (DFS).

Results

77 (71.3%) presented with early pT classification and 81 (75%) of were node-negative. The parotid was the commonest site of malignancy (86, 79.6%). Perineural invasion (PNI) was present in 40 (37%) and lymphovascular invasion (LVI) was present in 20 (18.5%). 63 (58.3%) underwent adjuvant therapy. Median follow up was 36 months. Five-year OS and DFS were 81.7% and 71%. Age [?]50, pT classification 3-4, high tumour grade, PNI, and advanced TNM stage were all associated with worse OS and DFS, and LVI with worse DFS. There was no survival difference between a close (1-<5 mm) or negative ([?]5 mm) resection margin.

Conclusions

Age >50 years, advanced TNM stage, PNI and LVI are predictors of poor DFS. There was no difference in OS or DFS between patients with negative and close resection margins, indicating that close margins may be adequate for maintaining good oncologic outcomes in this group of patients.

\sout

Key points:

- Salivary gland malignancies are a heterogenous and uncommon groups of cancers.
- This is a single centre retrospective study of clinicopathological variables that affect survival in these patients.
- PNI was present in 37% of patients.
- Five-year overall survival (OS) and disease-free survival (DFS) were 81.7% and 71%.
- Age [?]50, pT classification 3-4, high tumour grade, PNI, and advanced TNM stage were all associated with worse OS and DFS.
- No survival difference between close or negative resection margins

Ethical Considerations:

This study was registered with our clinical institution's audit department. Patient information was anonymised prior to data analysis.

Introduction

Malignancies of the salivary glands are uncommon and comprise 3-4% of all head and neck cancers [(1, 2)]. In the UK, the incidence was measured as 8-14 salivary gland cancers per million population [(3)]. The World Health Organisation has defined 22 subtypes, each with different clinical characteristics[(4)]. The low incidence and heterogeneity limit prospective study, and the sparsity of level I and II evidence makes it difficult to determine prognostic factors, optimise treatment, or assess long-term clinical outcome. The present study was carried out to evaluate clinicopathological determinants of oncological outcome in patients with malignant salivary gland tumours managed by curative intent with surgery.

Materials and methods

A retrospective analysis was conducted of patients with salivary gland malignancies treated at a London teaching hospital. We searched the pathology, radiation therapy and surgery databases for all major and minor salivary gland neoplasms treated by surgery from 2004 to 2019. We included only the malignant salivary gland tumours treated by primary curative-intent surgery. We excluded benign neoplasms, malignant

tumours treated by palliative intent, and patients with fewer than six months of follow-up. Clinical details, pathology, treatment and survival data were obtained from the electronic and paper medical records. Survival data were enriched in some cases by contacting GP surgeries, referring hospitals and patients or their families. There were a few patients who had a part of the definitive surgery done at another centre, and who were subsequently referred to us for completion surgery and/or neck dissection. The date of initial surgery was used for the survival analysis in these patients.

SPSS version 21 (IBM Corp®) was utilized for the statistical analysis. We assessed the distribution of various clinicopathological factors, such as age, gender, site, margin status, pT classification, pN classification, extra-nodal extension (ENE), lymphovascular invasion (LVI), perineural invasion (PNI), TNM stage of disease (AJCC, 8th Ed., 2017), and adjuvant radiation therapy. Tumours were grouped into higher-grade (carcinoma ex pleomorphic adenoma, salivary duct carcinoma, high-grade mucoepidermoid carcinoma, intermediate and high-grade adenoid cystic carcinoma, adenocarcinoma, poorly-differentiated carcinoma, squamous cell carcinoma, neuroendocrine carcinoma, spindle cell carcinoma and Merkel cell tumour) and lower-grade (acinic cell carcinoma, mammary analogue secretory carcinoma, low- and intermediate-grade mucoepidermoid carcinoma, low-grade adenoid cystic carcinoma, epithelial myoepithelial carcinoma). Margins [?] 5 mm were considered negative, 1-<5 mm were considered close, and <1 mm were considered positive. The survival analysis was conducted by the Kaplan-Meier method, and comparison between groups was determined with the log rank test. A multivariate analysis was undertaken using Cox regression to assess the impact of clinicopathological factors on overall survival (OS) and disease-free survival (DFS).

Results

During the study period, 410 patients with salivary gland neoplasms underwent surgery. Of these, 108 patients with salivary gland malignancies met the inclusion criteria. The clinicopathological data are shown in Table 1.

The median age was 57 years and 63 (58.3%) patients were male. Twelve (11.1%) patients had had definitive tumour resection prior to referral to this centre, and all subsequently had a revision resection and/or neck dissection at our centre. Among patients with parotid malignancies, 35 (40.7%) underwent partial or superficial parotidectomy, 41 (47.6%) underwent total conservative parotidectomy, and 10 (11.7%) underwent radical parotidectomy with facial nerve sacrifice. In 75 (87.2%) patients, the facial nerve was preserved.

Neck dissection was performed in 56 (51.8%) patients. Among those with parotid tumours, 35 (32.4%) underwent neck dissection. Of these, 14 (16.3%) underwent level II-III/IV dissection. A further 4 also included level I and 17 also included level V. Ten (11.6%) patients underwent selective sampling of level II alone. 50% of the patients with submandibular gland malignancies underwent neck dissection. Of these, 60% had level I-III/IV clearance while 40% underwent level V dissection as well. Among the minor salivary gland tumours, 5 (41.7%) underwent neck dissection. Of these, 80% had level I-III dissection and 20% had level II-V dissection. In addition, one patient (11.1%) had level II sampling alone.

Histological subtypes encountered are shown in Table 2. Mucoepidermoid carcinoma was the commonest histology seen (22 (20.4%) patients). This was followed by adenoid cystic carcinoma and acinic cell carcinoma (15 (13.9%) each). 71.3% had a pT1-2 tumour and 31% had a pT3-4 tumour. 75% of patients undergoing neck dissection were pN0 and 25% had N-positive disease. ENE was present in 9.3% of all cases and 37% among N-positive patients. There was no significant difference in the incidence of ENE by tumour site ($p = 0.91$).

Thirty (27.8%) patients had resection margins that were negative ([?]5 mm), 19 (17.6%) were close, and 59 (54.6%) were positive. Seventy-eight (72.2%) had either close or positive margins. When grouped by tumour grade, there was no difference in the incidence of close or positive margins (high grade, 72.7%; low grade, 71.4%). For survival analysis, we compared patients with close and negative margins to those with positive margins. 45.4% had close and negative margins and 54.6% had positive margins.

PNI was seen in 40 (37%) patients. On stratification by site, PNI was seen in 32.5% of parotid, 50% of

submandibular and 58.3% of minor salivary gland malignancies (p = 0.063). PNI was identified in 80% of adenoid cystic carcinoma, 58.3% of adenocarcinoma, 50% of salivary duct carcinoma, 40% of squamous cell carcinoma and 35.7% of carcinoma ex pleomorphic adenoma. LVI was found in 20 (18.5%) patients and there was no significant difference by site (p = 0.52). A higher incidence of LVI was seen in carcinoma ex-pleomorphic adenoma (35.7%), poorly differentiated cancers (33.3%), adenocarcinoma (33.3%), and salivary duct carcinoma (33.3%). Fifty-six (51.9%) of all patients received adjuvant radiotherapy, while 6.5% received adjuvant chemoradiotherapy. 36.7% of patients with negative margins received adjuvant therapy, whereas 57.9% of those with close margins and 67.8% with positive margins received adjuvant therapy.

Survival outcomes are summarised in Table 1 and Figures 1 and 2. The mean and median follow-up were 46.2 and 36 months. Five-year OS was 81.7%. Mean and median OS for the cohort were 116.1 months (95% CI: 99.2-133) and 128 months (95% CI: 105.4-150.6) respectively. On univariate analysis, age >50 years, pT stage 3-4, higher tumour grade, PNI, advanced TNM stage (III-IV), and adjuvant chemoradiotherapy adversely affected OS. Patients who received adjuvant radiotherapy had a superior mean OS (122.0 months) compared to those not given adjuvant therapy (101.7 months) (p = 0.025). Those who received adjuvant chemoradiation had an inferior OS (67.2 months).

When we compared patients by TNM stage (I-II versus III-IV), we found that even in early-stage disease, adjuvant radiation therapy improved the median survival (123.8 versus 114 months). In higher TNM stages, patients receiving adjuvant radiation had superior overall survival (73.3 months) compared to those treated with adjuvant chemoradiation (67.2 months) or no adjuvant therapy (44.2 months). There were no deaths in patients with submandibular gland or other minor salivary gland tumours. Owing to a lack of events, assessment based on site stratification could not be performed.

Recurrence and distant metastases were noted in 18 patients: 8 had local recurrence, 2 had regional recurrence, and 8 developed distant metastases. Of these, 13 patients were alive with disease at last known follow-up. Overall in the entire cohort, 17 (XX%) patients had died (3 from the index cancer and 14 from other causes).

At five years, 73 (71%) patients were alive and disease-free. The mean and median DFS were 98.4 months (95% CI: 82.3-114.5 months) and 118 months (95% CI: 61.4-174.6 months) respectively. DFS was found to be significantly better in patients with age <50 years, early pT classification, no PNI or LVI, lower-grade tumours, and early TNM stage (Table 1). We compared patients with close and negative resection margins to those with positive margins. Although the former had a better DFS (118 months versus 73 months), this finding was not statistically significant. Multivariate analysis using logistic regression was attempted to assess the impact of various covariates on OS and DFS using the covariates found to be significant on univariate analysis (Table 3). None of the factors was found to affect OS or DFS in a statistically significant manner.

Discussion

Owing to the rarity and heterogeneity of salivary gland malignancies, there is a paucity of high–level, large prospective studies. As a result, little information regarding the clinicopathological factors associated with these tumours and their long-term prognosis is available.

The epidemiological findings of our study are relatively consistent with those in the existing literature. The majority of our patients were male and over the age of 50 years which is similar to previous studies[5-8]{Lin, 2018 #170}. Cancers of the salivary glands are classified broadly as arising from either one of the major salivary or minor salivary glands. The most common site is the parotid gland, with an incidence ten times higher than the other glands (3). This is similar to our study, where 86% malignancies were seen in the parotid gland.

Five-year OS in the present study was 81.7% and 5-year DFS was 71%. This is in the context of over a third of patients presenting with stage III or IV cancers. In comparison, a review of the National Cancer Database (USA) reported a 5-year OS of 71%, whereas the Netherlands Cancer Registry noted OS to be 69% [9, 10].

In the UK, Public Health England reported a 5-year survival rate of 78.7%[11].

When examining the clinicopathological variables, we found that age, pT classification, tumour grade, TNM stage, PNI, and LVI significantly affected DFS. This is interesting because retrospective studies of similar size have revealed the following tumour-specific variables as indicative of a poor prognosis: T classification, positive resection margin status, PNI, involved lymph nodes, distant metastases, and a fixed neck mass [6, 12, 13]. Of these, PNI has been reported to be a prognostic factor for poor survival, a finding that is upheld by the present study. This may be linked to a greater risk of locoregional recurrence and distant metastases [14, 15]. In our study, PNI was present in almost 40% of the cohort (a third of parotid malignancies and over half of cancers at the other sites). Few studies have reported a high incidence (28.7-48%) of PNI, albeit in smaller cohorts than ours [7, 13]. Higher-grade histological subtypes were strongly associated with PNI and LVI, accounting for a poorer prognosis. In our study, contrary to others[7, 10, 11, 16], we did not find that pN classification, or the presence of ECS, affected survival. This could reflect the lower number of patients in these groups.

The resection margin in salivary gland cancers is often limited because in the presence of a functioning facial nerve and the absence of intraoperative signs of invasion the facial nerve is preserved. Sharp dissection along the perineurium allows good macroscopic resection though clearly often very close pathological margins. In the present study, DFS was comparable among patients with negative and close margins. Positive margins were associated with poorer survival, but this was not statistically significant, implying that more functional and less radical surgery may be acceptable, as long as it is followed by adjuvant therapy.

A large national cancer database review of 8,580 patients has shown that adjuvant radiotherapy improves survival regardless of TNM stage[18]. To explore this further, we categorised the patients undergoing adjuvant therapy into early- and late-stage. Nearly half of our early-stage patients (48.6%) received adjuvant radiotherapy. This was because of the presence of classical poor prognostic factors such as PNI, LVI, and higher grade. Adjuvant radiation improves survival in early and advanced stage tumours. Patients receiving adjuvant chemoradiation had poorer survival, but this was likely indicative of disease characteristics meriting aggressive adjuvant therapy. The majority of these patients had high-grade tumours, a positive margin, LVI (71.4% each) and PNI (100%). Multivariate analysis showed worse DFS for the following factors: advanced stage (HR, 2.59), presence of PNI (HR, 1.1) and age over 50 years (HR, 1.31). None of the factors had a statistically significant effect, but this was expected owing to the smaller number of patients in the subgroups as well as good survival and a low number of events.

Our study has some limitations that are associated with retrospective studies, including some missing data. The heterogeneity of data resulted in some analyses that were underpowered for the tumour subtypes. Nevertheless, our study has significant merit. The follow-up period was sufficient to capture relevant survival and recurrence-related data, the study included a larger cohort size for salivary gland malignancies from a single UK centre, and all patients were treated by a uniform philosophy from a multidisciplinary team at a major teaching hospital trust.

Conclusion

The study demonstrates that age >50 years, advanced TNM stage, and PNI and LVI are predictors of poor DFS. There was no difference in OS and DFS between patients with negative and close resection margins, indicating that close margins may be adequate for maintaining good oncological outcomes in this group of patients.

References:

1. Al-Mamgani A, van Rooij P, Verduijn GM, Meeuwis CA, Levendag PC. Long-term outcomes and quality of life of 186 patients with primary parotid carcinoma treated with surgery and radiotherapy at the Daniel den Hoed Cancer Center. International Journal of Radiation Oncology* Biology* Physics. 2012;84(1):189-95.

2. Ord RA, Ghazali N. Margin analysis: malignant salivary gland neoplasms of the head and neck. Oral and Maxillofacial Surgery Clinics. 2017;29(3):315-24.

3. Bradley PJ, McGurk M. Incidence of salivary gland neoplasms in a defined UK population. British Journal of Oral and Maxillofacial Surgery. 2013;51(5):399-403.

4. Slootweg PJ, El-Naggar AK. World Health Organization 4th edition of head and neck tumor classification: insight into the consequential modifications. Virchows Archiv. 2018;472(3):311-3.

5. Lin HH, Limesand KH, Ann DK. Current State of Knowledge on Salivary Gland Cancers. Critical Reviews in Oncogenesis. 2018;23(3-4).

6. Gutschenritter T, Machiorlatti M, Vesely S, Ahmad B, Razaq W, Razaq M. Outcomes and Prognostic Factors of Resected Salivary Gland Malignancies: Examining a Single Institution's 12-year Experience. Anticancer research. 2017;37(9):5019-25.

7. Kandaz M, Soydemir G, Bahat Z, Canyilmaz E, Yoney A. Prognostic factors and clinical outcome in parotid gland tumors: a single institution experience from the eastern black sea region of Turkey. Asian Pacific Journal of Cancer Prevention. 2016;17(3):1169-74.

8. Rapidis AD, Givalos N, Gakiopoulou H, Stavrianos SD, Faratzis G, Lagogiannis GA, et al. Mucoepidermoid carcinoma of the salivary glands.: Review of the literature and clinicopathological analysis of 18 patients. Oral oncology. 2007;43(2):130-6.

9. Ferrell JK, Mace JC, Clayburgh D. Contemporary treatment patterns and outcomes of salivary gland carcinoma: a National Cancer Database review. European Archives of Oto-Rhino-Laryngology. 2019;276(4):1135-46.

10. de Ridder M, Balm AJ, Smeele LE, Wouters MW, van Dijk BA. An epidemiological evaluation of salivary gland cancer in the Netherlands (1989–2010). Cancer epidemiology. 2015;39(1):14-20.

11. England PH. Epidemiology and management of major salivary gland cancers2016. Available from: https://kclpure.kcl.ac.uk/portal/files/77534661/Epidemiology_and_management_GIRDLER_-PublishedSeptember2016_GOLD_VoR.pdf.

12. Liu Y, Qin L, Zhuang R, Huang X, Su M, Han Z. Nodal Stage: Is It a Prognostic Factor for Submandibular Gland Cancer? Journal of Oral and Maxillofacial Surgery. 2018;76(8):1794-9.

13. Israel Y, Rachmiel A, Gourevich K, Nagler R. Kaplan–Meier analysis of salivary gland tumors: prognosis and long-term survival. Journal of cancer research and clinical oncology. 2019;145(8):2123-30.

14. Amit M, Eran A, Billan S, Fridman E, Na'ara S, Charas T, et al. Perineural spread in noncutaneous head and neck cancer: new insights into an old problem. Journal of Neurological Surgery Part B: Skull Base. 2016;77(02):086-95.

15. Terhaard CH, Lubsen H, Van der Tweel I, Hilgers F, Eijkenboom W, Marres H, et al. 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: Journal for the Sciences and Specialties of the Head and Neck. 2004;26(8):681-93.

16. Son E, Panwar A, Mosher CH, Lydiatt D. Cancers of the major salivary gland. Journal of oncology practice. 2018;14(2):99-108.

17. Guntinas-Lichius O, Silver CE, Thielker J, Bernal-Sprekelsen M, Bradford CR, De Bree R, et al. Management of the facial nerve in parotid cancer: preservation or resection and reconstruction. Eur Arch Otorhinolaryngol. 2018;275(11):2615-26.

18. Cheraghlou S, Kuo P, Mehra S, Agogo GO, Bhatia A, Husain ZA, et al. Adjuvant therapy in major salivary gland cancers: analysis of 8580 patients in the National Cancer Database. Head & neck. 2018;40(7):1343-55.

Hosted file

finaltable1.docx available at https://authorea.com/users/331061/articles/458350-malignant-salivary-gland-tumours-a-single-centre-experience

Hosted file

finaltable2.docx available at https://authorea.com/users/331061/articles/458350-malignant-salivary-gland-tumours-a-single-centre-experience

Hosted file

finaltable3.docx available at https://authorea.com/users/331061/articles/458350-malignant-salivary-gland-tumours-a-single-centre-experience