



AHNS Salivary Gland Section Edition

This Issue of the AHNS Journal Club has been compiled and reviewed by members of the AHNS Salivary Gland Section:

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[Distant metastasis of salivary gland cancer: Incidence, management, and outcomes.](#)

Mimica X, McGill M, Hay A, Karassawa Zanon D, Shah JP, Wong RJ, Ho A, Cohen MA, Patel SG, Ganly I.

*From the **Cancer**. May 2020.*

Review by Ameya Asarkar MD, Louisiana State University Shreveport

Background: Distant metastases (DMs) are the primary cause of treatment failure in patients with salivary gland carcinoma. There is no consensus on the standard treatment.

METHODS: Patients with DMs were identified from an institutional database of 884 patients with salivary gland cancer who underwent resection of the primary tumor between 1985 and 2015. Survival outcomes for patients with DMs were determined with the Kaplan-Meier method. Univariate and multivariate analyses were performed to identify factors associated with DM.

Results: Of the 884 patients identified, 137 (15%) developed DMs during follow-up. Most of the primary tumors (n = 77 [56%]) were located in a major salivary gland. At clinical presentation, 53% of the tumors were classified as T3 or T4, and 32% had clinical node metastases. The median time to DM was 20.3 months. The factors associated with shorter distant recurrence-free survival were male sex, high-risk tumor histology, and advanced pathological T and N

classifications. Patients with bone metastases had a lower survival rate than patients with lung metastases. The total number of DMs in a patient was inversely associated with survival. Patients who underwent surgical resection of DMs had a significantly higher 5-year rate of metastatic disease-specific survival than patients who underwent observation or nonsurgical treatment (44%, 29%, and 19%, respectively; $P = .003$).

Conclusions: In patients with DMs of salivary gland carcinoma, survival is negatively associated with high-grade histology, bone DMs, and the total number of DMs. Metastasectomy can help to lengthen disease-free survival.

Summary statements

- This study reviews the institutional database of 884 patients with salivary gland cancer and analyzes the incidence and outcomes of distant metastasis in these cancers. 12 patients were diagnosed with DM at presentation and 137 (15%) patients were diagnosed with DM during follow up.
- The median time to diagnosis of primary treatment was 20.3 months (1-194 months). Lungs were the most common site of distant metastasis (86/137; 63%)
- Adenoid cystic carcinoma (ACC) was the commonest histological subtype with DM (51/137; 37%)
- On multi-variate analysis significant independent predictors of shorter distant recurrence-free survival were male sex, tumor histological group (intermediate/high risk), pathological T classification, and pathological N classification.
- Median follow-up from time of DM diagnosis was 20 months (0-294 months), 2 and 5-years Metastatic Disease-Specific Survival (MDSS) were 47% and 28%, respectively.
- Patients who underwent surgical resection for DM had a higher 5-year rate of MDSS than patients who underwent observational management or nonsurgical treatment (44%, 29%, and 19%, respectively; $P = .003$)

Strengths

- This data represents patients from a single institution, thus the multidisciplinary management decisions are uniform
- Data has been stratified as per the treatment received and survival is compared among the three groups (Observation, nonsurgical, surgical)
- There was wide range of follow up of up to 194 months thus data on late occurring DM were captured as well. This is vital in ACC which runs an indolent course.

Weaknesses

- Retrospective analyses often have inherent patient and treatment biases
- As the current study included patients from 1985 to 2015, patients treated in the initial years of the study would not have been given targeted molecular therapies which are more commonly employed in the recent years in addition to other non-surgical treatments



Salivary gland pleomorphic adenoma in the Netherlands: A nationwide observational study of primary tumor incidence, malignant transformation, recurrence, and risk factors for recurrence

Valstar MH, de Ridder M, van den Broek EC, Stuiver MM, van Dijk BAC, van Velthuysen MLF, Balm AJM, Smeele LE.

From the *Oral Oncology*. March 2017.

Review by Trevor Hackman MD, University of North Carolina

Introduction: Whereas salivary gland pleomorphic adenoma (SGPA) is the most common type of salivary gland tumor, little is known about its epidemiology because national cancer registries do not register this disease.

Objectives: To establish SGPA incidence trends, rates of secondary malignant transformation and recurrence and associated factors in the Netherlands.

Materials and methods: Data on incidence, epidemiology, secondary malignant transformation, and recurrence were retrieved from the Dutch pathology registry (PALGA) for the years 1992, 1997, 2002, 2007, and 2012. Multivariate analysis was performed to discover the risk factors for recurrence.

Results: 3506 cases of SGPA were recorded implying an overall European standardized rate of 4.2-4.9 per 100,000 person-years. Our figures showed a female preponderance (1:1.43) with an annual 1% rise in female incidence (95% confidence interval [CI]: 0.2-1.8) and a bimodal age distribution in women ($p < 0.0001$). The overall 20-year recurrence rate was 6.7%, and median time to first recurrence was 7 years. Positive and uncertain resection margins and younger age at diagnosis were risk factors for recurrence, with odds ratios (ORs) of 4.62 (95% CI 2.84-7.51), 4.08 (95% CI 2.24-7.43), and 0.42 (95% CI 0.29-0.63) respectively. Tumor locations in the minor salivary glands had lower odds of recurrence than tumors in the parotid (OR 0.24; 95% CI: 0.07-0.77; $p < 0.016$). Malignant transformation occurred in 0.15% of SGPAs (3.2% of recurrences).

Conclusion: This first nationwide study clearly showed sex differences in SGPA epidemiology, possibly suggesting some underlying hormonal mechanism. Long-term recurrence risks were low, and secondary malignant transformation risks were very low.

Summary Statements

- This study is a nationwide observational analysis of salivary gland pleomorphic adenomas in the Netherlands retrieved from the Dutch pathology registry (PALGA) for the years 1992, 1997, 2002, 2007, and 2012.
- Primary objectives were to determine incidence rates and trends over time for these lesions, including a demographic breakdown. Secondary goals included analysis of demographic and surgical factors which impacted on incidence and recurrence of these lesions.

Pertinent Findings:



- Female incidence was on the rise (1% annual increase) with bimodal age distribution in women
- Incidence rate ranging between 4.2 and 4.9 per 100,000 person-years
- 4.6% first-recurrence rate after at least five years of follow-up
- 6.7% recurrence rate at 20 years of follow-up.
- Malignant transformation in 1.1% of primary & .15% of secondary SGPA's at 5 yrs.
- Risk factors for recurrence

§ positive or uncertain surgical margins

§ younger age at primary diagnosis

Mean age 40 y.o. for recurrent vs. 49 y.o. for non-recurrent

§ primary tumor location, with lower odds for minor-gland

Strengths

- Nationwide Comprehensive Database spanning multiple decades, which provided substantial data to look at incidence and trends for a specific diagnosis in a controlled population.
- Focused review of pleomorphic adenoma of all subsites
- Excellent long term follow up to assess for delayed recurrences in the national registry
- Unique findings of increasing trend of pleomorphic adenomas in females and increased risk of recurrence in younger patients (Mean age 40 y.o. vs. 49 y.o.)
- Confirmation of impact of surgical margins on recurrence, with expanded information of recurrence rates at various time points

Weakness

§ Netherland population database may not be generalizable to another population, which has unique genetic and environmental risk factors

§ Significant percentage of patients (28%) had unreported or unclear margin status

§ The authors only included histology diagnosis and exclude cytology, which may underestimate the recurrence rates

§ Lack of radiotherapy data

§ All information was obtained from non-standardized pathology reports, which potentially introduces interpretation bias with respects to margin status.

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Predictors of Nodal Metastasis in Parotid Malignancies: A National Cancer Data Base Study of 22,653 Patients

Xiao CC, Zhan KY, White-Gilbertson SJ, Day TA.

From the JAMA Otolaryngology Head Neck Surg. January 2016.

Review by William Ryan MD, University of California San Francisco

Objective: (1) To identify predictors of nodal disease in parotid malignancies using various clinical and pathologic variables. (2) To examine the effect of nodal disease on overall survival (OS) in parotid cancers.

Subjects and Methods: We identified all cases of primary parotid malignancies in the United States between 1998 and 2012 in the National Cancer Data Base. Eight histopathologies, constituting >80% of all cases, were examined for nodal metastasis and survival.

Results: We identified 22,653 cases of primary parotid cancer. Eight major histologies were studied, with mucoepidermoid carcinoma (31%), acinic cell carcinoma (18%), adenocarcinoma (14%), and adenoid cystic carcinoma (9%) being most common. Regional nodal disease incidence was 24.4% overall and varied by histopathology. Salivary ductal carcinoma had the highest incidence of both nodal metastasis and occult lymph node metastasis. Overall, N0 patients lived significantly longer than N+ (5-year OS, 79% vs 40%; $P < .001$). Low-grade disease had significantly better survival than high-grade (5-year OS, 88% vs 69%; $P < .001$). Occult nodal disease was found in 10.2% and varied by histopathology.

Conclusion: Regional lymph node metastasis significantly decreases survival in many parotid malignancies. High-grade cancers had higher incidences of regional disease than did low grade. Adenocarcinoma had the highest mortality when regional disease was present. Incidence of occult disease varied by histology, but incidence was <10% for all low-grade disease. High T stage and grade are significant independent predictors of nodal disease for most histopathologies.

Summary Statement

This is a retrospective analysis of the national cancer database (NCDB) evaluating neck dissection specimens for various parotid malignancies to determine the likelihood of overt neck metastases and occult metastases and the risk factors for them. Overall survival for parotid malignancies is also assessed. The information gleaned from this study are helpful in determining which patients meet indications for elective neck dissections or elective neck irradiation in parotid malignancies.

Strengths

This study's main strength is the practical information it provides to clinicians to help manage the neck in cases of parotid malignancy. The generalizability of the results are enhanced by the large sample size, multi-institutional nature of the NCDB, the focus on parotid malignancies only (as opposed to being a combination of salivary carcinomas), and the focus on the 8 most



common types of parotid carcinoma. This study, thereby, provides corroborative evidence to the body of literature of other single-institution and smaller-sample-sized retrospective studies that show the indications for elective neck dissections to be with high grade and advanced T-stage parotid malignancies. Noteworthy exceptions to meeting indications for elective neck dissection included all basal adenocarcinomas and epithelial-myoepithelial carcinomas.

Weaknesses

The NCDB carries with it the possibility of misclassification of data entry given the lack of study-specific verification; however, the NCDB is known to be of high quality. We do not know the imaging modality or process by which radiologists assessed clinical nodal positivity nor if cytologic confirmation was attained across the multitude of institutions in the NCDB. The extent of neck dissections is not known thus bringing on the possibility of selection bias. Also, better determination of the extent of elective and therapeutic neck dissections cannot be assisted by the NCDB data. The NCDB only shows overall survival data; thus, recurrence information and disease-specific survival were not assessed.

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Management of Salivary Gland Malignancy: ASCO Guideline

Geiger JL, Ismaila N, Beadle B, Caudell JJ, Chau N, Deschler D, Glastonbury C, Kaufman M, Lamarre E, Lau HY, Licitra L, Moore MG, Rodriguez C, Roshal A, Seethala R, Swiecicki P, Ha P.

*From the **Journal Clinical Oncology**. June 2021.*

Review by Kiran Kakarala MD, University of Kansas

Purpose: To provide evidence-based recommendations for practicing physicians and other healthcare providers on the management of salivary gland malignancy.

Methods: ASCO convened an Expert Panel of medical oncology, surgical oncology, radiation oncology, neuroradiology, pathology, and patient advocacy experts to conduct a literature search, which included systematic reviews, meta-analyses, randomized controlled trials, and prospective and retrospective comparative observational studies published from 2000 through 2020. Outcomes of interest included survival, diagnostic accuracy, disease recurrence, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

Results: The literature search identified 293 relevant studies to inform the evidence base for this guideline. Six main clinical questions were addressed, which included sub questions on preoperative evaluations, surgical diagnostic and therapeutic procedures, appropriate radiotherapy techniques, the role of systemic therapy, and follow-up evaluations.

Recommendations: When possible, evidence-based recommendations were developed to address the diagnosis and appropriate preoperative evaluations for patients with a salivary gland malignancy, therapeutic procedures, and appropriate treatment options in various salivary gland histologies. Additional information is available at www.asco.org/head-neck-cancer-guidelines.



Summary Statements:

This set of guidelines regarding the work-up and management of salivary malignancies was produced by a multi-disciplinary expert panel convened by the American Society of Clinical Oncology (ASCO). The panel included head and neck surgeons, radiation oncologists and medical oncologists. Evidence from the literature from 2000-2020 was used to guide discussions and arrive at expert panel consensus. Guidelines are laid out with varying degrees of evidence and strength behind them regarding common surgical questions such as extent of parotidectomy, management of the facial nerve, and the role of neck dissection in the management of salivary cancers. The role of adjuvant radiotherapy and chemotherapy in the primary and recurrent/metastatic setting are also addressed.

Strengths:

- A multi-disciplinary expert panel with representation from surgery, radiation oncology and medical oncology provides comprehensive guidelines for the management of salivary cancers.
- The full spectrum of care is addressed including work-up (imaging, FNA), surgery, radiation, chemotherapy, targeted therapies, and surveillance.
- Areas of weakness in the literature are highlighted, perhaps laying the groundwork for future research.
- The guidelines underscore the importance of treating salivary cancers in the multi-disciplinary setting.

Weaknesses:

- The literature relied upon is overwhelmingly retrospective in nature (229 out of 293 included articles), illustrating the relative dearth of high-quality evidence to guide management of salivary gland cancers.
- The role of reconstructive surgery to maximize cosmetic and functional outcomes (including facial nerve reconstruction and rehabilitation) is not addressed.

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[Sialendoscopy in Chronic Obstructive Sialadenitis Without Sialolithiasis: A Prospective Cohort Study](#)

Plonowska KA, Ochoa E, Ryan WR, Chang JL.

From the Otolaryngol Head Neck Surg. March 2021.

Review by Alexandra E. Kejner MD, University of Kentucky

Objectives: To evaluate long-term chronic sialadenitis symptoms in patients without sialolithiasis following sialendoscopy-assisted salivary duct surgery (SASDS) compared to a control group managed conservatively.

Methods: Thirty-six patients (52 glands) with chronic sialadenitis without sialolithiasis completed the Chronic Obstructive Sialadenitis Symptoms (COSS) questionnaire at presentation

and at 3-month time intervals thereafter for 1 year. Lower COSS scores represent lower symptom severity. We compared 27 patients who underwent SASDS to 9 control patients who elected conservative management.

Results: COSS gland-specific scores from 38 SASDS-treated glands (cases) and 14 control glands were similar at baseline. At 6 to 12 months (mean, 8.4 months), the surgically treated group had significantly lower scores and a greater score reduction from baseline compared to controls (mean score change [95% confidence interval] cases: 20.7 points [15.7-25.8]; controls: 11.7 points [4.9-18.4]; $P = .04$). There was a significant difference in scores between the 2 groups over time ($P < .001$). A greater proportion (72%) of cases reported partial or complete resolution of overall sialadenitis symptoms at 6 to 12 months compared to the controls (22%, $P < .05$).

Conclusion: Compared to patients electing for conservative management, patients with sialadenitis without sialolithiasis treated with SASDS had improved symptom scores and a greater reduction of symptom severity after 6 months. With SASDS, patients had higher rates of significant overall symptom improvement. In evaluating chronic sialadenitis, assessment at multiple time points is necessary to capture the intermittent and cyclical pattern of obstructive symptoms.

Keywords: Chronic Obstructive Sialadenitis Symptoms (COSS) questionnaire; outcomes; salivary duct stenosis; sialadenitis; sialendoscopy.

Summary Statement

- This is a prospective cohort study which was self-randomized, controlled trial. Patients were eligible for participation if they had 1) chronic obstructive sialadenitis without sialolithiasis (recurrent, episodic pain/swelling of salivary gland and no evidence of sialolith on exam/imaging) 2) no history of external beam radiation 3) no history of prior salivary surgery or procedures.
- Eligible patients were offered both conservative versus surgical management and then elected which arm they wanted to pursue. They were then followed every 3 months for 1 year. Surgical management consisted of sialendoscopy with interventions including sialodochotomy with sialodochoplasty for stenotic papilla, balloon dilatation, intraductal triamcinolone, possible stent placement, and for those with refractory symptoms, Botox injection to the affected gland. No repeat sialoendoscopy was performed during the study period. Conservative management consisted of gland massage, sialogogues, oral hydration, and avoidance of drying medication when possible
- The COSS (validated obstructive salivary disease questionnaire) is a validated questionnaire validated for patients with obstructive sialadenitis with a final score of 0-50. 10 specific questions assess pain/swelling/severity/frequency and then 10 questions regarding impact on QOL. Likert scale was also utilized.
- The authors found that symptom scores were significantly improved in patients undergoing operative management of their obstructive symptoms compared to those that continued conservative management.



Strengths

This study's main strength is the prospective aspect with a measurable outcome via a validated questionnaire. Prospective surgical trials are rare and assessing an intervention in the context of conservative management in this patient population is valuable, especially in the absence of a visible stone. Additionally, this may increase gland-sparing as an option for patients with chronic sialadenitis.

Weaknesses

The main weakness of this trial is that the surgical plans for those on the intervention arm were varied and not standardized. Some patients had dilation, some had stents placed, some had sialodochoplasty. However, this does indicate that with sialoendoscopy, a disorder that might not be recognized on ultrasound or other imaging may be recognized and treated and indicative that perhaps those with obstructive symptoms may benefit from evaluation and that sialoendoscopy-directed interventions are superior to conservative measures. Other weaknesses include the small sample size and self-randomization. Those with worse symptoms may be more likely to pursue surgical management and thus have more apparent findings on sialoendoscopy.

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