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This Issue of the AHNS Journal Club has been compiled and reviewed by members of the
AHNS Salivary Gland AHNS Salivary Gland Section:
(Danny Enepekides, Chair MD, MPH &, Kiran Kakarala MD, Vice-Chair)

Contributing Members*:*
William Ryan MD,
Pavel Dulguerov MD,
Becky Massey MD,
Ashok Jethwa MD,
Marco Mascarella MD,
Neerav Goyal MD

Dear Colleagues,

The AHNS ***Salivary Gland Section*** is pleased to present the issue of the AHNS Journal Club.

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Outcomes of Carcinoma Ex Pleomorphic Adenoma Compared to De Novo Adenocarcinoma of Major Salivary Glands

Patel EJ, Oliver JR, Liu C, Tam M, Givi B

From the **J Surg Oncol.** *February 2021.*

Background and objectives: Carcinoma ex pleomorphic adenoma (CXPA) is a rare disease of the major salivary glands that remains poorly characterized. Our objective was to compare the clinical outcomes of patients with CXPA of the major salivary glands to those with de novo adenocarcinomas.

Methods: Review of the NCDB between 2004 and 2016 to compare cases of CXPA and adenocarcinoma of major salivary glands. Demographics, clinical characteristics, and survival were analyzed.

Results: We identified 1181 patients with CXPA and 3326 patients with adenocarcinoma of major salivary glands. Adenocarcinomas presented with higher rates of nodal metastasis (54.7% vs. 30.4%, $p < .001$). Five-year survival of adenocarcinoma (55.8%) was worse than that of CXPA (68.5%, $p < .001$). When stratified by nodal status, there was no significant difference in 5-year survival between CXPA and adenocarcinoma node-negative (75.3% vs. 71.6%, respectively) and node-positive (40.4% vs. 36.1%, respectively) patients.

Conclusions: CXPAs of the major salivary glands present at an earlier stage with lower rates of regional metastasis compared to adenocarcinomas. After controlling for lymph node metastases, the outcomes are quite similar.

Summary Statement
This is a retrospective analysis of the national cancer database (NCDB) from 2004-2016 through a careful selection process evaluating overall survival of carcinoma ex pleomorphic adenoma (CXPAs) and adenocarcinoma of major salivary glands in comparison. Demographic, stage presentation tendencies, and treatment characteristics are presented thereby likely reflecting the general United States burden of these diseases over that time span. In comparison to CXPAs, adenocarcinomas have higher rates of presenting with nodal metastases and worse 5-year survival that is likely due to the nodal metastases. Adenocarcinomas and CXPAs have similar node negative and node positive 5-year survival outcomes. Treatment types for the two cancers have been similar over that period, mostly being surgery without or without adjuvant radiation. Age, high-grade tumors, advanced stage, and positive margins were independent risk factors for death. For CXPA, T3-T4 tumors and high-grade tumors were independently associated with having lymph node metastases. The information gleaned from this study are helpful in better understanding these rare salivary cancers.

Strengths
This study's main strength is in providing more information about CXPAs and adenocarcinomas given that they are rare cancers with limited data available to understand them. The

generalizability of the results is enhanced by the large sample size, multi-institutional nature of the NCDB, and the focus on these two malignancies.

Weaknesses
The NCDB carries with it the possibility of misclassification of data entry given the lack of study-specific verification and the general errors possible with the subjectivity of differentiating between CXPA and adenocarcinoma. The NCDB only assesses overall survival as an oncologic outcome. Thus, recurrence information and disease-specific survival are not available for the study.

Radiation Therapy After Surgical Resection Improves Outcomes for Patients with Recurrent Pleomorphic Adenoma

Nicholas SE, Fu W, Liang AL, DeLuna R, Vujaskovic L, Bishop J, Page BR, Quon H, Gourin C, Fakhry C, Eisele D, Kiess AP.

From the **Adv Radiat Oncol.** *March 2021.*

Background: Pleomorphic adenoma is a benign salivary tumor that may recur multifocally. Recurrent pleomorphic adenoma surgery remains challenging with increased re-recurrence rates, increased rates of permanent facial paralysis, and a risk of transformation into carcinoma ex pleomorphic adenoma. In case series, the benefit of adjuvant radiation therapy (RT) for recurrent pleomorphic adenoma remains unclear.

Methods and materials: Patients who received diagnoses of recurrent pleomorphic adenoma between 1980 and 2016 were identified using an institutional pathology database. Medical records were retrospectively reviewed to determine clinical, operative, pathologic, and imaging characteristics. Kaplan-Meier methods were used to estimate local control after surgery, stratified by completeness of resection and receipt of adjuvant RT. The association of variables with risk of subsequent local recurrence was analyzed using Cox proportional hazards model, and variance estimates were calculated to account for multiple recurrences in the same patient. Toxicities were prospectively recorded in a departmental database.

Results: A total of 49 patients presented with at least 1 recurrence, of which 28 were managed with surgery alone, and 21 were treated with surgery and RT. The median follow-up time after the initial recurrence was 48 months (range, 6-531 months). There were 35 subsequent recurrences; 34 after surgery alone and only 1 after surgery with RT. On multivariate analysis, adjuvant RT was associated with decreased risk of recurrence (hazard ratio, 0.09; 95% confidence interval, 0.02-0.41, $P = .002$), whereas increasing number of prior recurrences was associated with increased risk (hazard ratio, 1.23; 95% confidence interval, 1.13-1.35, $P < .001$). Common toxicities of RT included dermatitis, xerostomia, and mucositis.

Conclusions: For patients with recurrent pleomorphic adenoma, the addition of adjuvant RT after surgery is associated with a significant decrease in risk of subsequent tumor recurrence.

Summary Statement: This is a retrospective study of consecutive, not selected patients, spanning 36 years. Since a prospective randomized trial on this problem is probably not feasible, this study represents the best evidence of the utility of adjuvant radiotherapy for recurrent pleomorphic adenoma. The control following radiotherapy seems impressive, with few re-recurrences.

Strengths:

- Comparison of radiated and non-radiated patients treated in the same institution
- Consecutive non-selected patients
- About half of the patients were already at their second recurrence and thus having a high chance of further recurrences.
- Good follow-up

Weaknesses:

- Retrospective cohort
- Series spanning 36 years with marked variations for the indication of radiotherapy
- Insufficient follow-up

Extent and Indications for Elective and Therapeutic Neck Dissection for Salivary Carcinoma

Kejner AE, Harris BN.

From **Otolaryngology Clin North Am.** *June 2021.*

Background:
Although salivary gland malignancies account for only a small percentage of all head and neck cancers, the incidence is increasing. Furthermore, there is a wide variety of histologic subtypes which must be taken into account in the context of their location. Each is associated with a different rate of regional metastasis and overall survival. This article examines the incidence of salivary gland malignancies and provides evidence for the indications for and extent of elective or therapeutic neck dissection based on location, pathologic type, and histopathologic characteristics.

Purpose: Salivary gland malignancy has a low incidence and includes a variety of histologic subtypes with widely varying rates of neck metastasis. The purpose of this paper is to understand the indications for neck dissection for salivary gland carcinoma.

Methods: Because the rate of occult neck metastases varies based on subsite and histopathology, the authors sought to determine which neoplasms were associated with a high enough occult metastasis rate to require neck dissection. Case series, systematic review, SEER and NCDB studies were used to describe the rate of malignancy by site and then the rate of occult metastases by tumor type/site.

Recommendations: Mucoepidermoid, adenoid cystic and acinic cell carcinoma were confirmed as the most common salivary gland malignancies.
Elective neck dissection for major salivary gland carcinoma is recommended for high grade pathology (high grade mucoepidermoid carcinoma, salivary duct carcinoma, carcinoma ex pleomorphic, adenocarcinoma), T3/T4 acinic or adenoid cystic carcinoma and for high-risk clinical features of facial nerve or extra-parotid involvement. END is also recommended in cases where there is high grade transformation but this is not usually known until after the definitive surgery.

Elective neck dissection for high grade minor salivary gland carcinoma is indicated for extra-palatal oral cavity and nasopharyngeal malignancies but not larynx or trachea. PLGA variant, cribriform adenocarcinoma of minor salivary gland (CASMG), low grade outlier with recommendation for elective neck dissection due to ~50% risk neck metastasis.

Recommendations for extent of elective and therapeutic neck dissection were basically by historical pattern of drainage per site.

Summary Statement:
This chapter style Clinics paper sought to better delineate when neck dissection is indicated for salivary gland malignancy with additional attention to minor salivary glands for which indications are not easily discerned by the current NCCN guidelines.
The threshold for needing neck dissection was extrapolated from mucosal disease with a threshold risk of occult metastasis of 15 to 20%. The most common tumors were then described by site and histology. Neck dissection recommended for the very high-grade histologic tumors, for adverse primary features and advanced stage adenoid cystic and acinic cell. Note made of low risk of metastasis in submandibular adenoid cystic.

Strengths:
There were large series and database numbers for the adenoid cystic incidence and nodal metastasis information. The special cases of CASMG with high rate of metastasis and low rate in submandibular adenoid cystic carcinoma helpful to know.

Weakness:
There is not good data on the rate of occult metastasis which is an inherent weakness for this subject. The rate of occult metastasis and recommendations for acinic cell were confusing and seem discordant.
Newer WHO classifications and better type classification with recognized genomic alterations will likely make extrapolation from historical data difficult. The recommendations for extent of neck dissection in both elective and therapeutic necks are based on historical patterns.

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The Underappreciated Role of Auriculotemporal Nerve Involvement in Local Failure Following Parotidectomy for Cancer

Swendseid BP, Philips RHW, Rao NK, Goldman RA, Luginbuhl AJ, Curry JM, Keane WM, Cognetti DM

From **Head Neck.** *November 2020.*

Background: Locoregional recurrence rates following parotidectomy for cancer remain as high as 20-30%. The auriculotemporal nerve (ATN) may allow parotid cancers to spread from the facial nerve (FN) toward the skull base, causing local recurrence.

Methods: Retrospective review of 173 parotidectomies for malignancy. Preoperative and post-recurrence imaging were reviewed by a neuroradiologist for signs of tumor adjacent to the ATN.

Results: Clinical and imaging signs of possible ATN involvement correlated with FN weakness and sacrifice. Eight patients had pathologically confirmed tumor from the ATN or V3. Forty-four percent of local recurrences had post-recurrence imaging showing tumor along the course of the ATN. Locoregional failure along the ATN was also associated with preoperative FN weakness, intraoperative FN sacrifice, and failure to complete recommended adjuvant therapy.

Conclusions: Parotid cancers may invade the FN and spread to the skull base via the ATN. If not appropriately managed, this may lead to local recurrence.

Summary Statement

- This is a retrospective cohort study including 173 patients who underwent parotidectomy with pathologic confirmation of malignancy between 2012-2018.
- The purpose of the study was to use clinical signs, preoperative imaging, post-recurrence imaging, operative notes, and pathology reports to characterize the frequency of ATN involvement and its effect on tumor recurrence after parotidectomy.
- The primary outcome was local recurrence and secondary outcome was local recurrence along the course of the ATN.
- Clinical signs of possible ATN involvement (preauricular pain, numbness, otalgia, or jaw pain) were present in 57 patients (32.9%).
    - This was associated with preoperative FN weakness, PNI, and identification of the ATN intraoperatively.
- Seventy patients (40.5%) had tumor adjacent to the course of the ATN on preoperative imaging (posterior border of masseter, deep lobe of parotid, infratemporal fossa, Meckel's cave).
    - This was associated with preoperative FN weakness, PNI, intraoperative FN sacrifice, and ATN identification intraoperatively.
- Eight patients had pathologically involved ATN or V3 and all received adjuvant radiation therapy
    - All 8 patients required sacrifice of at least the upper division of the facial nerve
    - In 2 patients, a negative margin was obtained. In 6 patients, a positive margin was left at the skull base

    - Two patients suffered local recurrences at 2 years and 1 patient recurred distally at 5 months
- Local recurrence occurred in 25 patients.
    - Of these, 14 (56%) recurred in an area adjacent to the ATN course.
- Univariate associates with local recurrence-free survival included recurrent tumor, intraoperative FN sacrifice, T classification, ENE, and inability/refusal to complete adjuvant therapy. Recurrent tumor and inability/refusal of adjuvant therapy remained significant on multivariate analysis.
- Univariate associates with recurrence along the ATN included preoperative FN weakness, preoperative imaging consistent with tumor along the ATN, intraoperative FN sacrifice, T classification, ENE, positive margins, and inability/refusal to complete adjuvant therapy. Refusal of adjuvant therapy remained significant on multivariate analysis.

Strengths

- The greatest strength of this paper is that it raises awareness of the ATN and its importance as a pathway of spread that needs to be treated with local therapy
- One of just a few studies describing the relationship of the ATN and parotid malignancy
- First study, to my knowledge, to evaluate the effect of ATN involvement on recurrence rates of parotid malignancies
- Excellent description of the anatomy of the ATN
- This study supports prior pathologic risk factors for salivary malignancy
- Suggests the importance of including the ATN pathway in the radiation treatment field as about half of recurrences were along the course of the ATN
- Novel manner to evaluate local pattern of failure in parotid malignancies along the ATN. Also, the authors suggest possible options to address this region surgically in cases of ATN involvement.
- Large cohort for overall rare malignancies with a reasonable follow-up of patients (19 months) with parotid malignancies.

Weaknesses

- Involvement of ATN was predicted by tumor proximity to the ATN on imaging. Proximity of a tumor to a nerve on imaging does not always predict nerve involvement. Apart from V3 thickening, foramen ovale enlargement, or involvement of Meckel's cave, definitive invasion of the ATN is challenging to diagnose radiologically.
- It is not standard to identify the ATN during parotidectomy and as a result, the authors do not have pathologic evaluation of each patient's ATN
- Small number of patients with recurrence limits the data analysis
- Retrospective study from a single institution which allows for potential surgical selection and information biases (operative candidate, resectability, etc).
- Given the rarity of parotid tumors, there is a heterogeneity of both patients (treatment-naïve and recurrent) and tumor types (primary parotid malignancy, skin metastasis to parotid lymph nodes) which may limit the internal and external validity of the study.

- As mentioned by the authors, symptoms related to ATN involvement (preauricular pain, numbness or jaw pain) are non-specific and likely common in patients with a parotid malignancy.
- No information regarding radiation treatment field/dosing
- Unknown if V3, ATN, or Meckel's cave was included in the adjuvant radiation treatment field
- Did not report number of patients who "refused" adjuvant therapy

Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Salivary Glands

Skálová A, Hyrcza MD, Leivo I

From the **Head Neck Pathol.** *March 2022.*

Abstract: The salivary gland section in the 5th edition of the World Health Organization Classification of Head and Neck Tumours features a description and inclusion of several new entities, including sclerosing polycystic adenoma, keratocystoma, intercalated duct adenoma, and striated duct adenoma among the benign neoplasms; and microsecretory adenocarcinoma and sclerosing microcystic adenocarcinoma as the new malignant entities. The new entry also includes mucinous adenocarcinoma subdivided into papillary, colloid, signet ring, and mixed subtypes with recurrent AKT1 E17K mutations across patterns suggesting that mucin-producing salivary adenocarcinomas represent a histologically diverse single entity that may be related to salivary intraductal papillary mucinous neoplasm (IPMN). Importantly, the number of entities in the salivary chapter has been reduced by omitting tumors or lesions if they do not occur exclusively or predominantly in salivary glands, including hemangioma, lipoma, nodular fasciitis and hematolymphoid tumors. They are now discussed in detail elsewhere in the book. Cribriform adenocarcinoma of salivary gland origin (CASG) now represents a distinctive subtype of polymorphous adenocarcinoma (PAC). PAC is defined as a clinically, histologically and molecularly heterogeneous disease group. Whether CASG is a different diagnostic category or a variant of PAC is still controversial. Poorly differentiated carcinomas and oncocytic carcinomas are discussed in the category "Salivary carcinoma not otherwise specified (NOS) and emerging entities". New defining genomic alterations have been characterized in many salivary gland tumors. In particular, they include gene fusions, which have shown to be tightly tumor-type specific, and thus valuable for use in diagnostically challenging cases. The recurrent molecular alterations were included in the definition of mucoepidermoid carcinoma, adenoid cystic carcinoma, secretory carcinoma, polymorphous adenocarcinoma, hyalinizing clear cell carcinoma, mucinous adenocarcinoma, and microsecretory adenocarcinoma.

Introduction: Recognizing the diversity of neoplasms within the major and minor salivary glands, this article provides a summary of the updates in classification of these neoplasms between the 4th and 5th editions of the WHO Classification of Head and Neck Tumors.
The new benign classifications include:

- Keratocystoma

- Intercalated duct adenoma
- Striated duct adenoma
- Sclerosing polycystic adenoma - reclassified as a benign neoplasm.

The new malignant pathologies include:

- Microsecretory adenocarcinoma
- Sclerosing microcystic adenocarcinoma

The authors also note the increasing routine nature of molecular testing to classify salivary gland tumors. They recommend the use of the Milan system in classifying Fine Needle Aspirations (FNA). FNA is limited in having less architectural information than a core, however, they note that core biopsies often fail to distinguish between benign tumors and low-grade malignancies as they cannot capture the interface between the tumor and surrounding tissues. Histologic grading continues to be an important part of pathologic reporting as it impacts prognosis and management, however, a universal grading is not recommended across tumor types due to differences in biologic behavior.
They note several unresolved controversies following the publication of the 5th edition:

- Whether intraductal papillary mucinous neoplasm is a separate entity from mucinous adenocarcinoma though it often has the ATK1 mutation that mucinous adenocarcinomas are characterized by
- Whether intraductal carcinoma represents a biphasic neoplasm as occasionally these tumors extend beyond the ductal system and can have a loss of myoepithelial cells
- The classification of oncocytic carcinoma remains controversial and these tumors may instead be oncocytic variants of other tumor types when molecular testing is performed
- Carcinosarcoma remains a separate entity but may represent an epithelial-mesenchymal transition of another neoplasm and not a true sarcoma

New Entries in the 5th edition WHO

- Sclerosing Polycystic Adenoma (SPA)
    - This is a sclerosing tumor with histologic features similar to fibrocystic changes, sclerosing adenosis and adenosis tumor of the breast. These findings include fibrosis, cystic alterations, apocrine metaplasia, proliferations of ducts and acini with abundant eosinophilic granules, and myoepithelial cells of variable proportions. Mutations in the PI3K pathway is common, often in *PTEN*. This process has not been reported to be associated with metastatic disease, however invasive carcinoma has been seen with apocrine ductal carcinoma. There is a suggested close relationship between SPA, apocrine intraductal carcinoma, and high grade invasive salivary ductal carcinoma – suggesting it may even be a precursor to these pathologies
- Keratocystoma
    - This is a benign tumor with multicystic spaces lined by stratified squamous epithelium with keratotic lamella and focal solid epithelial nests. These tumors need to have bland lining without a granular layer within the cystic structures and sharply defined solid epithelial cell islands. They have only been identified in the parotid gland to date with a differential including squamous cell carcinoma,

mucoepidermoid carcinoma, metaplastic Warthin tumor and necrotizing sialometaplasia.

- Intercalated Duct Adenoma (IDA)
    - This is a benign proliferation of bilayered ducts with a cytologic appearance of normal intercalated ducts. IDA is on the spectrum of intercalated duct lesions which includes intercalated duct hyperplasia. The tumors stain positive for myoepithelial markers and cytokeratin 7, s100 (majority of tumors) and focal positivity for lysozyme and estrogen receptor. IDA differs from hyperplasia with the presence of a discrete partially or completely encapsulated tumor. This entity may be a precursor to other salivary tumors, which is supported by the presence of hybrid tumors. The main differential is basal cell adenoma which can be larger and show bilayering, prominent spindle sell stroma with prominent s100 expression in these cells and weak expression in the luminal cells.
- Striated Duct Adenoma
    - This is a benign encapsulated tumor with closely apposed ducts composed of a monolayer of cells resembling a normal striated duct with little to no stroma. They do not contain myoepithelial or basal cells. The cytoplasm is eosinophilic, and tumors are positive for S100, cytokeratin 7, cytokeratin 5 and negative for smooth muscle actin, with single cell p63 positivity. There can be features mimicking papillary thyroid cancer. There are fewer than 10 reported cases.
- Microsecretory adenocarcinoma (MSA)
    - It is a newly identified low grade salivary adenocarcinoma with a fusion of *MEF2C::SS18*. This tumor was previously within the adenocarcinoma, NOS category. Morphologic features that are present include small tubules, microcysts with flat duct-like cells, and basophilic luminal secretions, with uniform, oval nuclei and a lack of prominent nucleoli. These tumors are without a capsule and tend to have focal infiltration. 24 cases to date have been described, and none have shown a recurrence or metastases. The fusion gene can be evaluated using fluorescence in situ hybridization. The tumor is also positive for S100, SOX10, and p63, and negative for p40, calponin, SMA, mammaglobin. In contrast to these tumors, adenoid cystic carcinoma is biphasic, secretory carcinoma lacks myxoid stroma, polymorphous carcinoma lacks the microsecretory pattern.
- Sclerosing Microcystic Adenocarcinoma (SMA)
    - This rare malignant tumor demonstrates morphology similar to cutaneous microcystic adnexal carcinoma and has been reported minor salivary glands without documented local recurrence or distant metastases. It has small infiltrative cords and nests with the majority of the tumor volume consisting of a thick stroma. It is a biphasic tumor with bland ductal cells with eosinophilic to clear cytoplasm, flat peripheral myoepithelial cells and bland nuclei. Perineural invasion is common with rare mitoses. Luminal cells are positive for cytokeratin 7, while the other cells are positive for s100, smoot muscle actin, p63 and p40. Molecular testing can show a *MYB* gene rearrangement.

New concepts/Controversies/Emerging Entities

- Intraductal Carcinoma (IC)
    - Previously known as "low grade salivary duct carcinoma" and "low grade cribriform cystadenocarcinoma," IC is a rare low grade salivary gland malignancy with features similar to atypical ductal hyperplasia or ductal carcinoma in situ of the breast. The tumor demonstrates intraductal and intracystic proliferation of ductal cells in solid, cribriform, and papillary patterns with these luminal cells having S100 and SOX10 positivity. IC tumors tend to have *RET* gene rearrangements, with more novel fusions more recently identified
- Polymorphous Adenocarcinoma (PAC)
    - Previously known as "polymorphous low grade adenocarcinoma", PAC has an infiltrative growth pattern predominantly seen in minor salivary glands. The cribriform subtype also known as cribriform adenocarcinoma has been seen in the base of tongue and minor salivary glands and has multinodular growth pattern separated by fibrous septa. PAC is associated with gene point mutations in protein kinase D1 (*PRKD1*) while the cribriform subtype is associated with gene rearrangements in the *PRKD1, PRKD2, or PRKD3* genes. There is some controversy whether the cribriform type is a subtype or a separate entity of PAC.
- Mucinous Adenoma (MA) and Intraductal Papillary Mucinous Neoplasm (IPMN)
    - MA is a primary adenocarcinoma with evidence of mucin without other features of other salivary gland carcinomas and is typically seen in oral minor salivary glands with the presence of a *AKT1* E17K mutation. IPMNs are a proposed entity which have this mutation in low grade proliferations of intraductal epithelium with a mucinous component. There is controversy as to whether IPMN represents a distinct entity, a precursor lesion, or a variant of MA.

Summary:

For the head and neck surgeon and the head and neck pathologist, recognizing and incorporating newly identified classifications as well as changes to existing classifications are important. Additionally, there is an increasing importance on the use of immunohistochemistry as well as mutational profiling in appropriately classifying salivary gland tumors as noted in the 5th edition.

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