Salivary Gland Tumor Fine-Needle Aspiration Cytology

A Proposal for a Risk Stratification Classification

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ABSTRACT

Objectives: *Fine-needle aspiration (FNA) is useful in the evaluation of salivary gland tumors, but currently no standard terminology or risk stratification model exists.*

Methods: *FNA smears were reviewed and categorized based on cytonuclear features, stromal characteristics, and background characteristics. Risk of malignancy was calculated for each category. Classifications as benign, neoplasm of uncertain malignant potential (NUMP), suspicious for malignancy, and positive for malignancy were used to aggregate categories into similar risk groups.*

Results: *Categorization of salivary gland aspirates into morphologic categories resulted in the expected risk stratification. Grouping of categories maintained risk stratification, providing classes with malignancy risk as follows: benign, 2%; NUMP, 18%; suspicious for malignancy, 76%; and positive for malignancy, 100%.*

Conclusions: *Salivary gland FNA categorization into commonly encountered morphologic categories provides risk stratification, which translates to a simplified classification scheme of benign, NUMP, suspicious, and positive for malignancy similar to the paradigm in other organ systems.*

Salivary gland fine-needle aspiration (FNA) cytology has become an accepted method of evaluating salivary gland tumors preoperatively. Despite the relative rarity of these tumors, there is a wealth of literature on the diagnostic performance of FNA for salivary gland tumors. In a comprehensive meta-analysis, FNA of parotid gland tumors was shown to have a high specificity in differentiating benign and malignant lesions (97%) and in differentiating nonneoplastic from neoplastic lesions (98%).[1] Thus, FNA of salivary gland tumors has the potential to limit the need for surgery in nonneoplastic lesions that can often be followed clinically.[2] Indeed, a separate meta-analysis suggested that inclusion of salivary gland FNA in clinical decision making can reduce the overall cost of treating salivary gland tumors.[2] In addition, FNA can be used complementarily with intraoperative frozen section to help define the extent of initial surgery.[3,4]

Despite these strengths, the mediocre to poor performance of salivary gland FNA in providing specific diagnoses is also well documented.[5,6] Even when only the ability of salivary gland cytology in detection of malignancy is considered, FNA falls flat in terms of sensitivity (80%[1]; for comparison, the sensitivity of frozen section is noted to be 90%[3]). In addition, it has been noted that there is considerable performance heterogeneity across 64 studies included in the aforementioned meta-analysis.[1] Therefore, these aspects of salivary gland FNA—namely, the low sensitivity and high performance heterogeneity—show the greatest room for improvement, but the reasons behind these apparent limitations are multifactorial. While it is plausible that procedural performance, experience, and actual cytonuclear criteria for specific diagnoses can be improved somewhat, ultimately the intrinsic limitations (sampling, lack of architectural elements, and cytomorphologic overlap) among a variety of salivary gland lesions are likely to continue to represent effective barriers to diagnostic improvement. We postulate that a modification of the basic framework in which salivary gland FNA findings are interpreted and reported may be more appropriate.

One such model that might have potential to improve the clinical relevance of salivary gland FNA is a risk stratification scheme in which the likelihood of malignancy is provided for each diagnostic category. Ideally, such categories would be sufficiently broad so as to circumvent the pitfalls in overlap of specific diagnostic categories yet granular enough to add probabilistic information beyond just benign vs malignant. Conceptually, this is not novel; the best-known application of such a scheme in aspiration cytology is applied to thyroid gland cytology, for which the Bethesda System has revolutionized diagnosis and reporting to provide standardized and graded risk stratification.[7,8] A similar approach is to be adopted for pancreatic FNA.[9,10] While diversity, rarity, and diagnostic overlap present continued challenges in salivary gland cytology, we believe it is feasible to devise a limited but useful set of categories by incorporating cytoplasmic tinctorial characteristics, cell population diversity, background/stromal attributes, and nuclear atypia. We herein report our proposed classification scheme to provide risk stratification of salivary gland FNA with the aim of providing more useful information for refining management.

Materials and Methods

Selection of Cytology Aspirates for Retrospective Review

Our anatomic pathology laboratory information system (CoPath) was queried for cases of salivary gland FNA spanning 14 years (1999-2012, inclusive). A total of 794 salivary gland aspirations were identified. Cases were excluded from this analysis if no surgical excision of the same lesion occurred within 6 months (n = 333); the process was lymphoproliferative, mesenchymal, or metastatic (n = 120); or the original smears were not available for review (n = 47). In total, 294 aspirates were available from primary salivary gland epithelial lesions with corresponding surgical follow-up within 6 months. Clinicopathologic characteristics of these patients and tumors are shown in **Table 1**. In select cases, histologic sections of surgical resection specimens were also reviewed to confirm or change the diagnosis using modern criteria. This study was approved by the University of Pittsburgh Institutional Review Board.

Table 1
Clinicopathologic Characteristics

Characteristic	Value
No. of aspirates reviewed	294
No. of patients	281
Sex, No.	
Male	137
Female	144
Age, median (range), y	59 (16-92)
Site, No.	
Parotid	257
Submandibular	33
Other	4[a]
Surgical diagnoses, No. (%)	
Nonneoplastic	44 (15.7)
Benign neoplasm	166 (59.1)
Pleomorphic adenoma	79
Warthin tumor	54
Oncocytoma	11
Oncocytic cystadenoma	8
Basal cell adenoma	8
Other	6[b]
Malignant neoplasm	71 (25.3)
Salivary duct carcinoma	18
Mucoepidermoid carcinoma	16
Acinic cell carcinoma	11
Epithelial-myoepithelial carcinoma	9
Basal cell adenocarcinoma	5
Adenoid cystic carcinoma	4
Other	8[c]

[a] Other sites include one aspiration each of buccal, hard palate, parapharyngeal space, and neck not otherwise specified.
[b] Other benign neoplasms include two myoepitheliomas, two lymphadenomas, papillary cystadenofibroma, and oncocytic lipoadenoma.
[c] Other malignant neoplasms include two adenocarcinomas not otherwise specified, mammary analogue secretory carcinoma, polymorphous low-grade adenocarcinoma, poorly differentiated carcinoma, undifferentiated carcinoma, oncocytic carcinoma, and carcinoma not otherwise specified ex pleomorphic adenoma.

Classification of Retrospectively Reviewed Aspirate Smears

All aspirates were reviewed blinded to any clinical history and to the final histologic diagnosis. Smears were considered adequate if at least four high-power (×400) fields

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Table 2
Abbreviated Descriptions of Salivary Gland Aspiration Categories

Category	Description	Differential Diagnosis
Unsatisfactory/nondiagnostic	<4 hpf of epithelial cells and no definitive categorization can be made	
Cyst contents only	Unsatisfactory but with cyst content background (ie, histiocytes and granular debris)	
Nonneoplastic	Only benign acini and ducts or inflammatory background with only reactive epithelium	
Pleomorphic adenoma	Smears are characteristic for PA with bland ductal epithelial cells and myoepithelial cells embedded in a fibrillary myxochondroid stroma; stroma comprises at least 25% of the specimen	
Monomorphic cellular basaloid neoplasm	Neoplastic cells have scant cytoplasm with low to moderate nuclear grade; stroma comprises less than 25% of the specimen; the quality of the stroma determines the subclassification as follows:	
With fibrillary stroma	Mostly composed of cells with scant cytoplasm but with scant fibrillary stroma often with intermixed basaloid myoepithelial cells; stroma is metachromatic on Romanowsky stain	Cellular pleomorphic adenoma, epithelial myoepithelial carcinoma, basal cell adenoma/adenocarcinoma
With hyaline stroma	Stroma has a harder appearance than fibrillary stroma; neoplastic cells are usually excluded from the stroma	Basal cell adenoma/adenocarcinoma, adenoid cystic carcinoma, epithelial myoepithelial carcinoma
With mixed/other stroma	Stroma is difficult to classify as either fibrillary or hyaline; stroma may be scant to absent	Basal cell adenoma/adenocarcinoma, adenoid cystic carcinoma, epithelial myoepithelial carcinoma
Pleomorphic basaloid neoplasm	Smears show a predominantly basaloid neoplasm composed of pleomorphic nuclei suggestive of a high-grade malignancy; other high-grade nuclear features may also be seen (mitotic activity, apoptosis, nuclear membrane irregularities)	Salivary gland carcinoma with HGT, metastatic high-grade neuroendocrine carcinoma, metastatic nonkeratinizing SqCC
Warthin tumor	Smears are characteristic for WT; cellular constituents are truly oncocytic, highly cohesive, and have low to moderate nuclear grade; lymphocytes are present in the background or as lymphoid tangles mixed with epithelium; the background may be slightly mucinous or with cyst contents	
Monomorphic oncocytoid neoplasm	Cells have more cytoplasm than basaloid cells but may not represent true oncocytes; nuclear grade is low to moderate, but smears are not sufficiently characteristic of WT; prominent vacuoles excludes these categories; fine, dense granularity of an oncocyte is common but coarse foamy granularity excludes this category; background determines subclassification as follows:	
With cyst content background	Mostly histiocytes and finely granular debris comprise the background of smears	Warthin tumor, oncocytic cystadenoma
With mucinous background	Mucinous strands are present in the background; often cells with intracellular mucin can also be seen, but this is not required	Mucoepidermoid carcinoma, metaplastic Warthin tumor
With other background	Background material is not classifiable as cyst contents or mucinous; often these smears show a clean background	Oncocytoma
Oncocytoid neoplasm, coarsely granular/vacuolated cytoplasm	Neoplastic cells have prominent foamy and coarsely granular or vacuolated cytoplasm but are not characteristic of true oncocytes; in general, these smears are more dyshesive and have more naked nuclei than monomorphic oncocytoid neoplasms	Acinic cell carcinoma, mammary analogue secretory carcinoma, metastatic renal cell carcinoma
Pleomorphic oncocytoid neoplasm	Neoplastic cells have abundant cytoplasm and pleomorphic nuclei that often show other high-grade nuclear features (mitotic activity, apoptosis)	Salivary duct carcinoma, high-grade mucoepidermoid carcinoma metastatic carcinoma (adeno or squamous), metastatic melanoma

hpf, high-power fields; HGT, high-grade transformation; PA, pleomorphic adenoma; SqCC, squamous cell carcinoma; WT, Warthin tumor.

of epithelial cells were present across all available smears or a specific categorization could be applied confidently based on less material. Cases that did not meet our adequacy criteria but showed only cyst contents in the background (ie, little to no epithelium; prominent inflammatory cells, including prominent histiocytes; and granular debris) were considered unsatisfactory but were designated cyst contents only. All other aspirates were placed into a newly devised categorization system as detailed below and in **Table 2**:

- Nonneoplastic: aspirate smears did not show evidence of a neoplastic process and were characterized by only benign acini and ductal epithelium or an inflammatory background with only reactive epithelial cells.

Two "named" categories of pleomorphic adenoma and Warthin tumor were retained since these represent the most commonly encountered neoplasms of salivary glands and can often be accurately diagnosed on cytology aspirates.[11,12] To maintain a high specificity of these categories

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for our proposed system, we chose to require highly characteristic cytologic features of the respective diagnosis as follows:

- Pleomorphic adenoma: aspirate smears were characteristic for pleomorphic adenoma and specifically had fibrillary stroma comprising at least 25% of the lesional material (ie, relative cellularity <75%), and intermixed myoepithelial cells were present in the stroma and surrounding bland ductal structures. Stroma was metachromatic on Romanowsky stains when available.
- Warthin tumor: aspirates smears were characteristic for Warthin tumor with truly oncocytic cells in highly cohesive clusters and low to moderate nuclear grade. Lymphocytes were present in the background or as tangles intermixed with epithelial cells. While a prominent mucinous background was not allowed for categorization as Warthin tumor, a scant mucinous background was acceptable since occasional Warthin tumors can show mucinous metaplasia. Other features that exclude categorization as Warthin tumor included dyshesive epithelial cells, a lack of a lymphoid component, and high nuclear grade.

Neoplastic aspirates not characteristic for either pleomorphic adenoma or Warthin tumor were divided into either basaloid neoplasm or oncocytoid neoplasm categories. Basaloid neoplasms were composed predominantly of cells with scant cytoplasm as would be expected in myoepithelial or basal cells. Most of these had relatively high cellularity and low to moderate cytonuclear grade and were therefore termed *monomorphic cellular basaloid neoplasms*. Stroma/matrix production was common in these basaloid salivary gland neoplasms, and we theorized that differences in the stroma quality might offer additional risk stratification; therefore, monomorphic cellular basaloid neoplasms were further subcategorized based on stroma quality as follows:

- Monomorphic cellular basaloid neoplasm with fibrillary stroma: although aspirate smears demonstrated fibrillary stroma normally characteristic for pleomorphic adenoma, these smears were too cellular to meet criteria for pleomorphic adenoma (ie, >75% relative cellularity).
- Monomorphic cellular basaloid neoplasm with hyaline stroma: stroma was of hyaline quality (hard, more homogeneous appearance) lacking the fibrillary character of pleomorphic adenoma stroma. These aspirates were also usually cellular with relative cellularity greater than 75%.
- Monomorphic cellular basaloid neoplasm with mixed/other stroma: the stroma of these smears could not be easily classified as either fibrillary or hyaline. Some cases had stroma of intermediate quality between fibrillary and hyaline, a mixture of both hyaline and fibrillary stroma in different areas, stroma too scant to reliably classify, or entirely absent stroma. These aspirates were also usually cellular with relative cellularity greater than 75%.

For basaloid neoplasms with high cytonuclear grade, a pleomorphic basaloid neoplasm category was employed and defined as follows:

- Pleomorphic basaloid neoplasm: composed of predominantly cells having scant cytoplasm but pleomorphic nuclei. Other high-grade nuclear features were also commonly observed in these aspirates, including mitotic activity, apoptosis, and nuclear membrane irregularities.

Monomorphic oncocytoid neoplasm was used to describe neoplasms composed predominantly of low to moderate nuclear grade cells with abundant granular to vacuolated cytoplasm. These included but were not restricted to truly oncocytic neoplasms. While stromal characteristics were used to subcategorize basaloid neoplasms, we theorized that background characteristics could be used to subclassify monomorphic oncocytoid neoplasms into more specific risk categories as follows:

- Monomorphic oncocytoid neoplasm with cyst content background: background had typical cyst content features, including histiocytes and granular debris, but lacked other characteristic features of Warthin tumor. At least four high-power fields (hpf) of low- to moderate-grade oncocytoid cells were required or "unsatisfactory cyst contents only" was applied to these smears.
- Monomorphic oncocytoid neoplasm with mucinous background: mucinous strands were present in the background of an otherwise oncocytoid neoplasm. Goblet cells with a single large mucinous vacuole were often found in such aspirates.
- Monomorphic oncocytoid neoplasm with other background: background material was not classifiable as either cyst contents or mucinous. Often these aspirates had a clean background and were reminiscent of smears expected from an oncocytoma.

An additional oncocytoid neoplasm category was applied to those cases that showed coarsely granular or prominently vacuolated cytoplasm. The prototypical neoplasms predicted to fall into this category were malignant (acinic cell carcinoma and mammary analogue secretory carcinoma) and, although these cells lacked high-grade nuclear features, were predicted to represent a higher malignancy risk category. This oncocytoid neoplasm with coarsely granular/vacuolated cytoplasm was therefore separated from monomorphic oncocytoid neoplasms and was defined as follows:

- Oncocytoid neoplasm with coarsely granular/vacuolated cytoplasm: neoplastic cells had prominent coarse and often somewhat foamy granularity or a multivacuolated cytoplasmic character as would be predictive of acinic cell carcinoma or mammary analogue secretory carcinoma, respectively. Overall, the cytoplasmic character was not truly oncocytic in that the granularity was not as fine or tightly packed as that seen in true oncocytes. These aspirates

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were often differentiated from Warthin tumor or oncocytoma due to decreased cohesion (prominent single cells and/or very loose clusters). Naked nuclei were more commonly seen, indicative of the lability of tumor cell cytoplasm.

As with basaloid neoplasms, oncocytoid neoplasms composed of cells with high cytonuclear grade and pleomorphic nuclei were categorized as pleomorphic oncocytoid neoplasm:

- Pleomorphic oncocytoid neoplasm: the neoplastic cells had abundant cytoplasm and high cytonuclear grade with pleomorphism and often hyperchromasia, increased mitotic activity, and apoptosis.

Review of Aspirate Smears

Aspirate smears were reviewed blindly by three authors (C.C.G., R.K.P, and R.R.S.) and placed into the new proposed categories based on cytonuclear features (relative cellularity, stromal quantity and quality, cytoplasmic tinctorial quality and volume, and nuclear grade). All disagreements were resolved by consensus after review at a multiheaded microscope.

Histologic Classification of Surgical Cases

To determine the rate of malignancy and high-grade malignancy for each FNA category, we classified histologic diagnoses based on resection specimens as follows:

- Nonneoplastic: no specific pathologic change, inflammatory lesions (abscess, sialadenitis, reactive lymphoid hyperplasia), sialolithiasis, oncocytic cyst and hyperplasia, and lymphoepithelial cyst.
- Benign neoplasm: pleomorphic adenoma, Warthin tumor, basal cell adenoma, myoepithelioma, oncocytoma, oncocytic lipoadenoma, and papillary cystadenofibroma.

Malignant diagnoses were dichotomized based on intrinsic biologic behavior and cytonuclear grade as per our prior classification[13]:

- Low-grade malignancy: tumors with low local recurrence rates and metastatic potential, as well as those with low cytonuclear grade. These tumor types are generally treated with surgical resection alone, ensuring negative margins if there are no other adverse preoperative clinical parameters. These included acinic cell carcinoma, basal cell adenocarcinoma, epithelial-myoepithelial carcinoma, low- and intermediate-grade mucoepidermoid carcinoma, mammary analogue secretory carcinoma, carcinoma in situ ex pleomorphic adenoma not otherwise specified, and polymorphous low-grade adenocarcinoma.
- High-grade malignancy: tumors with established high propensities for local recurrence and metastasis. These tumor types generally require adjuvant treatment and/or neck dissection in addition to surgical resection. These included salivary duct carcinoma, acinic cell carcinoma with high-grade transformation, adenoid cystic carcinoma, high-grade mucoepidermoid carcinoma, high-grade adenocarcinoma not otherwise specified, oncocytic carcinoma, poorly differentiated carcinoma, and undifferentiated large cell carcinoma.

Statistical Analysis

Risk of malignancy for each FNA category was calculated as the number of low-grade and high-grade malignancies on final histologic diagnosis divided by the total number of cases in a given category. Similarly, the risk of high-grade malignancy was calculated as the number of high-grade malignancies diagnosed on final histologic examination divided by the total number of cases in a given category. Specificity, sensitivity, and accuracy were calculated. Receiver operator characteristic curves with area under the curve and χ^2 analysis were performed using SPSS version 22 (SPSS, Chicago, IL).

Results

Figure 1 demonstrates the categorization scheme with example cases in each category. **Table 3** shows the breakdown of histologic diagnosis for each of our retrospectively applied cytologic categories, and **Table 4** shows the risk of malignancy and high-grade malignancy on surgical follow-up based on cytologic categorization.

Inadequate, Cyst Contents Only, and Nonneoplastic Aspirates

No defined adequacy criteria are currently accepted for salivary gland FNA, but it has been suggested that low cellularity results in higher discrepancy rates.[6] On the basis of our experience, we required at least 4 hpf (×400) of epithelial cells to meet adequacy in this study. Only one case with fewer epithelial cells was considered adequate and was categorized as a pleomorphic oncocytoid neoplasm based on the finding of rare highly atypical cells with abundant cytoplasm. This tumor was salivary duct carcinoma on surgical excision.

The inadequacy rate was 28.2% (83/294). The rate of adequacy varied from year to year, with the highest rate occurring in 2003 (56.3%) and the lowest rates in 2008 and 2010 (10.3% each) (data not shown). There was a trend toward decreasing inadequacy rates from 2003 onward. Histologic diagnoses for inadequate aspirates included 32 (38.6%) nonneoplastic lesions (69.6% [32/46] of aspirates from nonneoplastic lesions were inadequate), 36 (43.4%) benign neoplasms, and 15 (18.1%) malignant lesions, including one high-grade malignancy (high-grade mucoepidermoid carcinoma).

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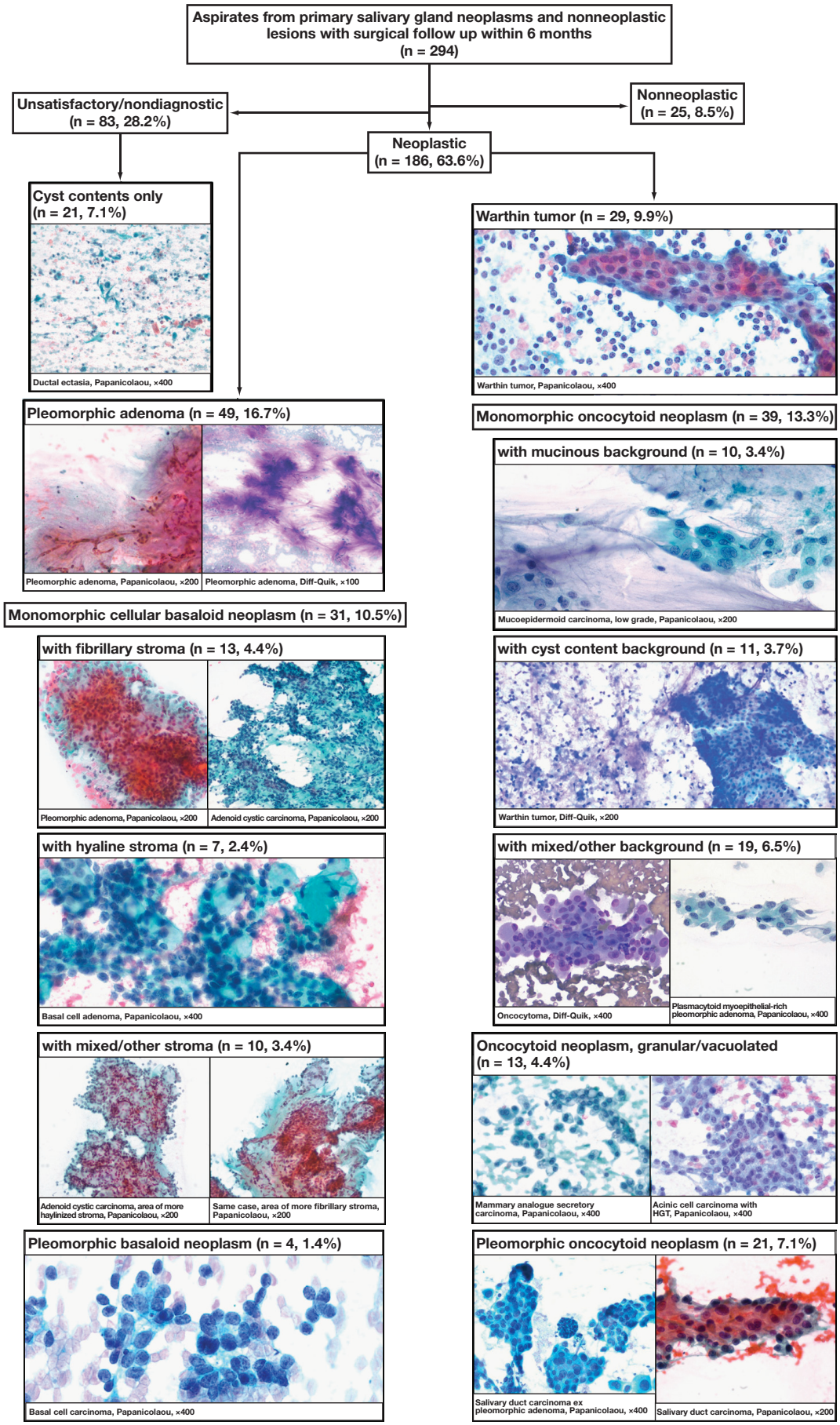

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Aspirate smears with cyst contents only (ie, granular debris and histiocytes and few to no epithelial cells) were included in the inadequacy rate (n = 21). Within this subgroup of inadequate cases, there were 12 (57.1%) nonneoplastic lesions, six (28.6%) benign neoplasms, and three (14.3%) low-grade malignancies (all mucoepidermoid carcinomas) on histologic follow-up.

A total of 25 (8.5%) of 294 aspirate smears were categorized as nonneoplastic. Of these, only eight (32%) of 25 were nonneoplastic on histologic follow-up, while the remaining 17 (68%) of 25 were benign neoplasms on histologic follow-up.

Benign Neoplasms—Pleomorphic Adenoma and Warthin Tumor, the Named Diagnostic Categories

Overall, pleomorphic adenoma and Warthin tumor FNA diagnostic categories were fairly specific, although not very sensitive for their respective histologic diagnoses. With regard to pleomorphic adenoma, the specificity was 98.8% (46/48), with only two malignancies being found on surgical follow-up (risk of malignancy 4.2%). These two cases were both carcinoma ex pleomorphic adenoma, and the inability to detect malignancy on these aspirates is most likely related to a sampling issue. Sensitivity was not as good for recognition of pleomorphic adenomas at 58.2% (46/79), with essentially all other "false-negative" cases falling into the basaloid neoplasm categories outlined below.

No malignant tumors were categorized as Warthin tumor (false negative), but three lesions found to be Warthin tumor on follow-up were overcategorized into suspicious for malignancy categories (two as monomorphic oncocytoid neoplasm with mucinous background and one as oncocytoid neoplasm with coarsely granular/vacuolated cytoplasm).

Basaloid Neoplasms

Thirty-one aspirate smears were categorized as monomorphic cellular basaloid neoplasm. Of these, 11 (35.5%) of 31 were malignant, and five (16.1%) of 31 were high-grade malignancies (four cases of adenoid cystic carcinoma and one salivary duct carcinoma ex pleomorphic adenoma). Low-grade malignancies, on the other hand, included epithelial-myoepithelial carcinoma (n = 3) and basal cell adenocarcinoma (n = 3).

Subcategorization by stromal characteristics of monomorphic cellular basaloid neoplasms, although definitionally scant, did appear to separate risk of malignancy somewhat. Fourteen aspirates were subcategorized as monomorphic cellular basaloid neoplasm with fibrillary stroma, and this category was not too dissimilar from the pleomorphic adenoma category in that 12 (85.7%) of 14 were benign, and 11 were actually pleomorphic adenoma. The malignancy risk for this subcategory was low at 14.3%, as was the risk of high-grade malignancy at 7.1%. On the other hand, three (42.9%) of seven aspirates subcategorized as monomorphic cellular basaloid neoplasm with hyaline stroma were malignant on surgical follow-up (although none were high-grade malignancies), while six (60%) of 10 monomorphic cellular basaloid neoplasms with mixed/other stroma were malignant (of these, four were adenoid cystic carcinoma, yielding a risk of high-grade malignancy of 40%).

Only four aspirate smears were categorized as pleomorphic basaloid neoplasm, and all of these were malignant on follow-up (epithelial-myoepithelial carcinoma, epithelial-myoepithelial carcinoma ex pleomorphic adenoma, basal cell adenocarcinoma, and acinic cell carcinoma with high-grade transformation), although interestingly, only one was in our high-grade category (acinic cell carcinoma with high-grade transformation).

Oncocytoid Neoplasms

Thirty-nine aspirate smears were categorized as monomorphic oncocytoid neoplasm. In this group, 12 (30.8%) of 39 were malignant, and only two (5.1%) of 39 were high-grade malignancies (both salivary duct carcinoma). Low-grade malignancies included low- and intermediate-grade mucoepidermoid carcinoma (n = 6), epithelial-myoepithelial carcinoma (n = 2), adenocarcinoma not otherwise specified (n = 1), and acinic cell carcinoma (n = 1).

As with monomorphic cellular basaloid neoplasms, further subcategorization based on background characteristics of oncocytoid neoplasms provided additional separation of malignancy risk. Eleven aspirates were subcategorized as monomorphic oncocytoid neoplasm with cyst content background, and all were benign (100%). This subcategory is most similar to the Warthin tumor category since most aspirates were Warthin tumors (n = 6) but had a higher proportion of other benign oncocytic lesions, including oncocytic cystadenoma (n = 3), oncocytoma (n = 1), and nodular oncocytic hyperplasia (n = 1). In comparison, four (22.2%) of 18 aspirates subcategorized as monomorphic oncocytoid neoplasm with other background were malignant on surgical follow-up, with only one (5.6%) of 18 high-grade malignancy (salivary duct carcinoma). Furthermore, eight (80%) of 10 monomorphic oncocytoid neoplasms with mucinous

Figure 1 Diagram of proposed salivary gland aspiration categories. Possible categories are laid out in an algorithmic approach with the major division among neoplastic aspirates being the distinction of basaloid from oncocytoid neoplasms. Photomicrographs demonstrate typical areas of aspirate for each of the proposed categories with the surgical follow-up being designated. The number and percentage of aspirates in each category are listed.

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Table 3
Retrospective Categorization of Aspirate Smears by Follow-up Histologic Diagnosis

	Unsatisfactory				Monomorphic Cellular Basaloid Neoplasm With		
	Unsatisfactory	Cyst Contents Only	Nonneoplastic	Pleomorphic Adenoma	Fibrillary Stroma	Hyaline Stroma	Mixed/Other Stroma
Nonneoplastic							
Chronic sialadenitis	7	4	4				1
Reactive lymphoid hyperplasia	3	1					
No significant pathologic change	4		2				
Lymphoepithelial cyst		3	1				
Abscess	1						
Chronic sclerosing sialadenitis	1						
Fibrosis		1					
Necrotizing granulomatous sialadenitis	1						
Suppurative xanthogranulomatous sialadenitis			1				
Ectatic duct		1					
Nodular intercalated duct hyperplasia	1						
Nodular oncocytic hyperplasia	1						
Oncocytic cyst		1					
Squamous lined cyst		1					
Sialolithiasis	1						
Benign neoplasm							
Pleomorphic adenoma	8	2	6	47	10	1	1
Basal cell adenoma	2		1		1	2	2
Myoepithelioma	1					1	
Lymphadenoma	4						
Papillary cystadenofibroma							
Warthin tumor	10	2	8				
Oncocytoma	3						
Oncocytic cystadenoma	1	2	2				
Oncocytic lipoadenoma	1						
Malignant neoplasm							
Epithelial-myoepithelial carcinoma	2 (1 ex PA)				1	1	1
Basal cell adenocarcinoma	1					2	1
Adenoid cystic carcinoma					1		3
Adenocarcinoma, NOS							
Polymorphous low-grade adenocarcinoma	1						
LG mucoepidermoid carcinoma	1	1					
IG mucoepidermoid carcinoma	2	2					
HG mucoepidermoid carcinoma	1						
Acinic cell carcinoma	4						
Mammary analogue secretory carcinoma							
Salivary duct carcinoma				1 (ex PA)			1 (ex PA)
Poorly differentiated carcinoma							
Undifferentiated carcinoma							
Oncocytic carcinoma							
Carcinoma, NOS				1 (in situ ex PA)			

HG, high-grade; HGT, high-grade transformation; IG, intermediate grade; LG, low grade; NOS, not otherwise specified; PA, pleomorphic adenoma.

background were malignant, mostly low- to intermediate-grade mucoepidermoid carcinoma (n = 6) and the only aspirated case of polymorphous low-grade adenocarcinoma (n = 1). One (10%) of 10 was high-grade malignancy (salivary duct carcinoma).

The oncocytoid neoplasm with coarsely granular/vacuolated cytoplasm was applied to 14 aspirates with 11 (78.6%) of 14 being malignant and four (28.6%) of 14 being high-grade malignancies on follow-up. Of these cases, half were acinic cell carcinoma (n = 7, two with high-grade transformation). Other low-grade malignancies classified as oncocytoid neoplasm with coarsely granular/vacuolated cytoplasm included mammary analogue secretory carcinoma (n = 1) and epithelial-myoepithelial carcinoma (n = 1), and other high-grade malignancies included salivary duct carcinoma (n = 1) and oncocytic carcinoma (n = 1).

The pleomorphic oncocytoid neoplasm category was more common (n = 21) than the pleomorphic basaloid neoplasm category but also showed a 100% rate of malignancy. All were high-grade malignancies, and most were salivary

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		Monomorphic Oncocytoid Neoplasm With				
Pleomorphic Basaloid Neoplasm	Warthin Tumor	Cyst Contents Background	Other Background	Mucinous Background	Oncocytoid Neoplasm With Granular/Vacuolated Cytoplasm	Pleomorphic Oncocytoid Neoplasm
			1			
	1					
		1	1			
	1					
	1		5			
			1			
					1	
	24	6	2	2	1	
	2	1	5			
		3				
2 (1 ex PA)			2		1	
1						
				1		1 (HG)
				3		
				3		
						3
1 (HGT)			1		7 (2 HGT)	
					1	
			1	1	1	15 (2 ex PA)
						1
						1
					1	

duct carcinoma (n = 15) on follow-up. Other tumor types falling in this category included high-grade mucoepidermoid carcinoma (n = 3), high-grade adenocarcinoma not otherwise specified (n = 1), poorly differentiated carcinoma (n = 1), and undifferentiated carcinoma (n = 1).

Classification of Cytologic Categories Based on Risk of Malignancy

Based on both the design of our risk categories and the discovered risk of malignancy, these new categories and subcategories were consolidated into classes of benign, neoplasm of uncertain malignant potential (NUMP), suspicious for malignancy, or positive for malignancy **Table 5**.

Benign classification included categories of nonneoplastic, pleomorphic adenoma, and Warthin tumor and showed the lowest risk of malignancy with only two (2%) of 102 being malignant. In addition, only one (<1%) of 102 was high-grade malignancy on follow-up.

NUMP was used as the overall class for neoplasms with a low rate of malignancy (<50% risk of malignancy).

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Table 4
Risk of Malignancy and HG Malignancy Based on Aspiration Category

Category	Class	No.	Malignant, No. (%)	Malignant, HG, No. (%)
Unsatisfactory/nondiagnostic		83	15 (18.1)[a]	1 (1.2)[a]
Cyst contents only		21	3 (14.3)[a]	0
Nonneoplastic	Benign	25	0	0
Pleomorphic adenoma	Benign	49	2 (4.1)[b]	1 (2.0)[b]
Monomorphic cellular basaloid neoplasm		30	11 (36.7)	5 (16.7)
With fibrillary stroma	NUMP	13	2 (15.4)	1 (7.7)[c]
With hyaline stroma	NUMP	7	3 (42.9)	0
With mixed/other stroma	Suspicious	10	6 (60.0)[c]	4 (40.0)[c]
Pleomorphic basaloid neoplasm	Malignant	4	4 (100)	1 (25.0)
Warthin tumor	Benign	29	0	0
Monomorphic oncocytoid neoplasm		40	12 (30.0)	2 (5.0)
With cyst content background	NUMP	11	0	0
With other background	NUMP	19	4 (21.1)	1 (5.3)[d]
With mucinous background	Suspicious	10	8 (80.0)[e]	1 (10.0)[d]
Oncocytoid neoplasm, granular/vacuolated	Suspicious	13	11 (84.6)[f]	4 (30.8)
Pleomorphic oncocytoid neoplasm	Malignant	21	21 (100)	21 (100)[d]

HG, high-grade; NUMP, neoplasm of uncertain malignant potential.
[a] Seven of 16 mucoepidermoid carcinoma (MEC) aspirates were unsatisfactory, and one was HG MEC; all three malignant cyst contents were MEC.
[b] Both malignancies categorized as pleomorphic adenoma (PA) on aspiration were carcinoma ex pleomorphic adenoma (ex PA); one was salivary duct carcinoma (SDC) ex PA.
[c] Most adenoid cystic carcinomas (three of four) fell in the monomorphic cellular basaloid neoplasm with mixed/other stroma category; one was classified as monomorphic cellular basaloid neoplasm with fibrillary stroma.
[d] Most SDCs (14 of 18) were categorized as pleomorphic oncocytoid neoplasm; one SDC each was categorized as monomorphic oncocytoid neoplasm with mucinous background and cyst content background.
[e] Monomorphic oncocytoid neoplasm with mucinous background is the next most common category for MEC (six of 16).
[f] Most acinic cell carcinomas (six of 11) fell into the oncocytoid neoplasm with granular/vacuolated cytoplasm category.

Categories grouped in this class included monomorphic cellular basaloid neoplasm with fibrillary stroma, monomorphic cellular basaloid neoplasm with hyaline stroma, monomorphic oncocytoid neoplasms with cyst content background, and monomorphic oncocytoid neoplasm with other background. Malignancy was found in nine (18%) of 50 of these cases, and only two (4%) of 50 were high-grade malignancy on follow-up.

Suspicious for malignancy was used for the categories with a risk of malignancy of 50% or more but less than 100% and included monomorphic cellular basaloid neoplasm with mixed/other stroma, monomorphic oncocytoid neoplasm with mucinous background, and oncocytoid neoplasm with coarsely granular/vacuolated cytoplasm. A total of 25 (73.5%) of 34 aspirates were malignant, and nine (26.5%) of 34 were high-grade malignancies.

Both pleomorphic basaloid neoplasm and pleomorphic oncocytoid neoplasm categories showed a 100% risk of malignancy on follow-up (n = 25) and were therefore grouped as positive for malignancy. The rate of high-grade malignancy in the positive for malignancy class was also very high, with 22 (88%) of 25 cases being high-grade malignancies.

The risk of malignancy was statistically significantly different among these classes of benign, NUMP, suspicious for malignancy, and positive for malignancy ($P < .0001$ by χ^2 analysis). With unsatisfactory cases excluded, the receiver operator characteristic curves for these classes looking at the specificity and sensitivity for malignancy and high-grade malignancy are shown in **Figure 2**. The area under the curve was 0.932 with malignancy as the end point and 0.929 with high-grade malignancy as the end point.

Discussion

The application of this proposed classification scheme successfully stratified aspirate smears by overall risk of malignancy and risk of high-grade malignancy. These differences in risk of malignancy between the benign, NUMP, suspicious for malignancy, and positive for malignancy classes were statistically significant and showed a receiver operator characteristic area under the curve of 0.932 in the determination of malignancy risk. We propose that the use of such a system could provide information to clinicians and surgeons in treatment planning and allow a more nuanced discussion with patients having salivary gland tumors.

The derivation of the proposed categories and subcategories was meant to mirror the histomorphologic commonality between and to circumvent the overlap among salivary gland tumors. Pleomorphic adenoma and Warthin tumor are the most common salivary gland tumors, often with characteristic cytomorphologic features, allowing accurate specific diagnosis.[11,12] Given the known established accuracy of cytologic diagnosis for these tumor types, we chose to maintain these diagnoses as "named categories" in our system. For cases with characteristic features for either of these tumor types, we used benign categories of pleomorphic

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Table 5
Consolidation of New Cytology Categories Into Classes

Categorization/Subcategorization	Risk of Malignancy, No./Total No. (%)	Classification	No./Total No. (%)	
			Overall Risk of Malignancy	Overall Risk of HG Malignancy
Nonneoplastic	0/25 (0)	Benign	2/103 (2.0)	1/103 (1.0)
Pleomorphic adenoma	2/49 (4.1)			
Warthin tumor	0/29 (0)			
Monomorphic cellular basaloid neoplasm with fibrillary stroma	2/13 (15.4)	NUMP	9/50 (18.0)	2/50 (4.0)
Monomorphic cellular basaloid neoplasm with hyaline stroma	3/7 (42.9)			
Monomorphic oncocytoid neoplasm with cyst contents background	0/11 (0)			
Monomorphic oncocytoid neoplasm with other background	4/19 (21.1)			
Monomorphic cellular basaloid neoplasm with mixed/other	6/10 (60.0)	Suspicious for malignancy	25/33 (75.8)	9/33 (27.3)
Monomorphic oncocytoid neoplasm with mucinous background	8/10 (80.0)			
Cellular basaloid neoplasm with coarsely granular/vacuolated cytoplasm	11/13 (84.6)			
Pleomorphic basaloid neoplasm	4/4 (100.0)	Positive for malignancy	25/25 (100.0)	22/25 (88.0)
Pleomorphic oncocytoid neoplasm	21/21 (100.0)			

HG, high-grade; NUMP, neoplasm of uncertain malignant potential.

adenoma and Warthin tumor with the intention of maintaining a high specificity.

Indeed, we did find a high specificity for the pleomorphic adenoma and Warthin tumor categories for the actual final diagnoses of pleomorphic adenoma and Warthin tumor, respectively, but had lower sensitivity. Importantly, in terms of diagnosing malignancy, there were only two "false negatives" categorized as pleomorphic adenoma, and both were carcinoma ex pleomorphic adenoma on follow-up, suggesting a sampling issue rather than interpretive error.

One of the major challenges in salivary gland cytology is the accurate separation of biphasic basaloid neoplasms such as pleomorphic adenoma, basal cell neoplasms (adenoma and adenocarcinoma), epithelial-myoepithelial carcinoma, and adenoid cystic carcinoma.[6] The inability to separate these tumor types with greater accuracy preoperatively is made more frustrating by the fact that the surgical approach can be quite different. Although several articles in the literature suggest morphologic features to resolve this differential diagnosis, these are often not practical.[14,15]

Given that most basaloid salivary gland neoplasms produce stroma of varying quality, we theorized that subcategorization of monomorphic cellular basaloid neoplasms based on stroma characteristics could offer additional risk stratification. Specifically, the strict requirement of at least 25% stroma for categorization as pleomorphic adenoma was predicted to exclude at least a small proportion of cellular myoepithelial cell-rich pleomorphic adenomas from this category. The application of a monomorphic cellular basaloid neoplasm with fibrillary stroma was meant to capture these and similar low-grade lesions into a low-risk category. In fact, the monomorphic cellular basaloid neoplasm with fibrillary stroma category clustered with pleomorphic adenoma, with 11 (84.6%) of 13 being pleomorphic adenoma on follow-up. Although the risk of malignancy in this study was slightly higher for the monomorphic cellular basaloid neoplasm with fibrillary stroma at two (14.3%) of 14, further study may allow this category to be collapsed into pleomorphic adenoma.

Likewise, the finding of hyaline stroma was predicted to identify those neoplasms of higher risk, specifically adenoid cystic carcinoma. While we did show a higher risk for the monomorphic cellular basaloid neoplasm with hyaline stroma category, this risk was intermediate (42.9%) with no high-grade malignancies. Surprisingly none of the four cases of adenoid cystic carcinoma were placed in this category. Instead, three of these four cases were categorized as monomorphic cellular basaloid neoplasm with mixed/other stroma, suggesting that the stroma of adenoid cystic carcinoma was harder to classify than we predicted. Partly as a result of most adenoid cystic carcinomas falling into this category, monomorphic cellular basaloid neoplasm with mixed/other stroma had the highest risk of malignancy (60%) and high-grade malignancy (40%) within the monomorphic cellular basaloid neoplasm group.

Subcategorization based on background characteristics of monomorphic oncocytoid neoplasms was also successful at providing further risk stratification of this group. Within this group, monomorphic oncocytoid neoplasm with cyst content background had the lowest risk of malignancy. In fact, none of the 11 neoplasms in this category were found to be malignant on follow-up, and most were Warthin tumors. As with monomorphic cellular basaloid neoplasm with fibrillary stroma and pleomorphic adenoma, further support

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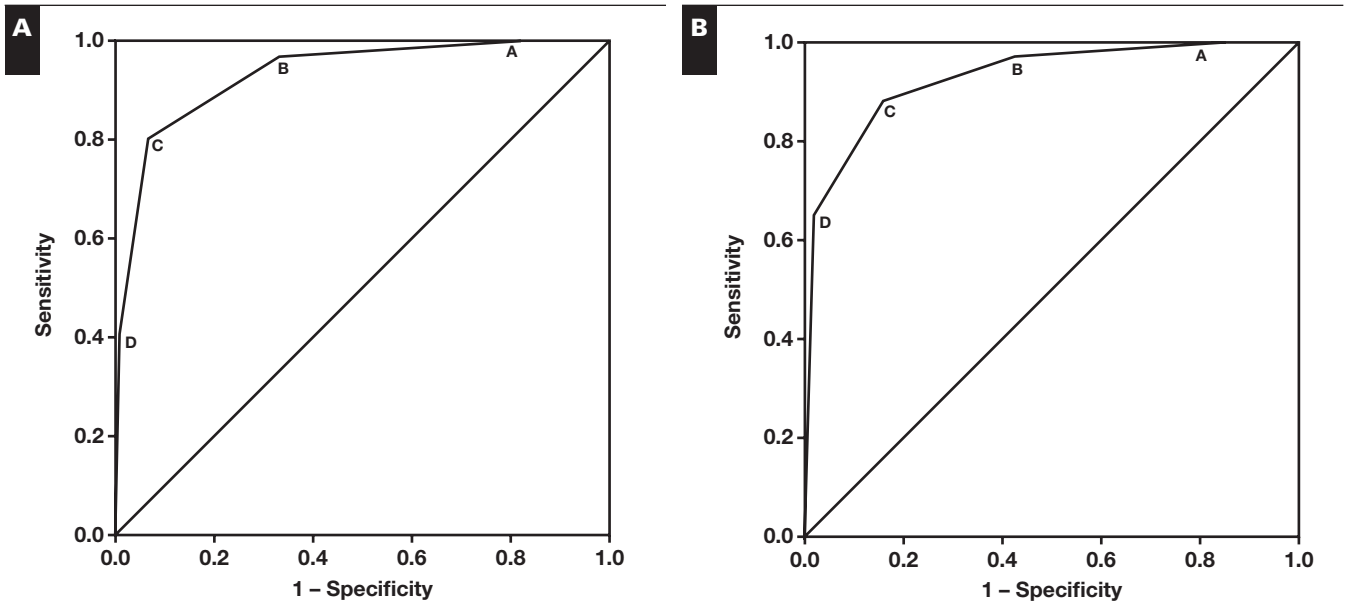

Figure 2 Receiver operator characteristic (ROC) curve analysis. **A**, ROC curve with malignancy on surgical follow-up as end point gives an area under the curve of 0.932. All but nonneoplastic = malignant (A), neoplasm of uncertain malignant potential (NUMP) + suspicious + malignant = malignant (B), suspicious + malignant = malignant (C), and malignant only = malignant (D). **B**, ROC curve with high-grade (HG) malignancy on surgical follow-up as the end point gives an area under the curve of 0.929. All but nonneoplastic = HG malignant (A), NUMP + suspicious + malignant = HG malignant (B), suspicious + malignant = HG malignant (C), and malignant only = HG malignant (D).

of this essentially zero risk of malignancy for monomorphic oncocytoid neoplasm with cyst content background may warrant its collapse into the Warthin tumor category.

The highest risk of malignancy (80%) within the monomorphic oncocytoid neoplasm group was seen for those with a mucinous background. It was predicted that this subcategory would capture most mucoepidermoid carcinomas, and in fact, that was found to be the case, with most low and intermediate mucoepidermoid carcinoma aspirates falling in this subcategory. Monomorphic oncocytoid neoplasm aspirates having neither cyst content background nor a mucinous background were categorized as monomorphic oncocytoid neoplasms with other background and showed an intermediate risk of malignancy (22.2%). These aspirates often showed nonspecific oncocytoid cells with low to moderate cytonuclear grade in a clean background and overall had one of the more diverse selections of histologic diagnoses on follow-up.

Cytomorphologically, acinic cell carcinoma is characterized by generally low cytonuclear grade cells with abundant foamy and coarsely granular cytoplasm.[16,17] Similarly, it has recently been shown that mammary analogue secretory carcinoma has similar cytomorphology but with more multivacuolated cytoplasm, in contrast to the granular cytoplasm of acinic cell carcinoma.[18] Oncocytoid neoplasm with coarsely granular/vacuolated cytoplasm was therefore designed as a special category in our system, in the hopes of capturing these two entities, and was expected to have a significant risk of malignancy. This category appears to have been quite successful in that most acinic cell carcinoma aspirates and the only mammary analogue secretory carcinoma aspirate were categorized as oncocytoid neoplasm with coarsely granular/vacuolated cytoplasm. Only a few other malignant neoplasms and a few benign neoplasms were also included in this category.

Not surprisingly, the pleomorphic basaloid and oncocytoid categories were invariably malignant. While the initial temptation was to designate these as high grade, not all tumors in these categories were actually high grade. To our surprise, only one (25%) of four pleomorphic basaloid neoplasms was high grade (acinic cell carcinoma with high-grade transformation), while the remaining three were low-grade malignancies (two epithelial-myoepithelial carcinomas and a basal cell adenocarcinoma). However, within the pleomorphic oncocytoid neoplasm group, follow-up showed universally high-grade malignancies (21/21). In keeping with the experience of salivary duct carcinoma cytomorphology in the literature, most of these 21 cases were salivary duct carcinomas but also included several other high-grade carcinoma types, including adenocarcinoma not otherwise specified and high-grade mucoepidermoid carcinoma.[19,20]

A novel aspect of our scheme is to also provide separate risk assessments for likelihood of high-grade malignancy. One of the fundamental flaws in thyroid tumor risk

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stratification on FNA (with or without molecular testing) is that the end point in most literature is simply malignancy. There is no discrimination between the end result of an indolent variant (ie, encapsulated follicular variant of papillary carcinoma) and an aggressive variant (ie, tall cell variant of papillary carcinoma). We felt that this additional risk evaluation may be useful for patient management even prior to surgery. While many salivary gland neoplasms will eventually undergo surgical excision, the extent of this surgery and the addition of elective neck dissection depend on the specific diagnosis or at least the aggressiveness of the neoplasm. For example, in patients being treated with the intent to treat malignancy, the rate of neck dissection is significantly higher, as is the rate of clear margins on final pathology.[21] The extent of surgery is clinically important since the incidence of morbidity is 2.7 times greater in patients undergoing at least total superficial parotidectomy vs those patients undergoing only a partial superficial parotidectomy.[22]

In addition to the benefits of risk stratification, this proposed categorization scheme also places salivary gland aspirates into fairly well-defined boxes with limited differential diagnostic considerations, as detailed in Table 2. Based on the literature and the manner in which categories were devised, it was expected that certain aspiration categories would favor a limited list of differential diagnostic considerations. For example, of the 10 aspirate smears categorized as oncocytoid neoplasms with mucinous background, six were mucoepidermoid carcinoma and two were adenocarcinoma on follow-up. Likewise, the categorization of aspirates as oncocytoid neoplasm with coarsely granular/vacuolated cytoplasm identified seven of 13 aspirates of acinic cell carcinoma, in line with previous reports showing a high sensitivity for FNA to identify malignancy in acinic cell carcinoma also with the common finding of foamy granular oncocytic-like cytoplasm.[16,17] In addition, mammary analogue secretory carcinoma has also been reported to show similar abundant granular to vacuolated cytoplasm, and the one aspirate from a mammary analogue secretory carcinoma in our series was also classified in this category.[18]

The limited number of differential diagnoses associated with some categories would be particularly useful in guiding the use of ancillary studies to reach a more specific diagnosis. This would be especially useful given the increasing number of diagnostic translocations in salivary gland tumors, including *CRTC1* or *CRTC3-MAML2* in mucoepidermoid carcinoma, *MYB-NFIB* in adenoid cystic carcinoma, *ETV6-NTRK3* in mammary analogue secretory carcinoma, and *PLAG1* in pleomorphic adenoma.[23,24]

While we feel the ability to determine the risk of high-grade malignancy is an important ancillary end point in this study, it does raise an issue in the definition of some tumors that were considered low or high grade. For example, we considered adenoid cystic carcinoma a high-grade malignancy given its high locoregional recurrence rate and the eventual high disease-related mortality, but the low rate of lymph node metastases in this disease means that a formal neck dissection is rarely required.[25] Conversely, we placed acinic cell carcinoma and mammary analogue secretory carcinoma in the low-grade malignancy group since these tumors are often locally less aggressive; however, the rate of lymph node metastases in these tumor types is not insignificant and may warrant elective neck dissection in some instances.[26] Given these stipulations, it would still be important to consider also the potential differential diagnoses based on the assigned aspiration category and not only the risk of high-grade malignancy in determining the best surgical management.

To our knowledge, adequacy requirements have not been established in salivary gland FNA. The requirement of 4 hpf of epithelial cells was used in this series since we were only examining the ability of this scheme to categorize nonlymphoproliferative and nonmesenchymal lesions. This requirement would clearly not be applicable to lymphoproliferative lesions or mesenchymal lesions. This study did have a high inadequacy rate at 28.2%, but this does fall within the range of other studies.[27-29] The rate of inadequate cases did trend in a downward direction, and this could indicate that increased experience with salivary gland FNA improves the adequacy rate. Also, while we did not collect data on whether clinicians or pathologists performed the aspirate, the general practice at our institution involves a mixture of these possibilities. Some studies suggest that clinician-performed FNA of salivary gland lesions results in a lower adequacy rate.[30,31]

While the strength of this study is the inclusion of only salivary gland lesions with surgical follow-up within 6 months, this does create selection bias for neoplastic lesions. This also leads to a potentially inflated risk of malignancy for at least some of the categories, particularly the inadequate/cyst contents only categories. However, the inclusion of aspirates without histologic follow-up as a gold standard in this initial design study would have created too great an uncertainty in the determination of malignancy risk.

We also excluded metastatic lesions in this series, which, during the real-time clinical evaluation of salivary gland aspirates, would clearly have the potential to be misinterpreted as primary salivary gland tumors. This proposed classification scheme is intended for risk stratification of primary salivary gland lesions, and if applied in the clinical setting, metastatic disease should be excluded whenever possible. While lymph nodes in the region of the parotid and submandibular gland are often the site of metastatic disease from both cutaneous and mucosal sites in the head and neck, cytomorphology (eg, keratinization

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would suggest a squamous cell lesion), clinical history, and ancillary testing with immunostains should be able to identify most metastatic lesions.[32,33] Future studies should include metastatic lesions to evaluate more clearly the ability to exclude these from categorization and to determine where particular metastatic tumors would most commonly be categorized if they are included. We would predict that metastatic lesions would mostly fall into the pleomorphic categories, especially the pleomorphic oncocytoid neoplasm category.

This first study is meant to introduce the concept of a risk stratification scheme in salivary gland FNA and propose a workable model. Validation of these results is imperative to determine if this system is reliable and accurate in different settings. Such validation will require testing of this scheme at different institutions to determine intra- and interobserver variability.

Here we propose for the first time a risk stratification scheme for salivary gland FNA. A similar concept of risk stratification has been applied to both thyroid and pancreas with success. While further studies will be required before clinical application of this scheme, we feel that there is great potential in this system to guide treatment and counseling for patients.

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