Concordance of second opinion diagnosis in salivary gland cytopathology: experience from a single academic institution

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Abstract

Interpretation of fine needle aspiration (FNA) material from salivary gland lesions has high interobserver variability due to the heterogenous and overlapping cytological features of various lesions. For this reason, second opinion consultation may play an important role in guiding appropriate clinical management for challenging cases. We aimed to report our experience with salivary gland cytology consultation cases at our academic center. Consecutive salivary gland FNA cases received from outside institutions for second opinion consultation between 2013 and 2022 were reviewed. Cases were divided into true consults (diagnostic assistance sought) or confirming consults (reviewed by in-house cytopathologists for patients being transferred to our institution for treatment). All diagnoses were re-classified using the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC). Discordance between reclassified consult diagnostic categories and preliminary diagnostic categories was recorded. Consultation resulted in a change in the diagnostic category in 15% of confirming and 18% of true consult cases. The overall distribution of diagnostic categories provided by outside pathologists was similar to consult diagnoses. Only 4 (5.4%) confirming and 3 (5.5%) true consult cases had major diagnostic discrepancies, which may impact the clinical treatment. Moderate interobserver variability is often expected with salivary gland FNA. However, in our consultation practice, we found a relatively high degree of concordance between submitting and consult diagnoses utilizing the MSRSGC.

Keywords Consultation; cytopathology; milan system; salivary gland; second opinion

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Salivary gland fine needle aspiration (FNA) has been widely used to evaluate salivary gland mass lesions because it can be easily applied in the outpatient setting and can effectively identify common benign tumors as well as discriminate between low-grade and high-grade malignant tumors.[1] However, interpretation of FNA material from salivary gland lesions has high inter-observer variability due to the heterogenous and overlapping cytological features of various lesions.[2,3] Clinical management of salivary gland lesions relies heavily on cytological findings, in conjunction with clinical presentation and imaging studies.[4] Therefore, second opinion review in salivary gland cytology may play an important role in guiding appropriate clinical management for challenging cases.

While the value of second-opinion consultation in surgical pathology has been well established, there have been only a few studies analyzing the effect of second-opinion consultation in cytopathology. Bailey G et al. reported an 8.4% major discrepancy rate between consult and outside diagnoses after retrospectively reviewing 928 non-gynecologic consult cases.[5] In another study regarding inter-institutional consultation for FNA cytopathology, 9.3% of 742 cases were documented to have major diagnostic disagreement.[6] A similar discrepancy rate was described by Layfield[7] and Lueck,[8] Nevertheless, there is limited data focusing on second opinion consultation for salivary gland cytology.

Various reporting practices and descriptive diagnoses have been used in reporting salivary gland cytology, which often causes confusion among pathologists as well as treating clinicians. The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) was introduced in 2017.[9] Instead of pursuing specific diagnoses, the MSRSGC included a limited number of diagnostic categories with clear definitions and the opportunity for each diagnostic category to be associated with a risk of malignancy (ROM), which made it easier for cytopathologists to apply in daily practice and for treating clinicians to guide their patient management.

In this study, we aimed to report our experience with salivary cytology consultation cases at our academic center, document the discrepancy rate, and discuss those cases with a major discrepancy. All the diagnoses were reclassified using the MSRSGC.

Materials and methods

Consecutive salivary gland FNA cases received at the University of Michigan from outside institutions for second opinion consultation between 2013 and 2022 were reviewed. Cases were divided into true consults (diagnostic assistance sought) or confirming consults (reviewed by in-house cytopathologists for patients being transferred to our institution for treatment). Both preliminary and consult diagnoses were reclassified using the MSRSGC as follows: I. Nondiagnostic; II: Non-neoplastic; III: Atypia of Undetermined Significance (AUS); IVA: Neoplasm:

Benign; IVB: Neoplasm: Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP); V: Suspicious for Malignancy; VI: Malignant.

The anatomic sites of these consult cases were documented. Discordance between reclassified consult diagnostic categories and preliminary diagnostic categories was recorded. Consult cases with no provided preliminary diagnoses from the referring institution were classified as "not applicable (N/A)". A minor discrepancy was defined by a one-step change in the discrete diagnostic category without a potential modification in patient treatment; for example, a change from "II: Non-neoplastic" to "III: AUS". Major discordance was defined by diagnostic differences which could potentially impact patient management; for example, a change from "III: AUS" to "IVB: Neoplasm: SUMP" was considered to represent a major disagreement. Cases with available clinical follow-up or subsequent surgical pathology reports were also reviewed and compared with the cytological diagnosis, focusing on cases with major diagnostic discrepancies.

Results

There were 138 cases (103 parotid, 12 submandibular, one sublingual, and 22 unspecified), of which 73 (53%) were confirming consults and 65 (47%) were true consults. Preliminary diagnoses from outside pathologists were provided in 83% (55 out of 65) true consult cases. The overall distribution of diagnostic categories provided by outside pathologists was similar to consult diagnoses (Table 1).

Comparison between preliminary and consult diagnosis for confirming consultation cases

Overall, consultation resulted in a change in diagnostic categories for 15% (11/73) of confirming consult cases (Table 2). All cases with discrepancies were parotid lesions. There were 4 (4/73; 5.4%) cases of parotid lesions that had a major disagreement between the outside and consult diagnosis. Among them was one "AUS" case that was upgraded to "Neoplasm: SUMP". Two cases of "Neoplasm: Benign" and "Suspicious for malignancy" were downgraded to "Non-Neoplastic" and "Neoplasm: Benign", respectively. In the other discrepant case of a parotid mass lesion, the outside pathologist diagnosed "Suspicious for malignancy, highly atypical squamous cells,". In contrast, the slides from this case showed only rare clusters of atypical keratinizing squamous cells with background benign salivary gland acini and lymphocytes (Figure 1). The diagnosis for this particular case was accordingly downgraded to "AUS, atypical squamous cells" after a second opinion review.

Comparison between preliminary and consult diagnoses for true consultation cases

There were ten true consult cases (10/55; 18%) that had a discrepancy between preliminary and consult diagnoses (Table 3). In 9 cases they were procured from the parotid gland and 1 was a submandibular gland lesion. The consult diagnosis of 3 parotid lesions had major disagreement with the corresponding outside diagnosis. Among them, two "AUS" cases were upgraded to "Neoplasm: SUMP" and "Malignancy" after second opinion review. Slides of the other outside "Non-Neoplastic, benign salivary gland component" case showed loose clusters of acinar cells with moderate to abundant granular cytoplasm, and scattered stripped nuclei that were also present. Immunohistochemical stains applied to this specific case showed that these cells were positive for cytokeratin, SOX-10 and DOG-1 (weak) (Figure 2). The diagnosis, in this case, was accordingly upgraded to "Neoplasm: SUMP, favor acinic cell carcinoma" after consultation.

Consultation cases with available clinical/surgical follow-up

There were 47 cases (49/73; 67%) with available clinical/surgical follow-up. This included all four of the cases with major diagnostic discrepancies that were parotid lesions, in which the consult diagnosis of the two cases that were downgraded after second opinion review was validated by clinical follow-up. The outside diagnosis of the other downgraded case was also supported by following histopathological examination of the surgical specimen. In one upgraded case, the interpretation rendered by the consult cytopathologist was confirmed by the surgical diagnosis. See Table 4.

Discussion

Cytopathology is reported to have low diagnostic reproducibility, and diagnostic error has been a major concern in this field.[10–12] For this reason, second opinion consultation may have a

Diagnostic category for outside versus consultation diagnoses

	Confirming consultation		True consultation	
	Outside diagnosis	Consult diagnosis	Outside diagnosis	Consult diagnosis
Non-Diagnostic	12 (16%)	14 (19%)	2 (4%)	4 (7%)
Non-Neoplastic	7 (10%)	6 (8%)	5 (9%)	2 (4%)
AUS	5 (7%)	5 (7%)	4 (7%)	2 (4%)
Neoplasm-Benign	19 (26%)	15 (21%)	13 (24%)	11 (20%)
Neoplasm-SUMP	21 (29%)	24 (32%)	24 (44%)	27 (49%)
Suspicious for Malignancy	3 (4%)	2 (3%)	1 (2%)	2 (4%)
Malignant	6 (8%)	7 (10%)	6 (10%)	7 (12%)
Total	73 (100%)	73 (100%)	55 (100%)	55 (100%)

(AUS: Atypia of Undetermined Significance; SUMP: Salivary Gland Neoplasm of Uncertain Malignant Potential).

Table 1

Concordance distribution of confirming salivary gland consultation cases

	Consultation Diagnosis							
Outside Diagnosis	**Non-Diagnostic**	**Non-Neoplastic**	**AUS**	**Neoplasm-Benign**	**Neoplasm-SUMP**	**Suspicious for Malignancy**	**Malignant**	**Total**
Non-Diagnostic	12							12
Non-Neoplastic	2	5						7
AUS			4		1			5
Neoplasm-Benign		1		14	3	1		19
Neoplasm-SUMP				1	20			21
Suspicious for Malignancy			1			1	1	3
Malignant							6	6
Total	14	6	5	15	24	2	7	73

(AUS: Atypia of Undetermined Significance; SUMP: Salivary Gland Neoplasm of Uncertain Malignant Potential).

Table 2

significant impact on clinical therapeutic decisions if a cytology specimen is the only available diagnostic material. Salivary gland neoplasm diagnosis by FNA is a well-known challenging area in cytopathology due to the diversity of tumors encountered in this region, the various cell types seen in salivary gland lesions, and overlapping features among different entities.[2,3] In the current study, after performing a retrospective review of 10 years involving salivary gland FNA consultation cases at our institution, an overall 5.5% of these cases were found to have major discrepancies between outside and consult diagnoses when utilizing the MSRSGC.

Four of seven cases with major diagnostic disagreement were upgraded. Two of them were initially diagnosed as "AUS" by outside institutions and were changed to "Neoplasm: SUMP" after a second opinion review. AUS represents a heterogeneous group of salivary gland lesions exhibiting morphologic overlap between non-neoplastic and neoplastic processes. The most common scenario seen in AUS diagnoses includes reparative and reactive changes, low cellularity and abundant mucin and/or aspirates with a scant epithelial component. In our study, two of the AUS cases showed small groups of basaloid cells, one of them with scant cellularity. A basaloid neoplasm of the salivary gland is known to have poor interobserver agreement.[13] Sometimes a benign or malignant neoplasm cannot be reliably differentiated on a cytology specimen. The "SUMP" category in the Milan reporting system is suitable for these lesions. A

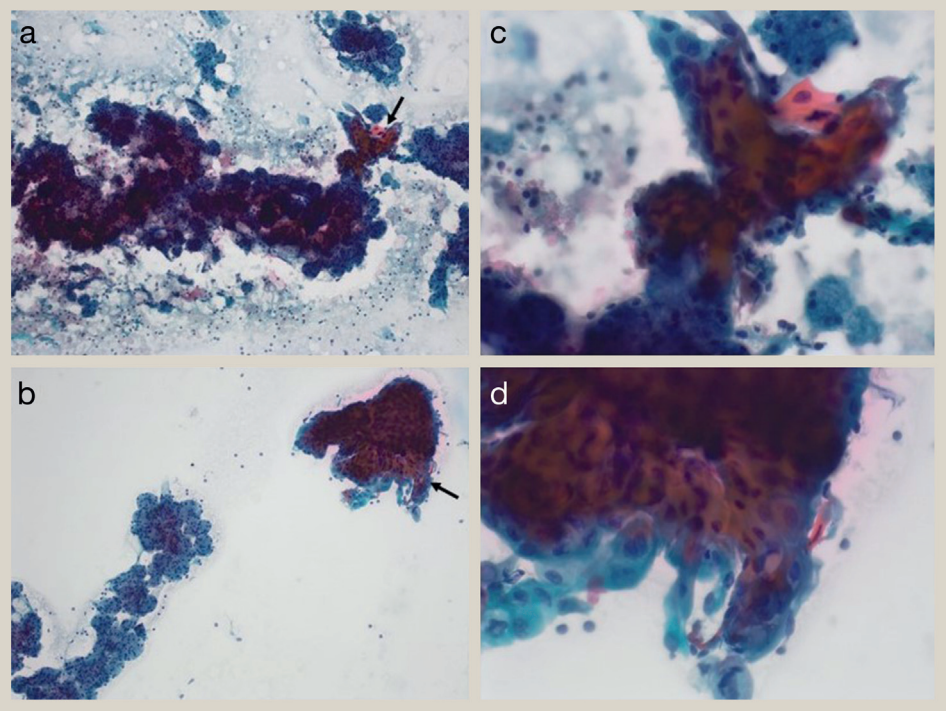

Figure 1 The FNA smears show predominantly benign salivary gland acini with rare atypical keratinizing squamous cells (arrow) and a background of small lymphocytes (Papanicolaou stain, **a**, **b**; 10X). The atypical squamous cells are characterized by moderate nuclear polymorphism and irregular nuclear contours (Papanicolaou stain, **c**, **d**; 40X).

Concordance distribution of true salivary gland consultation cases

	Consultation Diagnosis							
Outside Diagnosis	**Non-Diagnostic**	**Non-Neoplastic**	**AUS**	**Neoplasm-Benign**	**Neoplasm-SUMP**	**Suspicious for Malignancy**	**Malignant**	**Total**
Non-Diagnostic	2							2
Non-Neoplastic	2	1	1		1			5
AUS		1	1		1		1	4
Neoplasm-Benign				11	2			13
Neoplasm-SUMP					23	1		24
Suspicious for Malignancy						1		1
Malignant							6	6
Total	4	2	2	11	27	2	7	55

(AUS: Atypia of Undetermined Significance; SUMP: Salivary Gland Neoplasm of Uncertain Malignant Potential).

Table 3

diagnostic change from "AUS" to "Neoplasm: SUMP" is critical because the recommendation for most "AUS" lesions is clinical and radiological correlation with follow-up, or repeat FNA for further definitive diagnosis, while conservative surgical excision will normally be performed for "SUMP" masses. The consult diagnosis of "Neoplasm: SUMP" in our study was confirmed by surgical follow-up, which demonstrated a low-grade basal cell adenocarcinoma in one of these two cases. In the other "AUS" case, the aspirate consisted of monomorphic epithelial cells with vacuolated cytoplasm with focal nuclear atypia and pleomorphism. The diagnosis in this case was upgraded to "malignant", for which a radical resection is typically recommended. One true consult case with a major discrepancy represented a well-described pitfall, which is the interpretation of an acinic cell carcinoma as normal salivary gland. The smears in this illustrative case contained a few loose clusters of neoplastic cells with abundant granular cytoplasm and scattered stripped nuclei. Immunohistochemical stains performed at our institution for this case showed rare cells in the cell block that were positive for cytokeratin, SOX-10 and DOG-1 (weak). The interpretation of "benign" was thus upgraded to "SUMP, favoring an acinic cell carcinoma". Awareness of this pitfall may prevent a "false negative" diagnosis. This case also demonstrates the importance of a cell block coupled with ancillary studies in salivary gland cytology, especially if the cytological features are challenging.

One of the three downgraded cases with a major discordance was a squamous lesion of parotid gland, in which FNA smears showed predominantly a benign salivary gland component and rare groups of atypical squamous cells. The diagnostic consideration is broad in this case which includes a salivary tumor with squamous differentiation, mucoepidermoid carcinoma, metastatic squamous cell carcinoma, and primary squamous cell

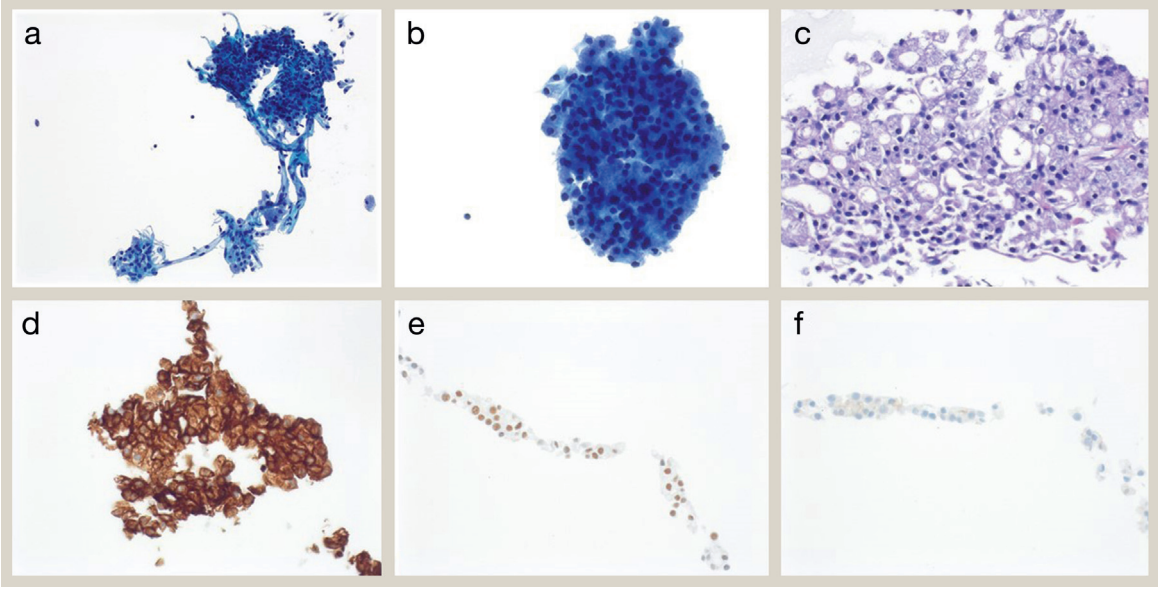

Figure 2 The FNA smears contain a few loose clusters of acinar cells with abundant granular cytoplasm and scattered stripped nuclei (Papanicolaou stain, **a**, 10X; **b**, 40X). Cell block material demonstrates these cells have finely vacuolated and basophilic granular cytoplasm (**c**, H&E, 40X). Immunohistochemical stains show that these cells are positive for cytokeratin (**d**, 40X), SOX-10 (**e**, 40X) and have weak staining with DOG-1 (**f**, 40X).

Clinical/surgical follow-up for cases with major diagnostic discrepancy

Outside diagnosis	Consult diagnosis	Clinical/surgical follow-up
Suspicious for Malignancy: Mucoepidermoid carcinoma	Neoplasm: Benign, favor Warthin's tumor	Two years clinical/image follow-up showed lack of growth and any symptoms
Neoplasm: Benign, consistent with pleomorphic adenoma	Non-Neoplastic	Treated with anti-inflammatory medications and the swelling was subsequently resolved
AUS	Neoplasm: SUMP	Low-grade basal cell adenocarcinoma
Suspicious for Malignancy: highly atypical squamous cells	AUS: atypical squamous cells	Squamous cell carcinoma

Table 4

carcinoma. The patient in this discrepant case had a history of lung squamous cell carcinoma. We downgraded the outside "suspicious for malignancy" diagnosis to "atypical squamous cells" based on the mild degree of atypia and inflammatory background. This patient had surgery, and the salivary gland mass turned out to be metastatic squamous cell carcinoma, corroborating the outside diagnosis. In another two consult cases, the outside diagnosis of "Benign neoplasm, consistent with pleomorphic adenoma" and "Suspicious for malignancy, mucoepidermoid carcinoma" were downgraded to "Benign salivary gland acini" and "Neoplasm, benign: favor Warthin's tumor". A repeat FNA was performed in the first case, which was essentially non-diagnostic. This patient was treated with anti-inflammatory medication, and the swelling of the parotid gland subsequently resolved. A neoplastic process was hence unlikely for this patient. In the second case, the clinician decided to observe rather than perform surgery based on the second opinion diagnosis. Two years of clinical/image follow-up showed there was a lack of growth and an absence of symptoms for this parotid lesion. A benign neoplastic process was hence favored. Unnecessary surgeries were thus prevented in both cases.

The majority of confirming consult cases (65%) had clinical/surgical follow-up. A cytology specimen was the only available anatomic specimen in many of these cases which demonstrates the importance of an accurate cytology diagnosis in guiding the clinical treatment of salivary diseases. Four cases had major disagreement, for which consult diagnoses were supported based on clinical/histopathologic follow-up in three of them. In our practice, a second opinion review of outside cytology material is mandatory before any major therapeutic decision is undertaken. We do not have follow-up data for three true consult cases with major diagnostic discrepancies, so there is, unfortunately, no way for us to know whether the outside or consult diagnoses were correct. However, the presence of a major disagreement should alert the clinician prior to making a radical treatment decision to consider perhaps further workup to establish a more accurate diagnosis.

Common challenges observed in our review of outside cytology cases included limited imaging/clinical information and FNA specimen preparation artifact. In some cases, only Papanicolaou stained slides were provided for review. However, extracellular matrix in salivary gland lesions is often better appreciated with a Romanowsky-type stain (such as a Diff-Quik stain), which is thus essential in providing a diagnosis of certain matrix-producing lesions such a pleomorphic adenoma, basal cell adenoma and adenoid cystic carcinoma. Despite these challenges, only a 5.5 % major discrepancy rate was identified in our study when the MSRSGC was applied, which is slightly lower than previous reports.[5–8] Of note, none of the prior studies focused specifically on salivary gland cytology, nor did they use the MSRSGC to reclassify any diagnosis.

In conclusion, moderate interobserver variability is expected when interpreting salivary gland FNAs. In our consultation practice, we found that an overall of 5.5% of cases had a major discrepancy between submitting and consult diagnoses when utilizing the MSRSGC. Available clinical/surgery follow-up for consult cases with major diagnostic disagreement showed that our consult diagnoses were more reliable in the majority of these cases (75%, 3 out of 4), which justifies the necessity of seeking a second opinion consultation for challenging salivary gland cytopathology cases before initiation major therapeutic intervention. ◆

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