MEDICAL RECORDS-International Medical Journal

Research Article

Correlation of Fine Needle Aspiration Cytology and Histopathological Evaluation in Salivary Gland Masses: A Single Center Retrospective Study

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Abstract

Aim: Fine-needle aspiration cytology (FNAC) in the preoperative diagnosis of salivary gland (SG) masses is a very fast, inexpensive, and reliable diagnostic method. In our study, the correlation of cytological-histopathological diagnosis in cases diagnosed with fine needle aspiration cytology in our clinic was investigated, and possible causes of diagnostic entrapment in discordant cases were discussed.

Material and Methods: Salivary gland FNAC cases with histopathological diagnosis between 2008 and 2019 were retrospectively analyzed.The age, gender, localization of the lesion, preoperative cytology, and postoperative histopathological diagnosis of the patients were recorded. Cytology results were analyzed in 5 categories: unsatisfactory, uncategorized, benign, suspected malignancy, and malignant. Histopathology results were recorded in 2 groups benign-nonneoplastic and malignant. Statistically significant difference level was accepted as $p<0.05$. The validity of the cytology result according to the biopsy result was evaluated by sensitivity, specificity, positive predictive value, and negative predictive value.

Results: 316 cases of salivary gland fine needle aspiration were detected. 156 (49.4%) of 316 cases had histopathological diagnosis. When calculating the cytological-histopathological diagnosis, the cases that were found to be inadequate and uncategorized by cytology were not taken into consideration. The suspected malignancy group was evaluated within the malignant category. Therefore, diagnostic agreement was calculated in 124 cases. Of these 124 cases, 116 (93.6%) cytology-histopathology diagnosis were compatible, and 8 (6.4%) were not.

In our series, the overall sensitivity and specificity were 83.3% and 97.7%, respectively. The positive predictive value was 93.7% and the negative predictive value was 93.4%. The accuracy rate was calculated as 93.5%.

Conclusion: In our study, high sensitivity and specificity values were determined by FNAC in accordance with the literature. It should be kept in mind that there may rarely be differences between preoperative cytological and histopathological diagnoses, possibly due to experience, method, and lesion-related limitations and pitfalls.

Keywords: Salivary gland, fine needle aspiration cytology, histopathology, sensitivity, specificity

INTRODUCTION

Fine-needle aspiration cytology in salivary gland (SG) masses is a reliable, fast, and inexpensive preoperative diagnosis method for centers with sufficient clinical experience. It is a minimally invasive application that can be performed in outpatient settings. In today's practice, the treatment approach to a detected SG mass is decided after evaluating the clinical-radiological-cytological data. Therefore, routine use of fine-needle aspiration cytology (FNAC) is recommended for preoperative diagnosis on an SG mass (2-11). In recent years, the 'Milan Reporting System' has been defined to ensure that cytological findings are reported using a common language in certain diagnostic categories and to analyze the malignancy risk for each diagnostic category and to develop a clinical approach algorithm (8).

CITATION

Gun S, Meydan BC. Correlation of Fine Needle Aspiration Cytology and Histopathological Evaluation in Salivary Gland Masses: A Single Center Retrospective Study Med Records. 2023;5(2):361-6. DOI:1037990/medr.1230522

Received: 06.01.2023 **Accepted:** 23.03.2023 **Published:** 27.03.2023

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Many non-neoplastic processes in SG can cause mass lesions. For example, intra-gland lymph node pathologies that do not require surgery can be confused with a primary tumor. Primary SG tumors have an extensive classification list with rare subtypes added daily (1). Even in a single tumor type, histomorphological heterogeneity may be evident. These features create difficulties in cytological and histopathological diagnosis. When the literature is examined, it has been reported that the diagnostic value of FNAC in SG masses is variable and its accuracy rate is relatively low compared to tumors of the other head and neck region (2-5). In recent years, the accuracy rate of FNAC in major SG masses is over 90% in studies based on large series of experience (6-11).

In our study, the correlation of cytological-histopathological diagnosis in cases diagnosed with fine needle aspiration cytology in our clinic was investigated, and possible causes of diagnostic entrapment in discordant cases were discussed.

MATERIAL AND METHOD

Our study was approved by the Ondkouz Mayıs University Clinical Research Ethics Committee with the decision dated 30.12.2021 and numbered B.30.2.ODM:0.20.08/843. A total of 316 salivary gland FNAC cases were diagnosed in Ondokuz Mayıs University, Pathology Department between 2008 and 2019 and the histopathological diagnoses of these cases were evaluated retrospectively.

Patient age, gender, and localization of the lesion were recorded. FNAC and histopathological diagnoses were compared. FNAC in our clinic; There were four main diagnostic categories: "Inadequate/Non-diagnostic", "Malignancy negative" (nonneoplastic or benign neoplasia), "suspicious malignancy" and "Malignant". In addition, there is a fifth separate diagnostic group for the cases that cannot be classified and reported as "not categorizable" in cases where cytological findings are not guiding. The histopathological diagnosis, which is accepted as the gold standard, was determined in 156 (49.4%) cases. The histopathological diagnoses given in the surgical materials were examined in two main diagnosis groups as "nonneoplastic or benign" and "malignant". The categories of "unsatisfactory" and "not categorizable" were not included in the statistical evaluation. The "suspicious malignancy" group was evaluated within the malignant diagnosis group. In the remaining 124 cases, cytological-histopathological agreement was calculated.

The research data were analyzed using the SPSS version 22.0 statistical program. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov test. Since the continuous variables do not follow the normal distribution while expressing the data, the median (1. Quarterly: Q1 - 3rd Quarter: Q3) and categorical variables were presented with frequency and percentage distributions. Mann Whitney U test was used to compare the age variable between the groups. Statistically significant difference level was accepted as $p<0.05$. The validity of the FNAC result according to the biopsy result was evaluated by calculating the sensitivity, specificity, positive predictive value, and negative predictive value.

RESULTS

Of 316 patients with salivary gland fine needle aspiration biopsy, 178 (56.3%) were male and 138 (43.7%) were female. The median age of the patients was 56 (Q1:42.25 - Q3:66.0). While the median age was 56.5 (46.0-66.0) in men, it was 54 (39.0-66.0) in women, and there was no age difference between the sexes (p:0.23). The number of children (18 years and younger) was 16 (5.06%). Of the FNACs, 274 (86.7%) belonged to the parotid gland, and 42 (13.3%) belonged to the submandibular gland. The distribution of the number of cases by year is given in Figure 1.

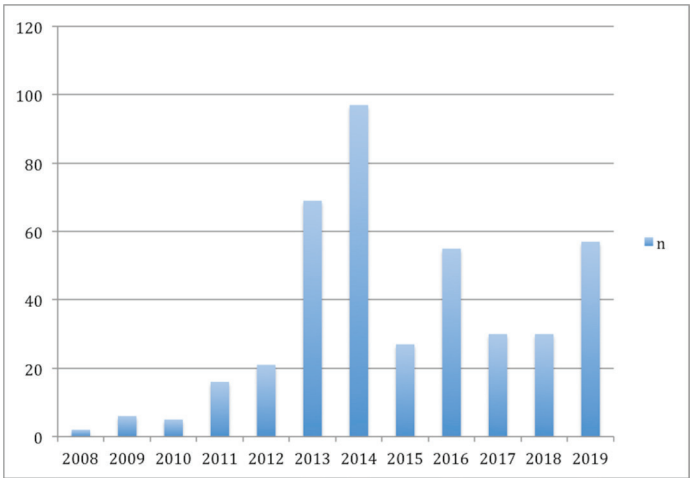

Figure 1. Number of salivary gland fine needle aspiration cytology material by years

Of 316 FNACs, 44 (13.9%) were categorized as "inadequate/non-diagnostic", 180 (57.0%) as "malignancy negative" (nonneoplastic-benign), 37 (11.7%) "categorized" undetectable", 20 (6.3%) "suspicious malignancy" and 35 (11.1%) "malignant" categories. 156 (49.4%) of 316 cases had histopathological diagnosis. FNACs of the patients in the inadequate and uncategorized group were not repeated. Repeated FNACs were not included in the calculation.When calculating the cytological-histopathological diagnosis, the cases that were found to be inadequate and uncategorized by cytology were not taken into consideration. The suspected malignancy group was evaluated within the malignant category. Therefore, diagnostic agreement was calculated in 124 cases.

While cytology-histopathology agreement was found in 116 (93.6%) of 124 cases included in the study, the diagnosis was inconsistent in 8 (6.4%). The cytological and histopathological diagnosis distributions of the cases are summarized in Table 1. It was interpreted as benign neoplasia in 79 (85.8%) and nonneoplastic processes in 13 (14.2%) of 92 cases in the "malignancy negative" group. 6 cases that we interpreted as benign neoplasia were diagnosed as malignant neoplasia, and 2 cases that we interpreted as malignant were diagnosed as benign neoplasia.

Table 1. Histopathological diagnoses of fine needle aspiration cytology evaluated for diagnostic compliance

Histopathological diagnosis distribution	n:124	%
Neoplastic (malignant)	**n:35**	**28.3%**
Squamous cell carcinoma	18	14.5%
Adenoid cystic carcinoma	6	4.8%
Malignant lymphoma	3	2.4%
Asinic cell carcinoma	2	1.6%
Carcinoma Ex pleomorphic adenoma	1	0.8%
Mucoepidermoid carcinoma	1	0.8%
Malignant melanoma	1	0.8%
Low graded salivary gland carcinoma	1	0.8%
High graded salivary gland carcinoma	1	0.8%
Adenocarcinoma, not otherwise specified	1	0.8%
Neoplastic (benign)	**n:77**	**62%**
Pleomorphic adenoma	48	38.7%
Warthin tumor	27	21.7%
Basal cell adenoma	2	1.6%
Nonneoplastic	**n:12**	**9.7%**
Sialadenitis	6	4.8%
Cyst	3	2.4%
Intraparotidal lymph node	2	1.6%
Vascular lesion	1	0.8%

In our series, the overall sensitivity and specificity were 83.3% and 97.7%, respectively. The positive predictive value was 93.7%, the negative predictive value was 93.4%, and our accuracy rate was 93.5% (Table 2). The sensitivity was 88.2%, the specificity was 97.4%, and the accuracy rate was 94.6% when calculated only for the cases for which we made a benign interpretation. When we made a malignant interpretation, the sensitivity was 76.9%, the specificity was 97.7%, and the accuracy rate was 92.9%.

Table 2. Cytological and histopathological diagnostic compatibility

	n
Number of cases included in statistical evaluation	124
True negative	86 (69.3%)
True positive	30 (24.1%)
False negative	6 (4.8%)
False positive	2(1.6%)
Sensitivity	83.3%
Specificity	97.7%
Positive predictive value	93.7%
Negative predictive value	93.4%
Accuracy rate	93.5%

The cytology of six cases with false negativity in FNAC were reported as cellular pleomorphic adenoma (PA) (n:4), reactive intraparotid lymph node (n:2). Three of the patients with PA in FNAC were diagnosed as adenoid cystic carcinoma (ACC) and one of them was mucoepidermoid carcinoma histopathologically after surgery. One of the 2 cases that we interpreted as intraparotidal lymph node in FNAC was diagnosed as follicular lymphoma and the other was diagnosed as diffuse large B-cell lymphoma (Figure 2-3).

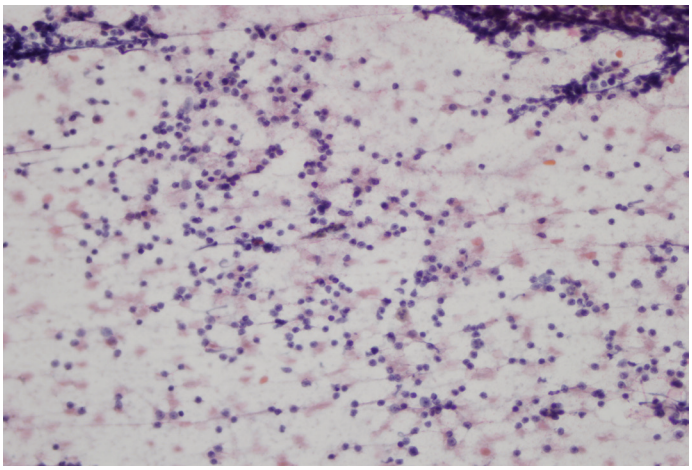

Figure 2. Lymphoid cells in salivary gland cytology diagnosed as malignancy negative, (PAPX400)

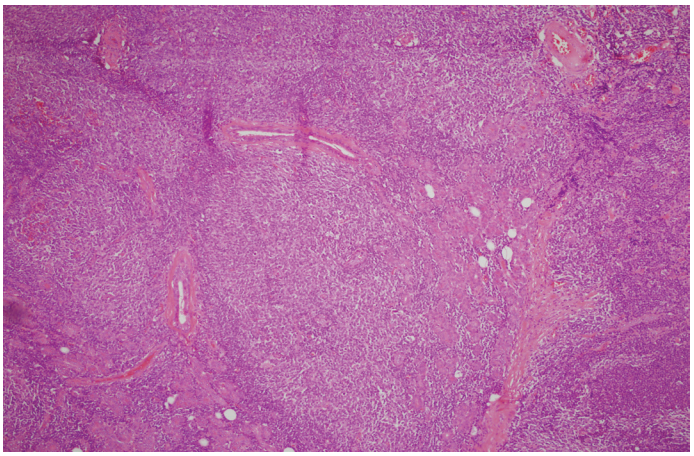

Figure 3. Histopathological section of cytology diagnosed as negative for malignancy. Follicular lymphoma (HEX200)

False positivity was detected in two cases. The tissue diagnosis of the case whose cytological diagnosis was ACC was basal cell adenoma (BCA)(Figure 4-5), and the tissue diagnosis of the case we interpreted as papillary thyroid carcinoma was PA (Table 3).

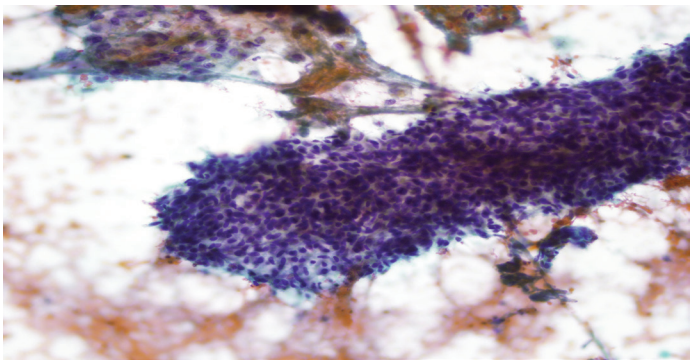

Figure 4. Crowded hyperchromatic basal cells diagnosed as malignancy positive (PAPx200)

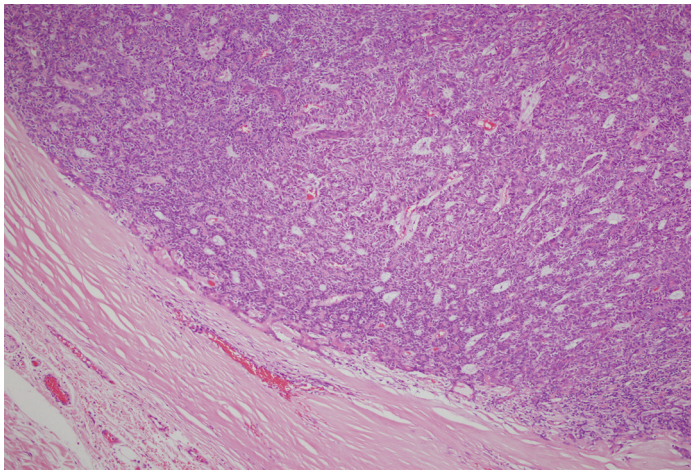

Figure 5. Basal cell adenoma (HEX100)

Table 3. The false negative and positive diagnoses given cytology cases

	n	Cytological diagnosis (n)	Histopathological diagnosis (n)
False negativity	6	Pleomorphic adenoma (4)	Adenoid cystic carcinoma (3)
			Mucoepidermoid carcinoma (1)
		Intraparotidal lymph node (2)	Follicular lymphoma (1)
			Diffuse large B -cell lymphoma (1)
False positivity	2	Adenoid cystic carcinoma (1)	Basal cell adenoma (1)
		Papillary thyroid carcinoma (1)	Pleomorphic adenoma (1)

DISCUSSION

Primary SG tumors constitute 3% of head and neck tumors (1,12-13). Most of these histologically complex tumors are benign. Especially well-differentiated malignant SG tumors have pathological findings overlapping with benign tumors. The primary treatment of salivary gland tumors is surgery and adjuvant radiotherapy and/or chemotherapy can be applied depending on the histopathological type, grade and stage of the tumor. Especially in the preoperative diagnosis of major SG primary tumors, FNAC is the most important diagnostic method. Its diagnostic accuracy is between 80-95% and it is superior to physical examination and imaging methods in the diagnosis of SG lesions (2-11). With FNAC, it is tried to answer whether the mass is inflammatory, neoplastic, benign or malignant. If a malignancy decision is made, it should be reported whether it is a primary salivary gland tumor or a metastatic tumor. If a primary salivary gland tumor is diagnosed, its grade (low/high) should be specified. Thus, the distinction between masses that require surgery and those that do not, or the type of surgery is partially determined, and complications related to the treatment of the patient are partially avoided (11,14-21).

The sensitivity, specificity, and accuracy of FNAC in the preoperative evaluation of primary SG tumors is over 90% (6,7,22). Sensitivity and specificity rates for FNAC in benign lesions have been reported as 64-100% and 75-100%, respectively, and the accuracy rate as 69-100% by various authors (6,7,23-27). Alphs et al. found the accuracy of FNAC to be 90-95%, and Al Salamah found 89% in their study (28,29). In a study conducted in our country, Yıldız et al. reported the sensitivity of preoperative FNAC as 59.09%, specificity as 97.85%, accuracy as 93.75%, positive predictive value as 76.47%, and negative predictive value as 95.2% for the diagnosis of malignancy (30).

Our results also showed that benign and malignant masses could be detected with a high accuracy rate (93.5%) with FNAC, similar to previous studies. Again, similar to the literature, 83.3% sensitivity and 97.7% specificity rates were obtained in benign and malignant SG masses, respectively.

In general, the factors that most affect the diagnostic value of FNAC are the adequacy of the cytological material, its preparation with a good technique, and the experience of the pathologist. Another important factor is the difficulties arising from salivary gland tumors having different cytological/histopathological features within the same tumor. Examples of reactive inflammatory conditions may be indistinguishable from low-grade lymphoma. Similarly, cases of ACC may be indistinguishable from cellular pleomorphic adenoma or cases of low-grade mucoepidermoid carcinoma from Warthin tumor or from non-neoplastic processes such as chronic sialadenitis and retention cysts (15-21). In the literature and in our study, it was seen that the diagnostic difficulties experienced during the cytological evaluation were concentrated in certain entities. It is difficult to distinguish reactive inflammatory conditions such as nonspecific or obstructive sialoadenitis and Mikulicz syndrome from primary SG low-grade lymphomas such as extranodal marginal zone lymphoma at the cytological level (31-34). Cohen et al. found that half of the false-negative results were low-grade lymphomas (31). Zurrida et al. They reported that only 2 of 7 parotid lymphoma cases were diagnosed correctly with FNAC and these were high grade (32). In our series, no lymphoma case was found in FNAC. However, two false-negative cases in our series were interpreted as reactive intraparotid lymph nodes. Follicular lymphoma and diffuse large B-cell lymphoma were diagnosed in the histopathological evaluation. Therefore, it should not be forgotten that flow cytometric examination should be added simultaneously with cytomorphological sampling in cases with clinical pre-diagnosis of lymphoma (35). It is also known that FNAC is very useful in differentiating lymphomas from SG carcinomas (33).

In the review of the American College of Pathologists, it was stated that approximately half (53%) of monomorphic adenomas were interpreted as "false positive" (36). ACC, which is usually rich in monotonous small blue cells with narrow cytoplasm in cytology smears, lacks the classical nuclear features of malignancy. Therefore, it can be diagnosed as cellular PA or BCA and vice versa. The cytological features of the tumor stroma and the cell-stroma interface may help differentiate benign and malignant entities but may be insufficient (3,36). Darvishian et al. stated that the presence of pleomorphism,

coarse chromatin, prominent nucleoli, mitotic figures, and necrosis was only observed in malignant myoepithelial lesions, and they suggested that the presence of any of these features may require wide excision and lymph node dissection with a more aggressive surgical approach (37). For these cases with overlapping cytomorphological findings, the term basaloid neoplasms and the diagnostic category "neoplasm with uncertain malignant potential" can be used (8). One of the false positive cases in our series is an example. It should be remembered that another primary SG malignancy with cytological features with an innocent appearance is ACC (5,23-27). If there is a suspicion of neoplasm, a consultation request from a pathologist/cytopathologist familiar with head and neck pathology will be the most practical and quick solution.

Mucoepidermoid carcinoma is another entity with which we have a diagnostic mismatch, as it contains heterogeneous cell populations, different grade foci, and cystic/solid areas (3,5,36). When the series in the literature are examined, the critical reason for the diagnosis mismatch is sampling errors (6,7,35).

In one case in our series, a false positive was caused by incorrectly filling out the pathology request form. Namely, the cytology sample taken from the submandibular gland was sent as "thyroid" and it was reported as papillary thyroid carcinoma instead of PA diagnosis by our colleague dealing with endocrine pathology because of overlapping cytomorphological findings.

Cytological sampling is insufficient in cystic, small, mobile or prominent fibrotic masses. It may be reported in the "non-diagnostic" category (3,25). Insufficient material ratios have been reported in many studies with variable values such as 1.1% and 12% (2-6,23-27,38). The inadequate rate in our study, which was slightly higher than in the literature, can be resolved by performing FNAC by an experienced radiologist/clinician and a rapid on-site evaluation until experience is gained. Attempting to make a diagnostic interpretation of unsatisfactory samples may indicate a diagnostic inconsistency, often in the form of false negatives; we did not encounter this situation in our series. The pathologist should be comfortable with having adequate data when making diagnostic interpretations. In our series, clinicians did not prefer re-aspiration from cases diagnosed as inadequate and uncategorized, and planned the treatment according to clinical- radiological findings.

The most common malignant tumors that metastasize to the salivary gland are squamous cell carcinoma (SCC), malignant melanoma, and less commonly kidney, breast, and thyroid carcinomas. Therefore, the possibility of metastasis should always be kept in mind, especially in the differential diagnosis of high-grade primary SG neoplasms (39). In our series, the diagnosis of SCC was high (14.5%). Primary SCC of SG is rare and cutaneous or mucosal regions, including the scalp, should be examined for a possible primary focus in the head and neck region (40). Adequate clinical information, radiological imaging findings and knowing the sampling site will prevent misinterpretation of cytological findings.In our study, the number of cases increased significantly over the years. In this process, the cases were reported by the cytopathologist, in-clinic consultation, and surgical pathologists, and only by the head and neck pathology team. Our clinic uses a conventional reporting system in FNAC, and the weak point of our study is the need to integrate our diagnostic categories with the Milan system. After accumulating retrospective analyses similar to our study and increasing cytology applications, the second stage will be the routine use of the Milan system introduced to clinicians.

Our study has shown that we have reached similar rates to the high sensitivity and specificity values reported in the literature regarding the diagnostic value of FNAC. In cases where a clear diagnostic categorization cannot be made, it may be useful to use the diagnostic approach of "Uncategorized; please read the comment", which can guide the clinician. Despite the false-negative and false-positive values, with limitations and pitfalls always in mind, our results showed that the application of FNAC is rapidly increasing and advantageous for clinicians and patients in preoperative diagnosis.

Financial disclosures: *The authors declared that this study has received no financial support.*

Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *This study was approved by the Ondkouz Mayıs University Clinical Research Ethics Committee with the decision dated 30.12.2021 and numbered B.30.2.ODM:0.20.08/843.*

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