A Review of Research on Cytological Approach in Salivary Gland Masses

Abstract
To evaluate the diagnostic accuracy of fine-needle aspirations (FNAs) in salivary gland pathologies. A comprehensive literature search was conducted in the PubMed database using related Medical Subject Heading terms “sensitivity and specificity of FNA in salivary gland” and “diagnostic accuracy of FNA in salivary gland” for the period 1980–2016, and we found that 414 research studies had been published. PRISMA technology was utilized to prepare flow chart for displaying data search strategy. A total of 385 articles were excluded based on the established inclusion and exclusion criteria of the study. Twenty-nine research studies were included. Those twenty-nine studies on the sensitivity and specificity of FNAs in salivary gland pathology consisted of 5274 cases of benign, malignant and inflammatory salivary gland lesions. The present study identified a range of 87%–100% sensitivity and 90%–100% specificity for the usefulness of FNAs in distinguishing benign and malignant salivary gland lesions. Although a considerable number of studies have been identified that reported on sensitivity and specificity of FNAs in salivary gland pathologies, each study had a different approach in reporting the sensitivity and specificity. We emphasize that standardized reporting protocols of sensitivity and specificity report supported with checklists would help future researchers to interpret this cytological method and make more accurate clinical utility and usefulness reports on salivary gland pathologies.

Keywords: Cytology, diagnosis, fine needle aspiration, pathology, salivary gland

Introduction
Cytology focuses at the cellular level on the structure, function and biochemical characteristics whereas cytomorphometric analysis is a qualitative and quantitative measurement of nuclear area, cytoplasmic area and nuclear to cytoplasmic ratio of normal cells. The principles of cytology are applied in diagnostic pathology diagnosis to observe the significance in the difference between normal and diseased cells. Fine needle aspirations (FNAs) are the most common cyto-methodology in salivary gland pathology practice. FNA is a cytological method that is used to describe the morphological findings of individual cells, groups of cells, and microparticles in tissue from samples that were acquired using a needle. The conventional biopsy procedure has a possible risk of intraoperative tumor cell implantation and damage to the facial nerve in parotid gland pathologies. FNAs are minimally invasive, simple, cost-effective, and minimal risk procedure than conventional biopsy procedure. Schröder et al. mentioned that FNAs have a minimal incidence of complication, have a reduced risk of tumor cell implantation (<1%). In addition, complications from surgical procedures such as hemorrhage, facial nerve damage and inflammatory reaction at the surgical site are rare. In routine FNAs practice, the needle used in aspiration is 25-gauge (i.e., 0.5 mm) and 10-mL syringe. Perkins in 2002 reported that larger syringes do not produce better specimens. In Sweden, a syringe holder is used, whereas in France a puncture is made without syringe aspiration. The material aspirated can be either prepared as direct smears or as cell blocks. The cell blocks are useful and are suitable for histochemical and immunocyto/histochemical staining methods. FNA methodology thus helps in recognizing inflammatory, reactive, cystic, benign, or malignant conditions of salivary gland tissue.

The focus of the pathologist, while evaluating the aspirated specimen, is on: (1) Whether the clinical condition had originated from salivary gland tissue? (2) The type of pathology (inflammatory, cystic, etc)
benign or malignant), (3) When the lesion is identified as malignant, the focus is made on detection of low grade versus high grade, (4) How specifically can the cytological diagnosis be derived? and (5) Cytological specimens that indicate atypical or malignant features mandate the need for surgical biopsy.

This review of the cytological approach to salivary gland masses will focus on the normal salivary gland cytology, report on FNA research that focused on sensitivity and specificity of salivary gland pathologies, cytological diagnosis in salivary gland pathology, specific cytological features of major salivary gland pathologies and problems, as well as pitfalls, in cytdiagnosis of salivary gland aspirates.

Descriptive Analysis on Research Report of Sensitivity and Specificity of Fine Needle Aspiration in Salivary Gland Pathology

The search for a reliable adaptation of FNA in salivary gland pathology practice has developed rapidly, encouraged by the fact that collecting a specimen is relatively easy, minimally invasive, economical, and rarely associated with complications. We conducted a comprehensive literature search in PubMed database using related Medical Subject Heading terms “sensitivity and specificity of FNA in salivary gland,” “diagnostic accuracy of FNA in salivary gland” from the early 1980s until the present, four hundred and fourteen research studies have been published in the PubMed database. The research papers were included based on: (1) full-text availability, (2) research papers that were available in English language, and (3) papers having Information on sensitivity and specificity of FNAs in salivary gland pathologies. However, research papers were excluded based on: (1) duplication of titles, (2) studies that focused on genetic and/or salivary analysis, and (3) incorrect weblink for full-text accessibility. Three hundred and eighty-five articles were excluded, 29 research studies were included [Figure 1].

The 29 studies on the sensitivity and specificity of FNAs in salivary gland pathology were all retrospective and consisted of 5274 cases of benign, malignant and inflammatory salivary gland lesions. The largest number of studies were reported from the Department of Pathology (8–20) (13 studies, 44.82%), followed by Departments of Otorhinolaryngology (21–24) (four studies, 13.79%), Head and Neck (25–28) (four studies, 13.79%), Surgery (29–31) (three studies, 10.34%), Surgical Oncology (32) (one study, 3.44%), Radiology (33) (one study, 3.44%), Stomatology (34) (one study, 3.44%), Laboratory Medicine (35) (one study, 3.44%), and one study (36) that did not specify their department details (one study, 3.44%) [Figure 2]. The rate of publication on sensitivity and specificity of FNAs has increased during the past 10-year period [Table 1].

A predominant number of studies focused on determining the diagnostic value of sensitivity and specificity of FNAs in salivary gland pathology. The overall accuracy rate of reporting on distinguishing benign from malignant salivary gland lesions was 87%–100% with a specificity of 90%–100%. A Taiwanese study evaluated the efficacy of Ultrasonography-Guided Fine Needle Aspiration Biopsy on malignant salivary gland lesions and revealed a sensitivity of 66.7% and specificity of 98.2%. So far, only three studies have been exclusively focused on FNAs sensitivity and specificity on parotid gland pathologies. Piccioni et al. assessed diagnostic accuracy of FNAs on benign and malignant parotid swellings that included Pleomorphic adenoma, Warthin’s tumor, mucoepidermoid carcinoma, adenocarcinoma, lymphoma, adenoid cystic carcinoma (ADCC), ductal carcinoma, oncocytoma, monomorphic adenoma and lipoma; and reported 81% sensitivity and 99% specificity on FNAs.[32] Awon and Ahmad evaluated the usefulness and accuracy of FNA cytology in the diagnosis of parotid gland tumors that included oncocytoma, mucoepidermoid carcinoma, pleomorphic adenoma and reported 74% sensitivity and 97% specificity.[39] Zurrida et al. assessed the accuracy of FNAs in planning therapy for parotid disease such as pleomorphic adenoma, Whartin’s tumor, oncocytoma, monomorphic adenoma, myoepithelioma, basal cell adenoma (BCA), acinic cell carcinoma, mucoepidermoid carcinoma, ADCC, malignant myoepithelialoma, metastatic squamous cell carcinoma and non-Hodgkin’s lymphoma by comparing the preoperative FNAs diagnosis with the postsurgical biopsy based specimen diagnosis; and reported 100% sensitivity and 90.40% specificity.[32] The results show higher specificity than sensitivity. Another study from the United States determined the accuracy of FNAs for establishing the diagnosis in lymphoproliferative, reactive and neoplastic salivary gland lesions as 100% sensitivity and 87% specificity.[20]

Two of the studies studied the preoperative efficacy of FNAs in salivary gland pathologies. Singh et al. established sensitivity and specificity of FNAs by correlating FNAC diagnosis with histopathology in benign, malignant, and nonneoplastic salivary gland lesions and revealed 76.90% sensitivity and 97.10% specificity. Their results concluded that FNAs can be used preoperatively to avoid unnecessary surgery and discomfort associated with open biopsy.[13] Tahoun and Ezzat evaluated the diagnostic accuracy of preoperative FNAs in benign and malignant salivary gland lesions and revealed 91.7% sensitivity and 92.5% specificity. Their results suggested that FNAC is complementary in usefulness for malignant salivary gland tumors. In contrast, FNAs does not influence the management of benign salivary gland lesions and routine FNAs for every patient may not be cost-effective.[14]
| Number | Study hypothesis                                                                 | Study sample size | Type of pathologies observed in the study | Specific information on pathologies observed                                                                 | Report on sensitivity and specificity on FNAs | Reporting country | Reporting specialty | Author/year (reference) |
|--------|----------------------------------------------------------------------------------|-------------------|------------------------------------------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------|---------------------|----------------------|
| 1      | To examine the sensitivity, specificity, and accuracy of FNAC of salivary gland lesions | 101               | Benign, malignant, and nonneoplastic lesions | Pleomorphic adenoma, Warthin’s tumor, adenoid cystic carcinoma, acinic cell carcinoma, squamous cell carcinoma, sialadenitis, cystic lesion, abscess, sialadenosis, and granulomatous inflammation | Sensitivity: 80%  
Specificity: 98.80%  
Malaysia  
Pathology  
Ameli et al., 2015[8] |                  |                    |                                   |                                                                                                               |
| 2      | To determine utility of FNAC in the diagnosis of salivary gland lesions           | 186               | Benign, malignant, and nonneoplastic lesions | Chronic sialadenitis, Kuttner’s tumor, lymphoepithelial cyst, pleomorphic adenoma, basal cell adenoma, Warthin’s tumor, mucoepidermoid carcinoma, acinic cell carcinoma, adenoid cystic carcinoma, carcinoma ex-pleomorphic adenoma, epithelial-myoepithelial carcinoma, and squamous cell carcinoma | Sensitivity: 86.60%  
Specificity: 94.60%  
India  
Pathology  
Arul et al., 2015[9] |                  |                    |                                   |                                                                                                               |
| 3      | To assess the diagnostic accuracy of FNAC for salivary gland lesions             | 187               | Benign, malignant, and nonneoplastic lesions | Chronic sialadenitis, Benign cystic lesion, granulomatous inflammation, pleomorphic adenoma, Warthin’s tumor, mucoepidermoid carcinoma, acinic cell carcinoma, adenoid cystic carcinoma, lympho proliferative disorder, and papillary adenocarcinoma | Sensitivity: 77.70%  
Specificity: 86.30%  
Pakistan  
Histopathology  
Naz et al., 2015[10] |                  |                    |                                   |                                                                                                               |
| 4      | To identify the spectrum of cytological diagnoses and evaluate the diagnostic effectiveness of FNAC in patients <20 years old | 909; salivary gland masses were 75 | Benign lesions                     | Pleomorphic adenoma, epidermal cysts, brachial cleft cyst | Sensitivity: 63%  
Specificity: 99%  
South Korea Pathology  
Kim et al., 2013[11] |                  |                    |                                   |                                                                                                               |
| 5      | To determine diagnostic value in patients with neck masses in Iranian patients   | 31                | Benign, malignant and nonneoplastic lesions | Inflammatory process, mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, squamous cell carcinoma, adenocarcinoma, lymphoma | Sensitivity: 72%  
Specificity: 87%  
Iran  
Pathology  
Saatian et al., 2011[12] |                  |                    |                                   |                                                                                                               |
| 6      | To correlate FNAC diagnoses with histopathology and to establish the sensitivity and specificity of FNAC in diagnosis of salivary gland swellings in our institution | 96                | Benign, malignant and nonneoplastic lesions | Pleomorphic adenoma, basal cell adenoma, Warthin’s tumor, lipoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, pleomorphic adenoma ex-carcinoma, metastatic tumor, inflammatory lesion | Sensitivity: 76.90%  
Specificity: 97.10%  
India  
Pathology  
Singh et al., 2011[13] |                  |                    |                                   |                                                                                                               |
| Number | Study hypothesis | Study sample size | Type of pathologies observed in the study | Specific information on pathologies observed | Report on sensitivity and specificity on FNAs | Reporting country | Reporting specialty | Author/year (reference) |
|--------|------------------|-------------------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------|---------------------|------------------------|
| 7      | Evaluation of diagnostic accuracy of preoperative FNAC in salivary gland lesions | 82                | Benign and malignant lesions               | Pleomorphic adenoma, Warthin’s tumor, and basal cell adenoma, acinic cell carcinoma and mucoepidermoid carcinoma | 91.70% 92.50% | United States | Pathology | Tahoun and Ezzat 2008\[14\] |
| 8      | To evaluate the sensitivity and specificity of FNA of SGTs | 115               | Benign and malignant lesions               | Pleomorphic adenoma, Warthin’s tumor, and basal cell adenoma, acinic cell carcinoma and mucoepidermoid carcinoma | 88.20% 100% | Japan | Pathology | Mihashi et al., 2006\[15\] |
| 9      | To evaluate utility of FNAC in salivary gland lesions | 70                | Benign, malignant and nonneoplastic lesions | Sialadenitis, cystic lesions, tuberculosis, pleomorphic adenoma, Warthin’s tumor, mucoepidermoid carcinoma, adenoid cystic carcinoma and squamous cell carcinoma | 94.54% 80.95% | India | Pathology | Khandekar et al., 2006\[16\] |
| 10     | The reliability of FNA biopsy as a the initial diagnostic procedure for palpable masses | 56                | Benign, malignant and nonneoplastic lesions | Pleomorphic adenoma, sialadenitis, hyperplasia, Warthin’s tumor, cyst, duct ectasia, lipoma, traumatic neuroma, dermoid cyst, carcinoma | 93% 100% | United States | Pathology | Florentine et al., 2006\[17\] |
| 11     | To evaluate FNAC in terms of accuracy along with its complications and limitations | 55                | Benign, malignant, and nonneoplastic lesions | Not available | 90.91% 93.18% | India | Pathology | Tilak et al., 2002\[18\] |
| 12     | To evaluate FNAC effectiveness in the interpretation of salivary gland disorders | 52                | Benign, malignant, and nonneoplastic lesions | Chronic sialadenitis, lymphoid hyperplasia, follicular lymphoma, acinic cell carcinoma, carcinoma ex-pleomorphic adenoma, monomorphic adenoma, Warthin’s tumor, lipoma, neurilemmoma, lymphoma, multiple myeloma and non-Hodgkin lymphoma | 66% 100% | Israel | Pathology and Lurie et al., 2002\[19\] otolaryngology |
| 13     | To determine the accuracy of FNA for establishing the diagnosis in salivary gland lesions | 43                | Reactive and neoplastic lymphoproliferative lesions | Lymphoid hyperplasia, multiple myeloma and non-Hodgkin lymphoma | 100% 87% | United States | Pathology | Chhieng et al., 2000\[20\] |
| 14     | To assess the efficacy of FNAC in preoperative diagnosis of parotid tumors | 93                | Benign and malignant lesions               | Pleomorphic adenoma, Warthin’s tumor, mucoepidermoid carcinoma, adenoid cystic carcinoma, acinar cell carcinoma, nondifferentiated carcinoma, lymphoma, melanoma, and oncocytic carcinoma | 57.10% 95.10% | Spain | Otorhinolaryngology | Zerpa Zerpa et al., 2014\[21\] |

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Table 1: Continued...

| Number | Study hypothesis                                                                 | Study sample size | Type of pathologies observed in the study | Specific information on pathologies observed                                                                 | Report on sensitivity and specificity on FNAs | Reporting country | Reporting specialty | Author/year (reference) |
|--------|----------------------------------------------------------------------------------|-------------------|------------------------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------------------|------------------|-------------------|------------------------|
| 15     | To identify the efficacy of FNA cytology by comparing cytodiagnoses with histopathology | 115               | Benign and malignant lesions             | Not available                                                                                                  | 80.80%                                      | Turkey           | Otorhinol aryngology | Inançli et al., 2013[22] |
| 16     | To assess the diagnostic accuracy of FNAC, on parotid gland swellings            | 176               | Benign and malignant lesions of parotid gland | Pleomorphic adenoma, Warthin’s tumor, mucoepidermoid carcinoma, adenocarcinoma, lymphoma, adenoid cystic carcinoma, ductal carcinoma, oncocytoma, monomorphic adenoma and lipoma | 81%                                         | Italy            | Otorhinol aryngology | Piccioni et al., 2011[23] |
| 17     | To determine the FNAs accuracy in malignant salivary gland lesions               | 51                | Malignant lesions                        | Sialadenitis, benign lymphoepithelial lesion, pleomorphic adenoma, myoepithelioma, acinic cell carcinoma, carcinosarcoma, squamous cell carcinoma, metastatic Merkel cell carcinoma, lymphoma, rhabdomyosarcoma | 79%                                         | Germany          | Otorhinol aryngology/ plastic surgery | Gerstner et al., 2003[24] |
| 18     | To determine the diagnostic value of FNAC in our institution in order to define its place in the diagnostic strategy | 249               | Benign and malignant lesions             | Lymphoepithelial cyst, pleomorphic adenoma, Warthin’s tumor, acinar cell carcinoma, follicularB-cell lymphoma, low-grade mucoepidermoid carcinoma, adenocarcinoma | 80%                                         | France           | Cervico-facial clinic | Fakhry et al., 2012[25] |
| 19     | To study the clinicopathological characteristics of SGTs in a Chinese population | 1176              | Benign and malignant lesions             | Pleomorphic adenoma, whartin’s tumor, basal cell adenoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, salivary duct carcinoma, acinic cell carcinoma, lymphoepithelial carcinoma, polymorphous low-grade adenocarcinoma, adenocarcinoma, carcinoma ex-pleomorphic adenoma, epithelial myoepithelial carcinoma, squamous cell carcinoma, metastatic carcinoma and lymphoma | 87.20%                                      | China            | Head and neck surgery | Wang et al., 2012[26] |
| 20     | To evaluate the diagnostic accuracy, sensitivity and specificity of FNAB of salivary gland tumours | 79                | Benign and malignant lesions             | Pleomorphic adenoma, whartin’s tumor, lipoma and acinar cell carcinoma | 68.20%                                      | Brazil           | Head and neck surgery | Stramandinoli et al., 2019[27] |

Contd..
| Number | Study hypothesis | Study sample size | Type of pathologies observed in the study | Specific information on pathologies observed | Report on sensitivity and specificity on FNAs | Reporting country | Reporting specialty | Author/year (reference) |
|--------|------------------|------------------|-----------------------------------------|-----------------------------------------------|-----------------------------------------------|------------------|---------------------|-----------------------|
| 21     | To review the FNAC and FS in salivary gland surgery and analyze the accuracy of both modalities | 114 | Benign, malignant and nonneoplastic lesions | Pleomorphic adenoma, Warthin’s tumor, basal cell adenoma, schwannoma, sialadenitis, inflamed salivary duct cyst, oncocytosis, lymphoid hyperplasia, castlemann’s disease, Kimun’s disease, acinic cell carcinoma, oncocytic carcinoma, adenoid cystic carcinoma, basal cell carcinoma, lymphoepitheliotumor-like carcinoma, mucoepidermoid carcinoma, recurrent nasopharyngeal carcinoma | Sensitivity: 89.70% Specificity: 100% | Singapore | Head and neck | Tan and Khoo 2006[28] |
| 22     | To determine the ability of FNA of the parotid gland to differentiate benign and malignant disease | 201 | Benign, malignant and nonneoplastic lesions | Pleomorphic adenoma, Warthin’s tumor, benign squamous cyst, lymphoma, nonspecific inflammation, lymphoepithelial cyst, basal cell adenoma, lipoma, salivary gland retention cyst, acinic cell carcinoma, adenocarcinoma, squamous cell carcinoma, mucoepidermoid carcinoma, adenoid cell carcinoma, oncocytic carcinoma, myoepithelial carcinoma, and pleomorphic ex-carcinoma | FNA showed 85% sensitivity among benign lesions FNA showed 76% specificity among benign lesions | United Kingdom | Surgery | Mallon et al., 2013[29] |
| 23     | To evaluate the usefulness and accuracy of fine needle aspiration cytology in the diagnosis of parotid gland tumors | 50 | Benign and malignant lesions of parotid gland | Oncocytoma, mucoepidermoid carcinoma, pleomorphic adenoma | Sensitivity: 74% Specificity: 97% | Pakistan | Surgery | Awan and Ahmad 2004[30] |
| 24     | To determine if in the light of development of these developments, disease of the parotid glands can be managed satisfactorily in a general surgical unit | 50 | Neoplastic and nonneoplastic conditions of parotid glands | Pleomorphic adenoma, Warthin’s tumor | The sensitivity of fine needle cytology for malignant parotid tumors was 66%. Whereas for benign tumors (pleomorphic adenoma or Warthin’s) 83%, specificity was 95%. | United Kingdom | Surgery | Deans et al., 1995[31] |
Table 1: Continued...

| Number | Study hypothesis                                                                 | Study sample size | Type of pathologies observed in the study | Specific information on pathologies observed                                                                 | Report on sensitivity and specificity on FNAs | Reporting country | Reporting specialty | Author/year (reference) |
|--------|----------------------------------------------------------------------------------|-------------------|------------------------------------------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------|----------------------|----------------------------------|
| 25     | The aim was to compare preoperative and postoperative diagnoses in this series and to assess the accuracy of FNA and its role in planning therapy for parotid diseases | 246               | Benign and malignant lesions of parotid gland | Pleomorphic adenoma, Warthin’s tumor, oncocytoma, monomorphic adenoma, myoepithelioma, basal cell adenoma, acinic cell carcinoma, mucoepidermoid carcinoma, adnoid cystic carcinoma, malignant myoepithelialoma, metastatic squamous cell carcinoma, and non-Hodgkin’s lymphoma | Sensitivity: 88% Specificity: 90.40 | Italy              | Surgical oncology      | Zurrida et al., 1993[32] |
| 26     | To evaluate the efficacy of UGFNAB in the diagnosis of salivary gland lesions    | 158               | Malignant lesions                        | Metastatic carcinoma, pleomorphic adenoma, lymphoid hyperplasia, Warthin’s tumor, lymphoma, myxoid liposarcoma, carcinoma | Sensitivity: 66.7% Specificity: 98.2% | Taiwan             | Radiology            | Huang et al., 2012[33]        |
| 27     | To evaluate the sensitivity, specificity and accuracy of FNAB in different staining techniques for nodular lesions from oral cavity and head and neck region | 39                | Benign and malignant lesions             | Not available                                                                                                  | FNAs stained with Papanicolaou staining showed sensitivity of 71.4% | Brazil             | Stomatology            | Santos et al., 2015[34]         |
| 28     | The accuracy of FNA cytology of salivary gland lesions by correlation between histology and cytology | 131               | Benign and malignant lesions             | Pleomorphic adenoma, Warthin’s tumor, basal cell adenoma, myoepithelioma, papillary mucinous cystadenoma, oncocytoma, sialolipoma, sialoadenitis, benign lymphoepithelial lesion, nodular oncocytic hyperplasia, sialolithiasis, lymphoepithelial cyst, Kimura’s | Sensitivity: 74% Specificity: 99% | Taiwan             | Laboratory medicine    | Jan et al., 2008[35]          |
Approach to Analyze Diagnostic Accuracy of Fine Needle Aspirations via Sensitivity and Specificity Report in Salivary Gland Cytodiagnosis

The sensitivity and specificity report of benign, malignant, and nonneoplastic salivary gland lesions on FNA cytology is shown in Table 1. The benign salivary gland conditions observed in present study are pleomorphic adenoma, Warthin’s tumor, lipoma, lipoma, oncocytoma, monomorphic adenoma, myoepithelioma, and schwannoma. The malignant salivary gland conditions observed in the present study are ADCC, acinic cell carcinoma, squamous cell carcinoma, mucoepidermoid carcinoma, carcinoma ex-pleomorphic adenoma, epithelial-myoepithelial carcinoma, adenocarcinoma, lymphoma, non-Hodgkin’s lymphoma, multiple myeloma, undifferentiated carcinomas, oncocytic carcinoma, ductal carcinoma, metastatic Merkel cell carcinoma, carcinomasarcoma, rhabdomyosarcoma, lymphoepithelial carcinoma, polymorphous low-grade adenocarcinoma (PLGA), nasopharyngeal carcinoma, myxoid liposarcoma, and basoloid squamous cell carcinoma.

The significance of utilizing FNA cytology practice in salivary gland pathology diagnosis is controversial due to lack of reliable recognition of true positive, true negative, false positive, or false negative cases. To achieve the reliable adaption of FNAs in salivary gland diagnosis, the preferred statistical tools to assess the positive and negative predictive values of FNA methodology were analyzed using sensitivity and specificity tests. If the FNAs were able to measure fewer false positives but more false negative cases, then the FNAs is highly specific but not very sensitive. Similarly, if the FNAs are able to measure fewer false negatives but more false positives, then the FNAs is highly sensitive but not very specific. When FNAs report was able to produce 100% sensitivity and 100% specificity results on the identification of salivary gland pathology then the FNAs should be considered as gold standard test and that it would never make an error. However, in routine practice that categorized a test as a gold standard may not be true gold standard because the gold standard is regarded as the best test under reasonable conditions.

The present study observed sensitivity of FNAs in recognition of salivary gland pathology was at a range of 57%–100% and specificity 80.95%–100%. Based on the current observation, the results can be generalized that FNAs are low sensitivity and highly specific, which means that there are many false negatives and few false positive results. Interestingly, the studies that focused on only benign salivary gland or inflammatory salivary gland conditions generated highly sensitive and highly specific results. The later observation is convenient to state that FNAs are useful diagnostic test in distinguishing benign and malignant salivary gland conditions. However, observations of the present study cannot be concluded as

| Specificities | Sensitivities |
|---------------|--------------|
| benign        | malignant    |
| squamous cell carcinoma | myoepithelial carcinoma |
| salivary duct carcinoma | adenoid cystic carcinoma |
| adenocarcinoma | carcinomasarcoma |
| mucoepidermoid carcinoma | rhabdomyosarcoma |
| carcinoma ex-pleomorphic adenoma | lymphoepithelial carcinoma |
| epithelial-myoepithelial carcinoma | polymorphous low-grade adenocarcinoma (PLGA) |
| adenocarcinoma | nasopharyngeal carcinoma |
| lymphoma | myxoid liposarcoma |
| non-Hodgkin’s lymphoma | basoloid squamous cell carcinoma |

Table 1: Specific information on pathologies observed in the study

| Type of pathologies observed in the study | Study sample size | Author/year (reference) |
|-----------------------------------------|------------------|-------------------------|
| squamous cell carcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, malignant lymphoma, lipoma, oncocytoma, basoloid squamous cell carcinoma | 73 | Not available |
| benign and malignant lesions | 29 | Not available |

FNAs showed sensitivity of 87.9% for benign tumors, whereas malignant tumors showed specificity of 42.5%.

FNAC=Fine needle aspiration cytology, FNAs=Fine needle aspirations, SGTs=Salivary gland tumors, FNAB=Fine needle aspiration biopsies, FS=Frozen section.
FNAs in salivary gland practice displays low sensitivity and highly specific reports due to the following reasons (1) the variation in reporting approach, (2) reports produced were clustered with benign, malignant and/or nonneoplastic salivary gland lesions, and (3) many studies did not show any evidence of standardized sample size calculation for reporting their results. The present study is the descriptive analysis of available reports on sensitivity and specificity of FNAs and the interpretations presented is not statistically acceptable. Systematic reviews are the best research tool to assess the diagnostic accuracy of FNAs in salivary gland diagnosis by investigating sensitivity and specificity reports of FNAs. The systematic reviews will come out with research questions on diagnostic accuracy with inclusion and exclusion criteria for selection of research reports. Following to the data collection from the reports available in literature, data analysis will be employed using statistical analysis. The results of the systematic reviews will be presented in the discussion exploring areas arising from research questions.

Normal Cytological Characteristics of Salivary Gland Aspirate

The three major salivary gland tissues are the parotid, submandibular, and sublingual. The normal cytological characteristics of salivary gland tissue are studied from the unintentional aspiration of normal tissue while aspirating abnormal tissue. FNAs of the normal salivary gland aspirate shows glandular (i.e., acinic cells), ductal elements, adipose tissue and scattered inflammatory cells. The acinic cells are either serous or mucous. The acinic cells are seen as cohesive ball like/grape-like arrangements, whereas ductal elements are identified as cohesive orderly sheets or more rarely as tubules and elongated myoepithelial cells attached to the epithelial elements.\(^{[7,38]}\) Acinic cells appear as a background field of bare nuclei. The acinic cells are composed of pyramidal cells that have uniform eccentric nuclei, and cytoplasm of serous cells is finely granular, foamy or vacuolated compared to the cytoplasm of ductal elements. Whereas ductal cells appear crowded, are smaller than acinar cells, and have less cytoplasm. When the nuclei of the ductal cells lose their cytoplasm, it is easy to misdiagnose these cells as lymphocytes.\(^{[38,39]}\)
### Table 2: Microscopic characteristics of salivary gland pathology

| Salivary gland pathology                   | Microscopic details of FNA                                                                 | Author/year (reference)                      |
|-------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------|
| Sialadenosis                              | Plenty of acinar epithelial cells, which appear normal or slightly increased in size. Microarchitectural pattern of regular acini joined by small ducts and fibrovascular stroma is that of normal salivary gland tissue is seen without inflammatory cells                                                                 | Ascol et al., 1993, Henry-Stanley et al., 1995, Gupta and Sodhani 1998(40-42) |
| Cysts                                     | Aspirate fluid of nonneoplastic cysts such as retention cysts, salivary duct cyst and lymphoepithelial cysts is poor in cells with presence of variable number of histiocytes, inflammatory cells and few degenerating epithelial cells and also few crystalloids. Aspirate of mucocele yields mucus with variable amount of mucinophages and inflammatory cells                      | Mavec et al., 1964, Elliott and Oertel., 1990, Zurrida, 1993, Layfield and Gomez, 2002(34,43-45) |
| Sialadenitis                              | Purulent aspirate (acute, infective sialadenitis) consisting of scanty ductal epithelial cells and acinar cells associated with fragments of fibrous stroma. Variable amounts of lymphocytes may be present in case of chronic sialadenitis. Sheets of ductal epithelium may show regenerative atypia and or squamous metaplasia | Qizilbash et al., 1985, Abad et al., 1992, Wax et al., 1994, Johnson et al. 1995(46-49) |
| Necrotizing sialometaplasia               | Cellular smear of squamous metaplastic cells showing regenerative atypia and degenerative changes such as nuclear pyknotosis with necrotic material in the background                                                                                                                                                                                                 |
| Benign lymphoepithelial lesion            | Smears from benign lymphoepithelial lesion are characterized by small clusters of ductal epithelial cells associated with lymphocytes and with a background of lymphoid cells                                                                                                                                                                                                                                                                 |
| Pleomorphic adenoma                       | Thick, sticky, fibrillary chondromyxoid ground substance like gel with variable cellularity consisting of and showing, mainly spindle shaped myoepithelial cells in single, in poorly cohesive clusters and sheets embedded in stromal matrix. Rounded, ovoid, plasmacytoid or spindle cells with abundant well defined cytoplasm, mesenchymal cells in a variable proportion. Sometimes metaplastic cells such as oncocytic, sebaceous and squamous cells may be seen. Whereas, monomorphic adenomas show lack of fibromyxoid material                                                                 | Klijjanienko and Vielh, 1996, Viguier et al., 1997(13,54) |
| Basal cell and canalicular adenoma         | Numerous small basoloid cells having scanty cytoplasm and rounded nuclei are found both singly and in multilayered clusters with occasional peripheral palisading with scanty inconspicuous stroma                                                                                                                                                                                                             | Hood et al., 1983, Stanley et al., 1996, Klijjanienko et al., 1992(55-57) |
| Warthin’s tumor                           | Aspirate is mucoid, murky fluid. There is the presence of bland oncocytic cells in cohesive, monolayered sheets and lymphoid cells in amorphous and granular debris background. Mast cells commonly associated with oncocyes                                                                                                                  | Klijjanienko and Vielh, 1997(58) |
| Oncocytoma and oncocytic carcinoma        | Contains cohesive oncocyes in sheets and three dimensional clusters with no fluid, debris and lymphoid cells                                                                                                                                                                                                                                                                                                                                 |
| Adenoid cystic carcinoma                  | Shows cellular smear with small uniform, basoloid cells with round hyperchromatic nuclei and coarse chromatin. Hyaline spherical globules with adherent tumor cells are characteristic                                                                                                                                                                                                                                                                  | O’Dwyer et al., 1986(59) |

Contd...
Table 2: Continued...

| Salivary gland pathology                  | Microscopic details of FNA                                                                 | Author/year (reference) |
|------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------|
| Mucoepidermoid carcinoma                 | Shows low cellularity with a dirty background of mucus and debris. Various cell types     | Cohen et al., 1990,     |
|                                          | predominantly intermediate cells, some mucous cells and infrequently squamous cells are    | Kumar et al., 1991,     |
|                                          | seen                                                                                      | Klijanienko and Vielh,  |
|                                          |                                             | 1997[62-64]               |
| Acinic cell carcinoma                     | Shows pure population of acinar cells in a clean background without ductal cells or       | Frierson et al., 1987,  |
|                                          | stroma. Cells arranged in clusters shows abundant, fragile, finely vacuolated cytoplasm  | Klijanienko and Vielh,  |
|                                          | with rounded medium sized nuclei. Mild to moderate anisokaryosis and bland chromatin is    | 1998, Gibbons et al.,   |
|                                          | present                                                                                  | 1999[65-66]              |
| Polymorphous low grade adenocarcinoma     | Cells with mildly enlarged pale ovoid homogeneous nuclei are arranged in                 | Carrillo et al., 1990,  |
|                                          | clustered tissue fragments with a trabecular pattern but also single cells. Hyaline       | Kocjan et al., 1993,     |
|                                          | stromal globules often present. Small basolaid epithelial cells or slightly larger        | Klijanienko and Vielh,  |
|                                          | cells resembling ductal epithelium or metaplastic squamous cells are also seen            | 1998, Ng et al., 1999,   |
|                                          |                                                                                          | Miliauskas and Orell     |
|                                          |                                             | 2003[68-69]               |
| Epithelial myoepithelial carcinoma       | Shows single cells or cell aggregates having strands of fibrous stroma and                | Smith, 1991[73]          |
|                                          | trabecular pattern. A biphasic population of clustered small epithelial cells and less    | Dee et al. 1993, Elsheikh|
|                                          | cohesive myoepithelial (clear) cells with pale fragile cytoplasm and large vesicular     | 1994, Fýrat et al. 1997,|
|                                          | nuclei showing mild to moderate nuclear enlargement and variation                        | Khurana et al., 1997,    |
|                                          |                                             | Klijanienko and Vielh, 1998|
|                                          |                                             | Ng et al., 1999,          |
|                                          |                                             | Miliauskas and Orell, 2003|
| Carcinoma ex pleomorphic adenoma         | Shows a dual population of malignant epithelial cells and benign cells and stromal        | Batsakis et al., 1992[81]|
| Salivary duct carcinoma                   | components of pleomorphic adenoma                                                        |                         |
| Adenocarcinoma of no special type         | Aspirate of salivary duct carcinoma shows clearly malignant epithelial cells, single     |                         |
|                                          | and in clusters. These cells show abundant cytoplasm, squamous,                         |                         |
|                                          | sometimes oncocytic like with no stromal component in the background of necrotic debris  |                         |
|                                          |                                             |                         |
|                                          | Shows poorly cohesive atypical epithelial cells with nuclear features of malignancy       |                         |
|                                          | with the presence of intracellular or extracellular mucin. Some glandular differentiation |                         |
|                                          | (microglandular pattern) may be present. These features do not suggest any specific entity|                         |

FNA=Fine needle aspiration

Cytological Characteristics of Aspirates from Salivary Gland Pathology

In responding to the call for detection of aspiration cytology diagnosis, oral and maxillofacial pathologists are expected to be knowledgeable of the cytological details of both normal as well as pathological conditions. Several excellent case studies and reviews have been previously published concerning the fine needle cytology diagnosis of various salivary gland pathologies. The microscopic characteristics of fine needle aspirate of salivary gland pathology are listed in Table 2.

Miller’s Approach in Salivary Gland Cytodiagnosis

The complexity of salivary gland lesions predisposes the cytodiagnosis to be challenging. Miller devised a five group approach to salivary gland cytodiagnosis: (1) myxoid-hyaline, (2) basolaid, (3) oncocytoid, (4) lymphoid, and (5) squamoid lesions [Figure 3]. The lesions that are included in myxoid hyaline lesions are benign mixed tumors, ADCC, carcinoma ex benign mixed tumor, PLGA; the lesions that show myxoid hyaline but are not of salivary gland origin are schwannoma, myxoma, myxoid lipoma, and myxoid neurofibroma. The basolaid lesions included BCA, basal cell carcinoma, solid variant of ADCC, PLGA, and small cell undifferentiated carcinoma. Intraglandular oncocytic lesions included Whartin’s tumor, oncocytoma, acinic cell carcinoma; and extraglandular oncocytic lesions include paraganglioma, carcinoid, granular-cell tumor, rhabdoid tumors, renal cell carcinoma, melanoma, medullary carcinoma, Hurthle cell carcinoma, and hepatocellular carcinoma. Lymphoid lesions included chronic sialadenitis, benign lymphepithelial lesions, intra-/peri-salivary gland lymph nodes. The misdiagnosis of lymphoid lesions included neoplastic lesions that are associated with lymphocytes such as Whartin’s tumor, lymphoepithelial carcinoma, and metastasis to intra-/peri-parotid lymph node. Squamoid lesions include retention cyst/mucoceles, squamous cell carcinoma and benign congenital cysts extrinsic to salivary glands such as branchial cleft, thyroglossal duct, thymic, and dermoid/epidermal inclusion cysts.[82]

Conclusion

The present study identified that the usefulness of FNAs in distinguishing benign and malignant salivary gland lesions were at a range of 87%–100% sensitivity and 90%–100% specificity. Although a considerable number
of studies have been identified that reported on sensitivity and specificity of FNAs in salivary gland pathologies, each study had a different approach in reporting the sensitivity and specificity. Hence, the present study results may not be conclusive to make a statement on overall sensitivity and specificity reports on FNA in salivary gland pathologies. However, we emphasize that standardized reporting protocols of sensitivity and specificity report with the means of checklists, would help future researchers interpret this cytological method and make more accurate clinical utility and usefulness reports on salivary gland pathologies.

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Conflicts of interest
There are no conflicts of interest.

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