International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2020; 3(2): 18-23
Received: 10-02-2020
Accepted: 12-03-2020

Dr. M Aswin Manikandan
SRM Medical College, SRM Medical College Hospital and Research center, Institute of Science and Technology (IST), Tamil Nadu, India

Dr. Jaison Jacob John
SRM Medical College, SRM Medical College Hospital and Research center, Institute of Science and Technology (IST), Tamil Nadu, India

Dr. CD Anand
SRM Medical College, SRM Medical College Hospital and Research center, Institute of Science and Technology (IST), Tamil Nadu, India

Dr. G Shivashekar
SRM Medical College, SRM Medical College Hospital and Research center, Institute of Science and Technology (IST), Tamil Nadu, India

Corresponding Author:
Dr. G Shivashekar
SRM Medical College, SRM Medical College Hospital and Research center, Institute of Science and Technology (IST), Tamil Nadu, India

An institutional study on salivary gland neoplasms and its challenges in diagnosis

Dr. M Aswin Manikandan, Dr. Jaison Jacob John, Dr. CD Anand and Dr. G Shivashekar

DOI: https://doi.org/10.33545/pathol.2020.v3.i2a.218

Abstract
Salivary gland neoplasms are uncommon, and its features are diverse and complex. In our study we have included 31 cases of salivary gland neoplasms for which final needle aspiration was done and classified according to Milan criteria. Application of Milan system of classification of salivary gland neoplasms is useful in evaluation and choosing appropriate management. These cases were followed up with histopathology which is the gold standard in diagnosis of salivary gland neoplasms. A correlation between Milan criteria and histopathology was done and the effectiveness of fine needle aspiration cytology was studied. It showed sensitivity of 64.38% and negative predictive value of 30.77% due to the fact salivary gland lesions are complex with lesions sharing common histological features.

Keywords: Milan system of classification of salivary gland neoplasm

1. Introduction
Salivary gland neoplasms are uncommon and have an incidence of 0.4 to 13.5 cases per 100,000 cases, mentioned in the study done by Curtis gregorie *et al*. [1] and Shivakumar *et al*. [2] Its features are diverse and many salivary gland neoplasms share common histological and cytological features.
FNAC is primary investigation of choice and is used to differentiate between non-neoplastic, benign neoplasm and malignant neoplasm of salivary gland lesions. If fine needle aspiration cytology is not confirmatory due to complexity of the lesion, histopathological diagnosis is considered the gold standard.
The newly devised Milan system of classification of salivary gland neoplasm has added two new categories which were not included in the previous reporting format-Atypia of undetermined significance and Salivary gland neoplasm of uncertain malignant potential to choose better treatment and patient care.

2. Materials and methods
Sample size: 31
Study: cross sectional study
Study duration: August 2017 to August 2019
Place of study: SRM Medical College and Research Centre, Potheri, Chennai – 603 210.
First brief clinical history and ultrasound findings were obtained, then physical examination was done to determine the size, consistency and warmth. Involvement of facial nerve was checked. Only cases which were diagnosed as salivary gland neoplasm on histology were included.
Fine needle aspiration was done and routinely stained by Hematoxylin and Eosin, Giemsa and Papanicolaou stain. For histopathological study, sections of 2mm thick were cut and stained after routine processing using Hematoxylin and Eosin.
Correlation between Milan criteria inference and histopathology have been done and the sensitivity, specificity and diagnostic accuracy of fine needle aspiration of salivary gland neoplasms have been calculated.

3. Results

Table 3.1: Milan criteria and histopathological correlation

Cytology inference			Histopathology inference		Total
			Benign	Malignant	
Milan criteria Inference	Benign	Count	17	1	18
		%	65.4%	20.0%	58.1%
	Malignant Neoplasm	Count	0	1	1
		%	0.0%	20.0%	3.2%
	Non diagnostic	Count	2	2	4
		%	7.7%	40.0%	12.9%
	Non neoplastic	Count	5	1	6
		%	19.2%	20.0%	19.4%
	Salivary gland tumour of uncertain malignant potential	Count	2	0	2
		%	7.6	7.6	6.4%
Total		Count	26	5	31
		%	100.0%	100.0%	100.0%

A correlation of cytological inference using Milan system of classification and histopathological diagnosis were done to study the effectiveness of salivary gland FNAC (table 3.1)

Table 3.2: Milan criteria inference

Milan Criteria Inference	Frequency	Percent
Benign	18	58.07
Malignant	1	3.2
Non-diagnostic	4	12.91
Non -neoplastic	6	19.36
Salivary gland tumour of uncertain malignant potential	2	6.46
Total	31	100.0

Milan inference

According to Milan criteria 18 cases were inferred as benign, 4 cases were non-diagnostic, 6 cases were non-neoplastic, 2 cases were diagnosed as salivary gland neoplasm of uncertain malignant potential, 1 case was found to be malignant. (table 3.2)

These cases have been followed up for histopathological diagnosis.

Table 3.3: Histopathological diagnosis

Histopathology Diagnosis	Frequency	Percent
Pleomorphic adenoma	22	70.97
Warthin tumour	3	9.67
Basal cell adenoma	1	3.2
Mucoepidermoid carcinoma (1 low grade and 1 high grade)	2	6.4
Myoepithelial carcinoma	2	6.46
Metastatic acinic cell carcinoma	1	3.2
Total	31	100.0

Histopathological diagnosis:

Out of 31 cases studied totally, 22 cases were pleomorphic adenoma. Out of 22 cases of pleomorphic adenoma 3 cases appeared cellular, Other cases were 3 cases of Warthin tumour, 1 case of basal cell adenoma, 2 cases were mucoepidermoid carcinoma, 2 cases were myoepithelial carcinoma, 1 case of acinic cell carcinoma. (table 3.3)

Discordant findings

Cases with discordant findings are,

In the 4 cases reported as non-diagnostic on cytology 1 case turned out to be Warthin tumour, 1 case was pleomorphic adenoma and 2 cases were myoepithelial carcinoma on histopathology. (table 3.1).

In the 6 cases diagnosed as non-neoplastic on cytology, 2 cases turned out to be Warthin

tumour, 3 cases turned out to be pleomorphic adenoma and 1 case was mucoepidermoid carcinoma on histopathology.

2 SUMP cases with increased cellularity and prominent nuclear atypia on cytology were diagnosed as pleomorphic adenoma on histopathology.

Table 3.4: Results

Senstivity	65.38%
Specificity	80.00%
Postive predictive value	94.44%
Negative predictive value	30.77%
Diagnostic accuracy	67.74
False negativity rate	34.62%

In our study after comparing inference of Milan criteria and histology, we got the sensitivity, specificity, diagnostic accuracy, false positivity and false negativity rates of application of salivary gland FNAC with Milan criteria; which had a sensitivity of about 65.38%, a specificity of 80%, diagnostic accuracy of 67.74%, false negativity rate of 34.62%. (table 3.4)

4. Discussion

A correlation of Milan criteria and histopathological diagnosis was done and sensitivity, specificity, positive predictive value, diagnostic accuracy of fine needle aspiration cytology in salivary gland neoplasms were studied.

In our study after evaluating cytology inference using Milan's system of classification of classification of salivary gland neoplasms.58% of the cases were benign, non-neoplastic were 19.4%, non-diagnostic cases were 12.9%, salivary gland neoplasm of uncertain malignant potential were 6.4%., malignant were 3.2%,

In studies conducted by Montezuma *et al*. [3] benign cases were 40.2%, non-neoplastic cases were 23%, non-diagnostic cases were 7.2%, SUMP cases were 14.2%, malignant cases were 3.6%, Findings were like that of our study.

In our study of 31 salivary gland neoplasms histopathologic diagnosis of majority of the cases (22) were pleomorphic adenoma which accounted for 62% of the neoplasms, 3 of these 22 cases were designated as cellular pleomorphic adenoma on histopathology.

Other neoplasms included Warthin's tumour (3 cases) 9.7%, basal cell adenoma (1 case) 3.2%. Malignant neoplasms in our study were myoepithelial cell carcinoma (2 cases) 6.5%, mucoepidermoid carcinoma 6.4% (2 cases), acinic cell carcinoma 3.2% (1 case).

This coincided with study conducted by Eveson and Cawson [4] who reported pleomorphic adenoma 63% cases, Warthin's tumour 14%, myoepithelial cell carcinoma 4.4%, mucoepidermoid carcinoma 1.5%, acinic cell carcinoma 2.5%,

Discordant cases

2 unusual cases on cytology,1 case inferred as non-diagnostic (figure 4.1) for which acellular aspirate might have been obtained from the cystic area, In the other case inferred as non- neoplastic(figure 4.2), cyst macrophages and inflammatory cells from the cystic area., Both the above cases were diagnosed as Warthin's on histology (figure 4.3).

As mentioned in the study done by Kala *et al.* [5] Warthin's tumour may have both solid and cystic component along with lymphoid cells, hence the aspirate might have macrophages from the cystic component and inflammatory cells leading to false labelling as non- neoplastic

2 cases given as non- diagnostic on cytology with acellular aspirate, which could have been could due to aspirate being obtained from areas of stromal fibrosis, was diagnosed as myoepithelial carcinoma on histology.

In myoepithelial carcinoma, adequate aspirate is cellular with tumour cells arranged singly, in sheets, clusters or crowded groups with metachromatic stromal globules and spheres. Variable nuclear atypia depending upon grade with plasmacytoid, spindled, clear and epithelioid morphology along with intranuclear pseudo inclusion.

In our case, fine needle aspiration material showed acellular aspirate devoid of epithelial or myoepithelial cells in a hemorrhagic background and we have given it as non-diagnostic.

The histological picture in this case showed a varied presentation with spindle cells, epithelioid cells, plasmacytoid cells, clear cells in a fibrosed and hyalinized background (figure 4.4). Prominent perineural invasion (figure 4.5) was also noted in this case indicating its aggressive behavior.

In the study conducted by Kala *et al*. [5] a case initially given as non- diagnostic on cytology and was postulated due to stromal fibrosis turned out to be myoepithelial cell carcinoma on histology.

This implies ultrasound guided FNAC might be needed for complex lesions like myoepithelial carcinoma which has diverse gross and histological features which may pose a diagnostic challenge.

One case reported as non- diagnostic on cytology showed cystic fluid with occasional macrophages in dispersion which turned out to be mucoepidermoid carcinoma (figure 4.6, 4.7) on histology. Prominent cystic areas seen within solid lesion and dense fibrosis in stroma may have given a dry aspirate. Similar findings were observed in a study conducted by kala *et al*. [5] showed lesion having cystic content interpreted as non-diagnostic.

Another case diagnosed on cytology as benign neoplasm suggestive of pleomorphic adenoma having cohesive clusters of epithelial cells turned out to be mucoepidermoid carcinoma on histology. This was due to presence of few clusters of epithelial cells with scant mucin, no mucin secreting cells and occasional squamoid cells in dispersion leading to false interpretation of pleomorphic adenoma.

Mucoepidermoid carcinoma has varied cytomorphological features with squamoid, intermediate and mucinous cells and there are variants like oncocytic and clear cell variant. It can be mistaken for squamous cell carcinoma, cystadenocarcinoma, squamous cell carcinoma, Warthin's or pleomorphic adenoma with squamous metaplasia in high grade mucoepidermoid carcinoma, the solid area is more and may resemble poorly differentiated adenocarcinoma. Stating that diagnosing this entity can be challenging. A study conducted by joseph *et al.* [6] had 6 cases of mucoepidermoid carcinoma on histology, of which two cases were diagnosed as pleomorphic adenoma with squamoid cells- interpreted as squamous metaplasia in pleomorphic adenoma in cytology

One case diagnosed as pleomorphic adenoma on cytology due to scant cellularity with epithelial cell clusters without any atypia and a mild fibrillary background turned out to be basal cell adenoma (figure 4.8) on histology

Usually Basal cell adenoma are composed of basaloid cells in sheets admixed with hyaline globules, acellular dense hyaline material with peripheral palisading of nuclei.

In our case, the smear had epithelial cells with scanty fibrillary material and peripheral palisading was not prominent. Which made us give the diagnosis of pleomorphic adenoma on FNAC.

A study conducted by Amoolya bhat *et al.* [7] stated that pleomorphic adenoma with increased cellularity may resemble basal cell adenoma with basaloid cells and fibro myxoid material giving rise to false interpretation.

2 cases were diagnosed as salivary gland neoplasm of uncertain malignant potential on cytology with increased cellularity and prominent nuclear atypia (figure 4.9) turned out to be benign on histopathological study with no significant atypia (figure 4.12,4.13). Both cases were proven to be pleomorphic adenoma on histology. Study conducted by Hanada *et al.* [8] showed that pleomorphic adenoma can present with atypical features with nuclear atypia and grooves along with metaplastic change and hyaline globules simulating malignancy as was seen in our case.

In a study conducted by Chowsilpa *et al.* [9] it is stated that SUMP cases have more chances of being benign (92.3%) and less propensity to be malignant (33.8%). As was seen in our case.

Out of five malignant cases in our study one case showed a submandibular lymph node swelling which was infiltrated by tumour cells having clusters of acinar cells with granular cytoplasm as well as in histology showing round to oval cells with abundant basophilic granular cytoplasm (figure 4.14). Patient did not follow up to investigate the origin of the primary.

Eberhard Stennert *et al*, [10] in their study showed major salivary gland neoplasms have high propensity to cause lymph node metastases with acinic cell carcinoma having incidence of only 44% among them.

In our study, A correlation of Milan criteria inference and histopathological diagnosis were done to study the effectiveness of salivary gland FNAC

A sensitivity of 65.38% was found, specificity was found to be 80% and diagnostic accuracy in our study was 67.74%. the low sensitivity and diagnostic accuracy of the study is

due to the fact salivary glands are complex with varied patterns, inadequate sampling and stromal fibrosis can also pose difficulties.

False negative rate was 34.62% in our series because three cases had unusual findings. Two case diagnosed as non-neoplastic on cytology- of which one case turned out to be mucoepidermoid carcinoma as only cystic component of the swelling has been sampled. Other case turned out to be myoepithelial carcinoma as only inflammatory component of the swelling has been sampled along with acellular hemorrhagic material. One case diagnosed on cytology as benign neoplasm suggestive of pleomorphic adenoma turned out to be mucoepidermoid carcinoma on histology, this was due to presence of few clusters of epithelial cells with scant mucin, no mucin secreting cells and occasional squamoid cells in dispersion leading to false interpretation of pleomorphic adenoma.

In a study conducted by Yegin[11] *et al.* it was shown that sensitivity, specificity of diagnosing salivary gland neoplasm on cytology are 57.2%,100% respectively. In their study, diagnostic accuracy for benign neoplasm was 91.4% and malignant neoplasm 42.8%. Their results were concurring with our studies.

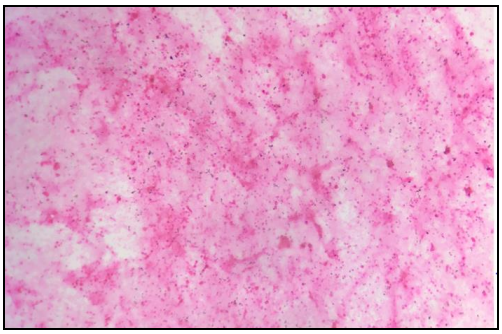

Fig 4.1: Non-diagnostic aspirate (CYTO H&E X40)

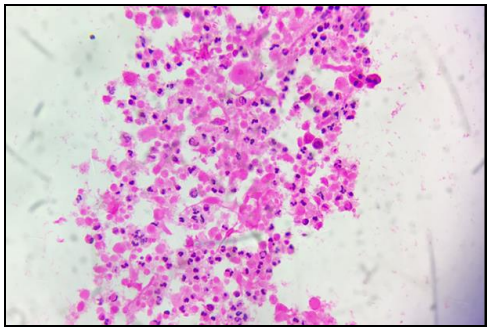

Fig 4.2: Non-neoplastic with inflammatory infiltrates and scanty epithelial cells (CYTO-H&E X400)

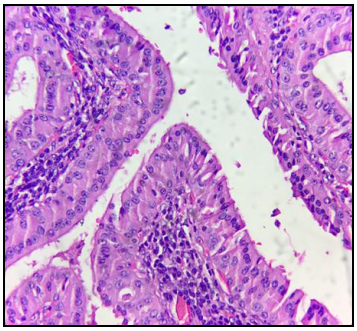

Fig 4.3: Dual lining epithelium in a lymphoid stroma-Warthin tumour (HPE H&E x100)

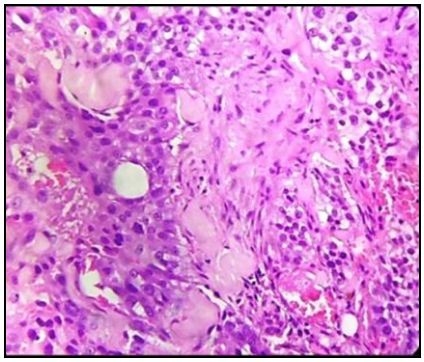

Fig 4.4: Myoepthelial carcinoma with spindle cells, epitheloid cells, plasmacytoid and clear cells in a fibrous background (HPE H&Ex40)

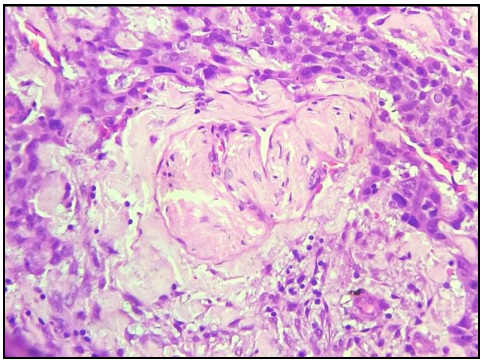

Fig 4.5: Perineural invasion seen in myoepithelial carcinoma (HPE H&Ex40)

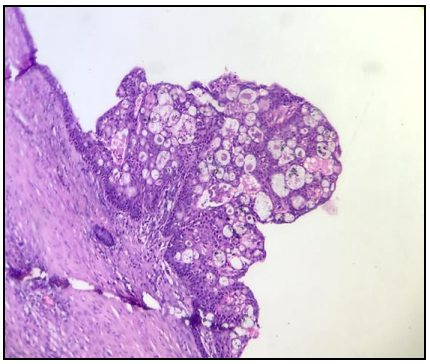

Fig 4.6: Cribriform architecture with multiple cyst lined by squamoid cells-mucoepidermoid carcinoma (HPE H&E x40)

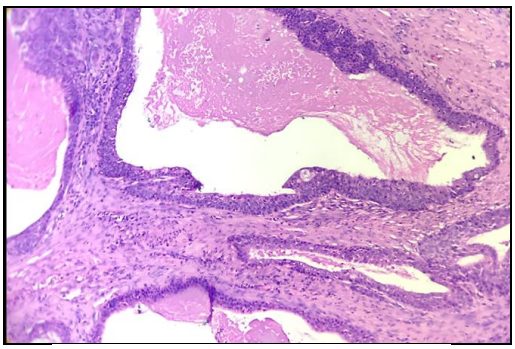

Fig 4.7: Cystic architecture lined by intermediate and squamoid cell in a fibrous stroma- mucoepidermoid carcinoma (HPE H&E x40)

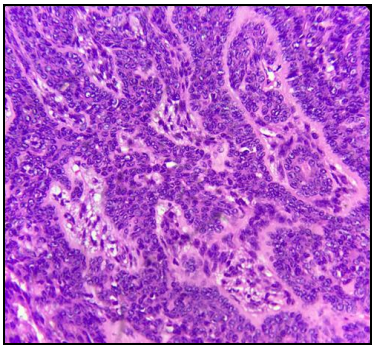

Fig 4.8: Arrangement of basaloid cells in nested pattern with peripheral palisading- basal cell adenoma (HPE H&E x400**)**

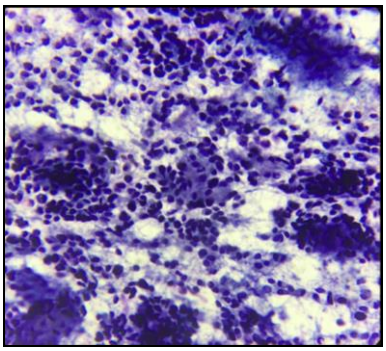

Fig 4.9: Case of pleomorphic adenoma showing mild nuclear atypia (CYTO PAP X400)

Fig 4.10: External surface of parotid swelling showing a capsulated lesion-pleomorphic adenoma

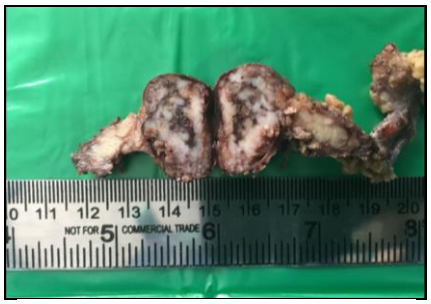

Fig 4.11: Cut surface shows appears grey white to grey brown, glistening with focal hemorrhagic areas-pleomorphic adenoma

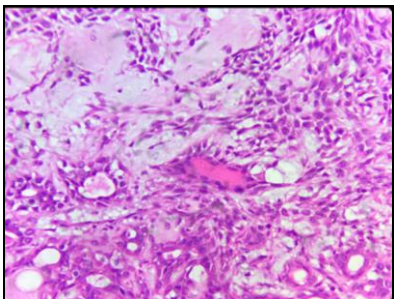

Fig 4.12: Epithelial and myoepithelial elements in a chondromyxoid stroma-pleomorphic adenoma (HPE H&E x400)

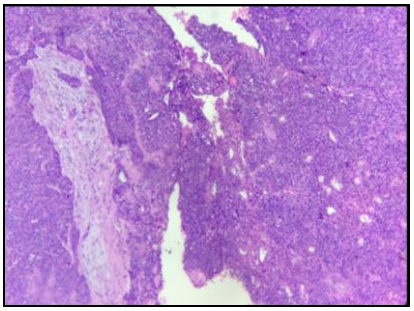

Fig 4.13: Pleomorphic adenoma with increased cellularity admixed with chondromyxoid stroma (HPE H&E x40)

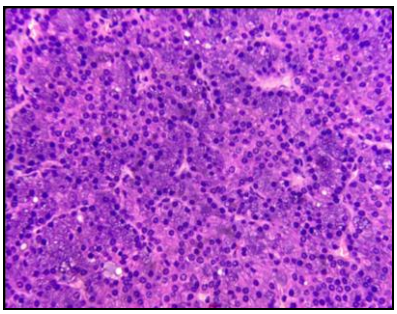

Fig 4.14: Solid sheets of cells with monomorphic cells with well-defined nuclear membrane with granular basophilic cytoplasm-acinic cell carcinoma (HPE H&E x40)

Conclusion

Salivary gland neoplasms are diverse with varied gross and microscopic features and share common cytological features which sometimes makes it difficult to differentiate the neoplasms. FNAC poses challenges as aspirates from the lesion may yield scanty material. It is important to obtain representative samples from at least from 2 sites of the same lesion, as said in a study conducted by Atheer talib *et al*.[12] to give a correct interpretation. Milan system of classification of salivary gland neoplasms has five different categories (Non diagnostic, Non-neoplastic, Atypia of undetermined significance, Neoplasm: benign, Neoplasm: Salivary gland neoplasm of uncertain malignancy) for which risk of malignancy is given. The addition of atypia of undetermined significance and SUMP is useful in evaluation and appropriate management. Histopathology is the gold standard; it gives the complete picture as multiple sections can be given from representative areas

References

1. Curtis Gregoire, Shahrokh C. Bagheri, R. Bryan Bell, Husain Ali Khan, Chapter 56 - Salivary Gland Tumors: The Parotid Gland, Current Therapy In Oral and Maxillofacial Surgery, W.B. Saunders, 2012, 450-460.
2. Thiagarajan S, Fathehi K, Nair D, *et al*. Surgical morbidities and outcomes of major salivary gland neoplasms treated at a tertiary cancer center. Indian J Cancer. 2018; 55(1):33-36.
3. Montezuma D, Canberk S, Aydın O, *et al*. A comparison study of the reporting systems for salivary gland fine needle aspirations: Are they really different? Diagn Cytopathol. 2018; 46:859-863.
4. Eveson JW, Cawson RA. Salivary gland tumours: a review of 2410 cases with particular reference to histological types, site, age, and sex distribution, J Pathol. 1985; 146:51-58.
5. Kala C, Kala S, Khan L. Milan System for Reporting Salivary Gland Cytopathology: An Experience with the Implication for Risk of Malignancy. J Cytol. 2019; 36(3):160-164.
6. Joseph TP, Joseph CP, Jayalakshmy PS, Poothiode U. Diagnostic challenges in cytology of mucoepidermoid carcinoma: Report of 6 cases with histopathological correlation. J Cytol. 2015; 32(1):21-24.
7. Bhat A, Rao M, Geethamani V, Shetty AC. Basal cell adenoma of the parotid gland: Cytological diagnosis of an uncommon tumor. J Oral Maxillofac Pathol. 2015; 19(1):106. doi:10.4103/0973-029X.157211.
8. Uma Handa, Neerja Dhingra, Rajan Chopra, Harsh Mohan Pleomorphic adenoma: Cytologic variations and potential diagnostic pitfalls. Diagn Cytopathol. 2009; 37(1):11-15.
9. Chowsilpa S, An D, Lose H, Huang X, Nayar R, Maleki Z. Risk of malignancy associated with cytomorphology subtypes in the salivary gland neoplasm of uncertain malignant potential (SUMP) category in the Milan System: A bi-institutional study. Cancer Cytopathology. 2019; 127:377-389.
10. Eberhard Stennert, Dilek Kisner, Markus Jungehuelsing, Orlando Guntinas-Lichius, Ursula Schröder, Hans Edmund Eckel, Jens Peter Klussmann. High incidence of lymph node metastasis in major salivary gland cancer. Arch Otolaryngol Head Neck Surg. 2003; 129(7):720-723.

11. Yegin Yakup *et al*. Diagnostic value of fine needle aspiration biopsy in parotid gland neoplasm. International Journal of Otorhinolaryngology and Head and Neck Surgery, [S.l.], v. 2, n. 2, p. 56-67.
12. Jiboon Atheer. Diagnostic Value of Fine Needle Aspiration Cytology (FNAC) in Salivary Gland Tumors, 2017, 1.