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A prospective study to assess the comparison of three different papanicolaou staining techniques in the evaluation of aspiration cytology smears and their cytohistopathological agreement

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Abstract

Background: Fine needle aspiration cytology (FNAC) is a minimally invasive clinical tool of investigation which produces a speedy result. Cytology samples are stained by Papanicolau stain. Many modifications are now available for the staining methods which take short duration and better efficacy. Correlation of cytological assessment and histopathological diagnosis facilitate the validity of aspiration cytology.

Aims & Objectives: The aims of this study were 1. To compare the efficacy of three Papanicolaou staining techniques in thyroid and breast aspiration smears by evaluating the cytomorphological features and staining characters in terms of quality index. 2. To obtain Cyto-histopathological agreement and assess the sensitivity, specificity and accuracy of FNAC.

Methods: Cross sectional study was conducted in department of pathology from January 2016 to October 2017. Sample size was scientifically calculated with n= $(2*\sigma 2*[Z\alpha+Z\beta]2)/\delta 2$ after reviewing literature. 40 samples each from thyroid and breast (total 80) was included. Three smears from sample were subjected to Conventional Pap stain, Rapid Pap stain and Modified ultra fast Pap stain. Quality index was calculated for staining quality. Cytology diagnosis was compared with histopathology diagnosis for all the samples and validity and reliability of FNAC was calculated.

Results: In this present study majority of patients were in the age group 20yrs to 40yrs (50%) in thyroid lesions and 40yrs to 60yrs (37.5%) in breast lesions. Mean quality index in breast samples were 0.84 with MUFP, 0.83 with CP and 0.70 with RP. Mean quality index in thyroid samples were 0.89 with MUFP, 0.91with CP and 0.69 with RP. Test of significance done and p value was statistically significant (<0.001) in both breast and thyroid samples. Sensitivity, specificity, accuracy were

100%, 96.5%, 97.5% in breast and 62.5%, 87.5% and 77.5% in thyroid samples respectively.

Conclusions: Modified ultrafast papanicolau stain takes only three minutes for staining the FNAC sample by giving equivocal quality similar to conventional papanicolau stain. For fast and emergency report dispatching as well as in medical camps, MUFP will provide a helping hand to the cytopathologist as well as the physicians without affecting the efficacy of morphology and diagnostic terms. FNAC diagnosis helps in the initial planning of prognosis and treatment.

Keywords: FNAC; Modified Ultrafast Papanicolau stain; Rapid Papanicolau stain; Conventional Papanicolau stain

Introduction

Fine needle aspiration cytology was introduced in 1950's.FNAC is an easy, cost effective minimally invasive and rapid diagnostic test. FNAC has become an important preoperative screening test which help as a guide to rational treatment.

The main focus of this cytology method is to recognize the malignant cells, which further help in the diagnosis investigation, diagnosis and management of the patient. FNAC is also reliable in degenerative , inflammatory and infectious disease which further adds to its unique importance in diagnostic cytopathology.

George N Papanicolaou, Father of Cytopathology introduced Pap stain in the year 1942 and further modified it himself in the year1954 and 1960. It yields polychromatic nuclear details, cell differentiation and transparency. Conventional Pap smear needs considerable amount of ethyl alcohol and long duration. So many modifications have been made to reduce the amount alcohol because of its cost and also to reduce the staining time. Need for laboratory license and renewal, mandatory for ethyl alcohol adds further difficulties.

Rapid Pap stain were further developed to cut short the staining time of conventional Pap by Kline ,T ao and Sato with respective staining time of 4minutes, 5minutes, 90 seconds. But they still require wet fixation and cell morphology is suboptimal.

Yang, Alvarez and Young introduced ultra-fast Papanicolaou staining technique in theyear 1995 which is a hybrid of Romanowsky stain and Pap stain to conclude the procedure in 90 seconds.It yields transparency and crisp nuclear details. But all reagents in ultrafast Papanicolaou stain are not readily available.

Kamal MM in the year 2000 studied the feasibility of reagents available in rural settings and further modified the MUF P, so that procedure can easily done in all settings. Shinde and Pandit adapted the Kamal modified MUFP technique with Gill's haematoxylin and EA-36 and studied the nuclear and cytoplasmic details in cytology of various organs. Maruta studied the MUFP with Gill's 5 haematoxylin and cytostain in the quick diagnosis of thyroid tissue in place of Yang's MUFP.

Choudhary and Sudhamani et al , Idris and Hussain et al studied efficacy of different staining procedures in the cytopathology by assessing the quality index by comparing the cell cytomorphology.

Histopathology is considered the gold standard; nevertheless FNAC is a diagnostic modality which assists the physician and the pathologist alike in arriving at a speedy diagnosis. Confirmation of all the diagnosis made by FNAC using histopathology technique is strongly advised.

Our aim of this study was to assess the efficacy of different Pap stain and implementation of a good staining technique that suits to our laboratory which is reliable for accurate diagnosis, enhance intraoperative

and emergency cytology and cost effective method in diagnostic cytopathology that can adapt in our secondary health center DR SMCSI Medical College, Karakonam.

Materials And Methods

Study Design: Cross Sectional Study

Study Setting: Department of Pathology Dr. SMCSI medical college, Karakonam.

Study Period: January 2016 to October 2017

Study Population: Patients referred to pathology department for FNAC from breast and thyroid

Study Sample: FNAC from thyroid and breast lesions as they are the most commonly encountered ones.

Inclusion Criteria: All breast and thyroid FNAC samples

Exclusion Criteria: Inadequate material on FNAC

Sample Size

Similar studies were reviewed. Quality of Index ranged from 0.92 to 0.97 for MUFP1,2, for conventional3 0.87 and for rapid1 0.90 with standard deviation 0.09. Formula used to calculate sample size in quality of index was $n=(2*\sigma 2*[Z\alpha+Z\beta]2)/\delta 2$ and reached sample size of 34.7~40(power 90%), $\alpha=0.05;\beta=0.1;Z\alpha=1.96;Z\beta=1.28;\delta=0.07$

Formula used for assessing sensitivity and specificity was 4PQ/D2. Precision (β error =10% and 1-α= 5%) and alpha as 5%.

Sensitivity from previous studies ranged from 93 to 95 % and specificity from 97 to 99%. Sample size required varied from 7 to 27.5~30.4

Thus decided to take 40 samples each for breast and thyroid lesions.

Exposure Variable: Age, sex, type, site, size of lesion.

Outcome Variable: Quality index, sensitivity and specificity.

Data Collection Tools and Techniques: Three smears from each sample was subjected to conventional Pap, rapid Pap and Modified ultrafast pap (MUFP) stains simultaneously

Conventional Pap Staining Technique Fixation

Fixation in 85% absolute alcohol for 15 minutes.

Procedure

- Descending grades of alcohol change 95% , 80% , 70% for 2 minutes each.
- Dip the slide in distilled water for 2 minutes.
- Dip the slide in harrishematoxylin from 2-5 minutes. Dip the slide in distilled water 2 changes for 2 minutes each.
- Then dip in 0.05% acid alcohol (4-5 dips)
- Again dip in distilled water for 2 minutes.
- Then 2 dips in ammonia water and further blueing in running tap water for 10 minutes.
- Ascending grades of alcohol change 70%, 80% , 95% for 2minutes each.
- Dip the slide in Orange G – 6 for 10-15 minutes.
- Then 3 change in 95% alcohol for 2 minutes each.
- Dip the slide in Eosin Azure 36 for 5 minutes.
- Then 3 change in 95% alcohol for 2 minutes each.
- Then 2 change in absolute alcohol for 2 minutes each.
- Dip the slide in Xylene – Alcohol for 5 minutes.
- 3 changes in xylene for 2minutes, 5minutes , 2 minutes.Mount in DPX.

Rapid Pap Staining Technique

Fixation

1. Fix wet smear with Biofix spray and wait for drying
2. Hydrate the smear by dipping the slide in tap water for 1 to 3 minutes.

Nuclear Staining

1. Blot out excess water from the slide and dip the slide in nuclear stain for

45 – 60 seconds.

2. Dip the slide in scott's tap water for 30-35seconds.

Preparation of Scott's tap water

1. 100ml tap water + 1ml Scott's tap water concentrate (Reg No 7)

3. Blot out excess Scott's tap water and dip the slide in dehydrant (Reg No 5) with 2 changes for 30 seconds each

Cytoplasmic Staining

- Dip the cytoplasmic working stain for 45 seconds. Preparation of cytoplasmic working stain
- Mix 2A and 2B equal volume (25ml +25ml stable for 3 months)
- Rinse in tap water , dip the slide in Scott's tap water for 20-30seconds , dry and see under the microscope.

Mounting

- Blot out excess water and dip the slide in dehydrant (Reg No 5) with 2 changes for 30 seconds each
- Dip the slide in xylene for 20 seconds.
- Mount with DPX.

Modified Ultra Fast Pap Staining Technique

Fixation

Air dried smear are kept in normal saline for 30 seconds and in alcoholic formalin for 10 seconds.

Procedure

- Tap water (6 slow dips)
- Harris Hematoxylin (30 seconds)
- Tap water (6 slow dips)
- Isopropyl alcohol 95% (6 dips)
- EA 36 (15 seconds)
- Isopropyl alcohol 95% (6dips)
- Isopropyl alcohol 100% (6dips)
- Xylene (10 slow dips)
- Mount with DPX

The smears was assessed by three different observers. Standardization by an experienced pathologist was done to reduce interobserver bias. Interpretation of smears was done as given by Sudhamani *et al* and PJ swetha .

Sl no	Parameters	Score 1	Score 2	Score 3
1	Background	Hemorrhagic	Clean	
2	Staining	Poor	Average	Good
3	Morphology	Poorly preserved	Moderately preserved	Well preserved
4	Cytoplasmic Details	Unsatisfactory	Suboptimal	Optimal
5	Nuclear Characteristics	Smudgy chromatin	Moderately crisp chromatin	Crisp chromatin
6	Drying Artifact	>50%	<50%	0%

- Maximum score was 17
- Quality Index = Actual Score Obtained / Maximum Score Possible
- Quality Index for the staining techniques is compared

Histopathological correlation with cytological diagnosis was done for assessing sensitivity and specificity

Data Analysis

- Data was entered in Microsoft excel and analysis done with the help of using IBM SPSS 25 trial version software.
- Qualitative variables expressed in percentage.
- Mean quality index was assessed with the formula : Quality Index = Actual Score Obtained / Maximum Score Possible
- Association between qualitative variables of three different stains was tested using Chi-square test. Non parametric test – Friedman test was applied to test for differences between groups (data was not normally distributed.)
- Sensitivity, Specificity, Accuracy and Predictive values were calculated for histopathological correlation.

- Cohen's kappa coefficient was done for assesing inter rater agreement between cytological and histopathological diagnosis.

Results

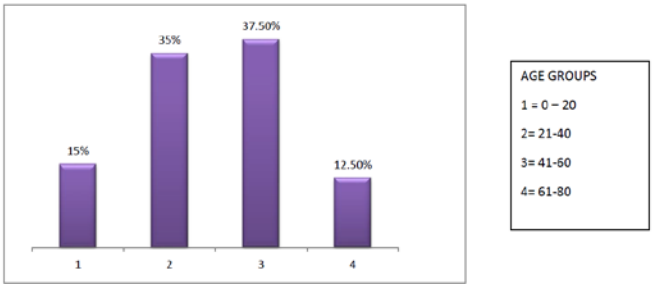

Figure 1: Age Wise Distribution – Breast Lesions

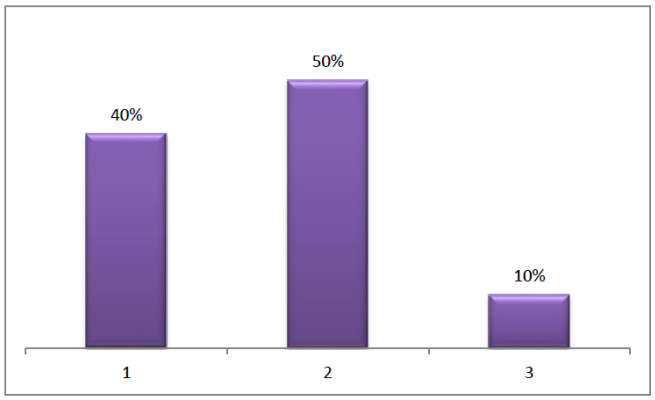

Figure 2: Age Wise Distribution – Thyroid Lesions

Figure 1 And 2

In The Present Study Breast Lesion Was Most Common In 40 To 60yrs And Thyroid Lesions In 20 To 40 Yrs

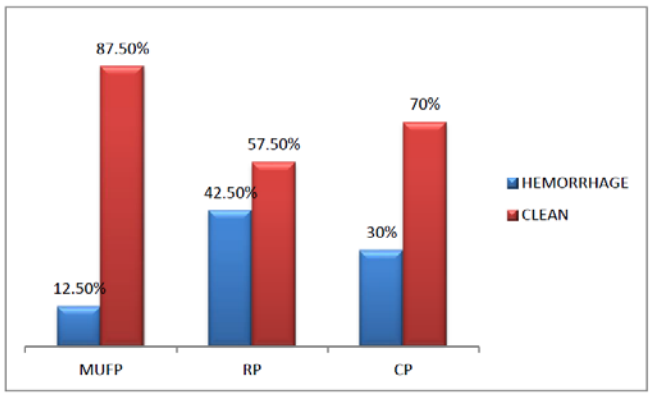

Figure 3: Background Staining Score

Mufp Showed A Clean Background In 87.5% , Cp In 70% And Rp In 57.50%

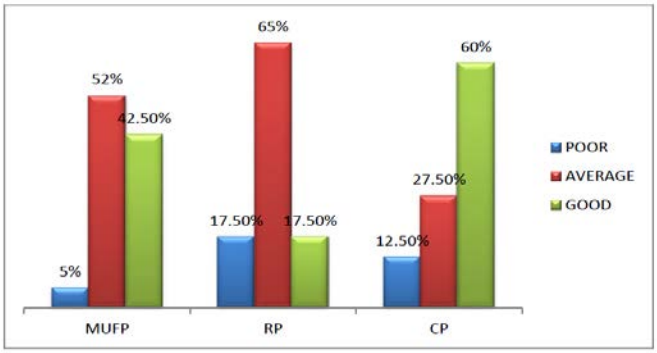

Figure 4: Overall Staining Score Distribution Among Breast Lesions In Each Stain

60% Showed Good Overall Staining With Cp And 42.5% With Mufp

65% Showed Average Overall Staining With Rp

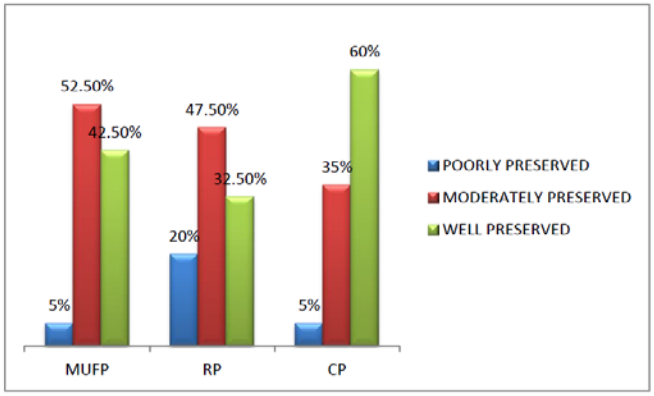

Figure 5: Cell Morphology Score Distribution Among Breast Lesions In Each Stain

Well Preserved Morphology Was Noted In 60% With Cp , 42.5% With Mufp And 32.5% With Rp

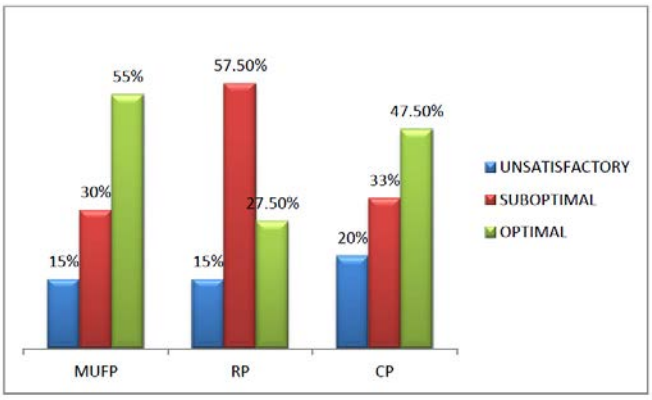

Figure 6: Cytoplasmic Details Score Distribution Among Breast Lesions In Each Stain

Mufp Showed Optimal Cytoplasmic Details In 55% , 27.5% With Rp And 47.5% With Cp

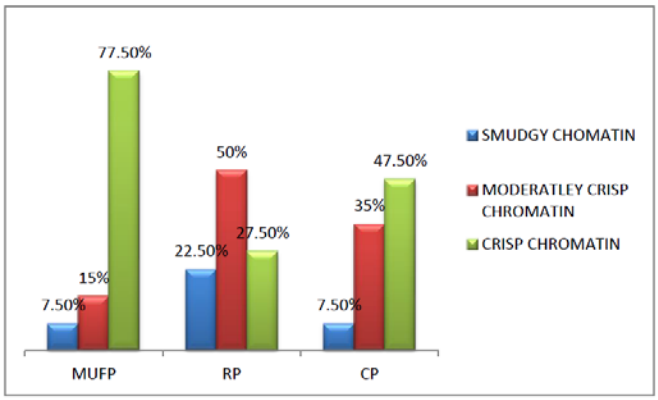

Figure 7: Nuclear Characteristics Score Distribution Among Breast Lesions In Each Stain

77.5% showed crisp chromatin with MUFP and 47.5% with CP

Moderately crsip chromatin was noted with RP in 50% and CP in 35%

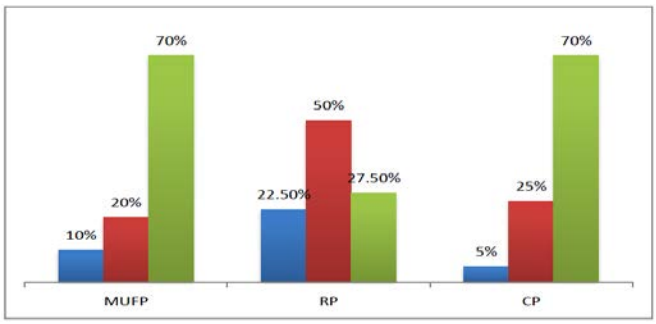

Figure 8: Drying Artefact Score Distribution Among Breast Lesions In Each Stain

Drying artifact <50% was noted in 70% in both MUFP and CP

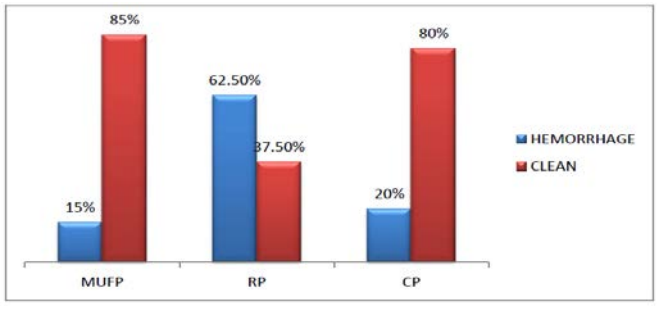

Figure 9: Background Staining Score Distribution Among Thyroid Lesions In Each Stain

85% in MUFP and 80% in CP showed a clean background

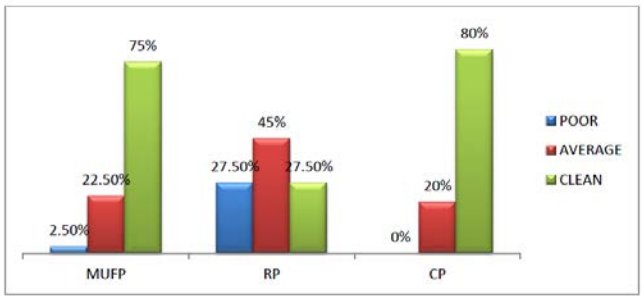

Figure 10: Overall Staining Score Distribution Among Thyroid Lesions In Each Stain

70% showed clean overall staining with MUFP , 80% with CP and average staining of 45% with RP

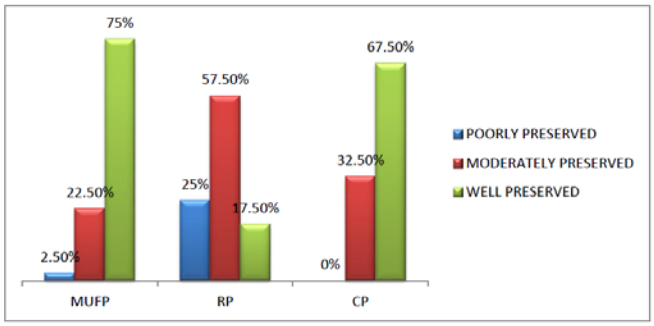

Figure 11: Cell Morphology Score Distribution Among Breast Lesions In Each Stain

Cell morphology was well preserved in 75% with MUFP and 67.5% with CP

57.5% showed moderately preserved cell morphology

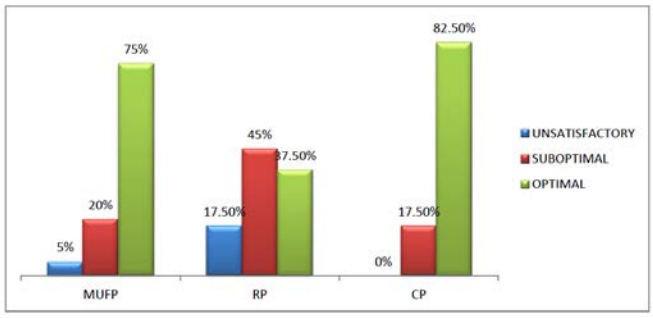

Figure 12: Cytoplasmic Details Score Distribution Among Thyroid Lesions In Each Stain

Cytoplasmic details was optimal in75% with MUFP, 82.5% with CP and 37.5% with RP

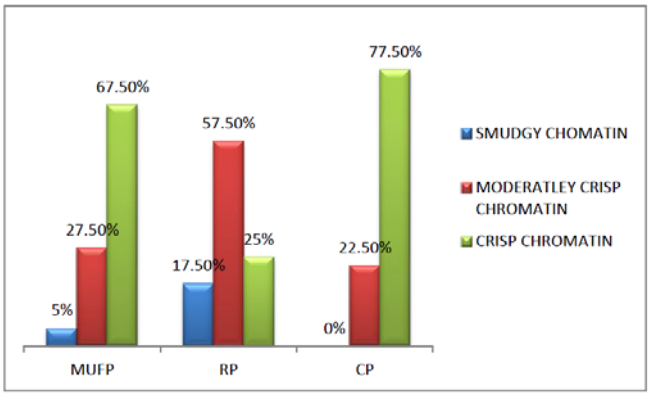

Figure 13: Nuclear Charecteristics Score Distribution Among Thyroid Lesions In Each Stain

77.5% showed crisp chromatin with CP , 67.5% with MUFP and moderately crisp chromatin in 57.5% with RP

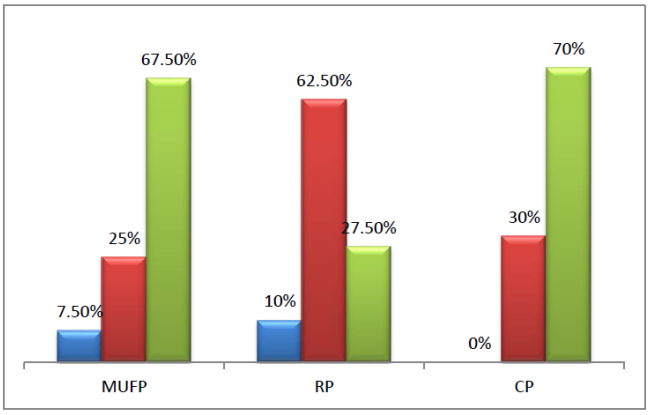

Figure 14: Drying Artefact Score Distribution Among Thyroid Lesions In Each Stain

70% with CP and 67.5% with MUFP showed drying artifact < 50%

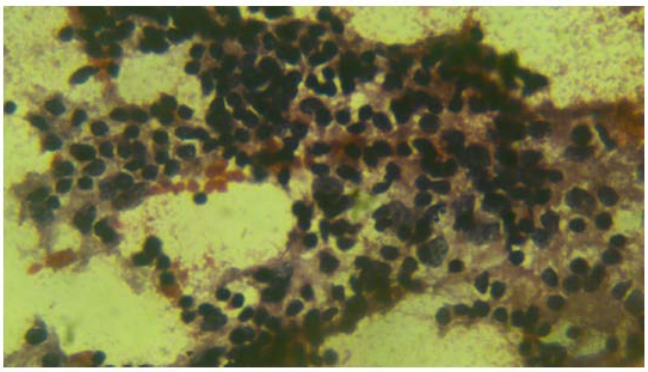

Figure 15: Conventional Papanicolau Stain – Thyroiditis (Oil Immersion)

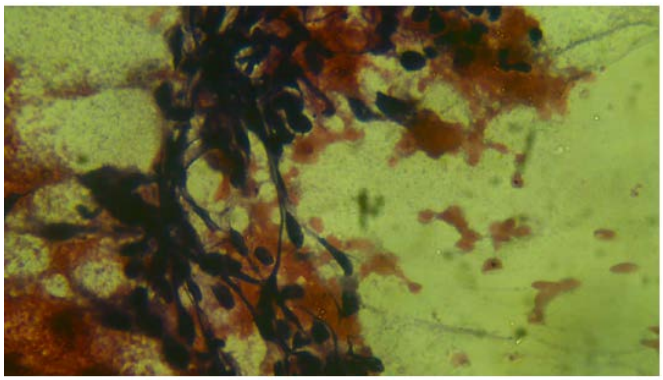

Figure 16: Conventional Papanicolau Stain – Carcinoma Breast (Oil Immersion)

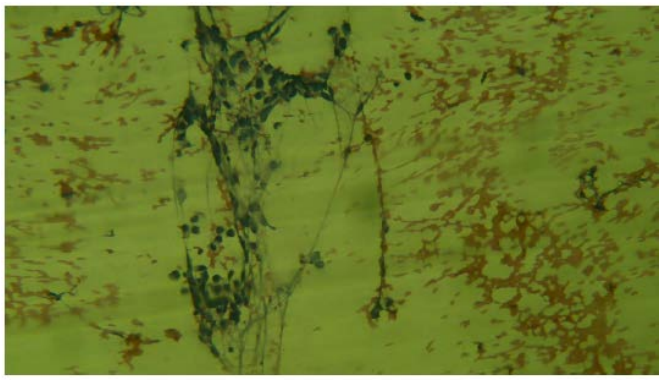

Figure 17: Conventional Papanicolau Stain – Carcinoma Breast (Oil Immersion)

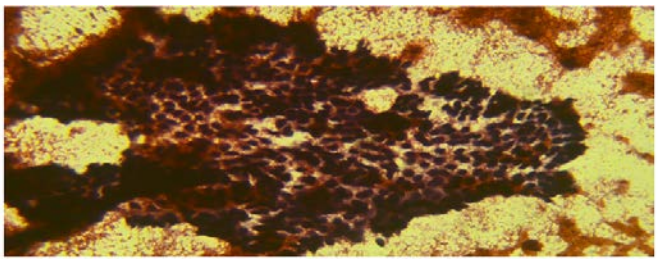

Figure 18: Conventional Papanicolau Stain – Follicular Neoplasm (Oil Immersion)

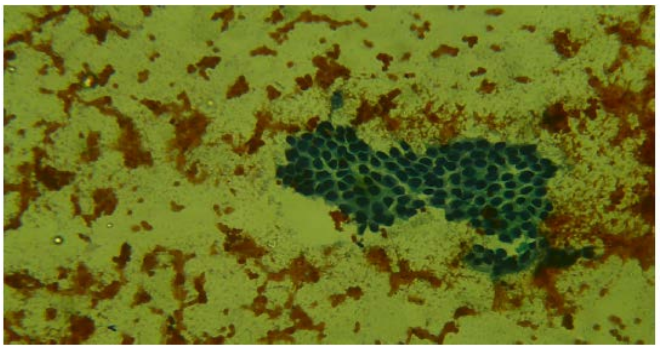

Figure 19: Rapid Papanicolau Stain – Follicular Neoplasm(Oil Immersion)

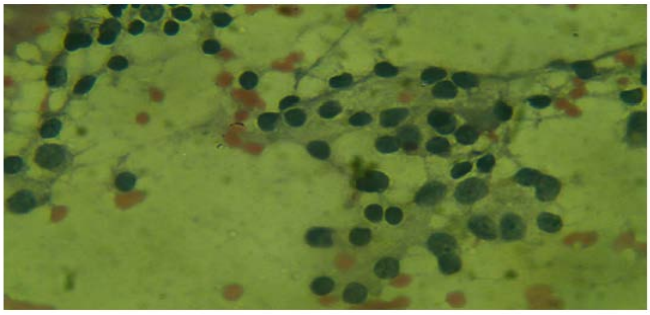

Figure 20: Rapid Papanicolau Stain- Follicular Neoplasm(Oil Immersion)

Discussion

FNAC is an accurate, low cost, and a rapid diagnostic test. The speed of reporting of FNAC can be improved further by rapid assessment of smears or on-site cytopathology. Quick diagnosis of FNAC plays an important role in efficient medical practice and management. Routine PAP staining is a commonly employed cytological procedure in the diagnosis of smears as it yields a polychromatic, transparent staining reaction with crisp nuclear/cytological features. Since its inception, PAP stain remains the traditional and preferred stain.

Age distribution of present study was 40yrs to 60 yrs (37.5%) in breast lesions and 20yrs to 40yrs (50%).Yelavarthy et al54 study shows majority of patient were between 21yrs-30yrs(45.12%) in breast lesions. Gupta et al45 shows majority of patients were in 3rd decade (44%) similar to our study

In this present study kamal's39 modified ultrafast pap staining and rapid pap kit staining was compared with traditional conventional pap staining technique in thyroid and breast lesions.40 samples from each organ was studied for the 6 parameters mentioned as in sewtha et al48 and sudhamani et al42. Efficacy was assessed by means of quality index and friedman test.

Like other studies MUFP gives a good quality index and shows efficacy similar to the traditional conventional papanicolau staining techniques. All the parameters (background , cell morphology , cytoplasm, nucleus, dry artefact) assessed showed an equivocal quality by MUFP like conventional pap. Present study also shows the relevance and role of FNAC as a minimally invasive procedure with key role in screening and prognosis along with limitations in few areas. Histopathology still plays its standard role in masking the difficulties and limitations by FNAC.

Summary

- The findings in the present study can be summarized as follows
- The present study had series of 40 FNAC samples each from both breast and thyroid lesions.
- Majority were in the age group 20yrs to 40yrs (50%) in thyroid lesions and 40yrs to 60yrs(37.5%) in breast lesions.
- All FNAC samples were stained with Conventional Papanicolau stain (CP), Rapid Papanicolau stain (RP) and Modified ultrafast Papanicolau stain(MUFP).
- Six parameters- background , overall staining , cell morphology, cytoplasmic details, nuclear characteristics and drying artifact were assessed.
- Score was given to each parameter
- Frequency of score distribution , mean quality index and friedman test were calculated for assessing the efficacy of each staining methods in both thyroid and breast samples. Assessing the efficacy of each staining methods in both thyroid and breast samples
- Mean quality index in thyroid samples were 0.89 with MUFP ,0.91with CP and 0.69 with RP.

- Test of significance (friedman test)done and p value was statistically significant(<0.001) in both breast and thyroid samples.
- Validity of cytology diagnosis was compared with histopathology diagnosis of the same samples.
- Sensitivity , specificity, accuracy were 100%,96.5% , 97.5% in breast and 62.5% , 87.5% and 77.5% in thyroid samples respectively.
- Cohen's Kappa statistics measured for assessing reliabity for cytohistopathology agreement.
- Kappa for breast lesions was 0.946% (excellent agreement beyond chance) and thyroid was 0.56%(fair to good agreement beyond chance).

Conclusion

- Papanicolaou stain is excellent in studying FNAC material.
- It maintain its efficacy in obtaining excellent nuclear and cytoplasmic features.
- Modified ultrafast papanicolau stain takes only three minutes for staining the FNAC sample by giving equivocal quality similar to conventional papanicolau stain.
- Conventional papanicolau stain takes about one and half hour for staining the cytology sample
- Rapid Papanicolau stain done with the help of commercially available rapid kit in this present study. By using better reagents this technique can be considered routinely as it still mainitains and above average efficacy in the assessment of all parameters.
- For fast and emergency report dispatching as well as in medical camps, MUFP will provide a helping hand to the cytopathologist as well as the physicians without affecting the efficacy of morphology and diagnostic terms.
- QUALITY INDEX assesed based on the cytomorphological parameters proved the relevance of MUFP in day today pathology laboratory activities.
- Technical factors like adequacy of material , spreading of the sample , skill of cytotechnician in staining also play an important role in FNAC staining.
- Cost effectiveness in terms of reagent use and availability also has its role in cytology laboratory quality assurance.
- MUFP stains with minimal reagents in lesser time with good staining quality
- Sample size also affects the results of a research work.
- Present study analyzed the morphology in total of 80 cases. More study in the same topic will further help and is needed in validating the relevance of this topic.
- Histopathology is the golden standard techinique in the field of pathology
- Cytology plays a unique role in clinical practice by giving an idea either confirming or rejecting a clinicians suspicion
- FNAC diagnosis helps in the initial planning of prognosis and treatment
- Inherent limitations of FNAC can be overcome by histopathology
- Both Cytology and histopathology has its own importance as diagnostic modalities in this modern era.

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