CORRELATION BETWEEN FNAC AND CNB IN PALPABLE BREAST LUMP WITH SPECIAL REFERENCE TO MYOEPIOTHELIAL MARKER CK5/6 AND CK7

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ABSTRACT

Background: Breast lump are the most common presentation in women attending a health clinic of which 80 to 85% are benign and rest is malignant. Breast carcinoma is the most common malignancy and the second most common cause of death in women with more than 1.7 million cases occurring worldwide annually. Breast cancer has ranked one in cancer among Indian females with age adjusted rate as high as 25.8 per 100000 women.

AIMS AND OBJECTIVES: Study was done to correlate FNAC and CNB in the diagnosis of palpable breast lump taking histopathological examination as the gold standard and to confirm myoepithelial marker Cytokeratin 5/6 and cytokeratin 7 positivity in cases which were histologically indeterminate.

MATERIALS AND METHODS: All 34 female patients attending the department of Pathology of JMCH with palpable breast lump were subjected to FNAC and CNB simultaneously for a period of 1 year. FNAC was performed by the standard technique and CNB was performed using 14G semiautomated core biopsy needles. Smears were stained by MGG, Papanicolau and H&E. Regarding diagnostic outcome of FNAC and CNB were reported using the '*INTERNATINAL ACADAMY OF CYTOLOGY YOKOHAMA SYSTEM*' on FNAC and UK '*National Health Service Breast Screening Programme'* (NHSBSP) on CNB respectively and their findings were correlated with their HPE results.

RESULTS: FNAC and CNB showed sensitivity (73.33% Vs 93.33%), specificity (100% Vs 100%), PPV (100% Vs 100%), NPV (82.61% Vs 95%), and accuracy (88.24% Vs 97.06%) respectively. Both FNAC and CNB showed statistically significant correlation with HPE of excision specimen (p value <0.05) in the diagnosis of breast lesions. Among 34 cases, diagnoses of 2 cases were histologically inconclusive, thus CK5/6 and CK7 were performed in both the cases and confirmatory diagnoses were made.

DISCUSSION : FNAC of breast lump is accepted and established method to determine the nature of lump but since there are various diagnostic pitfalls associated with FNAC, CNB has become an increasingly important diagnostic tool in the assessment of palpable breast

CONCLUSION: For diagnosing breast carcinoma, triple assessment of breast lump is most important diagnostic tool. FNAC continues to be a valuable and cost effective, and reliable method to diagnose breast lesions preoperatively particularly in India when used as a part of triple test but gradually CNB is introduced and replaced FNAC in correct diagnosis of breast carcinoma.

KEYWORDS : FNAC, Breast lump, CNB, IDC, NHSBSP

INTRODUCTION

Breast lump are the most common presentation in women attending a health clinic of which 80 to 85% are benign and rest is malignant .[1] Breast carcinoma is the most common malignancy and the second most common cause of death in women with more than 1.7 million cases occurring worldwide annually.[2]

Breast cancer has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100000 women. Young age has been found to be major risk factor for breast carcinoma in Indian women.[3] In North East, Upper Assam region, Dibrugarh district ranked 22nd with age adjusted rate 14.7 per 100000 population .[4]

X-ray screening mammography is the most sensitive noninvasive procedure for detecting early tumors of breast, besides there are various other nonradiation imaging technique develops for detection of cancer such as thermography, diaphenography (light scanning), whole breast ultrasound, and magnetic resonance imaging (MRI). Although other methods may refine screening mammography or clinical impressions, they are not sufficiently reliable, inexpensive, and ineffective as a mass screening test for large number of populations.[5]

Fine Needle Aspiration Cytology (FNAC) is a relevant and important method for diagnosing breast cancer. There are many advantages of Fine Needle Aspiration Cytology including as it is an outpatient procedure, easy to do, reliable and cost effective, and there is no risk of anaesthesia.

However, the major limitation of FNAC is the separation of atypical ductal hyperplasia (ADH) from ductal carcinoma in situ (DCIS) and differentiating DCIS from invasive carcinoma, which affects the patient treatment protocol. There are other limiting factors like occasional inability to make a definitive diagnosis of low grade carcinoma from ADH. Another major concern of breast [6].

Core needle biopsy preferred over FNA for the preoperative diagnosis of breast carcinoma. Core needle biopsy allows for evaluation of both cytological and architectural features, thus enabling a definitive diagnosis of invasive carcinoma if present. Conversely a benign lesion such as fibroadenoma can be easily recognized, and core needle biopsy allows for easier sampling and identification of micro-calcifications. Also it reduces the number of inadequate sampling [7].

Multiple tumor tissue biopsy samples can be taken and immune-histochemistry also can be done with Core Needle Biopsy sample. Recently introduced 14G core biopsy needle and automated large core biopsy gun improves the diagnostic efficacy and it makes the procedure even more easier. Disadvantage of CNB is that sometimes seeding of malignant cells along the needle tract can occur [8]

Cytokeratin (CK), is an intermediate filament protein, reflects the type of epithelial cell, the state of tissue growth, differentiation, functional status and is used to fingerprint of various carcinoma. The normal breast tissue is made up of luminal cells that express CK 8/18, CK7, CK19. The basal/ myoepithelial cells express CK5/6, CK14, CK17 and smooth muscle actin. A small subset of cells, representing less than 5% of total cell population, express CK5. These cells are dispersed throughout the inner layer of ductal system and differentiate into myoepithelial or glandular cells via intermediary cells [9].

Inclusion Criteria:
All women of age group more than 18 years presenting with palpable breast lump coming for FNAC with consecutive CNB in the department of pathology, JMCH during the study period.

Exclusion Criteria:
1) Inadequate and inconclusive sample
2) Inflammatory lesion, lactating adenoma cases are excluded
3) Patient having history of recurrence of breast carcinoma after mastectomy

4) Patient having history of chemotherapy and neoadjuvent chemotherapy or radiotherapy prior to mastectomy
5) Non compliant patient and those who refrained from giving the consent.

RESULTSAND OBSERVATIONS:
A total number of 34 cases were enrolled in the study with Mean age **39.47±10.58**. Among 34 cases, 2 cases presented with early menarche and 4 cases attained menopause on time while rest of them had normal regular history of menstruation.

The results of the study have been analyzed and observations are made in the following tables as follows:
I. Baseline Data
A total of 34 cases presented with palpable breast lump attended the Department of Pathology, Jorhat Medical College & Hospital, Jorhat during the study period. All patients were analyzed for a period of 1 year from June 2020 to May 2021 and the following findings were evaluated.

Table 1: Distribution Of Age In Patients With Palpable Breast Lump (n=34)

AGE (YEARS)	NUMBER OF CASE	PERCENTAGE(%)
≤ 20	0	0
21-30	10	29.41
31-40	2	5.89
41-50	20	58.82
51-60	1	2.94
61-70	1	2.94
>71	0	0
TOTAL	34	100

In this present study, the maximum numbers of cases present with palpable breast lump were in age group of 41-50 years (58.82%). No cases were reported in age group below 20 years and in more than 70 years. The youngest patient was 22 years old and the oldest one was 66 years old in our study population

Table 2: Distribution Of Cases Based On Marital Status

Marital status of the patient	Number of case	Percentage (%)
Married	28	82.35
Unmarried	6	17.65
TOTAL	34	100

In this study maximum number of cases were married (82.35%) while only 6 cases were unmarried (17.65%)

Table 3: Distribution Of Cases In Relation To Parity (n=34) :

Parity	Number of cases	Percentage (%)
Nulliparous	14	41.17
1-2	16	47.07
3-4	4	11.76
>4	0	0
Total	34	100

In this present study, out of 14 (41.17%) nulliparous cases, 6 cases were unmarried and rest were married. Whereas maximum number of cases i.e 16 (47.07%) had 1-2 children. Only 4 (11.76%) cases had 3-4 children.

Table 4: Distribution Of Cases Based On Positive Family History Of Breast Carcinoma (n=34)

Positive family history	Number of case	Percentage (%)
Present	4	11.76
Absent	30	88.24
Total	34	100

In this study, out of 34 cases, only 4 (11.76%) cases had positive family history of breast carcinoma.

Table 5: Distribution Of Cases According To Clinical Presentation (n=34)

Clinical presentation	Number of case	Percentage (%)
Only Lump	30	88.24
Lump with pain	4	11.76
Total	34	100

Out of 34 cases, 30 cases (88.24%) presented with painless breast lump

while only 4 cases (11.76 %) presented with painful breast lump.

Table 6: Distribution Of Cases According To Side Of The Breast Involved (n=34)

| Side of the breast	Number of case	Percentage (%)
Right side	32	94.12
Left side	2	5.88
Bilateral	0	0
Total	34	100

Among 34 cases, right side of the breast was most commonly involved (94.12%). Left side of the breast involved in 2 cases only (5.88%).

Table 7: Distribution Of Cases According To Quadrant Of The Breast Involved (n=34)

Quadrant of The Breast	Number of case	Percentage (%)
Upper outer quadrant	28	82.36
Upper inner quadrant	4	11.76
Lower outer quadrant	2	5.88
Lower inner quadrant	0	0
Central	0	0
Total	34	100

Among 34 cases, upper outer quadrant was involved in maximum number of cases (82.36%) followed by upper inner quadrant (11.76%) and lower outer quadrant (5.88%).

Graph 7: Bar Showing Quadrant Of The Breast Involved In The Study Population (n=34)
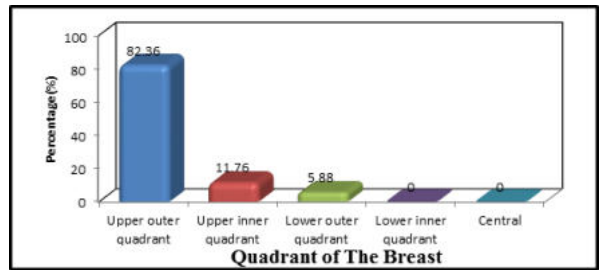
Among 34 cases, majority of them (20 cases) presented with lump more than 3 cm size while rest of them presented with lump less than or equal to 3 cm.

In our study, among 34 cases, 19 cases (55.88%) had symptom of more than 6 months duration while rest 15 (44.12%) presented with short duration of symptoms of less than 6 months.

Of total 34 cases, 24 (70.59%) had mobile lump while in 10 (29.41%) cases had fixed breast lump to the underlying tissue.

Table 8: cytological diagnosis of cases based on 'internatinal acadamy of cytology yokohama system' on fnac

Cytological diagnosis	Number of case	Percentage(%)
Inadequate (C1)	0	0
Benign (C2)	16	47.06
Atypia probably benign (C3)	4	11.76
Suspicious of Malignancy (C4)	3	8.82
Malignant (C5)	11	32.36
Total	34	100

Of total 34 cases, 16 cases (47.06) were diagnosed as benign lesion of breast while 11 cases (32.36 %) were diagnosed as malignant lesion of breast on FNAC.

Out of 34 cases, maximum number of benign cases were diagnosed in age group between 21-30 years while maximum number of malignant cases were diagnosed in age group between 41-50 years.

In this study, cases were categorized according to *YOKOHAMA SYSTEM* in C1- C5 for FNAC and B1- B5 for CNB. One case was placed in C2 category which was later found to be malignant on CNB, was missed on FNAC due to improper site of sampling. In C3 category (atypia but probably benign) had 4 cases, which was correctly categorized in B2 category (benign) of CNB. One case of C5 category (malignant) on FNAC was found to be in B3 category on CNB. C3 category (Atypia probably benign) had 4 cases as compare to B3

category of CNB which had only 01 case. Out of 11 malignant cases diagnosed on FNAC, only 10 cases were correctly diagnosed as malignant lesion on CNB (B5). Thus CNB helps in preoperative diagnosis more accurately than did FNAC, which was also observed in various other studies.

The comparison between FNAC and CNB diagnoses were as follows: The percentage of total malignant cases diagnosed on CNB (B5) was 41.18% while on FNAC (C5) was 32.35%. Thus CNB was able to detect 8.83% more malignant cases than FNAC. The suspicious rate of malignancy on FNAC (C4) was 8.82% while in CNB no case was reported in B4 category. The total percentage of benign cases diagnosed on FNAC (C2) and on CNB (B2) were 47.05% and 55.88% respectively. Out of 16 benign cases (C2) diagnosed on FNAC, 01 case was diagnosed as malignant on CNB. Out of 11 malignant cases diagnosed on FNAC, 1 case of C5 category found out to be in B3 (CNB AND HISTOPATHOLOGY OF C4 (SUSPICIOUS OF MALIGNANCY) CATEGORY OF FNAC:

In this category, 3 cases were highly suspicious for malignancy on FNAC. CNB was performed in all three cases and was diagnosed as malignant lesion (B5) of breast. On histopathology it was given a diagnosis of low grade DCIS. The diagnoses of CNB and histopathology were consistent in all three cases.

Table 9: Comparison Of Results Of Fnac With Cnb

CNB	FNAC		Total	Chi square test
	Malignant	Non malignant		
Malignant	10	4	14	P value =0.000046
Non malignant	1	19	20	

**Malignant: (C5/B5 category),   Non malignant: (C1-C4/B1-B4)
Chi square statistics is 16.6046. p value is < 0.05 is considered to be significant.**

Table 10: Comparison Of Results Of Cnb With Hpe

HPE	CNB		Total	Fisher exact test
	Malignant	Non malignant		
Malignant	14	1	15	P value= < 0.5
Non malignant	0	19	19	

Malignant: (C5/B5 category), Non malignant: (C1-C4/B1-B4 category)

Fisher Exact test statistic value is < 0.00001. p value < 0.05 is considered to be significant.

Table 11: Comparison Of Result Of Fnac With Hpe

HPE	FNAC		Total	Fisher Exact test
	Malignant	Non malignant		
Malignant	11	4	15	P value =0.00001
Non malignant	0	19	19	

**Malignant: (C5 category), Non malignant: (C1-C4)
p value is < 0.05 is considered to be significant.**

Immuno Histo Chemistry:
In our study, 1 case was reported as Ductal carcinoma on FNAC and ADH on CNB. But on following histopathology it was reported as low grade DCIS. Since the diagnosis was not conclusive, the case was further put forward for IHC to detect the presence or absence of microinvasion. Myoepithelial marker CK5/6 and CK7 were performed to confirm the diagnosis.

Table 12: Categorization Of Histological Subtype Based On Ck 5/6 And Ck7 Expression

Histological subtype	Number of cases	Basal keratin CK 5/6	Luminal keratin CK 7		Final Diagnosis
			Inside the duct	Outside the duct	
Ductal carcinoma in situ	1	Positive	Positive	Negative	DCIS
Ductal carcinoma with predominant cribriform pattern	1	Negative	Positive	Positive	Invasive Cribriform Carcinoma

In low grade DCIS, CK 5/6 stained myoepithelial layer positive in

involved ducts (staining index 4). CK7 stained luminal cell inside the duct positive (staining index 4) and outside the duct stained negative (staining index 0). In the case diagnosed with Ductal carcinoma with predominant cribriform pattern, CK5/6 stained negative (staning index 0) and CK7 stained luminal cell both inside and outside the duct positive (staining index 4) which confirms invasion and diagnosed as invasive cribriform breast carcinoma.

Table 13: Correlation Of Statistical Parameters Between Fnac, Cnb And Hpe

STATISTICAL PAERAMETERS	CNB IN COMPARISON OF HPE (%)	CNB IN COMPARISON OF FNAC (%)	FNAC IN COMPARISON OF HPE (%)
SENSITIVITY	93.33	71.43	73.33
SPECIFICITY	100	95	100
PPV	100	90.91	100
NPV	95	82.61	82.61
ACCURACY	97.06	85.29	88.24

The sensitivity and specificity of CNB in comparison with HPE considering histology as Gold standard was 93.33% and 100% respectively while with FNAC, sensitivity and specificity was 73.33% and 100 % respectively. Positive predictive value (PPV) and negative predictive value (NPV) for CNB was 100% and 95% respectively while that for FNAC was 100% and 82.61% respectively. The diagnostic accuracy for CNB was 97.06% while for FNAC diagnostic accuracy was 88.24%. Thus CNB was more helpful in accurate diagnosis of breast lesions than did FNAC.
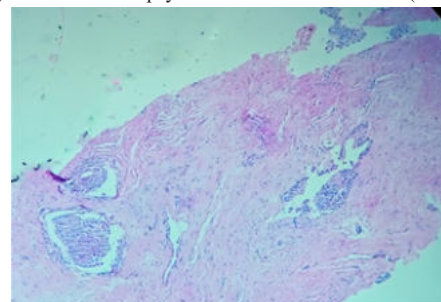
Photograph
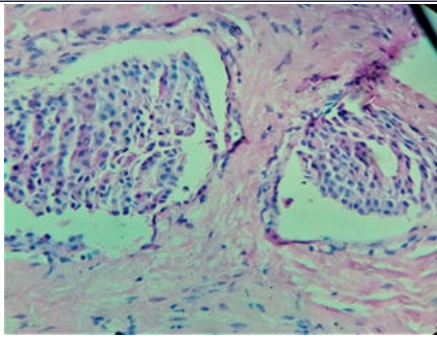**Photograph 1- Core Biopsy Needle 14g**
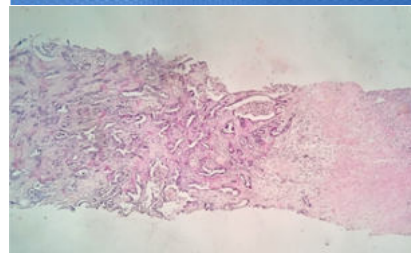
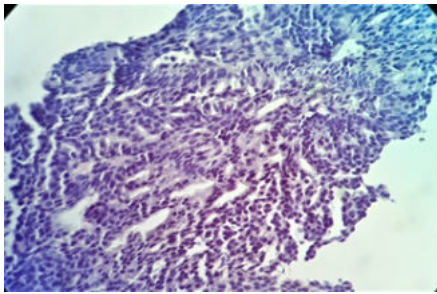**Microphotograph 3(a)- Low Power View Of Core Biopsy (10x)**

PHOTOGRAPH 2- Biopsy site cleaned with 10% betadine and infiltration of 2% lignocaine followed by stab incision given with 11 no. surgical blade and biopsy taken with automated CBC (14G)
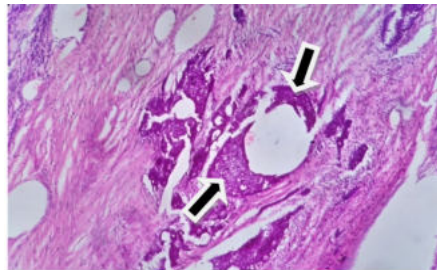

**Microphotograph 3(B)- Low power view of Atypical Ductal Hyperplasia (10x)**

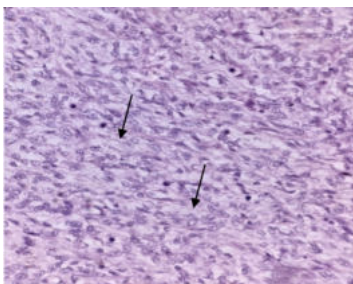**Microphotograph 3(C)- High power view of Atypical Ductal Hyperplasia (40x)**

Micrograpg 4(a)- High power view (40x)of Ductal Carcinoma

Microphotograph 3(D)- High power view of Ductal carcinoma in situ (40x)

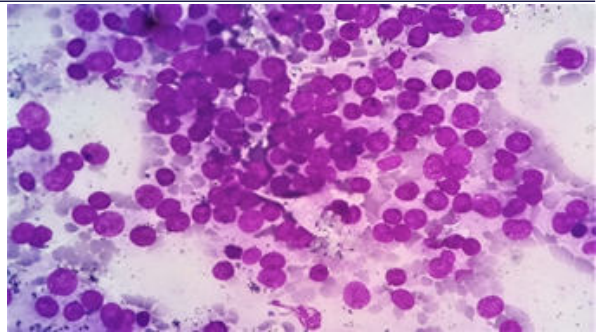**Microphotograph 4(B)- Shows CK5/6 positivitity in myoepithelial layer in DCIS**

Microphotograph 3(E)- Low power view (10x) shows malignant ductal component infiltrating stroma (Arrow) (idc Grade 1)

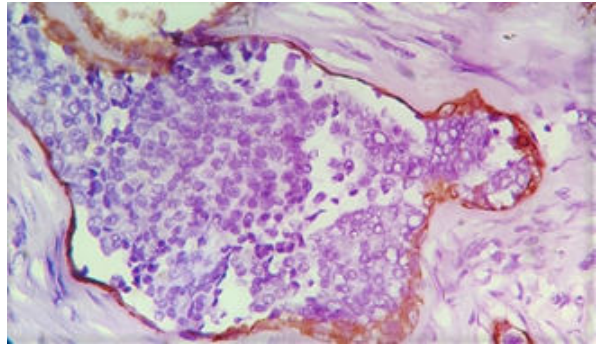**Microphotograph 4(C)- Low power view (10x) shows CK5/6 negative and CK7 positivitity in Cribriform carcinoma**
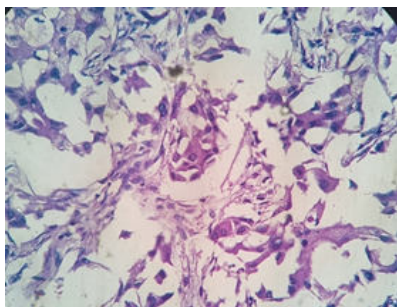
Microphotograph 3(F)- High power view (40x) shows IDC with medullary feature

MICROPHOTOGRAPH 4(D)- High power view show CK5/6 negative and CK7 positivity in Cribriform carcinoma

Statistical Analysis:

Entire data from the study was collected and analysed on Microsoft Excelsheet 2010 and SPSS 16 software. Statistical parameters like sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy were calculated and presented in the form of graphs, tables, and figures etc. The p value thus generated were
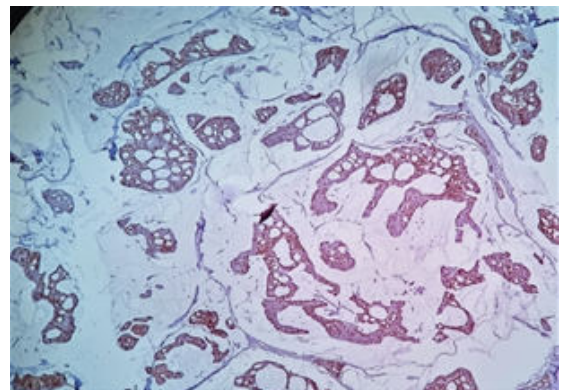

Microphotograph 3(g)- High Power View (40x) Of Malignant Phyllodes Tumor (black Arrow- Mitosis)
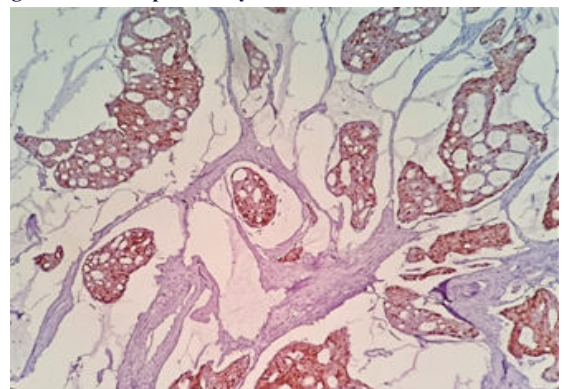**Microscopic Appearance Of Breast On Fnac-**

studied to indicate the presence or absence of significant differences in the parameters under consideration.

DISCUSSION

Comparison of age group in different studies:
In this study maximum numbers of cases were observed in age group between 41-50 years (64.71%). The same distribution of age group was also observed in the Indian studies by **Ganesan M. et al** (2016)[10] and **Srivastava N. et al** (2016)[11].

Comparison of mean age in different studies
In our study, mean age was 39.5 years which was comparable with the study done by **Okobia MN et al** (2001)[12] where mean age was 38 years. In another study carried out by **Srivastava N. et al** (2016)[11] mean age was reported as 45.2 years and in a study done by **Khattak MS et al.** (2020)[13] mean age was reported as 34.4 years.

Comparison of marital status with different other studies:
In our study 28 out of 34 patients were married (82.35%) which was comparable with the studies done by **Srivastava N. et al** (2016)[11] where 98.5% were married. In another study conducted by **Homesh et al** (2005)[14] they observed that 205 out of 296 cases (69.2%) were married.

Out of 34 cases, 30 cases (88.24%) presented with lump and 4 cases (11.76%) present with lump associated with pain. In a study conducted by **Srivastava N. et al** (2016)[11] similar presentation were seen.

Quadrant Wise Distribution Of Lump:
In this present study upper outer quadrant is most commonly involved (82.36%) followed by upper inner quadrant (11.76%). lower outer quadrant was least commonly involved. In the studies done by **Sandhu DS et al (2010)[15]**, **Rathi M et al (2015)[16]**, similar findings were observed.

Side Of The Breast Involved
In our study, right side of the breast was most commonly involved. Similar presentation was observed by **Saha A. et al** (2016)[17], whereas in previous studies done by **Rathi M. et al** (2015)[16] and **Das U. et al** (2015)[18] they found that left breast was more commonly involved than the right breast.

Comparison of cases diagnosed on FNAC with different studies:
A total of 16 (47.06%) cases were reported as benign and 11 (32.35%) cases were reported as malignant lesion of breast on FNAC. The frequency of benign and malignant lesion of breast on FNAC was found to be similar with the studies done by **Bukhari MH.et al** (2011)[19], **Rathi M. et al** (2015)[16] and **Badge SA et al** (2017)[20}

Comparison of expression of CK5/6 and CK7 in breast in different studies:
In our study 10 cases were diagnosed as malignant lesions of breast by both FNAC and CNB. Only 1 case was reported as histologically indeterminate on CNB and diagnosed as atypical ductal hyperplasia but it turned out to be DCIS on histology. Myoepithelial marker CK 5/6 and CK 7 was performed to confirm the diagnosis.

Out of 10 malignant cases, 8 cases were reported as IDC, NOS (GRADE 1) and another one was reported as IDC with medullary feature (GRADE 3) on histology. In rest of the case, it was very difficult to identify whether the lesion was invasive or not. To confirm invasion IHC with myoepithelial marker CK 5/6 and CK7 were performed in both the cases. In low grade DCIS, CK 5/6 stained myoepithelial layer positive in involved ducts while CK7 stained luminal cell inside the duct positive and outside the duct stained negative. In the case diagnosed with Ductal carcinoma with predominant cribriform pattern, CK5/6 stained negative and CK7 stained luminal cell both inside and outside the duct positive which confirms invasion and diagnosed as invasive cribriform breast carcinoma. Similar findings were observed in a study carried out by **Bhalla A. et al (2010)[21]** where they used ck 5/6 to differentiate invasive from non invasive lesions.

Comparison Of Sensitivity And Specificity Of Both Fnac And Cnb With Different Studies

	SENSITIVITY		SPECIFICITY		DIAGNOSTIC ACURACY	
	FNAC	CNB	FNAC	CNB	FNAC	CNB
SAHA A ET AL (2016)	69	88.3	100	100	74	86
TIKKU G ET AL (2010)	64.6	95.8	100	100		
SHAILA M ET AL(2016) (n=68)	84.6	97.4	72.4	96.5	79.4	92.6
GARG S. ET AL(2007) (n=50)	78.15	96.5	94.44	100		
PRESENT STUDY 2021 (n=34)	73.33	93.33	100	100	88.24	97.06

On evaluation we found that the sensitivity and specificity of CNB in detecting malignancy was 93.33% and 100% respectively which correlate well with various different other studies. Studies regarding the correlation between FNAC and CNB in palpable breast lump within the same individual are relatively few in comparison with the studies regarding mammographically detected breast lesions. In this present study, sensitivity and specificity of FNAC in detecting malignancy was 73.33% and100% respectively which was similar to other studies where FNAC and CNB was done subsequently in palpable breast lumps.

SUMMARY AND CONCLUSION
Breast carcinoma is one of the leading causes of cancer in women, worldwide and the second most common cancer after carcinoma cervix in India. Breast lump is the most common presenting symptoms in breast carcinoma however; clinically it is often hard to determine whether a palpable lump is benign or malignant. thus it has become mandatory for the clinician and the oncologist to evaluate a suspicious palpable breast lump with accurate and highly specific diagnostic test.

Since last few years, there is a continuous evolution from the use of FNAC to CNB as a diagnostic method of choice in palpable breast lesion. In comparison with FNAC, CNB provides the more accurate and optimal diagnostic information as it is possible to differentiate invasive from in situ malignancy and lobular from ductal carcinoma on a core biopsy. Preoperative evaluation of hormonal status is also possible in core biopsy sample. The availability of automated large core biopsy gun with 14/16 G core biopsy needle make the procedure more easier and improves the diagnostic yield. In various studies CNB is reported to have higher sensitivity and specificity than FNAC while in other studies FNAC was found to be more sensitive and cost effective than CNB. The choice between FNAC and CNB should be individualized for the patient presenting with palpable breast lump. In our study, CNB was found to be more superior to FNAC in terms of sensitivity, suspicious rate, diagnostic accuracy and correct typing of benign and malignant cases. Thus we can say that CNB is more useful than FNAC for the preoperative evaluation of palpable breast lump.

Ethical Clearance
Ethical clearance certificate was obtained from the Human ethics committee (H) OF Jorhat Medical College and Hospital prior to the commencement of the study

Limitation Of The Study
The current study has many limitations, the major being the study was undertaken in a short span of 1 year (June 2020- May 2021) time which coincided with ongoing COVID-19 pandemic.

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