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Upgrade Rate and Associated Predictive Factors of Papillary Breast Lesions on Core Needle Biopsy in a Private Tertiary Institution: A Cross-sectional Study

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ABSTRACT

Objective. The aim of this study was to determine the upgrade rate in diagnosis of biopsy-proven papillary breast lesions on core needle biopsy and their respective surgical excisions, and to assess for predictive factors associated with an upgrade at St. Luke's Medical Center – Global City.

Methodology. A retrospective review of our institution's database identified 184 papillary breast lesions diagnosed by core needle biopsy. The study population consisted of 71 samples that met the inclusion criteria. The overall upgrade and concordance rates were determined and analyzed if there was any significant association with clinical demographics, radiologic findings, and core diameter on gross examination. Continuous variables were presented as mean and median, and Shapiro-Wilk test was used to assess normality of data. Categorical variables were expressed as frequencies and percentages. Simple logistic regression analysis with Firth's bias correction was performed to determine the variables associated with a diagnostic upgrade. *P* values ≤0.05 were considered statistically significant.

Results. A total 71 patients, all female, were included in the study. The overall upgrade rate was 8.45% (95% CI: 3.16-17.49%) in comparison with the diagnosis of the initial CNB and SE alone. This translated to 6/71 samples in this study. The overall concordance was 91.55% based on clinical significance, and an individual diagnosis concordance rate of 78.87%. None of the predictive factors (i.e., age, history of breast cancer, BI-RADS score, and gross core diameter) assessed showed an association with a diagnostic upgrade.

Conclusion. The computed overall upgrade rate is within range of currently published literature. The concordance rates for both clinical significance and individual diagnosis were quite high, suggesting good reproducibility of histopathologic diagnosis within our institution. This was also found to be consistent with other studies. Of the predictive factors, none showed an association to a diagnostic upgrade. Despite the latter, our findings may be of value within the medical center in further exploring and expanding the data set at hand, such that it may hopefully contribute to local guidelines in managing PBLs in the future.

Key words: papilloma, papillary breast lesions, upgrade rate, core needle biopsy

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INTRODUCTION

Papillary breast lesions (PBL) are a diverse and heterogeneous group of breast lesions that include benign intraductal papillomas (IDP), papillomas with atypical ductal hyperplasia (ADH, atypia measuring <3 mm), papillomas with ductal carcinoma in situ (DCIS; atypia >3 mm), papillary DCIS, encapsulated papillary carcinomas (EPC), solid papillary carcinomas (SPC), and invasive papillary carcinomas (IPC).[1-3] A conundrum frequently faced by surgical pathologists is that papillary morphology alone – epithelial cells lining arborizing, delicate fibrovascular cores, with or without a myoepithelial cell (MEC) layer and are attached to the ductal walls – is challenging in the face of core biopsies, where commonly, only portions of the papillary lesion are sampled and submitted for analysis. The characteristics of the epithelial cells, as well as the presence of the MEC layer, determine whether a papillary lesion is categorized as benign or atypical.[1-4] In many cases, immunohistochemical stains are utilized to further determine characteristics where morphology is difficult in determining the lesion's nature.[1,2,5-7]

Determination of the upgrade rate, and factors associated with the upgrade rate of papillary lesions on core biopsy to atypical or outright malignant in resection, can be useful in the management of papillary breast lesions – especially in those that could potentially benefit the patient if a more severe underlying lesion cannot be totally ruled out. The data gathered can serve as a guide to both the pathologist and surgeon, for the next best course of action if a patient should undergo surgical excision (SE) of the lesion or not, and thus the possibility of avoiding an unnecessary procedure.[4]

A common dilemma encountered by pathologists after a diagnosis of an atypical papillary lesion made on core needle biopsy (CNB) is whether to recommend conservative management or excision of the lesion.[8,9] A core biopsy only provides a representative picture of the lesion found in radiographic studies. Nonetheless, an overly aggressive management of the patient may occur depending on the diagnosis reported by the pathologist.

Immunohistochemical techniques that detect the MEC layer or epithelium have been of great utility in identifying and differentiating benign versus atypical lesions.[1,5-7] However, other factors such as age (demographic), lesion size, and radiologic findings have been also found to correlate with the upgrade to an atypical papillary lesion.[1,4,5,8-11] At present, there has been no uniform consensus as to the criteria that should be employed in the management of patients with papillary breast lesions.[12] This is exhibited by European guidelines preferring a more conservative approach through regular patient follow-up,[13] while guidelines proposed by the American Society of Breast Surgeons suggest surgical excision is more appropriate.[14]

Papillary breast lesions evaluated on core needle biopsy is not an uncommon task in the realm of surgical pathology. As part of cancer screening programs, Image Guided CNB (IGCNB) has become more utilized, and becoming the "gold standard" in diagnosing breast masses and lesions and in further evaluating their malignant potential.[1,15,16] Particularly difficult are PBLs, due to their wide range of disease potentials from benign to frank malignancy.[1-5,8-12,15-17]

Another layer adding to the difficulty in diagnosing papillary lesions is sampling, wherein the architecture of the lesion may be distorted due to fragmentation, infarction, or inadequacy of the specimen. Further, the presence of cellular atypia cannot be entirely ruled out since a biopsy takes only a snapshot of the lesion identified through imaging.[3,13,18] In Europe,[13] the uncertainty this raises has led to the consensus that PBLs are lesions of uncertain malignant potential, or B3 on a biopsy category scale of 5 (B1 to B5), regardless of cellular atypia identified in the sample. All these factors are taken into consideration when evaluating for the upgrade rate i.e., the percentage of benign neoplasm that becomes classified as atypical papillary neoplasm or frank malignancy. Qiu et al., suggests that the upgrade rate for PBLs may vary up to 31%.[5]

This variance in upgrade rate has therefore led to some controversy as to which factors associated with the upgrade of the lesion can be used in the subsequent clinical and surgical management of PBLs. Various publications have identified common factors including: older age (ranging from 45 to 65 years),[1,9,19] larger lesion size (between 1 to ≥2 cm)[1,19-21] and presence of atypia.[5,6,13,19,2-28] Other factors such as location (central or peripheral), radiologic grade (Breast Imaging Reporting and Data System - BI-RADS score), microcalcifications, and history of breast cancer had less than conclusive results.[1,10,22,24,29,30] The inconsistencies in these findings may be attributed, but not limited to sample size and interobserver variability as well as other confounding variables.

To note, interobserver variability has been reduced due to in no small part by the utilization of immunohistochemical (IHC) studies.[5] Myoepithelial markers (i.e. p63, SMMS) and epithelial markers (i.e. ER, CK5/6) have aided in reducing the ambiguity in the diagnosis of lesions that by morphology alone are difficult to discern for atypia.[1,3,10] Despite this, it should be reiterated that the presence of atypia regardless of using IHC stains, can still be confounded if the IGCNB sampling of the lesion was unable to hit the area containing the atypical cells in the first place, hence the need for criteria in whether clinical observation or surgical excision should be the next step in the management of the patient's case. Establishing an upgrade rate within our tertiary medical center with a breast care center should be of benefit within the institution for clinicians and pathologists alike.

The study primarily aims to determine the upgrade rate of papillary breast lesions on core needle biopsy and its subsequent surgical excision (SE) specimens. Moreover, the association between clinico-demographic (age), history of breast cancer, gross core diameter, radiographic findings and the various papillary breast lesions will be examined.

METHODOLOGY

This is a single center, analytical, cross-sectional study approved by the Institutional Ethics Review Committee (IERC) of St. Luke's Medical Center – Global City (SLMC-GC), which abided by the Principles of the Declaration of Helsinki (2013) and conducted along the Guidelines of the International Conference on Harmonization - Good Clinical Practice (ICH-GCP) on privacy and confidentiality.

Patient selection

A retrospective review of breast core needle biopsies with papillary lesions from the time period of January 1, 2020 to December 31, 2023, were sourced from the records of the Section of Histopathology of SLMC-GC, where an initial total of 184 records were found. Those included into the study were the surgical pathology reports of CNBs with an initial diagnosis of a PBL, age as demographic data, core diameter from the gross description, history of breast cancer, an available BI-RADS score from the Breast Care Center via breast ultrasonography or mammogram, and the CNB must have a subsequent SE specimen. Those excluded were as follows: 1) an initial biopsy done through incision or excision biopsy; 2) excision and resection specimens who had no initial CNB; 3) incomplete demographic data; and 4) those without radiographic data (BI-RADS score) done within the medical center.

Data analysis

Data collection was done via utilization of the laboratory information system (LIS) and electronic medical records (EMR). The following keywords were used to search through both databases: "breast," "papilloma," and "papillary." Radiologic data (BI-RADS score) was accomplished through assistance of the records kept within the Breast Care Center of SLMC-GC.

Data gathered included an initial core biopsy of a PBL, its respective subsequent surgical excision, patient characteristics (age at the time of biopsy, history of breast cancer), core diameter from the gross description of the surgical pathology report, and BI-RADS score. MS Excel was used to input the data.

Patient characteristics were analyzed as follows: age was categorized as <55 years old, and ≥55 years old; and history of breast cancer as "yes" or "no." Radiologic data of the BI-RADS score was group together into three categories: "1,2,3;" "4," and "5,6." Core gauge was set as a continuous variable.

The PBLs were classified as benign, atypical, or malignant. Intraductal papilloma was categorized as benign. For atypical lesions, inclusive was papilloma with atypical ductal hyperplasia. Within the malignant category, the following were included: papillomas with DCIS, papillary DCIS, encapsulated papillary carcinomas, solid papillary carcinomas, and invasive breast carcinomas (IBC) with papillary features/ invasive papillary carcinomas.

For the purposes of this study, surgical pathology reports that stated "*ductal carcinoma in situ in papillary pattern*" were included, as it is common to have multiple DCIS morphological patterns in one specimen.[31] In addition, "*invasive breast carcinoma with papillary features*" are also included in the study, as invasive papillary carcinoma in its pure form is rare.[2]

Upgrade rate is defined as the percentage in which a benign neoplasm is upgraded to an atypical papillary neoplasm, and by which an atypical papillary neoplasm is upgraded into a frank malignancy. Concordance is the percentage at which the initial diagnosis of the core needle biopsy matches that of the SE specimen.

Data was encoded in MS Excel by the researcher. Stata MP version 17 software was used for data processing and analysis. Continuous variables (i.e., age and diameter of needle) were presented as mean (standard deviation/SD) and median (interquartile range/IQR) depending on the data distribution. The Shapiro-Wilk test was used to assess the normality of data. Categorical variables (i.e., history of breast cancer, BI-RADS score and histopathologic results) were expressed as frequencies and percentages. To determine the variables associated with upgrade of lesions, simple logistic regression analysis with Firth's bias correction was performed. P values ≤0.05 were considered statistically significant.

RESULTS

A total of 184 patients with core needle biopsies showing PBLs were identified between January 2020 to December 2023. Seventy-one (39%) of the 184 patients were recorded as having underwent a subsequent SE and met the inclusion criteria and thus included into the study. The characteristics of the patients (age, history of breast cancer), BI-RADS score, and core diameter are noted in Table 1. All the samples in this study were taken from female patients.

Patient characteristics

The mean age was found to be 58.2 ± 14.1 years old, with a range of 24 to 90 years old. Forty-five (63%) of the samples were from patients with an age of ≥55 years, with the remaining 26 (37%) below 55 years of age. Of the 71 samples, only 1 (1%) patient had a previous history of breast cancer prior to CNB. For BI-RADS score, 32 (45%) samples were found to be category 4, followed by category 5, 6 with 28 (39%) samples, and BI-RADS category 1, 2, and 3 with 11 (16%) samples. The median core diameter was found to be 0.2 cm in 44 (62%) of the samples.

Distribution of papillary breast lesions

Figure 1 illustrates that based on the CNB (1.a) and subsequent SE (1.b) results of the included patients, most were noted to have been diagnosed with invasive breast carcinoma with papillary features / invasive papillary carcinoma. None were found to have a papilloma with DCIS.

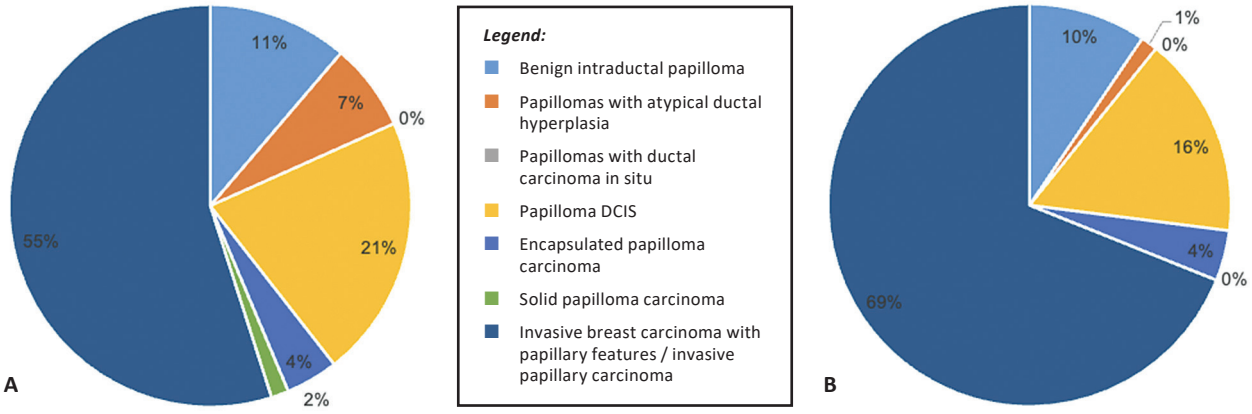

Figure 1. Distribution of papillary lesions based on **(A)** CNB results and **(B)** histopathology result of resection specimen (n = 71).

Concordance rate and upgrade rate

Table 3 shows the concordance of the CNB and their subsequent SE results based on specific diagnosis. Pertinent findings include that one patient had SPC on CNB, which was then found to have been DCIS with papillary features / papillary DCIS upon SE. Further, all IBC with papillary features / invasive papillary carcinoma diagnosed on CNB retained the diagnosis on SE.

Table 3 further classifies concordance based on clinical significance, namely, benign, atypical, or malignant. Noteworthy was that all (100%) four atypical lesions on CNB were upgraded to a malignancy. Also, all 58 malignant PBLs on CNB remained malignant upon SE.

After data analysis, the results of the overall upgrade and concordance rates are summarized in Table 4.

Predictive factors

A simple logistic regression model was used in determining the significance of the predictive factors and their potential association with an upgrade in diagnosis.

Table 1. Characteristics of patients with papillary lesions on CNB and underwent resection (N = 71)

Characteristics	n (%) Mean ± SD; Median [IQR]
Age (in years), mean	58.2 ± 14.1
<55	26 (37)
≥55	45 (63)
History of breast cancer, % yes	1 (1)
BI-RADS score	
1, 2, 3	11 (16)
4	32 (45)
5, 6	28 (39)
Core diameter (in cm), median	0.2 [IQR: 0.2-0.2]

The analysis of age-related findings revealed that among individuals younger than 55 years, 8% (2 out of 26 samples) experienced an upgrade in diagnosis, while the remaining 92% (24 samples) did not. Similarly, for those aged 55 and older, 9% (4 out of 45 samples) saw an upgrade in diagnosis, with 91% (41 samples) showing no change.

The findings regarding breast cancer history indicated that 9% (6 out of 70 samples) with no history of breast cancer experienced an upgrade in the diagnosis of their PBL, while 91% (64 samples) did not. Among those with a history of breast cancer, none (0 out of 1) had an upgrade in diagnosis.

Analysis of BI-RADS score groups revealed that for BI-RADS 1, 2, and 3, none of the samples (0%, 11 out of 11) showed an upgrade in diagnosis. In the BI-RADS 4 category, 19% (6 out of 32 samples) experienced an upgrade, while 81% (26 samples) did not. Similarly, all samples in the BI-RADS 5 and 6 groups (100%, 28 out of 28) showed no diagnostic upgrade.

Across all samples, regardless of whether an upgrade in diagnosis occurred, the median core diameter was consistently 0.2 cm, with an interquartile range (IQR) of 0.2 to 0.2.

The simple logistics regression model analysis revealed that none of the factors were significantly associated with an upgrade in diagnosis of PBLs (Table 5); thus, a multiple logistic regression model was no longer created.

DISCUSSION

The diversity of PBLs account for 1 to 4% of breast lesions diagnosed though CNB.[23] Patients with benign IDPs have a

Table 2. Specific diagnosis: concordance of CNB and SE results (N = 71)

CNB results	Histopathologic result of subsequent excision specimen						
	IDP	Papillomas with ADH	Papilloma with DCIS	DCIS with papillary features / papillary DCIS	EPC	SPC	IBC with papillary features / IPC
IDP [a]	7	0	0	1	0	0	0
papillomas with ADH [b]	0	1	0	1	0	0	3
papillomas with DCIS [c]	0	0	0	0	0	0	0
DCIS with papillary features / papillary DCIS	0	0	0	9	0	0	6
EPC [d]	0	0	0	0	0	0	3
SPC [e]	0	0	0	1	0	0	0
IBC [f] ***papillary features / IPC*** [g]	0	0	0	0	0	0	39

a = benign intraductal papilloma
b = atypical ductal hyperplasia
c = ductal carcinoma in situ
d = encapsulated papillary carcinoma
e = solid papillary carcinoma
f = invasive breast carcinoma
g = invasive papillary carcinoma

Table 3. Clinical significance: concordance of CNB and SE results (n=71)

CNB results	Histopathologic result of subsequent excision specimen		
	Benign	Atypical	Malignant
Benign	7	1	1
Atypical	0	0	4
Malignant	0	0	58

Table 4. Summary of upgrade and concordance rates

Overall upgrade rate	8.45%
Overall concordance rate	91.55%
Concordance Rate for Specific Diagnosis	78.87%

Table 5. Predictive factors associated with upgrade of lesion on subsequent excision (N = 71)

Characteristics	Upgrade		Crude OR (95% CI)	*P* value
	Yes	No		
Age (in years)	N (%)			
<55	2 (8)	24 (92)	Ref	Ref
≥55	4 (9)	41 (1)	1.06 (0.21-5.39)	0.942
History of breast cancer				
No	6 (9)	64 (91)	Ref	Ref
Yes	0	1 (100)	3.31 (0.12-89.74)	0.477
BIRADS score				
1,2, 3	0	11 (100)	Ref	Ref
4	6 (19)	26 (81)	5.64 (0.29-108.71)	0.252
5, 6	0	28 (100)	0.40 (0.01-21.58)	0.655
Core diameter (in cm), median	0.2 [IQR: 0.2-0.2]	0.2 [IQR: 0.2-0.2]	0.06 (0.00-3662.43)	0.611

Ref: Reference category

1.5 to 2 times higher incidence of breast cancer, and those with atypia are found to have a higher risk of 4.3 times than that of the general population.[6] As such, several groups and institutions have attempted to establish criteria for the consistent management of PBLs. Based on European guidelines, PBLs are classified under breast lesions of uncertain malignant potential (B3). Qualifiers such as IDP without atypia and IDP with atypia are considered prior to further management, resulting in either with vacuum assisted biopsy (VAB) or surgical excision, respectively.[13]

Continuity of the histological picture of a PBL is also considered. ADH and DCIS in PBLs are qualified by the extent of the atypia present within the sample. While CNBs, and indeed, VABs may be of aid in excising papillary lesions, the continuity and wholeness of the lesion is not guaranteed. Hence, for a more thorough examination of the PBL, surgical excision may be preferred in some cases.[33] However, agreement with a more uniform consensus on whether to proceed with SE has been nebulous at best, as different groups variably prefer conservative or aggressive management within and between institutions.

The findings in this study revealed that 6 of the 71 PBL samples included had a computed overall upgrade rate of 8.45% (95% CI: 3.16-17.49%) and fall within the range of several studies published previously. However, it must be noted that these studies have varying upgrade rates with no consistent values, ranging from 1.58% to 31%.[1,2,5,7-11,18-23,30,32,34-36] As such, the setting of a guideline for clinical and surgical management proves to be of some difficulty still.

It was found that 2 of the 9 (22%) of the benign PBLs had been upgraded in our study. One was noted as atypical, and the other as malignant. This is well beyond the upgrade found in several publications, where the range only values from 1.58% to 8.8%.[8,9] This can be accounted for by the smaller sample size this study has in comparison to those currently published. Of note, however, is that some studies have pointed out that some of their upgraded cases were seen to have more aggressive lesions in the periphery of the index lesion than the actual index lesion itself, as well as intralesional heterogeneity, thus raising the possibility of sampling error.[22,35] In theory, this may also explain the one sample diagnosed as SPC on CNB that was later to be found as papillary DCIS on SE.

For atypical PBLs, 4 of 4 (100%) were found to have been upgraded to a malignant PBL. This is inconsistent with other studies, where 27% to 30% of the samples with atypia were upgraded to malignant.[8,9,25,27] Finally, all 58 malignant samples remained malignant, and hence classified as no upgrade. This is in keeping with other studies citing at least an 80.2% to 100% concordance rate for the diagnosis of malignant lesions from their initial CNBs in comparison with their excisions.[32,27] Consequently, the overall concordance rate in our study was found to be 91.55%, similar to the findings of a study by Fuentes et al (88.7%).[37]

An attempt to describe the concordance of the specific CNB and its respective excision diagnosis was made in this study, regardless of the clinical significance. It was of interest to the researchers to evaluate if at least the *sameness* of the initial final diagnosis yielded any significant data that could be investigated. The concordance rate (Table 2) for this aspect of the study yielded a result of 78.87%. This is comparative to a ten-year study where B3 lesions underwent CNBs, with a concordance rate of 83.3%[38] upon SE.

The demographics of this study showed a median age of 58.2 ± 14.1, 63% (45 of 63 patients) of which were older than 55 years of age. While not significant in our study, older patients, particularly those considered post-menopausal[27] and/or ≥55 years of age, were found to be associated with an upgrade in diagnosis.[1,10,21,23,28] A Turkish study recommended an even lower cut off, at 40 years of age.[11]

History of breast cancer was a predictive factor of interest in our study. Unfortunately, of the 71 included samples, only 1 had a previous personal history of invasive breast carcinoma, of which the CNB and SE revealed the same diagnosis. In larger studies such as those of Albert-Oller et al.,[29] it was found that 32.5% of those with history of IBC did show an upgrade in diagnosis after SE. On the other hand, those with no personal history had an overall upgrade rate of 11.2% in diagnosis, of which only 0.8% upgraded to a malignancy. Here, they suggest that even if the CNB was not suggestive of atypia, the personal history of IBC alone might suggest further management with SE. Chen and colleagues also had similar findings, where presence of atypia resulted in an upgrade rate of 27%; further, when paired with personal history of breast carcinoma, this was increased to 31%. Timing of the history was not significant

(i.e., recently as less than 1 year, or more than 1 year), suggesting history alone would suffice.[26]

BI-RADS score also did not yield any significant association with the upgrade rate in our study. However, it should be noted that those assigned BI-RADS 4 on imaging, 19% (6 of 32 samples) did show an upgrade in diagnosis. Those grouped as BI-RADS 1, 2, and 3, and BI-RADS 5 and 6 showed no samples having any change in their clinical significance. Upon review, some studies also did not show any significance in association with BI-RADS score. Yet, descriptively speaking, in the same instance, Salisbury et al.,[1] stated that lesions categorized as BI-RADS 4 were still likely to receive an upgrade. Other publications have found that a higher BI-RADS score, most those of 4c and 5, did show an upgrade in clinical significance.[7,10,22,35]

Core diameters in many studies have varied,[18] most using the gauge 14 size as a standard in their medical centers. In a meta-analysis by Zhang et al.,[22] wider core gauges such as those of vacuum assisted breast biopsies (VAB) were found to be able to identify PBLs with atypia better than those of the standard CNB. This led to a lower upgrade rate when performing VAB over CNB, as a thicker core diameter yields more tissue. In contrast, a ten-year single-center study found no significant difference in needle gauges in the underestimation of malignancy.[38] The latter study compares to ours, in that no association was found between core diameter and upgrade rate.

Admittedly, the small sample size of this study is a glaring limitation. Examination of the incidental findings from our data may shed some light as to why many samples were excluded from the final data analysis. A total of 184 patients with PBLs on CNB were initially recorded, of which 113 (61%) did not undergo subsequent SE. When stratified based on clinical significance, 62 of 71 (87%) of benign lesions, 19 of 23 (83%) of atypical lesions, and 32 of 90 (36%) of malignant lesions did not have any data on SE.

There is evidence that suggests that benign PBLs less than 1 cm may not warrant an excision.[1,13,16,21,22,28,39,40] A publication by Ko et al.,[39] found that their overall upgrade rate to a malignancy was only 2.3% in small, solitary, PBLs. Some have agreed that recommending close clinical follow-up instead of SE with these studies in mind. Despite these findings, not all publications agree. Glenn et al.,[34] and the American Society of Breast Surgeons[14] recommend surgical excision of the papillary lesions, regardless of size, arguing there is no safe limit at which papillomas could be managed with observation.

Unfortunately, data on the exact size of the PBLs in this study were not always available, hence, it was not included as a predictive factor. Instead, we noted 62 patients with a histopathological diagnosis of a benign PBL without atypia (i.e., intraductal papillomas) on CNB may have been recommended by their respective clinicians to be conservatively managed by close clinical follow-up. This is consistent with many studies recommending the same.[8,10,25,27,39,40] The remaining patients with an atypical or malignant diagnosis, however, are more likely to have been lost to follow-up in our center.

Circling back, a similar conundrum of the lack of lesion size was encountered by Khan et al. Instead, crediting to the 15-year length of their study, they were able to generate findings showing 10-year cancer free survival rates of PBLs without atypia (93.80%) and those with atypia (77.4%).[25] Extending the study period within our medical center may be of some merit if the investigators were to follow this example.

Regarding clinical significance of the diagnosis, our study grouped PBLs into three main groups, namely benign, atypical, and malignant. As observed during data collection, signed out surgical pathology reports for CNBs may state that a PBL in a specific sample could only be diagnosed as an atypical lesion at most. Recommendations for further immunohistochemical staining or an excision may or may not be stated in addition to the diagnosis. Yet it remains that the specific sample was insufficient to diagnose it as firmly benign or malignant with the data at hand at the time.[5] The sometimes fragmented or infarcted nature of a PBL in biopsy samples may account for this; and in rare instances, sampling error and cellular paucity of the sample further increases the difficulty at arriving at a more definite diagnosis.[18] As noted by Petrolla et al., the exercise of caution in diagnosis in accounting for the aforementioned confounding factors may also affect the upgrade rate.[37] Perhaps this may also account for the non-existence of the diagnosis of DCIS within a papilloma for our study, as some results opt to report this lesion as a whole as an "atypical papilloma." In addition to this, a literature review by Tay et al.,[17] found that the definitions for an upgrade in clinical significance differ in many studies, citing that one in particular did not actually consider atypia/ADH an upgrade, and thus may add to the inconsistencies in the body of literature available in the *uniformity* of what an upgrade is in the first place!

Limitations

As a retrospective study in a single center, selection bias must be accounted for. The exclusion of 113 samples from the initial 184 that was collected due to the patient not undergoing further surgical excision must also be raised as potential selection bias. During literature review, it was found that categorization was inconsistent across several publications. Some had opted to only include PBLs with or without atypia and excluding in-situ lesions and carcinoma altogether;[25] while others were more extensive, separating lesions based on radiologic-pathologic concordance or discordance.[38] The predictive factors selected for this research were also less in comparison to other investigations. Factors such physical palpability of a breast mass, radiologic size, radiologic-pathologic concordance/discordance, bloody nipple discharge, calcifications associated with or without a mass on imaging, location (central versus peripheral), core needle gauge, distance from the nipple, and family history of breast cancer were explored for any significant associations with an upgrade in clinical significance from their initial biopsies compared to their surgical resections.[13,16,21,27,29,40,41] The previously mentioned factors, then, can be included in future research endeavors.

Another limitation was found during the process of data collection. Our medical center is home to a number of different practitioners with varied exposures to international

and local training. In line with this is a possible difference among their own practices, and as such, may contribute to the differences in their style of management which may in turn reflect as to why some patients may be managed with or without an excision. In addition, perhaps the lack of data with regard to the patient's own decision to proceed with an excision and cosmetic concerns in relation to the clinician's medical advice were actually noted by Rizzo et al., to be a possible contributing factor that may be missed out as to why some are lost to follow-up.[18]

Racial diversity may be also of some interest for additional data input in the future. Noted by some authors, that inclusive of their limitations was that their studies skewed to one or another racial group, specifically African American or Caucasian women.[18,24] As our medical center caters to a more internationally diverse populace, it might be some benefit to include this as a predictive factor.

Previously mentioned is the lack of recording of lesion size. During the process of data collection, it was found that while the radiologic size was stated within the reports of the Breast Care Center, there was lack of consistency of measuring the PBL in surgical pathology reports. Most of the benign and atypical lesions were not measured, perhaps due to the inherent nature of PBLs' tendency for fragmentation during processing of a CNB.[18] Also, adding to this conundrum is the possibility of sampling in the form of fewer passes on CNB that may yield a smaller histologic sample for assessment.[24] Nevertheless, there might be value in recording the measurements of the PBLs on histomorphology moving forward.

Beyond the scope of this study was if IHCs were used to diagnose atypical PBLs on CNB, and if it had any impact for further surgical management. Though it is a fact that immunohistochemical markers have proven to be of utility in the diagnosis in differentiating among benign, atypical, and malignant PBLs,[1,2,4,29,37] there were only a few samples wherein IHCs had been performed to warrant investigation for the time period set (2020 to 2023) for this paper.

This study also raises the consistency of record keeping within the medical center. Not limited to the Institute of Pathology where the diverse ways patient data were kept and notated. Initially, we had considered *core gauge* instead of *core diameter* as a factor that may or may not have an association with a clinically significant upgrade in diagnosis. However, not all patient records had input the gauge or type of core used in performing the biopsy. Further, some core needle biopsies were not necessarily stated to be image guided – another interesting variable to be explored in future studies.

CONCLUSION

In conclusion, we found that the overall upgrade rate of our study was 8.45%. This is consistent with several publications. However, in part due to the small sample size, none of the predictive factors investigated showed any association with an upgrade in clinical significance in the diagnosis of PBLs. This is demonstrated by the wide confidence intervals computed during data analysis.

Despite this, of some benefit was this study revealed that there was a good concordance in diagnosis between CNB and SE within our center, revealing an overall concordance rate of 91.55% in terms of benign, atypical, and malignant PBLs. In assessing individual diagnoses of PBLs, the concordance rate was 78.87%. This suggests that there is merit to the reproducibility of results within our medical center.

The 4-year period of this study did impact on the sample size, and thus it is recommended to expand the time period in future endeavors. Also, exploring and collecting data, moving forward, on other predictive factors such as but not limited to lesion size, radio-pathologic concordance on lesion characteristics, and clinical symptoms is suggested, as this could potentially aid in adding to the current body of data in crafting standardized guidelines on how to manage patients with PBLs within our medical center and possibly for the Philippines.

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STATEMENT OF AUTHORSHIP

All authors certified fulfilment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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