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ORIGINAL ARTICLE – BREAST ONCOLOGY

Management of Papillary Lesions of the Breast: Can Larger Core Needle Biopsy Samples Identify Patients Who May Avoid Surgical Excision?

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ABSTRACT

Background. The ability to distinguish benign from atypical/malignant papillary lesions on core needle biopsy is limited by the representative nature of the biopsy method, thus follow-up excision is usually recommended. We aimed to determine if larger samples of tissue obtained by core needle biopsy can more reliably predict the true benign nature of a papilloma.

Methods. We reviewed the pathology slides and medical records of 51 patients who were diagnosed with benign papillomas on core needle biopsy from 2000 to 2010, who subsequently underwent surgical excision. The characteristics of the core needle biopsy that were associated with retention of benign histology on excision were determined and analyzed.

Results. Atypical ductal hyperplasia and carcinoma were identified in 5.8 % (3/51) and 5.8 % (3/51) of papillary lesions, respectively, when excised. Patients whose lesions were diagnosed as benign on excision were significantly distinguished by the area (mm^2) of tissue sampled by core needle biopsy (mean ± standard deviation (SD): 101.5 ± 106.5) compared with those with atypia or carcinoma on excision (mean ± SD: 41.7 ± 24.0, $P = 0.003$). All biopsies performed with 12-gauge or larger needles retained benign features on excision. Core needle biopsy tissue samples consisting of ≥7 cores, or measuring >96 mm^2 in aggregate, had a negative predictive value for atypia/malignancy of 100 %.

Conclusions. Larger tissue samples significantly improved the predictive value of benign histology on core needle biopsy. A papilloma sampled by a 12-gauge or larger needle, ≥7 cores, or >96 mm^2 retained its benign features upon excision.

Papillary lesions of the breast comprise a spectrum of neoplasms, which range from benign intraductal papilloma to in situ or invasive papillary carcinoma.[1] The majority of patients with papillary lesions present with nipple discharge and/or a subareolar mass-like lesion.[2] However, it is difficult to further characterize these lesions preoperatively. Patient characteristics, clinical presentation, and radiographic features are unreliable for distinguishing benign from malignant papillary neoplasms.[3–5]

Atypical and malignant papillary lesions evade clinical distinction from benign papillomas because their defining features are typically appreciable only by microscopy. In addition, papillary lesions frequently show intralesional heterogeneity. Benign-appearing papillomas can harbor areas of duct epithelial atypia (equivalent to atypical ductal hyperplasia, "ADH") or even ductal carcinoma in situ (DCIS), which often comprise less than 25 % of the entire lesion.[6] Core needle biopsy (CNB) of these lesions may not sample the most pathologically significant area, as noted by numerous studies comparing characteristics of papillary lesions on CNB and subsequent excision.[6–16] It has been reported that up to 34 % of papillary lesions that appear benign on core biopsy are found to be associated with ADH or malignancy when surgically excised.[7–16] These findings

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suggest that excision of all papillary lesions would be prudent, even in the absence of atypia in the core biopsy.

Several recent studies have reported that vacuum-assisted biopsies provide more accurate diagnoses of benign papillomas, decreasing the requirement for subsequent excision.[17–19] This biopsy technique, which typically utilizes 11-, 9-, or 8-gauge needles, yields a substantially larger sampling of breast tissue, significantly improving the predictive value of the core biopsy. Berg et al.[20] reported average specimen weights of 94 mg for 11-gauge vacuum-assisted specimens compared with 18 mg for those acquired with a 14-gauge automated biopsy gun (Fig. 1).

It has been our practice to recommend excision of all papillary lesions diagnosed on core biopsy, even those that appear benign. In recent years, we have noted a significant increase in the number of patients referred to our institution with papillary lesions sampled by vacuum-assisted and large gauge CNB. We hypothesized that some patients whose benign-appearing papillomas are generously biopsied by CNB may not require surgical excision. We sought to determine if a larger amount of tissue obtained by CNB, in terms of the needle gauge, number or cores sampled, or the overall aggregate area of tissue obtained, could distinguish a group of patients who may be safely followed with close surveillance, and thereby spared surgical excision.

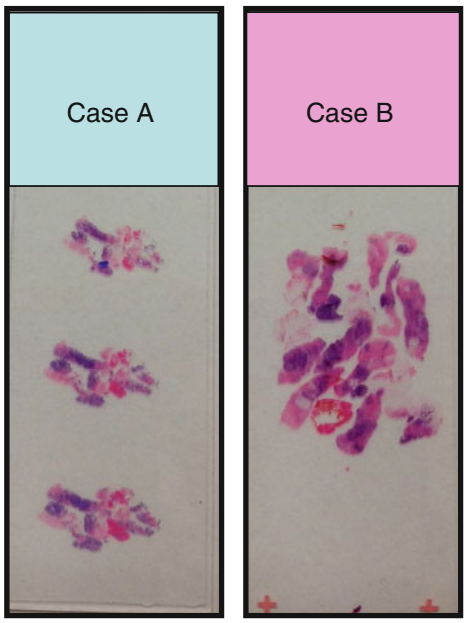

FIG. 1 Case A shows a gross photo of slide containing tissue biopsied with a 14-gauge needle. The tissue measured 72 mm^2 on the slide. Compare with case B biopsied with an 11-gauge needle. The tissue measured 312 mm^2 on the slide. The biopsy for case B procured 4.3 times the area of tissue

MATERIALS AND METHODS

We identified 183 female patients older than age 18 years from the SJHC pathology database who were diagnosed with a papillary lesion by CNB between January 2000 and December 2010. CNBs were performed at SJHC or various referring institutions; however, all biopsies were reviewed by the SJHC department of pathology prior to surgical excision. A total of 113 patients were excluded from the study due to the presence of atypia or malignancy on core biopsy; 19 patients were excluded from the study due to the lack of a subsequent excisional biopsy at our institution. A total of 51 patients with the diagnosis of benign papilloma on core biopsy who had subsequent excisional biopsy were studied.

Medical records were reviewed for clinical and radiographic characteristics, including the radiographic size of the lesion, needle gauge, ultrasound, or mammographic characteristics, and BIRADS classification. One subspecialty-trained breast pathologist (JS) reviewed all CNBs and all excision specimens revealing atypia or malignancy. In accordance with our standard institutional practice, at least three tissue levels were examined on all core biopsy samples. Several cases were further examined with deeper levels and/or myoepithelial immunohistochemistry markers when deemed necessary by the original pathologist. Pathology review confirmed the absence of atypia or malignancy and confirmed the benign histologic features of the papilloma on CNB. The lesions were evaluated according to published histologic criteria.[1,2,21] For the diagnosis of benign papilloma, we required a uniform, single-layer proliferation of ductal epithelium with fibrovascular core formation, presence of myoepithelial cells, and absence of pleomorphism or cellular monotony. Foci of slight epithelial hyperplasia minimally exceeding a single layer of ductal cells were acceptable for benign lesions, provided there were no associated secondary lumens, micropapillary fronds, or solid areas of epithelial proliferation present. The aggregate area of tissue present on the slide(s), recorded in square millimeters (mm^2) was calculated by multiplying the total aggregate length of tissue by the total aggregate width of tissue on the slide(s). The excisional biopsy results were reviewed to determine the histologic characteristics of the papillary lesion on excision, including presence of atypia or carcinoma, and the relationship of these significant findings to the originally biopsied papilloma. This study was approved by the John Wayne Cancer Institute's (JWCI) Institutional Review Board.

Chi-square analysis was used to compare the clinical and radiographic characteristics of patients whose final pathology on surgical excision demonstrated atypical or malignant papillary lesions with those who had benign

papillomas. Continuous variables were analyzed using the Student's *t* test and Wilcoxon rank-sum test. Multivariable logistic regression model was built with atypia/malignancy as a dependent variable using stepwise selection method. Any variable that showed $P < 0.15$ in the univariate analysis was entered into the multivariable model. Receiver operator characteristic curves and the area under the curve (AUC) were determined for the variables that were found to be significant predictors of benign histopathology, including number of cores sampled and aggregate area of tissue biopsied. *P* values <0.05 were considered statistically significant. The analyses were performed using SAS 9.2 (Cary, NC).

RESULTS

We identified 51 patients with CNB of benign papilloma without atypia, who subsequently underwent surgical excision at SJHC. Six of 51 (11.7 %) excisions revealed pathologically significant lesions that were not sampled by the core biopsy. Atypical ductal hyperplasia (ADH) was identified in 5.8 % (3/51) of excised papillary lesions (see cases 1–3 in Table 1; Fig. 2). Excision revealed an invasive and/or in situ carcinoma in close proximity to the papilloma in an additional 5.8 % (3/51) of cases. Among the malignant cases, one excision showed DCIS within the residual papilloma, one excision showed DCIS within ducts surrounding the papilloma and an immediately adjacent 0.15-cm invasive carcinoma, and one excision revealed ADH within the excised papilloma with an adjacent incidental 0.1-cm tubular carcinoma (see cases 4–6 in Table 1).

Clinical and radiographic characteristics did not distinguish the atypical and malignant lesions from benign papillomas. The mean patient age at core biopsy was 50.2 years (range 24–81). The clinical presentation and radiographic features are unknown for one patient. The CNB was most frequently prompted by an abnormal screening imaging study (62 %; 31/50 patients). Five of 50 (9.8 %) patients initially presented with nipple discharge, and 14 of 50 (28 %) of patients initially present with a palpable mass. All 19 patients who presented with nipple discharge or palpable mass were subsequently demonstrated to have a corresponding radiographic abnormality on diagnostic mammogram and/or ultrasound. For all patients, a solid or hypoechoic mass on ultrasound or mammogram was the most common abnormality (38/50, 76 %). Several patients with masses identified on ultrasound additionally showed various forms of calcifications on mammogram in the corresponding area of interest; however, none of these cases were atypical or malignant upon excision. The two cases revealing DCIS on excision did not show mammographic or histologic calcifications. BIRADS scores were known for 40 of the 51 patients, including all six patients with ADH/DCIS/IDC on excision. Thirty-seven lesions were categorized as BIRADS 4 and three lesions were categorized as BIRADS 3; these three were benign upon excision. Most lesions were relatively radiographically small, with 71 % (32/45) measuring ≤1.0 cm. Papillomas that were benign on excision ranged 3–30 mm in greatest radiographic dimension, 9.1 mm (standard deviation (SD): ±4.34) in average. Lesions containing atypia or malignancy on excision ranged 4–22 mm in greatest radiographic dimension, 10.8 mm (SD: ±8.52) in average. This difference is not statistically significant ($P = 0.51$). These data are presented in Tables 2 and 3.

CNB needle size ranged from 9 to 18 gauges (median 14). Of the nine patients who were biopsied with 12-, 11-, or 9-gauge needles, none had atypical or malignant lesions at excision. The number of tissue cores sampled ranged from 3 to 16 (median 4). Mean number of cores sampled did not significantly differ between the two groups. By logistic regression we show that CNB tissue samples consisting of ≥7 cores, independent of needle gauge, had a negative predictive value for ADH/malignancy of 100 % (AUC of 0.69). These data are presented in Table 3.

The aggregate area of tissue present on all slides ranged from 20 to 450 mm^2 (mean 93.7 mm^2, median 60 mm^2, SD: ±101.5). Biopsies obtained with 9-, 11-, and 12-gauge needles biopsies yielded a 5.1-fold greater area of tissue compared with the 14- and 18-gauge needles. Patients whose excisions revealed ADH or malignant lesions had significantly less tissue sampled by CNB than those whose excisions confirmed benign histology (41.7 mm^2, SD: ±24.0 vs. 101.5 mm^2, SD: ±106.5, respectively, $P = 0.003$, Table 3). By logistic regression, CNB tissue samples measuring >96 mm^2 in aggregate had a negative predictive value for ADH/malignancy of 100 % (AUC of 0.68). A total of 15 core biopsies accurately predicting benign papillomas upon excision measured greater than 96 mm^2. Ten of these cases were biopsied with 12-gauge or larger needles; 5 of the 15 cases measuring >96 mm^2 were biopsied with a 14-gauge needle (Table 4).

DISCUSSION

The management of patients with a core needle biopsy showing papilloma has been guided by data from several studies reporting up to a 34 % upgrade rate to ADH or malignancy on excision.[6–16] The representative nature of a core biopsy procedure largely accounts for the initial underestimation of atypical and malignant features. Additionally, the pathologists' ability to reliably distinguish

TABLE 1 Characteristics of cases with excision findings of ADH/DCIS/IDC

	Radiographic features	Core biopsy	Excision diagnosis	Excision specimen details
Case 1 40 years old	U/S: 2.2 complex cystic mass M: nonspecific increased density (interpreted as "normal")	18-gauge needle U/S guided core biopsy three cores, 30 mm^2 obtained	ADH	1.5-cm residua of the papilloma contains foci of ADH within the neoplasm
Case 2 46 years old	U/S: 0.5-cm hypoechoic lesion M: no abnormality	14-gauge needle U/S guided core biopsy three cores; 20 mm^2 obtained	ADH	0.4-cm residua of the papilloma contains foci of ADH within the neoplasm
Case 3 54 years old	Ipsilateral IDC in a different quadrant. Separately noted: U/S: 0.8-cm hypoechoic mass M: no abnormality	14-gauge needle U/S guided core biopsy three cores; 40 mm^2 obtained	ADH	Papilloma is separately excised from the IDC during the same surgical procedure. The 0.6-cm papilloma contains ADH, bordering on low-grade DCIS within the neoplasm
Case 4 78 years old	U/S: not performed M: 1.2-cm mass	14-gauge needle Stereotactic core biopsy two cores; 20 mm^2 obtained	DCIS	1.0-cm residua of papilloma. Papilloma contains atypia, including a focus of DCIS.
Case 5 81 years old	U/S: 0.8-cm oval hypodense mass M: no abnormality	14-gauge needle U/S guided core biopsy four cores; 60 mm^2 obtained	DCIS IDC	0.7-cm residua of papilloma. Several surrounding small ducts contain DCIS with no associated calcifications. In addition, a 0.15-cm low-grade IDC is immediately adjacent to the DCIS and papilloma. See Fig. 2
Case 6 63 years old	U/S: ill-defined hypoechoic mass M: 1.2-cm mass	14-gauge needle U/S guided core biopsy five cores; 80 mm^2 obtained	ADH IDC	1.3-cm residua of the papilloma contains atypia (ADH). 0.4-cm from the papilloma is a 0.1-cm incidental tubular carcinoma

U/S ultrasound, *M* mammogram, *G* gauge, *ADH* atypical ductal hyperplasia, *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma

benign, atypical, and malignant papillary lesions often is limited by the small and fragmented nature of the biopsy material obtained by these core biopsies. The fragmented nature of core biopsy specimens is analogous to a jigsaw puzzle, necessitating a spatial reassembly of the lesion of interest. This task is all the more challenging for lesions like papillomas, which typically arise in large ducts and are best evaluated in one contiguous and inclusive section. In 2012, Lu et al.[22] reported that the average size of the lesions that were biopsied with a 14-gauge needle and upgraded after excision was only 13 mm, suggesting that even small lesions may not be adequately and accurately sampled by core biopsy. Given this reported underestimation rate for atypia or malignancy, our institution routinely offers surgical excision for most patients with a papillary lesion diagnosed on core biopsy, regardless of core biopsy size, histologic features, or radiographic characteristics.

Several authors have recently suggested that larger core biopsy needles, i.e., 8- to 11-gauge, and vacuum-assisted techniques may decrease the underdiagnoses of atypical or malignant papillary lesions.[23–29] The preceding CNB studies that quote high excision upgrade rates largely included patients who underwent first-generation CNB procedures with stereotactic mammography or ultrasound

for localization using an automated biopsy gun equipped with a 14-gauge or smaller needle.[10,15,22] An 8- to 12-gauge vacuum-assisted device allows for significantly greater sampling of a lesion, potentially improving the predictive value of a biopsy. Berg et al.[20] showed that an 11-gauge device typically yields a fivefold greater volume of material per core compared with a 14-gauge automated biopsy gun. Accordingly, we noted that the 9-, 11-, and 12-gauge needles in our study obtained a five times greater yield of tissue (average 215 mm^2) compared with 14- and 18-gauge needles (average 42.5 mm^2). Several investigators report lower upgrade rates for papillary lesions sampled with these larger vacuum-assisted devices [30–32] and argue that surgical excision may be avoided in many such cases.

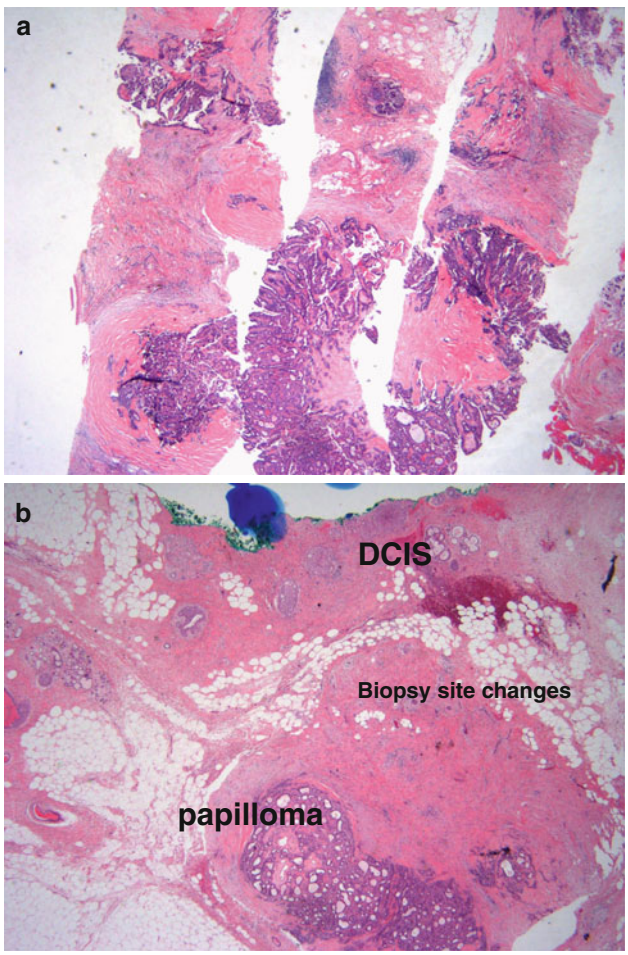

FIG. 2 Histology photos taken from case 5 (see Table 1). **a** Core biopsy showing portions of papilloma with benign histology. **b** Follow-up excisional biopsy showing biopsy site changes, adjacent to residual papilloma and previously unsampled ductal carcinoma in situ (DCIS). The DCIS is not associated with calcifications and does not seem to correspond to a mass-like lesion; thus, the only radiographic abnormality is the 0.8-cm mass identified by ultrasound. In addition a 0.15-cm low-grade IDC is immediately adjacent to the DCIS and papilloma, not present in photo

Our study supports the well-established principle that benign, atypical, and malignant papillary lesions are not preoperatively distinguishable by patients' clinical or radiographic features. Our 13 % overall upgrade rate from benign papilloma to atypical or malignant papillary lesion is consistent with that reported in the literature. In excision specimens, five of the six upgraded cases revealed ADH or DCIS within the completely excised papilloma. This finding supports prior authors' observation that papillary lesions are frequently heterogeneous lesions and may harbor ADH or DCIS in less than 25 % of the neoplasm.[6] It is notable that all of the upgraded cases had significantly smaller core biopsies, as measured by needle gauge, number of cores sampled, and area of tissue present on the slide. Papillomas that were sampled by 9-, 11-, or 12-gauge needles, $\geq$7 cores, or >96 mm^2 of tissue on the slide retained their benign features upon excision.

We appreciate that some percentage of papillary lesions that appear to be "upgraded" at the time of excision have actually been underdiagnosed, or miscategorized, at the time of original core biopsy; however, this is unlikely to account for our findings. We performed retrospective review of all core biopsies to confirm that all of the cores included in our study showed benign features only. We intentionally imposed strict histologic inclusion criteria to consider a papilloma benign. Any equivocal atypical features present in a core biopsy excluded the patient from our study.

To the best of our knowledge, this is the first study to measure and report the area of tissue on the slide as a predictive variable. We used this method to determine sample size for two reasons:(1) By determining the actual dimension of tissue on the slide, we have calculated a more accurate measurement of the tissue biopsy than needle gauge alone would provide. The needle gauge is a surrogate marker for biopsy size, but it does not account for other factors determining the quantity of tissue, including the number of tissue cores taken. This point is evidenced by our finding that 5 of the 15 core biopsies that measured greater than 96 mm^2 (our cutoff for 100 % positive predictive value) were procured with 14-gauge needles.(2) The needle gauge often is not known at the time of biopsy review. Our pathology department reviews CNBs from several referring radiology practices in addition to our hospital-based group. A diversity of biopsy techniques and needle sizes are utilized in our community. Pathologists and surgeons are frequently uncertain of the needle gauge used to procure the biopsy upon which they must base their management. However, the dimensions of the tissue sampled are easily calculated from the slides. Measuring aggregate area of tissue on the slide allows the pathologist to make a determination of biopsy size without having knowledge of the CNB method, needle gauge, or number of cores taken.

TABLE 2 Imaging characteristics in benign and atypical/malignant cases (missing data = 1)

		Benign excision ($N = 44$)	ADH/DCIS/IDC excision ($N = 6$)	P value
Initial presentation ($N = 50$)	Abnormal screening mammogram or ultrasound	28	3	0.41
	Palpable mass	11	3	
	Nipple discharge	5	0	
Ultrasound characteristics ($N = 50$)	Hypoechoic solid mass or complex mass	29	5	0.83
	Dilated duct + solid component	7	0	
	Small cysts	1	0	
	Normal	1	0	
	U/S not performed	6 all have abnormal mammogram	1 mass by mammogram	
Mammographic characteristics ($N = 50$)	Mass	11	2	0.89
	Clustered microcalcifications	3	0	
	Pleomorphic calcifications	2	0	
	Coarse calcifications	2	0	
	Linear calcifications	1	0	
	Normal	21	4 hypoechoic mass on U/S	
	Mammogram not performed	4 all have abnormal U/S	0	

ADH atypical ductal hyperplasia, *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma

Comparison by Chi-squared test

TABLE 3 Patient and lesion characteristics in benign and atypical/malignant cohorts

	Student's t test			Logistic regression predicting atypia/malignancy
	Benign ($n = 45$) mean ± SD	ADH/DCIS/IDC ($n = 6$) mean ± SD	P value	Value that gives 100 % NPV for atypia (AUC)
Patient age	50.2 ± 11	60.33 ± 16.7	0.07	NA
Radiographic size of lesion (mm)	9.8 ± 5.8 Missing data $n = 6$	11.0 ± 7.3	0.52	NA
Size of biopsy (mm^2)	101.5 ± 106.5	41.7 ± 24.0	0.003	96 mm^2 (0.68)
Number of cores sampled	4.8 ± 2.4	3.3 ± 1.1	0.11	≥7 cores (0.69)

U/S ultrasound, *ADH* atypical ductal hyperplasia, *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *SD* standard deviation, *AUC* area under the curve, *NPV* negative predictive value

Group comparison by Student's t test and AUC; NPV by logistic regression

TABLE 4 Biopsy characteristics by needle gauge (missing data = 2)

Needle gauge	N	Mean # cores sampled	Mean area of tissue (mm^2)	Benign excision	ADH/DCIS/IDC excision
9	5	7.8	321.6	5	0
11	3	9.3	204	3	0
12	1	5	120	1	0
14	31	3.8	55.8	26	5
18	9	3.7	29.2	8	1

G gauge, *ADH* atypical ductal hyperplasia, *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma

Our results show that biopsies of a certain aggregate dimension showing benign papilloma may spare patients a subsequent excision. Patients may ultimately benefit from radiologists' selection of a larger needle gauge, and/or a greater number of tissue cores, when feasible, particularly when the diagnosis of papilloma is clinically or

radiographically suspected. In our series, the mean biopsy size with 100 % negative predictive value for atypia/malignancy of 96 mm^2 is significantly smaller than the 204 mm^2 average size of the biopsies procured by 11-gauge needles. Extrapolating these results support prior authors' assertion that benign papillomas diagnosed by US-guided 11-gauge vacuum-assisted biopsy should provide adequate predictive value that the lesions are indeed benign.[28,31]

The lesions included in our study ranged in size from 0.3 to 3.0 cm; however, it should be noted that the average size of the targeted lesions was relatively small at approximately 1.0 cm. When sampling a potentially heterogeneous lesion, the adequacy of a representative biopsy is a function of both core biopsy size as well as the size of the targeted lesion. The size of the lesion sampled by core biopsy should be considered when interpreting our findings, particularly with lesions measuring significantly greater than 1.0 cm.

As with any CNB, the primary issue in the evaluation of these benign-appearing lesions is confirming that the histologic findings in the CNB specimens provide an accurate representation of the radiographically detected target lesion. Discordance between the radiographic abnormality and the biopsy findings must be reconciled, even if the core biopsy findings appear benign. We believe that papillary lesions sampled with smaller core biopsies should still be excised, however close surveillance may be a reasonable option for certain patients whose benign papillomas are generously sampled at the time of CNB.

Disclosures None.

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