

Management of Benign Intraductal Solitary Papilloma Diagnosed on Core Needle Biopsy

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ABSTRACT

Background. The purpose of this study was to determine whether surgical excision of benign solitary intraductal papillomas (BSIP) diagnosed by core needle biopsy (CNBx) without an associated high-risk lesion and concordant with imaging is justified.

Methods. A review of all papillary lesions diagnosed by CNBx from January 2003 to June 2010 was performed. Available histologic and radiologic materials were evaluated in a blinded fashion by three pathologists and three dedicated breast radiologists, respectively, to assess for concordance. The papillary lesions were designated as benign, atypical, or malignant. There were 16 BSIPs excluded because of an adjacent high-risk lesion or same-quadrant ipsilateral cancer. All immediate and delayed excisional specimens were reviewed. Clinical and radiologic data were recorded.

Results. A total of 299 papillary lesions diagnosed on CNBx and concordant with imaging were identified. Of these, 240 (80 %) were classified as benign, 49 (16 %) atypical, and 10 (3 %) malignant. After exclusions, 77 of 224 women in our study cohort (34 %) underwent surgical excision with no atypical or malignant upgrades. Of the remaining 147 women diagnosed with a BSIP on CNBx, 47 (32 %) were lost to follow-up and 100 (68 %) were observed. All 100 observed patients had stable imaging findings at follow-up (4.8–93.8 months, mean 36.0 months).

Conclusions. The likelihood of diagnosing atypia or malignancy after surgical excision of a BSIP diagnosed on CNBx without associated high-risk lesion or ipsilateral

quadrant malignancy is extremely low. For this distinct subset of patients with a BSIP, these data justify close imaging follow-up, rather than surgical excision.

Papillomas are intraductal epithelial proliferations with a central fibrovascular core lined by myoepithelium with a second layer of cuboidal or columnar cells. Papillomas can be classified into solitary papillomas or multiple papillomas. Most often, a solitary papilloma is a benign process that occurs in the subareolar ducts and is often palpable or found incidentally on imaging (see Fig. 1). Alternatively, papillomas can manifest as multiple peripherally located lesions. Our study exclusively examines benign solitary intraductal papillomas. As proliferative lesions, solitary intraductal papillomas can be involved with usual-type ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS). The criteria for these epithelial processes involving papillomas is similar to those found elsewhere in the breast.^{1,2}

It is generally accepted that papillary lesions with atypia or malignancy, diagnosed on core needle biopsy CNBx, require surgical excision.^{3–13} However, several authors have suggested that surgical excision is also warranted when a benign papillary lesion is diagnosed by CNBx, while others have proposed that close observation is appropriate.^{3,6,7,10,11,13–19} Proponents of each stance vary in their estimates of the risk of potential undersampling of atypia or malignancy. We undertook this study to determine whether surgical excision of BSIPs diagnosed by CNBx without an associated high-risk lesion and concordant with imaging findings is justified.

METHODS

Institutional Review Board approval was obtained for this study. A text search of our institution's pathology database



FIG. 1 Solitary breast papilloma by ultrasound. Ultrasound reveals an isoechoic, circumscribed intraductal mass

for papillary lesions diagnosed by CNBx was performed between January 2003 and June 2010. All potential cases in women who underwent breast CNBx were reviewed by 3 breast imagers, divided equally among them. No prior knowledge of the final histologic diagnosis or patient outcome was known. Only concordant papillary lesions diagnosed on CNBx were included. Discrepant cases were resolved by consensus of all three radiologists. All available histologic materials were evaluated by two pathologists (RES, CR), one with expertise in breast pathology, and without knowledge of the original histologic diagnosis or patient outcome. The papillary lesions were designated as benign, atypical, or malignant. Atypical lesions included those with any cytologic or architectural atypia (see Fig. 2a, b). Cases diagnosed as BSIP with concordant imaging but an adjacent associated high-risk lesion or concurrent malignancy in the same quadrant of the breast were excluded to maintain a “pure” cohort of BSIPs. The remaining BSIPs were either followed clinically or excised. All immediate (<6 months from the date of CNBx) and delayed (>6 months) excisional specimens were reviewed and diagnosed as benign, atypical, or malignant. Any discrepant case between the initial diagnosis and second histopathologic review was reviewed by a third “tiebreaker” breast pathologist (DWV), also without knowledge of the initial or second review diagnosis. Details regarding clinical presentation, core biopsy technique, radiologic histopathologic concordance, and follow-up imaging were recorded.

RESULTS

A text search including variations of the word “papillary” in the diagnosis field of CNBx of the breast yielded

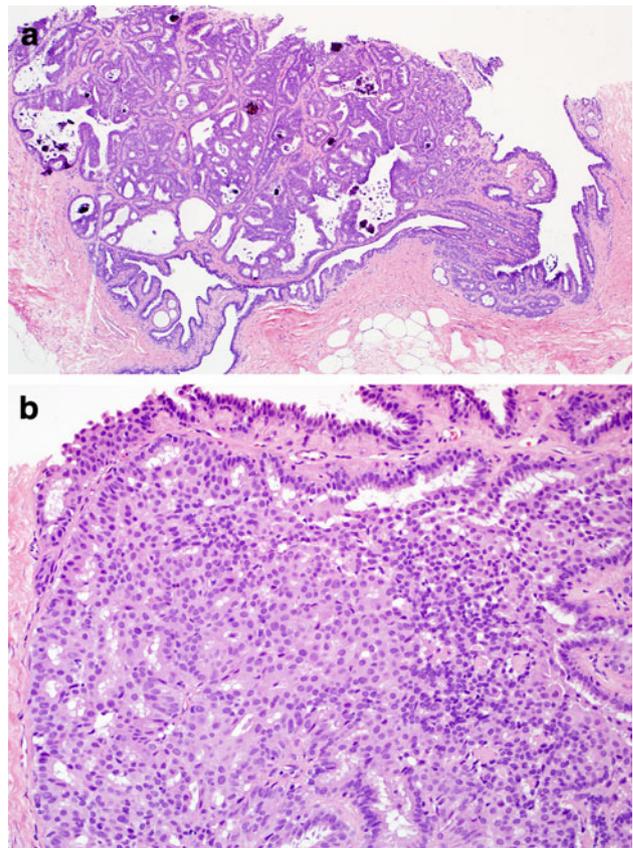


FIG. 2 a Papilloma with architectural atypia. Atypical papilloma with complex architecture demonstrated by rigid secondary lumens. Although architecture is cribriform, extent and cytologic atypia are insufficient to meet criteria for DCIS (hematoxylin and eosin, $\times 40$). **b** Papilloma with cytologic atypia. Atypical papilloma with abnormal cytology consisting of variable nuclear enlargement occupying several regions within the papillary lesion and without architectural complexity (hematoxylin and eosin, $\times 200$)

887 potential papillary lesions. Histopathologic and radiologic evaluation of this cohort led to a total of 299 solitary papillary lesions diagnosed on CNBx that were concordant with imaging (Fig. 3). Of these, 240 (80 %) were classified as benign, 49 (16 %) atypical, and 10 (3 %) malignant. Of the BSIPs, 16 cases (7 %) were excluded because of an associated high-risk lesion [atypical lobular hyperplasia (4), atypical ductal hyperplasia (3), complex sclerosing lesion (1), flat epithelial atypia (1), apocrine atypia (1)] adjacent to but not involving the papilloma or concurrent malignancy [invasive carcinoma (6)] in the same quadrant of the breast. The remaining 224 BSIPs comprised the study cohort.

All 224 BSIPs were from women with near equal distribution in the right (49 %) and left (51 %) breast (Table 1). The average patient age was 57 years (range, 30–78 years). Patients presented after a screening mammogram or ultrasound (US) in 109 cases (49 %), nipple discharge in 61 cases (27 %), and palpable mass in 36

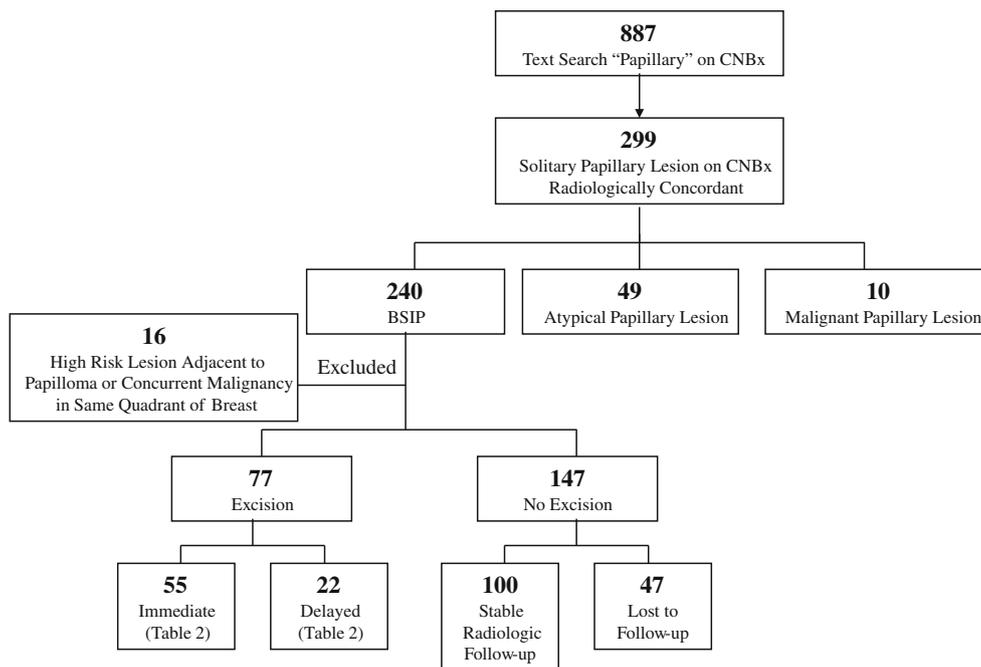


FIG. 3 Case flow of papillary lesions

cases (16 %). The mean size of the papillary lesion on imaging was 0.9 cm (range, 0.3–4.0 cm). CNBx was obtained with US guidance in the majority of cases (88 %). Only 4 cases (2 %) were biopsied with MRI guidance because of an enhancing lesion. Irrespective of the imaging technique, a 14-gauge needle was used in 97 cases (43 %), a 9-gauge needle in 61 cases (27 %), and an 11-gauge needle in 34 cases (16 %).

There were 55 of 224 women (25 %) who opted for immediate excision (Table 2). Surgical excision resulted in 48 benign papillomas (87 %) and four specimens with no residual papilloma (7 %). Also, three women (5 %) underwent mastectomy for an ipsilateral invasive carcinoma in a different quadrant of the breast, and no discernible gross findings were noted at the initial papilloma CNBx site. The mean time to immediate excision was 1.0 month (range, 1 day–5.9 months).

A total of 22 women (10 %) underwent an ipsilateral excisional biopsy at a mean of 19.5 months (range, 6.0–74.4 months). Of these 22 surgical excisions, eight (36 %) were in a different quadrant than the prior CNBx showing BSIP and were excluded. All 14 of the remaining surgical excisions (100 %) revealed a benign papilloma. Reasons for delayed excision included persistent nipple discharge (5), increase in size radiographically (5), new calcifications (2), suspicious radiographic findings (1), and surgery for contralateral DCIS with concomitant excision of the papilloma CNBx site at the time of operation (1).

Of the remaining 147 women diagnosed with a benign papilloma on CNBx, 47 (32 %) were lost to follow-up,

while 100 (68 %) had available follow-up information. All 100 patients were found to be stable clinically and radiologically at last follow-up (4.8–93.8 months, mean 36.0 months).

Of the 59 cases classified as atypical or malignant, 14 (24 %) were originally diagnosed as benign papilloma and reclassified as atypical (13) or malignant (1) upon histopathologic second review. Seven cases reclassified as atypical were not excised. All 7 were stable clinically and radiologically at last follow-up (36.3–86.4 months, mean 54.9 months). The remaining reclassified cases were surgically excised. Of the six reclassified atypical cases, one showed no residual papilloma, one was benign, two were atypical, and two were malignant (DCIS involving a papilloma). Of the one reclassified malignant papillary lesion, an encapsulated papillary carcinoma was found at surgical excision.

DISCUSSION

Management strategies for benign papillary lesions of the breast continue to be controversial and highly variable. It is universally accepted that intraductal papillomas with atypia or carcinoma should be excised. However, some clinicians advocate for immediate surgical excision of BSIPs, while others find close clinical and radiologic observation to be adequate, including several recent studies.^{3,4,6,7,10,11,13–24} Some of the differences in these perspectives lie in the design of the studies purported to support each view, as well as in the definition of an

TABLE 1 Clinical and radiologic characteristics of BSIP cohort

Demographics and size	
Mean age, years (range)	57.0 (30–78)
Laterality	
Right	110
Left	114
Mean lesion size, cm (range)	0.9 (0.3–4.0)
Clinical presentation	
Nipple discharge	61
Palpable mass	36
Screening mammogram/ultrasound	109
Special imaging (PET/MRI/MBI)	17
Unknown	1
Biopsy method	
Ultrasound	196
Stereotactic	24
Magnetic resonance imaging	4
Needle size	
9 gauge	61
11 gauge	34
12 gauge	4
14 gauge	97
16 gauge	16
18 gauge	8
20 gauge	1
Unknown	3
Total	224

PET positive emission tomography, *MRI* magnetic resonance imaging, *MBI* molecular breast imaging

“upgrade.” Other disparities in the data appear to be genuine differences. We carefully selected our cohort to include only cases that were radiologically concordant with a BSIP and in the absence of an adjacent high-risk lesion or concurrent malignancy in the same quadrant of the breast. As our cohort did not include patients with multiple or peripheral papillomas, our findings are not generalizable to patients with these conditions.

Of 299 papillary lesions diagnosed on CNBx in our cohort, 240 (80 %) were classified as benign, 49 (16 %) atypical, and 10 (3 %) malignant. These findings are similar to those reported in the most recent and largest studies,

which further supports the representative nature of our cohort.^{3,14,21,25} In our cohort, the likelihood of finding undetected atypia or malignancy after surgical excision of a benign papilloma diagnosed on CNBx was extremely low. None of the 77 BSIPs diagnosed on CNBx, without associated high-risk lesion or concurrent malignancy in the same quadrant of the breast, were upgraded to atypia or malignancy on surgical excision. Furthermore, none of the 100 patients observed with follow-up were upstaged, with the caveat that our mean follow-up time for this group was relatively short (4.8–93.8 months, mean 36.0 months). Given our experience, it may be appropriate to recommend careful follow-up in the proper clinical, pathologic, and radiologic setting.

Our data corresponds with and supports many reports in the literature. Bennett et al. report only one atypical upgrade from 44 BSIPs on CNBx, with no malignant upgrades. Others report similar findings of no upgrades to malignancy.^{8,9} Ahmadiyah et al. report 1 upgrade to malignancy of 86 BSIPs on CNBx, with 29 of those being excised and 42 followed without incident¹⁸. Chang et al. recently reported two atypical upgrades from 34 BSIPs on CNBx with no malignant upgrades.¹³ However, there are many reports with significantly higher malignant upgrade rates. Rizzo et al. published an atypical upgrade rate of 17.9 % and 8.1 % malignant upgrade rate from a total of 171 BSIPs.²¹ Other publications report similarly high upgrade rates, although the nature of the “upgrade” is not always clear.^{6,14,15}

One major reason for variability in reported upgrade rates is the inclusion of patients who are being managed for a more concerning lesion in which the finding of an intraductal papilloma is incidental. Several studies fail to take into account the importance of concordance of radiologic and histologic findings when calculating upgrade rates of a benign papillary lesion to one involving atypia or malignancy, as is pointed out by Georgian-Smith and Lawton.⁴ Specifically, patients who have a radiologically worrisome lesion adjacent to a BSIP should not be included as an “upgrade.” Likewise, patients who have clinical findings (e.g., palpable mass, nipple discharge, etc.) are not “upgrades.” These patients would be evaluated for and undergo excision in the normal course of

TABLE 2 Immediate and delayed excision diagnosis of BSIP on CNBx

	Benign	Atypical	Malignant	No residual	Different site	Total
Immediate excision (<6 months)	48	0	0	4	3 ^a	55
Delayed excision (>6 months)	14	0	0	0	8 ^b	22

^a Patients were diagnosed with cancer in a different quadrant from the papilloma CNBx site, and the papilloma CNBx site was not grossly visible at mastectomy

^b Excision performed at site other than previous papilloma CNBx site

treatment. For example, Liberman and colleagues report a malignant upgrade rate of 14 % (5 of 35 cases).⁶ However, of these five cancers (four DCIS, one invasive carcinoma), three of them were found on follow-up due to interval growth and one presented at follow-up with new, bloody nipple discharge at a median of 22 months. The fourth patient presented with a 1.8 cm palpable malignant mass at the biopsy site at follow-up, after a stereotactic biopsy of a 0.6 cm mass. The fifth and final patient elected surgical excision, and histology showed DCIS 1.0 cm from the previous biopsy site and no residual papilloma was found. This inaccurate use of incorporation of clinical and radiologic data is also present in other studies.^{7,26} Mercado et al. states that in 9 of 42 patients (21 %) the diagnosis was upgraded to either ADH or DCIS.⁷ However, in four cases, the BIRADS category was 5, indicating discordance of a benign papillary diagnosis with highly suspicious imaging findings, thereby necessitating surgical excision. This discrepancy is important. It is clear that any patient with new clinical findings such as a palpable mass or nipple discharge, or alternatively with new, worrisome mammographic findings, should be evaluated for surgical excision. Therefore, these patients should be excluded from calculations of malignant or atypical “upgrades” on excision.

Proper tissue sampling is known to be an issue in papillary lesions. Kim et al. found that of 271 papillary lesions, 195 (80.0 %) were benign, 21 (7.7 %) were atypical, and 55 (20.3 %) were malignant.²⁷ There were no false negatives or underestimated atypical papillomas in the US-guided vacuum-assisted group; however, in the 14-gauge CNBx group, their false-negative rate was 7.5 % (12 of 157 benign papillomas), and their atypical papilloma underestimation rate was 33 % (5 of 15 atypical papillomas). The histological upgrade rates for papillary breast lesions were 0 % for vacuum-assisted group and 10.2 % for the 14-gauge CNBx group. Undersampling does not appear to be an issue in our study cohort since a wide range of needle gauge sizes were used at CNBx and no cases were upstaged to atypia or malignancy.

As previously mentioned, all papillary lesions in this cohort were reviewed and classified without prior knowledge of original histologic diagnosis. There were 14 cases (24 %) originally classified as benign intraductal papilloma that were reclassified as atypical or malignant. In general, most pathologists would agree that papillary lesions are diagnostically challenging. Benign papillomas are intraductal lesions that have an arborescent architecture with a well-developed fibrovascular core. They may have a complex glandular architecture, but are always composed of two cell types, an inner ductal epithelial cell layer, and a second outer myoepithelial cell layer. The distinction between these two subtypes in practice can be subtle, leading to misinterpretation. Benign papillomas can also

show marked fibrosis leading to distortion of the tumor and entrapping epithelial elements in the duct wall so as to simulate invasion, leading to diagnostic error. The histologic changes characteristic for atypia in a papilloma can also be quite subtle. Any atypia within a papilloma diagnosed on CNBx should warrant surgical excision. These histologic features are usually characterized by cytologic or architectural atypia, but these are subtle findings that cause much angst among pathologists. As seen in our series, 13 of the 49 atypical papillomas and 1 of the 10 malignant papillomas were initially classified as benign, but on second histopathologic review demonstrated areas of atypia or malignancy. Of these reclassified cases, 7 had no further excisions and were stable clinically and radiologically at follow-up. The remaining 7 reclassified cases went to surgical excision. If a formal pathologic review was not undertaken in this study, five cases would have been considered an upgrade at surgical excision, with three being malignant.

Our results contrast with the recent claim of Lopez et al. that pathologists are overly cautious of papillomas on CNBx, as they report 7 of 8 cases originally called atypical were later diagnosed as benign on excision.²² In our cohort, of the six reclassified atypical papillary lesions on CNBx that eventually went to surgical excision, one showed no residual papilloma and one was benign, while two were atypical and two malignant at surgical excision. At least some of the variability found in the literature and, indeed, the variability among pathologists at our institution, underscores the diagnostic challenge that papillary lesions represent. Jakate et al. recently stated that reasons for this difficulty include limited and fragmented samples, prominent epithelial hyperplasia that form complex architecture, and sclerosis that entraps glands simulating invasive carcinoma.²⁸ This study also stresses the importance of second histologic review of pathological materials for these type of studies.

In conclusion, we attribute the lack of upstaging to atypia or malignancy on excisional biopsy after the diagnosis of a BSIP on CNBx to a carefully selected cohort of patients. Identifying these patients is highly dependent on strong communication between radiology and pathology. In medical centers where a multidisciplinary breast program is used for patient management, these data support the option of clinical follow-up, rather than mandated surgical excision, for patients diagnosed with a benign papilloma on CNBx when imaging findings are concordant and in the absence of associated high-risk lesion or concurrent malignancy in the same quadrant of the breast. In centers without a multidisciplinary approach, observation may not be an acceptable means of patient management. Given the variability in collaboration among providers, management practices should be adjusted by individual

health care systems in accordance with the system in place and the patient population.

ACKNOWLEDGMENT Many thanks to Natalie S. Campbell and Benjamin J. Barrett for their help with data analysis.

DISCLOSURE None.

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