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Papilloma on Core Biopsy: Excision vs. Observation

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ABSTRACT

Background. Intraductal papillomas (IPs) are commonly seen breast lesions with variable clinical presentation. For a palpable lesion and/or evidence of cellular atypia and/or pathologic nipple discharge, excision is warranted to rule out adjacent carcinoma, while for asymptomatic IPs lacking atypia current data for excision vs. observation are controversial. We reviewed outcomes of IPs diagnosed at our institution.

Methods. With IRB approval, we reviewed consecutive patients with IPs seen on core biopsy (CBx) between 2005 and 2013. All patients had an excision, with subspecialty breast pathology review of CBx and excisions. The rate of upgrade to cancer on excision was recorded. Differences between atypia and no-atypia groups were determined by two-tailed *t* test and Fisher's exact test.

Results. We identified 97 patients (age range 31–83 years) with IPs on CBx. Among 52 atypical IPs, DCIS was seen in 11 (upgrade 21 %). In 45 IPs without atypia, 3 cancers were seen (upgrade 6. %): 2 had palpable lesions and were found to have DCIS, and 1 invasive cancer was found in a non-palpable mammographically detected BIRADS 4C lesion, whose Cbx result was discordant. If the 2 palpable lesions are excluded, the upgrade rate for IPs without atypia is 2.2 %.

Conclusions. This series shows a low upgrade rate for IP without atypia seen on CBx in the absence of a palpable mass and radiographic/pathologic discordance, suggesting that a surgical biopsy may not be necessary. Further prospective studies to better estimate the upgrade rate for IPs without atypia may be helpful.

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Intraductal papilloma (IP) is a commonly identified breast lesion with variable clinical presentations, such as pathologic nipple discharge, a palpable mass, or as an asymptomatic lesion seen only on breast imaging. Carcinoma is the underlying etiology for 2–15 % of cases of pathologic nipple discharge (defined as spontaneous, persistent, bloody or clear nipple discharge, emanating from a single duct), regardless of the presence of suspicious clinical and/or breast imaging findings. Therefore, the presence of pathologic nipple discharge has been perceived as an independent indication for a surgical excision.[1] Excision of a palpable papilloma often is performed, as a benign diagnosis obtained via a palpation- or an image-guided core needle biopsy may be felt insufficient to rule out carcinoma.[2]

Historically, the rate of upgrade from IP without atypia to ductal carcinoma in situ (DCIS) or invasive carcinoma for an asymptomatic lesion has been reported to range between 2 and 12 %.[3–6] With this range in upgrade the role of excision of this lesion identified by core biopsy remains controversial.

Our institution has previously reported on a retrospective series of 29 excisions of IPs without atypia where the upgrade rate was found to be 3 % and have suggested that when there is radiologic/pathologic concordance, an excisional biopsy of IP is not necessary.[3] The purpose of the current study is to document the upgrade rate in a larger cohort of IPs with and without atypia, accrued subsequent to the prior publication, and to evaluate the impact of the BI-RADS category and of the presence of radiologic-pathologic concordance on the likelihood of finding carcinoma on excision.[3]

METHODS

With institutional review board approval, we conducted a retrospective review of consecutive patients diagnosed with IPs on core biopsy at Brigham and Women's Hospital

between 2005 and 2013. Patients who presented with pathologic nipple discharge as well as those who also had atypical ductal hyperplasia (ADH) on core biopsy were excluded. All core biopsies were performed under stereotactic, ultrasound, or MRI guidance by dedicated breast imagers. Percutaneous core biopsies were performed using 8-, 9-, 11-, 12-, 14-, or 15-gauge biopsy devices. All the excisional biopsies reported in this study were performed by a breast surgical oncologist at our institution. Dedicated breast pathologists reviewed all the core and excision specimens. Although there is no official institutional policy in place regarding the management of IPs found on core biopsy, most commonly all IPs with atypia or with radiologic/pathologic discordance are excised and IPs without atypia, which are concordant are excised at the discretion of the surgeon.

Atypia with IP was defined by the presence of focal monotonous cells or cytological and architectural features of low-grade ductal neoplasia in IP, according to the WHO criteria. Baseline characteristics analyzed included patient age, indication for core biopsy, BI-RADS category, radiologic-pathologic concordance, the imaging modality to perform the core biopsy, the gauge of the core biopsy needle, the number of core samples and additional pathologic findings, such as flat epithelial atypia, atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), and complex sclerosing lesion (CSL).

Baseline characteristics of the two cohorts found to have IPs with and without atypia on core biopsy were compared using two-tailed Fisher's exact test for categorical variables and two-tailed t test for continuous variables, with $p < 0.05$ considered statistically significant.

RESULTS

Between 2005 and 2013, more than 9,000 patients underwent breast core needle biopsy at Brigham and Women's Hospital. We identified 180 patients with the diagnosis of IP on core biopsy. We excluded from this analysis 37 patients who had ADH in the same core needle biopsy, 12 patients with pathologic nipple discharge, 6 patients with concomitant DCIS in the same core biopsy, and 28 patients treated on the outside after the initial core biopsy. The remaining 97 patients, diagnosed with IP by core biopsy (mean age 52 years, range 31–83 years), who subsequently underwent an excision at our institution, were analyzed. In this cohort, the initial core biopsy indications were the presence of a palpable mass ($n = 16$, 16 %), mammographic mass lesion ($n = 51$, 53 %), distortion ($n = 1$, 1 %), calcifications ($n = 18$, 19 %), and MRI-detected mass or non-mass-like enhancement ($n = 11$, 11 %). The initial core biopsy details are described in Table 1.

TABLE 1 Core needle biopsy details, $n = 97$ total patients

	Number of patients	%
Core biopsy indications		
Palpable mass	16	16
Mammographic calcifications	18	19
Nonpalpable, mammographic mass and/or distortion	50	52
Nonpalpable mammographic mass and calcifications	2	2
MRI-detected enhancement	11	11
Core biopsy type		
Ultrasound-guided core biopsy	69	71
Stereotactic core biopsy	20	21
MRI-guided core biopsy	8	8
Core needle gauge		
8	4	4
9	12	12
11	20	21
12	2	2
14	58	60
15	1	1

TABLE 2 Baseline characteristics of patients with IP with and without atypia on core biopsy

Atypia	Yes	No	p value
Clinical and radiographic characteristics			
Patients, N	52	45	NA
Mean age	56	51	0.02
Lack of palpable mass (%)	46 (88 %)	35 (78 %)	NS
BI-RADS 4	51 (98 %)	43 (96 %)	NS
Radiographic-pathologic concordance	40 (77 %)	21 (47 %)	0.02
Mean number of cores	5.2	5.2	NS
Mean core biopsy gauge	12.5	12.5	NS
Core biopsy modality used			
Ultrasound	34 (65 %)	35 (78 %)	NS
Stereotactic	14 (27 %)	6 (13 %)	
MRI	4 (8 %)	4 (9 %)	

In 52 (54 %) patients, the diagnosis of IP on core biopsy was associated with atypia, in the remaining 45 (46 %) no atypia was documented. The baseline characteristics of the two cohorts are shown in Table 2. Our patients with and without atypia did not differ on most measures; however, patients diagnosed with atypia were older than patients

TABLE 3 An overview of more recent published literature pertaining to upgrade rates for IP with and without atypia

Author, year	Excisions, *n*	Nipple discharge included	Concordance	IP with atypia upgrade (%)	IP without atypia upgrade (%)
Mercado,[9] 2006	36	No	Reported	NA	2/36 (5 %)
Sakr,[6] 2008	63	Yes	Not reported	2/3 (33 %)	4/48 (8 %)
Ahmadiyeh,[3] 2009	69	Yes	Not reported	9/40 (22.5 %)	1/29 (3 %)
Rizzo,[10] 2012	276	Yes	Not reported	16/42 (38 %)[a]	21/171 (12 %)
Nayak,[2] 2013	30	Yes	Not reported	NA	3/30 (10 %)
Nakhlis et al.	97	No	Reported	11/52 (21 %)	3/45 (6.7 %)[b]

[a] In this study, IP lesions with atypical ductal hyperplasia (ADH) and/or atypical lobular hyperplasia (ALH) were contrasted to IP lesions without atypia and the 38 % upgrade rate pertains to IP with ADH and/or ALH on core biopsy

[b] If discordant and palpable upgraded lesions are removed from the analysis, the upgrade rate is 0 %

without atypia (56 vs. 51 years, $p < 0.05$) and there was more radiographic-pathologic discordance in those whose cores were initially classified as lacking atypia (47 vs. 23 %, $p < 0.05$). For the 52 patients with atypical IPs on core biopsy, 11 DCIS lesions were found in association with the core biopsy site on subsequent excision, an upgrade rate of 21 %.

Among the 45 IPs without atypia on core biopsy, 3 cancers were found on excision (an upgrade rate of 6.7 %). Of these, one was an invasive carcinoma (grade 2, 1.9-cm invasive ductal carcinoma, BI-RADS 4C) and the other two were DCIS (both of these lesions were palpable). For all three upgraded cases, the core biopsy result was reported as being discordant by the radiologist and pathologist. Patients with papillomas without atypia on core needle biopsy underwent excision at the discretion of the surgeon. In the prior study from this institution, 34 % of patients in this group underwent surgery.[3] If the imaging and/or clinical findings are discordant with a papilloma, excision is recommended. In the current study, 47 % (21 patients) were considered to be in the discordant group and three of these patients (14 %) were found to have cancer. All of the upgrades to carcinoma were found only in excisions of IPs without atypia with discordant radiographic/pathologic results; therefore, no concordant lesions excised were upgraded to carcinoma.

In the cohort of 45 IPs without atypia on core biopsy, excisional biopsies yielded 2 IPs associated with ADH, 2 IPs associated with ADH, and ALH and 2 IPs associated with LCIS; all of these lesions were concordant.

Cancers Found in Patients with Papillomas Without Atypia

The first patient presented with a 3.6-cm palpable irregular mass. The core-needle biopsy showed fragments of a sclerosing lesion, including papillary areas and a radial sclerosing lesion. The lesion was considered sufficiently suspicious on clinical examination and imaging to warrant excision. On excision, the mass was confirmed to be a benign sclerosing lesion with a 0.4-cm incidental grade III, estrogen receptor (ER)-negative DCIS in the adjacent breast tissue.

The second patient presented with a 2.2-cm palpable lobulated mass. The core needle biopsy showed an IP, but because this was a new finding in a postmenopausal woman, it was felt to be discordant, and an excision was recommended. On excision the palpable mass was confirmed to be a papilloma, associated with a 0.8-cm area of grade I, ER-positive DCIS, confined to the papilloma.

The third patient also was a postmenopausal woman who presented with multiple new palpable circumscribed masses, the largest of which was 1.5 cm. The core-needle biopsy showed an IP with florid epithelial hyperplasia, but this diagnosis was felt to be discordant, and an excision was recommended. The pathology report from the excisional biopsy of the larger lesion demonstrated a grade 2, 1.9-cm invasive ductal carcinoma, ER-positive, progesterone receptor-positive, HER2-negative. On definitive surgery, this patient had multiple foci of moderately differentiated invasive carcinoma associated with encapsulated papillary carcinoma and extensive papillary DCIS. One sentinel lymph node was free of carcinoma. Although the original core needle biopsy sampled the lesion, the features were insufficient to recognize the lesion as fragments of a papillary carcinoma.

Cancers Found in Patients with Papillomas with Atypia

Excision is recommended for all patients who are diagnosed with a papillary lesion with atypia on core needle biopsy. Eleven of 52 patients (21 %) in this group were found to have cancer. In all cases, the cancer was ER-positive DCIS and all but one had low to intermediate nuclear grade. For eight patients, the imaging finding was a mass.

Six of these patients had benign papillomas that were focally involved by DCIS. For two patients, the mass was

an in situ papillary carcinoma. The diagnosis of carcinoma had been suspected on the core needle biopsy in both cases.

Three patients presented with mammographic calcifications. In one patient, the calcifications were associated with DCIS. In another they were associated with the papilloma, and in the third case the papilloma and the DCIS may have been incidental findings as both lacked calcifications.

DISCUSSION

While the natural history of papillary lesions with and without atypia is not well understood, Lewis and colleagues have reported a slight increase in long-term breast cancer risk.[7,8] The likelihood of detecting carcinoma on excision of papillary lesions without atypia diagnosed by an image-guided biopsy has ranged from 3 to 12 % when discordant cases are included (Table 3). In an earlier report by Mercado and colleagues, two DCIS lesions found on excision of 36 IP without atypia: 1 of these patients had a BIRADS 5 lesion, which prompted the initial core biopsy, and in the second upgraded case the core biopsy pathology was felt to be discordant.[9] This is consistent with our findings: in 45 patients with a core biopsy diagnosis of IP without atypia three cancers were seen (upgrade 6.7 %), 2 of which were palpable, and the third one was discordant. If the two palpable lesions are excluded, the upgrade rate for IPs without atypia is 2.2 %. Because all three upgraded lesions were discordant and thus would have been excised, in our limited series of IPs without atypia no concordant lesions would have been upgraded. In a more recent study by Rizzo and colleagues, which reviewed the results of excisional biopsies for 171 IP without atypia and demonstrated a 12 % upgrade rate, some of the patients had pathologic nipple discharge (although their number is not specified), and radiographic-pathologic concordance is not discussed, making it difficult to determine how any of the upgraded cases could have been attributable to discordance.[10]

The limitation of this study is its retrospective nature with a moderate sample size, approximately 2 % of our core biopsies. Its strength is a subspecialty breast pathology, surgery, and imaging review of all the cases in this series as well as a detailed documentation of other factors that may contribute to upgrade to cancer on excision other than the presence of IP on core biopsy, including BI-RADS classification, radiographic-pathologic correlation, or the presence of a palpable lesion. An additional strength of the study is that patients with ADH, which may contribute to an upgrade to cancer by itself, have not been included in the analysis.

Another interesting observation of our study is that in our cohort more diagnoses of IPs without atypia were reported to be discordant than those with atypia (47 vs. 23 %, $p < 0.05$). Therefore, with nearly a half of the core biopsies showing IP without atypia being discordant, one may anticipate a substantially higher upgrade rate in this group than what was observed.

In summary, our study demonstrated that for IP without atypia seen on core biopsy of BI-RADS 4 lesions exhibiting radiologic-pathologic concordance the upgrade rate to carcinoma on subsequent excision was 0 %, suggesting that a carefully selected group of patients with IP can be safely monitored and not need excision. These include patients with asymptomatic, nonpalpable lesions whose core biopsies reveal IP with no atypia, and for which there is clear radiographic-pathologic concordance. Prospective studies are being planned to better estimate the upgrade rate for IPs without atypia and will allow for more accurate counseling and risk assessment.

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