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RESEARCH

Non-Malignant Breast Papillary Lesions - B3 Diagnosed on Ultrasound - Guided 14-Gauge Needle Core Biopsy: Analysis of 114 Cases from a Single Institution and Review of the Literature

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Abstract One-hundred-fourteen consecutive cases of breast ultrasound-guided 14-gauge needle core biopsy (14G NCB) performed from January 2001 to June 2013 and diagnosed as non-malignant papillary lesion (PL)-B3, were reviewed and compared with definitive histological diagnosis on surgical excision (SE) to evaluate the diagnostic accuracy of ultrasound-guided 14G NCB. PL with epithelial atypia on 14G NCB were associated to malignancy on definitive histological diagnosis on SE in 22 (7 DCIS and 15 invasive carcinomas) of 46 cases with an underestimation rate of 47.8 %, while 9 (4 DCIS and 5 invasive carcinomas) cases out of 68 cases of PL without epithelial atypia were upgraded to carcinoma with an underestimation rate of 13.2 %. In cases of PL with epithelial atypia on ultrasound-guided 14G NCB, SE appears mandatory due to the high risk of associated malignancy. The diagnosis of PL without epithelial atypia on ultrasound-guided 14G NCB does not exclude malignancy at subsequent SE, consequently further assessment (by surgical or vacuum-assisted excision) is recommended to avoid the risk of delaying a diagnosis of malignancy, although this tends to be lower (1 in 8 patients).

Keywords Papillary lesions · 14-gauge needle core biopsy · Epithelial atypia · Excision · Associated carcinoma

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Introduction

Papillary lesions (PL) of the breast are characterized by the presence of fingerlike fibrovascular stromal cores lined by epithelium. According to WHO classification (2012) [1] PL encompass a heterogeneous group of epithelial lesions including intraductal papilloma, intraductal papilloma with atypical ductal hyperplasia, intraductal papilloma with ductal carcinoma in situ, papillary ductal carcinoma in situ, encapsulated papillary carcinoma, solid papillary carcinoma and invasive papillary carcinoma.

PL may have a significant microscopic intralesional heterogeneity showing the presence of simultaneous benign and morphologically malignant areas. It is well recognized that benign PL may arbor foci of atypical ductal hyperplasia or ductal carcinoma in situ (DCIS) in only a small part of the papilloma, although this appears to be more common in patients with multiple peripheral papillomas than in those with solitary central papilloma [2]; thus the limited sampling achieved with core biopsy (CB) may miss areas of cancer elsewhere within the lesion or in the immediately adjacent breast tissue due to the frequent concurrent presence of

atypical ductal hyperplasia or DCIS in the surrounding breast parenchyma.

Even if some malignant PL may be reliably diagnosed on CB, the majority of PL, due to difficulties in excluding or confirming a diagnosis of malignancy on a small tissue sample and depending on the extent and degree of atypical epithelial proliferation, are classified as "B3/uncertain malignant potential" according to UK [3] and European guidelines [4] with a recommendation for diagnostic excision to permit examination of the lesion and surrounding breast tissue.

There is a general consensus that surgical excision (SE) should be performed when a non-malignant PL with epithelial atypia is diagnosed in a CB due to the high risk of associated malignancy. On the contrary, the need for SE in patients in whom a PL without epithelial atypia is found on CB remains a controversial issue although it is well known that imaging findings cannot reliably distinguish between benign and potentially malignant papillary lesions [5].

The aim of our study was to evaluate the surgical outcome of a consecutive series of PL B3, with a particular attention to PL without epithelial atypia, diagnosed on ultrasound-guided 14-gauge needle core biopsy (14G NCB) in a 12.5-year period at a single institution.

Materials and Methods

The institutional review board (IRB) approval was obtained for this retrospective study, which was performed in a large university referral hospital for breast disease. Written informed consent of patients was not required by the IRB.

Histological records of core biopsies diagnosed from January 2001 to June 2013 as PL B3 were retrieved from the archival files of Pathological Anatomy Unit of Careggi University Hospital. One-hundred twenty-nine cases diagnosed as PL B3 were identified; all core biopsies, except for 3 cases performed under vacuum assisted devices, were performed under ultrasound guidance with a 14-gauge needle (14G NCB).

Inclusion criteria

The inclusion criteria for the study were: histological diagnosis of PL B3 on 14G NCB; histological report of performed SE (our standard routine is to recommend SE whenever a diagnosis of PL B3 on CB is performed); absence of synchronous associated DCIS or invasive carcinoma in the same breast.

One-hundred-fourteen cases of PL B3 in 114 women (age range: 35–85 years; mean age: 55.7 years) were included in the present study. The remaining 15 cases were excluded: 3 performed with a vacuum-assisted device, 8 associated with synchronous breast cancer in the same breast and 4 with no histological diagnosis on SE available.

Ultrasound Protocol

All 114 patients underwent whole breast sonography performed using a broadband 10–13 MHz linear transducer (Technos, Mylab 70 XS Esaote, Genoa, Italy). Percutaneous CB were performed under ultrasound guidance with a semiautomated biopsy gun (Precisa, Hospital Service, Rome, Italy) with a 14-gauge, 15 cm long needle; a mean of 3.5 core samples (range 1–6) were obtained per lesion.

Histological Findings on 14G NCB

All histological slides of PL B3 were reviewed by two pathologists (SB and VS) and the following histopathological features were evaluated: extent of PL in CB (≤25 %; between 25 and 50 %; >50 %); extent of epithelial hyperplasia of usual type (HUT) in PL (absent; focal in less than 25 % of lesion; focal between 25 and 50 % of lesion; diffuse if more than 50 % of lesion); extent of epithelial atypia in PL (absent; focal in less than 25 % of lesion; focal between 25 and 50 % of lesion; diffuse in more than 50 % of lesion). According to absence (Fig. 1) or presence of HUT (Fig. 2) and epithelial atypia (Fig. 3a and b) in CB, the following histopathological score has been created: 1) HUT absent/epithelial atypia absent; 2) HUT present/epithelial atypia absent; 3) epithelial atypia present.

Histological Findings on Surgical Excision

Definitive histological diagnosis after SE for each case was reviewed and classified according to the highest grade lesion in one of the following categories: malignant lesion (DCIS or invasive carcinoma); high risk lesion (atypical ductal hyperplasia, lobular intraepithelial neoplasia); benign lesion

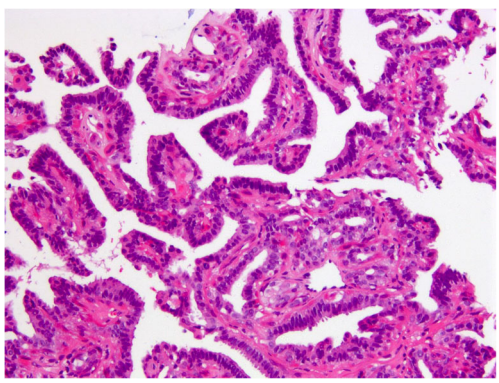

Fig. 1 Papillary lesion without epithelial hyperplasia of usual type and epithelial atypia. Papillary fronds show fibrovascular cores lined by a layer of epithelium composed of cuboidal to columnar epithelial cells and myoepithelial cells

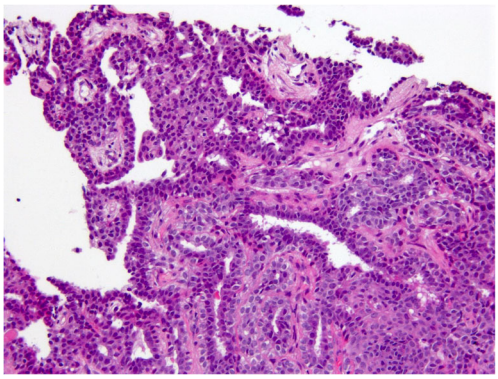

Fig. 2 Papillary lesion with epithelial hyperplasia of usual type and without epithelial atypia. Hyperplasia of usual type produces an increased thickness of the epithelial layer and bridging of epithelium across spaces between fronds, resulting in formation of microlumens

(intraductal papilloma, other benign breast lesions). The percentage of malignancy according to histopathological score was calculated. Definitive histological diagnosis after SE served as the "gold standard".

The following clinical-ultrasound features were evaluated: presence or absence of nipple discharge; presence or absence of microcalcification; presence or absence of hypoechoic nodule.

Statistical Analysis

Among all cases of PL B3 distributions were calculated, according to malignancy as detected after SE, for the following histopathological and clinical-ultrasound variables: extent of PL in CB (≤25 %; 25–50 %; >50 %); number of cores (≤2, 3, >3, range 1–6); histopathological score (1, 2, 3); presence of nipple discharge (yes/no); presence of microcalcification (yes/no); presence of hypoechoic nodule (yes/no). P values from Fisher exact test were calculated. A logistic regression model including all histopathological and clinical-ultrasound variables and age (quintiles) was used to compute odd ratios (ORs) and 95 % confidence intervals (95 % CIs) as estimate of malignant breast cancer risk.

Results

In Table 1 the distribution of 114 PL is reported according to histopathological score and malignancy on SE. At histological review of the 114 PL, 10 (8.8 %) cases resulted benign papillomas without epithelial hyperplasia of usual type (age range 34–74 years, mean age: 59.4 years), 58 (50.9 %) resulted benign papillomas with epithelial hyperplasia of usual type (age range 24–81 years, mean age: 52.9 years) and 46 (40.4 %) were classified as papillomas with epithelial atypia (age range 26–54 years, mean age: 58.3 years). At SE, overall, out of the 114 PL B3 cases, 31 cases (27.2 %) proved to be associated with malignancy: 12 (38.7 %) DCIS and 19 (61.3 %) invasive carcinomas.

In Table 2 the distribution of 114 PL on 14G NCB according to histopathological, clinical-ultrasound features and malignancy on SE is reported. There were no statistically significant associations between clinical-ultrasound features and subsequent malignancy revealed at SE. Among histopathological features an increased risk of malignancy at SE emerged according to histopathological score (OR 5.82; 95%CI 2.23–15.20; p 0.0003).

Papillary Lesions with Epithelial Atypia

Of the 46 cases of PL with epithelial atypia, 22 (7 DCIS and 15 invasive carcinomas) were associated with malignancy at SE with an upgrade rate of 47.8 %; of the remaining 24 cases, 7 resulted benign lesions and 17 resulted high-risk lesions i.e.,

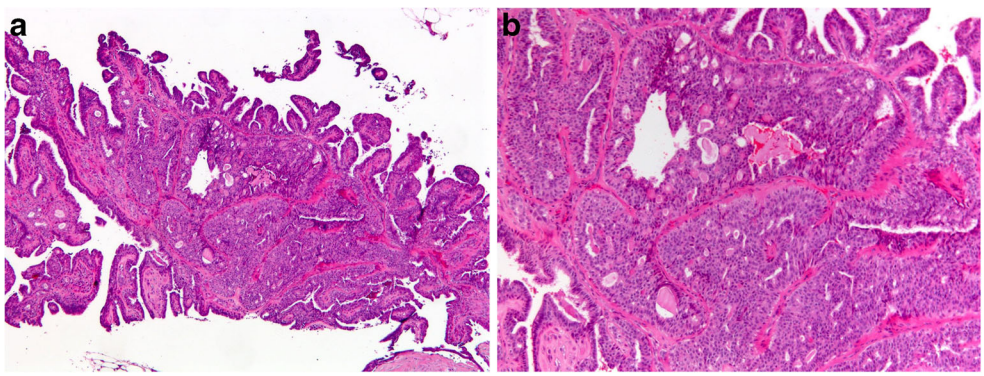

Fig. 3 **a** Papillary lesion with epithelial atypia. At central part of core an area of epithelial atypia is seen. **b** Higher-power view shows atypical epithelial proliferation forming a solid pattern with scattered rigid lumens. The atypical epithelial proliferation is of limited extension and only partially involves basement membrane-bound spaces; irregular, slitlike lumens and lack of cellular monotony - tipical of hyperplasia of usual type - are still evident

Table 1 Distribution of 114 PL on 14G NCB according to histopathological score and benignity/malignancy on SE. Heterogeneity p value 0.0002

Histopathological score on 14G NCB [1]	Benignity on SE	Malignancy on SE		Total
	n	n	%	n (%)
1	9	1	10.0	10 (8.8 %)
2	50	8	13.8	58 (50.9 %)
3	24	22	47.8	46 [2] (40.4 %)
Total	83	31	27.2	114 (100 %)

[1] Histopathological score: 1=HUT absent/epithelial atypia absent; 2=HUT present/epithelial atypia absent; 3=epithelial atypia present

[2] Nine (19.6 %) with focal epithelial atypia in less than 25 % of lesion; 11 (23.9 %) with epithelial atypia in 25–50 % of lesion; 26 (56,5 %) with diffuse epithelial atypia in more than 50 % of lesion

HUT=hyperplasia usual type; *PL*=papillary lesion; *SE*=surgical excision; *14G NCB*=14-gauge needle core biopsy

associated with atypical ductal hyperplasia and/or lobular intraepithelial neoplasia.

Papillary Lesions Without Epithelial Atypia

Of the 10 PL without HUT, one was associated with malignancy (invasive carcinoma) at SE with an upgrade rate of 10 %. Of the other 9 cases, 6 resulted benign lesions and 3 resulted high-risk lesions i.e., associated with atypical ductal hyperplasia and/or lobular intraepithelial neoplasia.

Of the 58 PL with HUT, 8 (5 DCIS and 3 invasive carcinomas) were associated with malignancy at SE with an upgrade rate of 13.8 %. Of the remaining 50 cases, 34 resulted benign lesions and 16 resulted high-risk lesions i.e., associated with atypical ductal hyperplasia and/or lobular intraepithelial neoplasia. Overall in 68 PL cases without atypia, 9 (13,2 %) resulted underestimated.

Table 2 Distribution of 114 PL on 14G NCB according to age, histopathological, clinical-ultrasound features and outcome at SE (malignancy yes/no). For each variable ORs from logistic analyses (95 % CIs and p values) are reported as estimate of malignant breast cancer risk

		Malignancy on SE			Logistic analysis		
		No *n*=83	Yes *n*=31	p value [a]	OR [b]	95%CI	p
Histopathological features							
% of PL on 14G NCB [c]	≤25 %	21	9	0.16	0.71	0.36–1.38	0.31
	25–50 %	34	7				
	≥50 %	28	15				
Number of cores [c]	≤2	5	5	0.13	0.97	0.45–2.10	0.94
	3	44	11				
	>3	34	15				
Histopathological score [c, d]	1	9	1	0.0002	5.82	2.23–15.20	0.0003
	2	50	8				
	3	24	22				
Clinical-ultrasound features							
Nipple dicharge	No	74	25	0.23	1	0.75–11.86	0.12
	Yes	9	6		2.98		
Microcalcification	No	75	28	1.00	1	0.16–4.03	0.79
	Yes	8	3		0.80		
Hypoechoic nodule	No	74	29	0.72	1	0.08–2.79	0.41
	Yes	9	2		0.47		
Age (quintiles) [c]	24–43 y	19	3	0.04	1.53	1.08–2.15	0.02
	44–49 y	19	6				
	50–57 y	16	5				
	58–69 y	19	5				
	70–84 y	10	12				

[a] P values from Fisher exact tests

[b] OR from logistic model simultaneously adjusted for all the variable reported in table and subjects age

[c] Variable included as an ordinal term in the logistic model

[d] Histopathological score: 1=HUT absent/epithelial atypia absent; 2=HUT present/epithelial atypia absent; 3=epithelial atypia present

HUT=hyperplasia usual type; *PL*=papillary lesion; *SE*=surgical excision; *14G NCB*=14 gauge needle core biopsy

Discussion

Although image-guided CB is generally highly accurate in non-operative diagnosis of benign and malignant breast lesions, particular difficulties may be encountered with PL because of their histological heterogeneity and/or association with malignancy within PL or in the immediately adjacent breast tissue. This may result in failure to sample an area of malignancy, resulting in under-diagnosis of the lesion [6].

A number of studies [5, 7–60], some of them with very limited case numbers, have been published concerning the surgical outcome of PL diagnosed on image-guided CB.

Papillary Lesions with Epithelial Atypia

Our study based on homogeneous series of non-malignant PL B3 diagnosed on CB performed under ultrasound guidance with a 14G needle showed that the presence of epithelial atypia on PL was significantly correlated with upgrade to malignancy, thus confirming the almost unanimous consensus of previous studies [5, 7–9, 12–47] as regards the mandatory follow-up SE in PL with epithelial atypia, due to high risk of associated malignancy.

A review of existing studies concerning PL with epithelial atypia diagnosed on CB and subsequent SE results is reported in Table 3. PL with epithelial atypia is an uncommon diagnosis at image-guided CB representing about ¼ of PL reported in literature. The upgrade rates to malignancy at surgery after a diagnosis of PL with epithelial atypia on CB has been reported ranging from 0 to 100 % with a mean value of 34 % (274 out 805) (Table 3) and the general consensus, confirmed also in a recent meta-analysis [61], is to progress to SE to establish in these cases a definitive histological diagnosis.

However, many of the published studies are difficult to interpret as they report a very limited number of cases with follow-up SE (10 cases or less) [5, 7–14, 16–19, 25, 27, 32, 33] or more than 10 cases, but a variety of biopsy techniques and needles of different gauges [15, 20–24, 26, 28–31, 34, 37, 40, 41, 43, 46, 47]. Moreover in some studies [9, 12, 14, 32, 33, 35, 45] guidance method, type of CB and needle gauge were not specified.

To our knowledge, our study is one of the largest single-centre series reporting on SE outcome of PL with epithelial atypia diagnosed on ultrasound-guided 14G NCB. We found at SE an incidence of malignancy of 47.8 % that is higher than the mean value (34 %) of the literature; a possible explanation is that our series is exclusively composed of 14G NCB, while in the majority of published series CBs resulted to be performed in part by 14G NCB and in part by vacuum-assisted needle core biopsy (VANCB) using 11G or larger needle (Table 3), confirming that VANCB is more accurate than NCB in diagnosing PL with epithelial atypia [61].

Seven studies [7, 22, 36, 38, 39, 42, 44] are comparable to our study considering the homogeneity of series reported (US 14G NCB). These studies report a range of underestimation rate between 15 and 47 %, and our value of underestimation rate (47.8 %) results to be very close to superior limit of this range. The largest series [42] using 14G NCB reported the lowest underestimation rate (15 %) not only among comparable studies, but also among all published series (Table 3) using different devices and excluding two studies [28, 40] reporting a low number of cases (16 and 11 cases with underestimation rate of 6 and 9 % respectively).

In our series 68 % (15 out 22) of cases of malignancy found on SE after a diagnosis of PL with epithelial atypia on 14G NCB were invasive carcinomas: six cases of small (5 mm or less) carcinomas of several histological types (2 tubular, 3 cribriform and 1 ductal), five cases of "encapsulated papillary carcinoma"; three cases of papillary carcinoma and one case of mucinous carcinoma. All six cases of small invasive carcinomas and mucinous carcinoma were found in the surrounding breast parenchyma; all small invasive carcinomas were associated to DCIS of low or intermediate nuclear grade present within the PL and in the immediately adjacent breast tissue. Of the remaining seven cases of DCIS (32 % of malignancy found on SE) with low or intermediate nuclear grade, 3 cases were only within the PL, and 4 cases were within and outside PL, in adjacent breast tissue.

From our review a difference, although not significant, in the rate of underestimation of the "before 2007" group of series [5, 8–19] in comparison with the "2007 or later" group of series [24–52] was found among PL with epithelial atypia (40 versus 33 %, p-value from test of proportion 0.14) (Table 3). This finding, in our opinion, could be attributable to a selection bias due to the fact that the majority of series with a small number of cases is concentrated in the years from 1999 to 2006 and the widespread use of VANCB procedure, providing larger volumes of tissue for histopathological examination, decreases the underestimation rates for carcinoma especially in breast lesions associated with epithelial atypia.

Papillary Lesions Without Epithelial Atypia

Our study showed that the absence of epithelial atypia on PL was associated with a lower underestimation rate. However the risk of an upgrading to malignancy still involves 1 out of 8 patients thus maintaining the management of PL without epithelial atypia diagnosed on CB still a matter of debate.

Published series report a significantly higher prevalence of PL without epithelial atypia diagnosed by imaging (sonography, mammography or magnetic resonance imaging) as compared with PL with epithelial atypia (Table 4). From a comprehensive review of the literature, in the last 15 years, among 3032 lesions diagnosed as PL without epithelial atypia on image-guided CB (from 54 series, Table 4), 231 cases of

Table 3 Papillary lesions with epithelial atypia on CB and malignancy on SE: review of the literature

Study	Year	Guidance method, type of core biopsy, needle gauge	Mean N of cores (ranges)	N of papillary lesions	N upgraded to DCIS	N upgraded to invasive carcinoma	N upgraded to malignancy (DCIS or invasive carcinoma)	PPV %
Liberman et al. [8]	1999	US, STX NCB 14G STX VANCB 11, 14G	NCB 5 (1–20) VANCB 14G 13 (1–50) VANCB 11G 14 (5–34)	10	3	0		30
Ioffe et al. [9]	2000	NS	NS	3	1	2		100
Philpotts et al. [10]	2000	STX NCB 14, 11G	7 (5–12)	2	0	0		0
Mercado et al. [11]	2001	STX VANCB 11G	11 (6–18)	6	0	0		0
Rajendiran et al. [12]	2001	NS	NS	10			2	20
Rosen et al. [13]	2002	US, STX NCB 14G STX VANCB 14, 11G	NS	10	3	0		30
Masood et al. [14]	2003	NS	NS	4	1	1		50
Puglisi et al. [5]	2003	US, STX NCB 14G	5 (3–6)	5			3	60
Agoff et al. [15]	2004	STX NCB 14G VANCB 11, 9G	NS	25	10	2		48
Ivan et al. [16]	2004	US NCB 20, 18, 16G STX VANCB 14, 11G	NCB 5 (3–12) VANCB 11 (5–22)	8	5	0		63
Renshaw et al. [17]	2004	US NCB 14G STX VANCB 11G	NS	7			2	29
Carder et al. [18]	2005	US NCB 18G STX NCB 14G	NS	4*	3	1		100
Shah et al. [19]	2006	US, STX NCB 14G	2.7 (1–9)	10	3	0		30
Arora et al. [20]	2007	US NCB 14, 12G STX VANCB 11G MRI VANCB 9G	NS	66	13	7		30
Ashkenazi et al. [21]	2007	US NCB 16, 14G STX VANCB 12, 11, 9G	NS	18			12	67
Ko et al. [22]	2007	US NCB 14G	NS	17			8	47
Sohn et al. [23]	2007	US NCB 14G US VANCB 11G STX VANCB 14G, STX VANCB 11G	NCB NS (2–10) VANCB NS (8–12)	19	4	1		26
Sydnor et al. [24]	2007	STX NCB 14G STX VANCB 14, 11G	NS	15			10§	67
Kil er al.[25]	2008	US NCB 14G STX VANCB 11G	NS	9	1	2		33
Rizzo et al. [26]	2008	US, STX VANCB 11G	NS (8–12)	23	5	0		22
Sakr et al. [27]	2008	US NCB 14G STX VANCB 11, 10G	NS	3	1	1		67
Shin et al. [28]	2008	US NCB 14G US VANCB 11, 8G	NCB 5 (4–7) VANCB NS	16	1	0		6
Ahmadiyeh et al. [29]	2009	US, STX, MRI NCB or VANCB 14, 11, 8G	NS	40	8	1		23
Bernik et al. [30]	2009	US NCB 16, 14G STX VANCB 11G	NS	16			7	44
Bode et al. [31]	2009	US NCB 16, 14G	3 (1–6)	19	6	5		58
Cheng et al. [32]	2009	NS	NS	8			4	50
Tseng et al. [33]	2009	NS	NS	7			5	71
Bennett et al. [34]	2010	US NCB 14G STX VANCB 11G	NCB 6 (2–15) VANCB 10 (2–30)	50			15	30
Tse et al. [35]	2010	NS	NS	11			6	55
Youk et al. [36]	2010	US NCB 14G	5 (1–6)	30	6	1		23
Chang et al. [37]	2011	US VANCB 11G	NS	11	2	0		18
Kim et al. [38]	2011	US NCB 14G	5 (NS)	15			5	33

Table 3 (continued)

Study	Year	Guidance method, type of core biopsy, needle gauge	Mean N of cores (ranges)	N of papillary lesions	N upgraded to DCIS	N upgraded to invasive carcinoma	N upgraded to malignancy (DCIS or invasive carcinoma)	PPV %
Rakha EA et al. [39]	2011	US NCB 14G	NS	30	10	1		37
Richter-Ehrenstein et al. [40]	2011	US NCB 14 G STX VANCB 11G	NS	11	0	1		9
Destounis et al. [41]	2011	US NCB 14G STX, MRI VANCB 14, 12, 9G	NS	52	13	6		37
Fu et al. [42]	2012	US NCB 14G	NS	65	6	4		15
Holley et al. [43]	2012	US NCB 14G STX VANCB 9G	4 (1–21)	35			13	37
Lu et al. [44]	2012	US NCB 14G	NS	12	2	1		25
Rizzo et al. [45]	2012	NS	NS	42	14	2		38
Al-Hassan et al. [46]	2013	US NCB 18, 14, 10G STX VANCB 11, 9G	NS	19			7	37
Koo et al. [7]	2013	US NCB 14G	NS (4–6)	10			3	30
Wiratkapun et al. [47]	2013	US NCB 14G STX VANCB 11G	6 (2–16)	32	10	2		38
TOTAL				805	274			34
Present study	2014	US NCB 14G	3 (1–6)	46	7	15		48

* diagnosed as B4 /suspicious of malignancy

§ including 2 cases of lobular carcinoma in situ considered as "malignancy" at surgical excision

DCIS: ductal carcinoma in situ; *G*: gauge; *MRI*: magnetic resonance imaging guidance; *NCB*: needle core biopsy; *NS*: not specified; *PL*: papillary lesion; *PPV*: positive predictive value; *STX*: stereotactic guidance; *US*: ultrasound guidance; *VANCB*=vacuum assisted needle core biopsy

malignancy (DCIS and/or invasive carcinoma) after subsequent SE were reported with a mean underestimation rate of 7.6 %. Underestimation rate of malignancy, however, differed widely among studies [5, 7–22, 24–60], ranging from 0 to 29 %. The mean value of 7.6 % of incidence of malignancy of PL without epithelial atypia on CB can be considered low, nevertheless it is sufficiently high to warrant further assessment even in consideration that imaging characteristics are not able to predict which PL without epithelial atypia diagnosed on CB will result malignant at SE. From the analysis of the literature it results that about the 57 % of the studies concerning PL without epithelia atypia on CB concluded that routine SE is recommended for complete evaluation of lesion to exclude the possibility of concomitant malignancy; on the contrary about 28 % of studies suggested that these lesions can be managed with clinical-imaging follow-up alone and SE may not be required (Table 4) particularly if the imaging studies are concordant with diagnosis, although it is well known that intraductal papillomas and papillary carcinomas have a considerable overlap in imaging features [51].

In consideration of higher prevalence of PL without epithelial atypia in comparison with PL with epithelial atypia, from the review of the literature results that about 1/3 of the published studies report a very limited number of cases with follow-up SE (20 cases or less) [8–11, 13–18, 20–22, 49, 51–53]; in single series reporting more than 20 cases, often a variety of biopsy techniques and needles of different gauges have been used [5, 12, 19, 24–31, 34, 37, 40, 41, 43, 46, 47, 50, 54–57, 59]; a certain number of studies [9, 12, 14, 32, 33, 35, 45, 48, 50] did not specified guidance method, type of CB and needle gauge.

In our series, we found a percentage of upgrade of 13.2 % that is higher than the mean value (7.6 %) of the literature; as for PL with epithelial atypia, this could be attributable to widespread use of VANCB that results to be more accurate than NCB in diagnosing PL without epithelial atypia [61].

Eight studies [7, 22, 36, 38, 39, 42, 44, 58] are comparable to our study considering the homogeneity of series reported (US 14G NCB). These studies report a range of underestimation rate between 4 and 12.9 %, and our value of underestimation rate (13.2 %) results to be very close to superior limit of this range. The five larger series [7, 36, 38, 39, 42] using 14G NCB reporting more than one-hundred cases (160, 131, 155, 203 and 191) show a wide range of underestimation rate (5, 9, 12.9, 6 and 5 % respectively).

Chang et al. [58] reported that the mean lesion size was significantly larger for lesions upgraded to malignancy and recommended excision of PL without epithelial atypia diagnosed on 14G NCB especially for lesions larger than 15 mm. Size of papillary lesion has been evaluated in a recent meta-analysis [61] as a possible variable associated with underestimation. The median lesion size across 10 of the examined studies was 13.5 mm.; there was no statistical association between larger lesions (> or=13.5 mm.) and a higher rate of

Table 4 Papillary lesions without epithelial atypia on CB and malignancy on SE: review of the literature

Study	Year	Guidance method, type of core biopsy, needle gauge	Mean N of cores (ranges)	N of papillary lesions	N upgraded to DCIS	N upgraded to invasive carcinoma	N upgraded to malignancy (DCIS or invasive carcinoma)	PPV %	Routine excision recommended
Liberman et al. [8]	1999	US, STX NCB 14G STX VANCB 14, 11G	NCB 5 (1–20) VANCB 14G 13 (1–50) VANCB 11G 14 (5–34)	9	1	0		11	NS
Ioffe et al. [9]	2000	NS	NS	8			2	25	NS
Philpotts et al. [10]	2000	STX NCB 14, 11G	7 (5–12)	6	1	0		17	NO
Bazzocchi et al. [48]	2001	NS	NS	26	0	0		0	YES
Mercado et al. [11]	2001	STX VANCB 11G	11 (6–18)	6	1	0		17	YES
Rajendiran et al. [12]	2001	NS	NS	27			2	7	NS
Irfan et al. [49]	2002	STX VANCB 8G	12.4 (11–17)	3	0	0		0	NS
Jacobs et al. [50]	2002	NS	NS	38			3	8	NS
Rosen et al. [13]	2002	US, STX NCB 14G STX VANCB 14, 11G	NS	4	0	0		0	NO
Masood et al. [18]	2003	NS	NS	6	1	0		17	YES
Puglisi et al. [5]	2003	US, STX NCB 14G	5 (3–6)	31			2	6	YES
Agoff et al. [15]	2004	STX NCB 14G STX VANCB 11, 9G	NS	11	0	0		0	NO
Gendler et al. [51]	2004	US NCB 14G STX VANCB 11G	NS (5–15)	13			2	15	YES
Ivan et al. [16]	2004	US NCB 20, 18, 16G STX VANCB 14, 11G	NCB 5 (3–12) VANCB 11 (5–22)	6	0	0		0	YES
Renshaw et al. [17]	2004	US NCB 14G STX VANCB 11G	NS	18	0	0		0	NO
Carder et al. [18]	2005	US NCB 18G STX NCB 14G	NS	16	0	0		0	NO
Lam et al. [52]	2006	US NCB 16G	NS	11	1	0		9	NS
Liberman at al. [53]	2006	US NCB 14 G STX VANCB 11G	NCB 4 (1–6) VANCB 14 (8–35)	20	1	0		5	YES
Mercado et al. [54]	2006	US NCB 14 G STX VANCB 11G	NCB 4 (3–5) ANCB 9 (3–18)	36	2	0		6	YES
Shah et al. [19]	2006	US, STX NCB 14G	2.7 (1–9)	40	1	0		2.5	NO
Arora et al. [20]	2007	US NCB 14, 12G STX VANCB 11G MRI VANCB 9G	NS	18	0	0		0	NO
Ashkenazi et al. [21]	2007	US NCB 16, 14G STX VANCB 12, 11, 9G	NS	20			4	20	YES
Ko et al.[22]	2007	US NCB 14G	NS	19			1	5	NO
Sydnor et al. [24]	2007	STX NCB 14G STX VANCB 14, 11G	NS	23			4	17	NO
Kil et al. [25]	2008	US NCB 14G STX VANCB 11G	NS	67	0	3		5	YES*
Rizzo et al. [26]	2008	US, STX VANCB 11G	NS (8–12)	101	9	0		9	YES

Table 4 (continued)

Study	Year	Guidance method, type of core biopsy, needle gauge	Mean N of cores (ranges)	N of papillary lesions	N upgraded to DCIS	N upgraded to invasive carcinoma	N upgraded to malignancy (DCIS or invasive carcinoma)	PPV %	Routine excision recommended
Sakr et al. [27]	2008	US NCB 14G STX VANCB 11, 10G	NS	56	6	1		12	YES
Shin et al. [28]	2008	US NCB 14G US VANCB 11, 8G	5 (4–7)	86	10	2		14	YES
Skandarajah et al. [55]	2008	US NCB 14G STX NCB 11, 9G	4 (1–13)	80	8	7		19	YES
Ahmadiyeh et al. [29]	2009	US, STX, MRI NCB 14, 11, 8G	NS	29	1	0		3	NO
Bernik et al. [30]	2009	US NCB 16, 14G STX VANCB 11G	NS	47			4	9	YES
Bode et al. [31]	2009	US NCB 16, 14G	3 (1–6)	23	1	1	–	9	YES
Cheng et al. [32]	2009	NS	NS	77			3	4	YES
Jaffer et al. [56]	2009	US NCB 20, 18, 16G STX VANCB 14G	NCB 5 (3–12) VANCB 15 (10–20)	104	6	3		9	YES
Tseng HS et al. [33]	2009	NS	NS	24			7	29	YES
Jung et al. [57]	2010	US, STX NCB 14G	NS	160	3	7		6	NO
Bennett et al. [34]	2010	US NCB 14G STX VANCB 11G	NCB 6 (2–15) VANCB 10 (2–30)	45	0	0		0	NS
Chang et al. [58]	2010	US NCB 14G	NS	100	3	1		4	YES§
Tse et al. [35]	2010	NS	NS	68			7	10	YES
Youk et al. [36]	2011	US NCB 14G	NS	160	6	2		5	NS
Chang et al. [59]	2011	US NCB 14G US VANCB 11G	NCB 6 (2–10) VANCB 7 (3–19)	64	2	0		3	YES
Chang et al. [37]	2011	US VANCB 11G	NS	49	0	0		0	NO
Kim et al. [38]	2011	US NCB 14G	5 (NS)	131			12	9	NO
Rakha EA et al. [39]	2011	US NCB 14G	NS	155	14	6		12.9	YES
Richter-Ehrenstein et al. [40]	2011	US NCB 14G STX VANCB 11G	NS	45	2	0		4	NO
Destounis et al. [41]	2012	US NCB 14G STX, MRI VANCB 14, 12, 9G	NS	53	2	0		4	NO
Fu et al. [42]	2012	US NCB 14G	NS	203	12	0		6	YES
Holley et al. [43]	2012	US NCB 14G STX VANCB 9G	4 (1–21)	51			1	2	YES
Lu et al. [44]	2012	US NCB 14G	5	66	4	0		6	YES
Rizzo et al. [45]	2012	NS	NS	234	19	2		10	YES
Shouhed et al. [60]	2012	US NCB 14G STX VANCB 11G	NS	59			6	10	YES
Al-Hassan et al. [46]	2013	US NCB 18, 14, 10G STX VANCB 11, 9G	NS	37	7	3		27	YES
Koo et al. [7]	2013	US NCB 14G	NS (4–6)	191			9	5	YES

Table 4 (continued)

Study	Year	Guidance method, type of core biopsy, needle gauge	Mean N of cores (ranges)	N of papillary lesions	N upgraded to DCIS	N upgraded to invasive carcinoma	N upgraded to malignancy (DCIS or invasive carcinoma)	PPV %	Routine excision recommended
Wiratkapun et al. [47]	2013	US NCB 14G STX VANCB 11G	6 (2–16)	52	0	0		0	YES°
TOTAL				3032	231			7.6	YES: 31 (57.4 %) NO: 15 (27.8 %) NS: 8 (14..8 %)
Present study	2014	US NCB 14G	4 (2–14)	68	5	4		13.2	YES

* if PL ≥1.5 cm or peripheral lesion

§ if PL≥1.5 cm

° if symptomatic PL and/or high BIRADS

DCIS=ductal carcinoma in situ; *G*=gauge; *MRI*=magnetic resonance imaging guidance; *NCB*=needle core biopsy; *NS*=not specified; *PL*=papillary lesion; *PPV*=positive predictive value; *STX*=stereotactic guidance; *US*=ultrasound guidance; *VANCB*=vacuum assisted needle core biopsy

underestimation (p=0.250); according to the authors [61], this finding my result from the fact that breast papillary lesions are generally small, 10 mm. or less.

Regarding the histological features of cancers detected on SE in our series of PL without epithelial atypia, we found that the frequency of DCIS (5 out 9, 56 %) and invasive carcinoma (4 out 9, 44 %) was similar.

Of the 5 cases of DCIS, 3 of low and 2 of intermediate nuclear grade, 2 cases were only within the PL and 3 cases were within PL and in surrounding breast tissue. Of the 4 cases of invasive carcinoma, diameters were 1.5, 3, 4 and 5 mm, respectively, three of them were grade 1 (1 tubular, 1 cribriform and 1 encapsulated papillary carcinoma) and one was grade 2 ductal carcinoma; three out four were outside PL in the adjacent parenchyma.

A recent study [7] evaluated whether the upgrade to malignancy rate of PL without epithelial atypia on ultrasound guided 14G NCB could be decreased using immunohistochemistry (IHC) staining and whether IHC can replace SE in these cases. The authors found that, even if IHC may decrease the upgrade to malignancy rate for PL without epithelial atypia on 14G NCB, a misdiagnosis still occurred, suggesting that IHC can not replace SE for a definitive diagnosis of papillary lesion of the breast.

Recently, vacuum-assisted excision has been proposed as an acceptable alternative to SE in the treatment of PL without epithelial atypia diagnosed on image-guided CB, provided thorough multidisciplinary discussion has taken place before the type of treatment is decided [62].

According to European guidelines [4] histological diagnosis of non-malignant PL on CB is reported as B3 category (lesions of uncertain malignant potential); the possibility of using vacuum-assisted excision [62–64] as an alternative to SE in the management of cases of PL without epithelial atypia on image-guided CB implies from the pathological point of view the categorization of the histological diagnosis of PL on CB into two groups: B3a for PL without epithelial atypia and B3b for PL with epithelial atypia; this subcategorization can be helpful for guiding treatment decision (surgical or vacuum-assisted excision) during multidisciplinary discussion meeting.

The mean number of core samples on reported series, when stated, ranges from 2.7 to 11 (Tables 4), however it would seem not have an influence on the accuracy of diagnosis of PL without epithelial atypia on image-guided CB.

In the meta-analysis by Wen et al. [61] a statistically significant difference in the rate of underestimation of PL without epithelial atypia was found between the “before 2007” group of series [5, 8–19, 48–54] and the “2007 or later” group of series [7, 20–47, 55–60], this did not result from our review (6.0 versus 7.8 %, p-value from test of proportion 0.23) (Table 4).

Conclusions

In conclusion our results show that, in agreement with data resulting from a comprehensive review of the literature, in cases of a diagnosis of PL with epithelial atypia on ultrasound-guided 14G NCB, SE appears mandatory due to the high risk of associated malignancy (approximately 1 out of 2 patients).

The diagnosis of PL without epithelial atypia on ultrasound-guided 14G NCB does not exclude malignancy at subsequent SE, and consequently further assessment (by surgical or vacuum-assisted excision) is recommended to avoid the risk of delaying a diagnosis of malignancy (independently from the concordance between the imaging features and the pathological diagnosis). This risk tend to be lower but still involves 1 out of 8 patients.

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Conflict of Interest The authors declare that there is no conflict of interest

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