UICC
global cancer control

IJC
International Journal of Cancer

Characterization and outcome of breast needle core biopsy diagnoses of lesions of uncertain malignant potential (B3) in abnormalities detected by mammographic screening

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In the setting of breast cancer screening, 5–9% of needle core biopsies are diagnosed as lesions of uncertain malignant potential (B3). The management of these lesions is potentially problematic as the data on their outcome remains limited. In our study, we aim to assess the outcome of screen-detected lesions diagnosed as B3 in a large series to validate previous studies and to characterize the malignant lesions detected after a B3 diagnosis. Therefore, the results of 1,025 needle core biopsies of women screened over a 7-year period (1999–2006) in two different regions in the UK with B3 diagnoses who underwent surgical excision were reviewed and compared to the final excision histology. Final histology showed that 25% of cases were malignant (17% ductal carcinoma *in situ* and 8% invasive). Predictors of malignancy included calcification on imaging and epithelial atypia on needle core biopsy particularly atypical ductal hyperplasia [positive predictive value 50%]. Pure flat epithelial atypia showed the lowest positive predictive value amongst all epithelial atypia groups (21%). The positive predictive value was low for complex sclerosing lesions (9%) and papillary lesions (13%) without epithelial atypia. Malignant tumors detected after B3 diagnosis showed favorable histological features, the majority were *in situ*, and most belonged to the low grade breast neoplasia family that is associated with indolent behavior. The underlying radiological abnormality was calcification in 44% of cases and the imaging classification was malignant/suspicious in 38%. In conclusion, our results further emphasize the heterogeneity of B3 lesions and that the likelihood of malignancy varies substantially between different histological subtypes. Malignancy is particularly associated with epithelial atypia suggesting the use of two categories of with and without epithelial atypia. Radiological findings provided useful information regarding the nature and outcome of B3 lesions.

Needle core biopsy (NCB) is now considered the method of choice for triple assessment,[1] which combines the results of imaging, clinical and pathological examination (FNA or NCB). The published data suggest that the use of core biopsy has significantly increased the preoperative diagnosis rate in screen-detected breast cancers.[2–4] The majority of NCB are classified as normal (B1), benign (B2) or malignant (B5).[5] The accuracy of benign and malignant NCB diagnoses is supported through the use of two borderline categorizations; lesion of uncertain malignant potential (B3) and suspicious of malignancy (B4). The B3 category consists of a heterogeneous group of lesions which may yield only benign histology on initial NCB sampling but are recognized to show heterogeneity and may harbor malignancy elsewhere or to have an increased risk of associated adjacent malignancy.[5,6]

Although the B3 category constitutes a relatively small proportion of all NCB (3–9%; average 6%[4,7–12]), most cases progress to surgical intervention to establish an excision histology diagnosis. This has significant implications particularly in screen-detected (nonsymptomatic) breast lesions in which final benign diagnoses after surgical intervention is a drawback of mammographic screening. In a previous study, we reported the positive predictive value (PPV) of B3 diagnosis of screen-detected mammographic abnormalities from the Trent region, UK (523 subjects).[13] In our study, we aimed to assess the outcome of screen-detected lesions diagnosed as B3 category on routine practice in a large series of cases to validate and confirm our previous findings. One key goal of

Key words: screen-detected breast lesions, Needle core biopsy diagnosis, B3, positive predictive value, atypical ductal hyperplasia, epithelial atypia, lobular neoplasia, radial scar, complex sclerosing lesion, papillary lesion, papilloma, breast cancer, ductal carcinoma *in situ*
DOI: 10.1002/ijc.25801
History: Received 11 Sep 2010; Accepted 4 Nov 2010; Online 2 Dec 2010
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our study was to attempt to characterize the malignant lesions diagnosed after B3 in routine breast screening practice. For this reason we chose to concentrate on cases where subsequent surgical biopsy was performed allowing accurate final diagnostic classification.

Material and Methods

This was a retrospective study of all women who attended one of the seventeen breast screening units in the West Midlands and South Central regions, UK from 1st of April 1999 until 31st of March 2006. Women aged 50–70 are invited for screening by two view mammography without breast examination every 3 years. The reason for performing NCB was usually the presence of a mammographic abnormality which was not definitively benign. A small proportion of NCB (<2%) were performed because of a clinical abnormality detected by or reported to the radiographer at the time of mammography. NCB results were categorized B1 to B5 according to UK guidelines.[5] All patients diagnosed as B3 category on core biopsy were discussed at a multidisciplinary meeting with a breast radiologist, histopathologist and surgeon present at which time decisions on further action were made. Those patients not undergoing an excision biopsy were therefore subject to multidisciplinary discussion to ensure that this conclusion was appropriate.

Histology reports of B3 NCB and the subsequent diagnostic biopsy results of all patients were reviewed by one pathologist (EAR) for our study. No slides were reviewed and no diagnosis made in routine practice was altered. Data collected included region and units, date of core biopsy and surgical procedure (1st, 2nd and 3rd operation data as appropriate), radiological and clinical abnormalities, core biopsy type and imaging technique (*i.e.*, guidance *via* Ultrasound or stereotaxis or vacuum assisted biopsy), NCB diagnosis (including presence and type of epithelial atypia and presence of calcification), final diagnosis including histological type, grade and size where appropriate. For the purpose of our study, excision histology findings were reported as a) malignant; invasive carcinoma and ductal carcinoma *in situ* (DCIS), in addition to other malignant lesions such as sarcomas and lymphomas, and b) benign lesions including atypical ductal hyperplasia (ADH), lobular neoplasia (LN; [ALH and LCIS]) and benign and borderline phyllodes. Positive predictive values (PPV) for detection of malignancy were calculated for all B3 core cases and for each subcategory. PPV was determined as follows: PPV = (number of malignant cases/total number of subjects) × 100%.

In our study, we classified B3 diagnosis into the following subcategories; 1-Epithelial atypia, which included cases diagnosed as atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), apocrine atypia and sclerosing adenosis with atypia, 2-Lobular neoplasia (LN) including both atypical lobular hyperplasia (ALH) and lobular carcinoma *in situ* (LCIS), 3- Radial scar complex/sclerosing lesion with or without epithelial atypia (RS/CSL), 4-Papillary lesion (PL) with or without epithelial atypia, 5-Fibroepithelial lesion with cellular stroma (FE), and 6-B3 unclassified / not otherwise specified including lesions which cannot be categorized into any of the previous categories but are sufficiently suspicious to be classified as B3 (*e.g.*, Mucocoele-like lesion, vascular lesion, entrapped glands, adenomyoepithelioma and possible malignant soft tissue neoplasm, multiple lesions difficult to classify accurately) and where excision is recommended for definite diagnosis.

Results

Out of the 1,082 cases collected, 33 did not have a core biopsy report available for review. Initial analysis showed that 19 cases were miscoded/ incorrectly interpreted (*e.g.*, should have been reported as benign B2 or suspicious B4). Therefore, in our study, 1,025 subjects, who were diagnosed as B3 and underwent subsequent excision biopsy, were included in the final analysis. Of those 81% were diagnosed on the first surgical intervention, 17% on the second and 2% on the third intervention. Of all cases, 763 (74.4%) were benign; including 82 ADH (10.7%), 66 lobular neoplasia (8.6%; 34 ALH and 32 LCIS), 198 RS/CSL (25.9%) and 119 papillary lesions (15.6%). Malignant lesions included 177 (17.3%) DCIS and 85 (8.3%) invasive cancers; giving an overall PPV of 25.6%. However, the PPV varied between the 2 regions (24% and 29%; $\chi^2 = 3.1$, $p = 0.08$), and among different units (15–39%; $\chi^2 = 31.2$, $p = 0.008$). Although there was a decline in PPV over years from 31% in 1999 to 19% in 2006, a rise was noted in the years 2002 and 2005 (31% [43/140] and 31% [65/212], respectively) and the overall difference was not significant ($\chi^2 = 12.5$, df = 7, $p = 0.086$).

Relationship between radiological and histological findings

The associations between pre-NCB findings (radiological and/or clinical) and core biopsy procedures and the histological outcome are shown in Tables 1 and 2. Of 670 cases with radiological data, the main mammographic abnormalities were calcification (44%), mass (25%) and architectural deformity (31%). Screen-detected calcifications showed higher incidence of malignant outcome (40%) when compared to mass lesions (22%) or architectural deformities (16%) ($\chi^2 = 49.5$, $p < 0.001$). Of the cases diagnosed radiologically as suspicious or malignant (R4/5 and/or U4/5; 38%), 30% were malignant on final histology. Of these cases, when radiological abnormality was considered, 50% were malignant when the abnormality was calcification, 28% for mass lesions and 20% were malignant when the abnormality was architectural distortion ($\chi^2 = 6.9$, $p = 0.031$).

When calcification was the main radiological abnormality, the lesion diagnosed on NCB was frequently epithelial atypia (74%; 69% of all atypia) or lobular neoplasia (10% but 73% of all lobular neoplasia). Indeterminate calcification (R3) was the main abnormality in 77 cases and this group showed

Table 1. Association between radiological and clinical findings and core biopsy procedure final histological outcome of B3 lesions

Variables	No (%)	Final outcome			PPV	χ^2 p-value
		Benign	DCIS	Invasive		
Radiological finding[1]						
Calcification	294 (44)	177	88	29	40%	48
Mass	166 (25)	130	17	19	22%	<0.001
Architectural distortion	210 (31)	177	24	9	16%	
Radiological category[2]						
2 (Benign)	48 (14)	42	4	2	13%	9
3 (Equivocal)	165 (48)	130	23	12	21%	0.161
4 (Suspicious)	97 (28)	65	20	12	33%	
5 (Malignant)	35 (10)	28	4	3	20%	
Clinical category						
1 (Not palpable)	44 (68)	37	5	2	16%	8
2 (Benign)	7 (11)	4	1	2	43%	0.207
3 (Equivocal)	11 (17)	7	2	2	36%	
4 (Suspicious)	3 (4)	1	1	1	67%	
Core biopsy procedure						
NCB	988 (96)	731	173	84	13%	3
Vacuum assisted	37 (4)	32	4	1	26%	0.210
Core biopsy procedure						
Stereotaxic	169 (17)	110	46	13	35%	3
Other method (Ultrasound/clinical)	812 (83)	613	128	71	24%	0.002

[1]Data on radiological findings were available on 670 cases, radiological categories on 345 cases and clinical categories on 65 cases. [2]Highest category [mammography (R), or ultrasound (U)].

33% malignant outcome. In this group, when NCB diagnosis was considered, atypia (65 cases) showed malignant outcome in 37%, papillary lesion (7 cases) in 29% while none of the RS/CSL or mucocele-like lesion showed malignant outcome (0/5). All but one case diagnosed as columnar cell change with atypia/flat epithelial atypia (FEA) on NCB presented with calcification. In contrast, 62% of architectural distortions were diagnosed as RS/CSL, 34% of mass lesions were diagnosed as papillomas (53% of papillomas were diagnosed as mass) and 20% of mass lesions were diagnosed as FE (91% of FE diagnosed as mass). RS/CSL and papillomas were frequently classified as suspicious or malignant on radiology (47% and 45%, respectively), while FE, LN and AIDEP groups were usually associated with benign/uncertain (R/U 2/3) diagnoses.

B3 NCB and subsequent final histology

Initial analysis showed that when epithelial atypia was mentioned explicitly in NCB report, 42.4% (190/448) were malignant, whereas when the absence of epithelial atypia was mentioned, only 8.1% (10/135) were malignant on final histology ($\chi^2 = 53.9$, $p < 0.001$). Moreover, some recent reports contained formal subdivision of B3 category into B3a (without atypia) and B3b (with atypia) where 36.2% (21/58) of B3b and 7.1% (3/42) of B3a were malignant ($\chi^2 = 11.3$, $p = 0.001$).

Table 3 summarizes all NCB histological categories, excision histology outcomes and category-specific PPV. The most frequent entities diagnosed as B3 on NCB were epithelial atypia with or without other lesions (50% including LN and 43.5% without LN) and RS/CSL (32%), while papillomas comprised 18% of cases and the least frequent diagnoses were FE lesions (5%).

The PPV varied widely among different categories with the highest rates in epithelial atypia particularly for ADH (50%), while the lowest rates were seen in FE (1.9%) ($\chi^2 = 125$, df = 5, $p < 0.001$). PPV for papillary lesion and RS/CSL without epithelial atypia were 12.9% and 8.9%, respectively.

Of all malignant lesions, 77% were diagnosed as epithelial atypia on NCB; 64% of those were diagnosed as ADH. The overall PPV of ADH was 50%; of all DCIS, 53% were diagnosed as ADH on NCB, whilst 40% of invasive tumors were diagnosed as ADH.

Table 4 shows the correlation between preoperative radiological abnormality and final diagnosis in the different NCB B3 subgroups based on the presence of atypia. When NCB shows B3 lesion without atypia, PPV is 8% if radiological abnormality is distortion and 24% if the radiological

Table 2. Association between radiological findings and histological findings on both core and surgical specimens

Histological findings	Radiological findings			
	Calcification	Mass	Distortion	χ^2 *p*-value
Calcification				
Seen	216	34	75	137
Not seen	19	25	22	<0.001
Not mentioned	59	106	107	
Atypia				
Atypia present	240	54	62	171
No atypia	54	112	148	<0.001
Diagnostic B3 category				
ADH	137	22	23	
FEA	14	0	1	55
LN	39	3	11	0.001
Papilloma	35	54	15	
RS/CSL	19	36	152	
FE	0	29	3	
Final histological outcome				
Benign	177	130	177	49
DCIS	88	17	24	0.001
Invasive	29	19	9	

abnormality is calcification. Contrasting this B3 lesions present as calcification and show atypia on NCB demonstrate PPV of 46%.

Clinicopathological features of malignant lesions after B3 diagnosis

Of the invasive tumors (85 cancers), 54 were of no special type (NST), 18 pure tubular, and 13 invasive lobular carcinomas; 64% were grade 1, 31% grade 2 and 5% grade 3. Of the DCIS cases, 39% were low grade, 37% intermediate grade and 24% were high grade (Table 5). Of the invasive cancers, 29 had comments on lymph nodes number in the report (total lymph node number varied from 3 to 25; median 13). Of those, 4 cases (14%) were positive for metastatic deposits (1/12, 1/22, 2/25 and 4/10). Interestingly, out of the 4 lymph node positive cases, 1 case underwent mastectomy with lymph node dissection directly after B3 diagnosis (based on MDT discussion) whilst the other 3 cases, lymph nodes were sampled on a subsequent surgery after invasive diagnosis on the initial excision histology. Details of carcinoma size are shown in Table 5.

Discussion

Management of lesions as of uncertain malignant potential (B3) by needle core biopsy histological examination, is particularly important in the screening setting where the main aims are early detection and management of breast cancer (BC) and reducing mortality from BC, yet at the same time, the program aims to avoid of unnecessary surgery for benign disease in screened 'asymptomatic' women. Therefore, there is a need for data that can be applied to clinical practice to increase the accuracy of nonoperative diagnosis avoiding unnecessary surgery for benign conditions. Moreover, in the screening setting, clinical follow-up is not advocated and the outcome of any screening episode should ideally be either a return to normal screening cycle or a diagnosis of malignancy. The follow-up of women with a more intensive surveillance program than the 3 yearly NHSBSP is considered as unacceptable outcome. Hence all the more reason for more accurate categorization of B3 lesions to enable one of these two outcomes to be reached in a timely fashion.

In a previous study,[13] we provided data on the PPV for malignancy of screen-detected B3 lesions (523 subjects) diagnosed in the East Midlands region UK. In our study we provide more detailed data on a larger series (1025 subjects) of screen-detected B3 lesions diagnosed in 2 different regions in the UK during the same period. Our data showed that the PPV of a B3 diagnosis is 25.6%. Although this is slightly higher than reported in the Trent region (20%[13]), this may reflect a regional variation amongst different practices as evidenced from the variation observed in our study between the two regions, and between the different units and over the different years in both studies (see Table 6 for the combined results of both studies). It may also reflect the difference in the proportion of B3 diagnostic subtypes since 50% of the lesions in our study showed epithelial atypia compared to 42% in the previous study. Supporting this, view previous reports of PPV have shown that the overall rate of malignancy for B3 lesions after excision varied in frequency; 10,[14] 16,[15] 21,[10] 26,[12] 34[16] to 35%[7] (average 23.5%, which is expected to be less in recent years[4]).

In our study, there was an association between radiological finding and outcome. Calcification as the main radiological abnormality was more likely to be associated with malignant outcome compared to mass lesions or architectural distortions. When the abnormality was calcification, the PPV of the lesion was 50% if the radiological diagnosis was suspicious or malignant and 33% if indeterminate regardless of the NCB finding. However, it is important to mention that calcification was frequently associated with epithelial atypia, particularly ADH, and LCIS and it was rare in papillary lesions, radial scars and cellular fibroepithelial lesions. Our results support the findings of previous studies,[7,12,17,18] and emphasize that the clinical and radiological features are helpful in deciding further management after a B3 needle core biopsy diagnosis, that this should form part of the evidence discussed at multidisciplinary meetings and the management decision should be tailored to individual patient circumstances.

In agreement with previous studies,[7,10–13,19–21] our results showed that the most frequent B3 lesion identified was epithelial atypia, and the PPV for detection of malignancy for this diagnosis was 40.5%. However, the PPV also varied

Table 3. Details of histological outcome of the different groups of lesions reported on NCB

		Final excision diagnoses			
Reason for B3 diagnosis on NCB	No (% of the total)	Benign	Malignant in-situ	Malignant invasive	PPV%
Epithelial Atypia present[1]	511 (50)	304	144	63	40.5
Pure ADH	248	123	92	33	50.4
Pure FEA	24	19	4	1[2]	20.8
Atypia unspecified	189	119	46	24	37.0
All LN	79	56	8	15	29.1
Pure ALH	33	25[3]	3	5	24.2
Pure LCIS	20	17[3]	1	2	15.0
LN unspecified	8	6	1	1	25
LN and ADH	13	5	3	5	61.5
LN and RS/CSL	5	2	1	2	60.0
No Epithelial Atypia (other B3 lesions)	514 (50%	459	33	22	10.7
Papillary lesion	185 (18)	154	24	7	16.7
With atypia	30	19	10	1	36.7
Without atypia	155	135	14	6	12.9
RS/CSL	329 (32)	284	26	19	13.6
With atypia	51	31	12	8	39.2
Without atypia	278	253	14	11	8.9
FE lesions	52 (5)	51[4]	0	1	1.9
B3 miscellaneous	52 (5)	44	4	4	15.4
Total	1,025	763	177	85	25.6

Abbreviations: FEA: flat epithelial atypia; LN: lobular neoplasia (ALH and LCIS); RS/CSL: radial scar/complex sclerosing lesion; FE: fibroepithelial lesion.
[1]All cases with atypia including LN with or without other lesion showing architecture and/or cytological atypia. [2]This case was grade 1, NST tumor, 1.5 mm in size. [3]Of the benign outcome, LCIS was the final diagnosis in 4 ALH (25%) and 8 in LCIS (47%) diagnosed on NCB. [4]Benign outcome of FE lesions included 17 benign phyllodes tumor and 1 borderline phyllodes.

Table 4. Correlation between preoperative radiological abnormality and final diagnosis in the different NCB B3 subgroups based on the presence of atypia

	Final histologic outcome					
	Atypia present on NCB			No atypia on NCB		
Radiological abnormality	Benign[1]	Malignant *in situ*	Malignant invasive	Benign	Malignant *in situ*	Malignant invasive
Calcification	131 (56)	77 (33)	25 (11)	47 (76)	11 (18)	4 (6)
Mass	25 (58)	9 (21)	9 (21)	105 (85)	8 (7)	10 (8)
Distortion	40 (66)	15 (24)	6 (10)	136 (92)	9 (6)	3 (2)
Total	196 (58)	101 (30)	40 (12)	288 (87)	28 (8)	17 (5)

[1]Final diagnosis on based on excision histology [number (percentage)].

among the different subtypes of epithelial atypia, with the highest rate detected for ADH whilst the lower rates were associated with FEA and pure lobular neoplasia. This supports the standard clinical practice of performing excision biopsy of all lesions with a diagnosis of epithelial atypia. In our study, 14 out of 15 FEA presented with calcification. The PPV for pure FEA was 21%, which was lower than that of ADH. The malignant lesions identified after FEA were mainly of favorable prognosis. Consistent with our results, Lee *et al.*,[22] found that 14% (1/7) of pure FEA were malignant on excision whilst 29% (9/31) of FEA combined with ADH were malignant. These authors also noted that tumors excised after NCB diagnosis of pure FEA had favorable prognostic factors.[22] Moreover, Ingegnoli *et al.*[23] have reported similar results where 20% of pure FEA were malignant (3/15).

The PPV of pure lobular neoplasia (without other B3 lesion) was 22.5%. The PPV when lobular neoplasia was combined with ADH was 61.5%, but the number of cases

Table 5. Details of malignant outcome (grade and size) in relation to the main pure B3 categories diagnosed on NCB

Reason for B3 diagnosis on NCB	Invasive cancer				DCIS			
	Histologic grade			Size (mm) range (median)	Nuclear grade			Size (mm) range (median)
	1	2	3		1	2	3	
Pure ADH	22	8	3	2-30 (8)	35	30	20	2-60 (9)
Pure FEA	1	0	0	2	2	0	1	–
Atypia unspecified	9	8	1	2 29 (12)	9	15	12	3-40 (10)
Pure lobular neoplasia	6	4	0	2-8 (5)[1]	1	1	4	3-20 (7)
Papillary lesion	4	2	0	2-29 (10)	4	9	1	3-48 (9)
RS/CSL	10	1	0	4-29 (10)	10	3	1	3-23 (4)
Total*	52^	23	4	2-29 (7)	61	58	39	3-60 (9)

Of the invasive tumors following pure LN on NCB (10 cases), 4 were lobular, 2 tubular and 4 were NST. Following ADH, 22 were NST, 6 tubular and 5 were lobular.
Following RS/CSL, 5 were tubular, 4 NST and 2 were lobular. Following papilloma, 6 were diagnosed as NST; 2 were associated with papillary carcinoma in-situ. Of the 4 grade 3 invasive cancers, 1 was diagnosed as a mass lesion on imaging and ADH was found on NCB, and one was incidental/synchronous mass (tubular carcinoma 6 mm with low grade DCIS but also there was another mass of grade 3 invasive NST cancer.
[1]79/85 of invasive tumor reports included histological grading (2 were microinvasive). ^ Of grade 1 invasive tumors, 2 were associated with high grade DCIS.

Table 6. Positive predictive values (PPV) of the different groups of B3 lesions reported on NCB in this study (1,025 cases) combined with the previous study (523 cases) from the East Midlands region [13] (Total 1,548 B3 NCB)

Reason for B3 diagnosis on NCB	Current study		Previous study		Total	
	No (%)	PPV%	No (%)	PPV%	No (%)	PPV%
Epithelial atypia	432 (42)	42.5	188 (36)	32.4	620 (40)	39.5
Lobular neoplasia	79 (8)	29.1	33 (6)	33.3	112 (7)	30.3
No atypia (other B3 lesions)	514 (50)	10.7	302 (58)	7.9	816 (53)	9.9
Papillary lesion	185 (18)	16.7	124 (24)	10.5	309 (20)	14.2
With atypia	30	36.7	25	36	55	36.4
Without atypia	155	12.9	99	4	254	9.4
RS/CSL	329 (32)	13.6	156 (26)	12	485 (31)	13.2
With atypia	51	39.2	24	29	75	36.0
Without atypia	278	8.9	132	9	410	9.0
FE lesions	52 (5)	1.9	32 (6)	0	84 (5)	1.2
B3 miscellaneous	52 (5)	15.4	21 (4)	23.8	83 (5)	21.7
Total	1,025	25.6	523	20	1,548	23.7

was small. Lobular neoplasia is often associated with calcification in adjacent fibrocystic change and less commonly with calcification in the lobular neoplasia itself[24,25] and rarely forms a mass lesion and therefore it is usually an incidental finding in NCB that has been performed for other reasons.[24] In our study, we were not able to review all the clinical and radiological features of these patients in detail to determine whether there was discordance between radiological/clinical and pathological findings; a frequent occurrence in patients found to have malignancy after NCB diagnosis of LN.[25,26] In our study no LN variants (pleomorphic LCIS or LCIS with necrosis) were identified.

The PPV% of RS/CSL (14%) in our study was similar to previous studies.[10,13,27–29] When we excluded cases associated with epithelial atypia (PPV = 39%) from the analysis, the PPV of RS/CSL was 9%, similar to that reported in our previous study (9%).[4] These findings in addition to the fact that most of the malignant lesions detected after a diagnosis of RS/CSL were low grade (80%) and often of pure tubular morphology (55%) may support consideration of nonsurgical management, such as removal by vacuum assisted biopsy, in selected cases.

The PPV for malignancy for papillary lesions with atypia on core biopsy is clearly higher than if no atypia is present (37% *vs.* 13%). Although the PPV of papillary lesion without atypia was higher than that found in our previous study[13] (4%), it is consistent with those reported by Liberman *et al.*[30] and by Dillon *et al.*[10] (both 14%). These findings in addition

to other published studies[13,17,31–33] indicate that removal by vacuum assisted biopsy may be a safe alternative to surgical excision in selected cases. However, papillary lesions associated with epithelial atypia require surgical excision for definitive diagnosis because histologic underestimation occurs at a frequency similar to that in other atypical lesions undergoing NCB.[31,32,34,35]

Although only one lesion diagnosed as cellular fibroepithelial lesion on core was malignant on excision, 36.5% were phyllodes tumors.

Our study also provides further support to the use of subcategorization of B3 lesions into B3a and B3b (without and with epithelial atypia)[9] since the difference in the PPVs of both subcategories was significant (7% *vs.* 36%). Our findings support the use of this subcategorization for guiding treatment decision during multidisciplinary discussion meeting (MDT).

In this series, the carcinomas detected after a B3 diagnosis showed favorable histological features: (a) 68% of carcinomas were DCIS (b) 63% of invasive cancers were grade 1 and 39% of DCIS were low nuclear grade whilst only 5% of invasive and 25% of DCIS were high grade. The low grade breast neoplasia family is reported to be associated with good prognosis and indolent behavior.[36] (c) Only 14% of invasive cancers showed lymph node positivity. (d) The majority of invasive carcinomas were of small size (median 7 mm, and 64% were $\leq$10 mm). (e) 22% were pure tubular carcinomas that are associated with excellent outcome.[37] To compare the features of malignant lesions detected after B3 diagnoses with those of screen-detected cancers which usually follow B5 diagnosis (93%[4]), we analysed the Nottingham series (1990–2004; unpublished data). We found that 25% of screen-detected 1,294 invasive cancers were grade 3 and 25% were lymph node positive. The size ranged from 1 to 60 mm (median 13 mm and 33% were =10 mm). Moreover, data from the East Midlands region from 2001 to 2006 showed that of the 3,763 screen-detected invasive cancers diagnosed by NCB as malignant (B5b), 21.1% were grade 3 and 21.6% were node positive. The median size was 13 mm (range 1–100 mm) (JJ and EAR unpublished data). Furthermore, 80% of malignant lesions diagnosed after a B5 NCB are invasive cancers compared to 40% after B3 diagnoses.[4,7] Similar figures have also been published.[18,38] Thus the carcinomas detected after a B3 diagnosis have better histological prognostic features than carcinomas detected after a B5 diagnosis.

In view of the wide variation of PPV, outcome and behavior of these lesions, informed discussion with women presenting with screen-detected B3 lesions is challenging, particularly as it may be increasingly important to include details which address the fact that although the outcome may be the diagnosis of malignancy, the favorable behavior of these lesions should be taken into consideration. The UK screening program has been extended to the age of 73 with women self-referring thereafter. As many carcinomas identified after a B3 diagnosis were low grade, are surveillance or hormonal prevention viable options to excision surgery for some elderly women? Our study should allow more informed choice based on its findings.

In conclusion, our results further emphasize the heterogeneity of lesions of uncertain malignant potential B3 and their risk of associated malignancy. Radiological findings provide useful information regarding the nature and outcome of these screen-detected lesions. Radiological calcification with suspicious or malignant characteristics and histological evidence of epithelial atypia were the most frequent abnormalities observed in B3 NCB's associated with malignancy. Epithelial atypia detected on NCB has a high PPV for malignancy requiring surgical excision. Pure ADH showed a higher PPV than FEA amongst the epithelial atypia group. The PPV is low for papillary lesions and radial scars without atypia. Alternative strategies such as removal by vacuum assisted biopsy after a multidisciplinary discussion may be appropriate. Malignant tumors detected after B3 diagnosis generally showed a favorable prognostic characteristics being, mainly *in situ* and belonging to the low grade breast neoplasia family which is recognized to be associated with indolent behavior. Our study also supported categorization of the B3 NCB into two groups: B3a (lesions of uncertain malignant potential without epithelial atypia) and B3b (lesions of uncertain malignant potential with epithelial atypia). Finally, it is important to emphasize that multidisciplinary discussion is important for appropriate management of all patients with a B3 NCB diagnosis.

Acknowledgements

The authors thank the administrative staff and pathologists involved in provision of the NHS breast screening service in the UK West Midlands and South Central regions for their help and support in conducting this study.

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