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An audit of mammographic screen detected lesions of uncertain malignant potential (B3) diagnosed on initial image guided needle biopsy: how has our practice changed over 10 years?

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AIM: To review all cases of B3 lesion diagnosed at initial image-guided needle biopsy over two 5-year cohorts to identify upgrade rates to malignancy and the effect of changing guidance on the management of such lesions.

MATERIALS AND METHODS: Data was collected retrospectively. Mammographic features, biopsy type and management were recorded for each lesion. Upgrade rates for each B3 histological category were quantified. Statistical analysis was performed using SPSS.

RESULTS: There were 224 cases in 2005–2010 and 240 cases in 2010–2015. Mammographically 211 lesions were microcalcifications, 182 masses, 65 distortions and six asymmetric densities with no difference in the mammographic features in the two cohorts. Two hundred and eight 14 G core biopsies and 256 initial vacuum-assisted biopsies were performed. There was a statistically significant reduction in benign surgical biopsies and an increase in second-line vacuum biopsy/excision in the latter cohort, with no significant change in the upgrade rate. There was an overall 6% upgrade to invasive malignancy and 13% upgrade to ductal carcinoma in situ (DCIS). The upgrade rates for the following histological categories were atypical intraductal epithelial proliferation (AIDEP) 33.2% (21/63); classical (not pleomorphic) in situ lobular neoplasia (ISLN) 18.2% (6/33); flat epithelial hyperplasia (FEA) 21.7% (20/92); papilloma with atypia 53.8% (7/13), without atypia 12.1% (8/66); and radial scar/complex sclerosing lesion with atypia 16.7% (2/12), and without atypia 7.9% (6/76).

CONCLUSION: Upgrade rates remain high for some histological categories even with first-line use of vacuum biopsy. Management of borderline lesions should be considered carefully in a multidisciplinary meeting. In many cases, the need for diagnostic surgical excision has been replaced by image-guided vacuum sampling.

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Introduction

The management of lesions of uncertain malignant potential (B3) found on image-guided needle biopsy has been increasingly discussed following criticism of over-diagnosis within breast screening and the requirement within the NHS Breast Screening Programme (BSP) to minimise the number of benign diagnostic surgical biopsies.[1,2] The introduction of vacuum-assisted biopsy (VAB) has revolutionised the management of these lesions both in terms of initial diagnosis and further management. King's College Hospital has been one of the early adopters of VAB for image-guided needle biopsies for mammographic-only visible lesions in the UK since 2003–2004.

B3 lesions make up 5–11.9% of all core biopsies performed.[3–6] The B3 category includes a spectrum of lesions that demonstrate heterogeneity or carry an increased risk of malignancy.[7] It is well recognised that B3 lesions with atypia have even higher malignant potential.[8] This overall upgrade rate to non-invasive and invasive disease has been shown to range between 9.9–35.1% depending on study design and upgrade criteria for each histological subtype.[9] Several studies have shown that open surgical biopsy/excision of many benign lesions can be safely avoided with the use of VAB or vacuum-assisted excision (VAE).[10,11]

New assessment guidelines from the NHS BSP have recommended that surgical biopsy for many B3 lesions may no longer be required and that VAE should be performed for further sampling, or in the cases of small lesions, for complete excision.[12,13] Further management of such cases after initial needle biopsy should be decided following careful consideration of the imaging and histology at a multidisciplinary meeting (MDM). Papillary lesions with atypia and cellular fibroepithelial lesions still require surgical excision. A comprehensive description of the radiological and pathological features of B3 lesions and management guidelines has been detailed by Pinder *et al.*[14]

In the present audit, all screen-detected cases of B3 lesions at initial biopsy were reviewed over two consecutive 5-year cohorts to quantify upgrade rates to malignancy. In addition, ways in which practice has changed was assessed and areas where the new NHS BSP guidance could be safely adopted were identified.

Materials and methods

Patient population

Ethics approval was not required for this audit. Data was collected retrospectively using the National Breast Screening System (NBSS) of all B3 lesions from 1 April 2005 to 31 March 2010 and 1 April 2010 to 31 March 2015 as diagnosed at initial 14 G ultrasound-guided core biopsy or stereotactic VAB. During the first cohort, VABs were performed using the 11 G Mammotome biopsy system (Devicor Medical Products, Cincinnati, OH, USA) and during the second cohort, either the Hologic Suros Atec (Hologic, Marlborough, MA, USA) or the BARD EnCore (Bard Biopsy Systems, Tempe, AZ, USA) 9 G needles.

All cases were discussed at the MDM to determine the most appropriate method for performing further sampling with VAE when required. Lesions that were biopsied under ultrasound-guidance (e.g. papillomata) were usually sampled further with 9 G ultrasound-guided VAE. Microcalcification and distortions were generally sampled further with stereotactic-guided VAE as these lesions are more easily identified on mammography as opposed to ultrasound.

Data collection

For each lesion, the mammographic sign, mammographic grade and lesion size (if available) was recorded. Lesions were documented to have undergone either an initial 14 G ultrasound-guided core biopsy or stereotactic 11 or 9 G VAB. The initial histology, including presence or absence of atypia, and histology from VAE or surgical biopsy were recorded. Clinical outcomes following discussion at MDM were documented. Where data was incomplete on NBSS, it was collected from the patient record.

All data was input into Microsoft Excel with statistical analysis performed by using SPSS for Windows (version 22, IBM, Chicago, IL, USA). Chi-square tests were performed to determine whether significant differences could be seen between individual subgroups (two-tailed p-value for significance is <0.05).

Histological categorisation

Lesions were divided into nine histological groups: atypical intraductal epithelial proliferation (AIDEP), classical (not pleomorphic) in situ lobular neoplasia (ISLN), flat epithelial hyperplasia (FEA), papillary lesion (PL), radial scar/complex sclerosing lesion (RS/CSL), mucocoele-like lesion (ML), cellular fibroepithelial lesion or suspected phylloides tumour (CFL), and other. The presence or absence of atypia was recorded for PL and RS/CSL.

In cases where the initial histology showed two pathological entities that would have been classified as B3, the lesion was assigned to the category with the highest malignant potential. For example, if the initial histology showed ISLN and AIDEP then the lesion was put into the AIDEP group for the purposes of this audit. Similarly, if the initial histology showed a papilloma and RS/CSL then the lesion was categorised into the papillary lesion group.

Upgrade rates

All cases were discussed at the departmental breast cancer MDM to agree on appropriate management. Upgrade rates have been calculated based on the cohort of lesions that underwent vacuum sampling or diagnostic surgery. For the purposes of this study, if further histology from VAE or surgery showed ductal carcinoma in situ (DCIS), invasive carcinoma, or other malignant lesions, such as sarcomas or malignant phylloides tumours, the lesion was considered an upgrade. Cases of ISLN that were then found to have the

same pathology on the surgical specimen or VAE were not considered to be upgraded to malignancy. Where there was ISLN found on surgical pathology for another B3 category, the case was not considered to be upgraded to malignancy.

Results

A total of 438,941 women were screened during the 10-year period and 5,517 lesions underwent core biopsy or VAB at assessment; 464 of these lesions were categorised as B3 (8.4% of all screen-detected lesions biopsied). There were 224 B3 lesions in 2005–2010 and 240 in 2010–2015. Fifty-seven percent (127/224) of B3 lesions were diagnosed following initial VAB in 2005–2010 compared to 14 G core biopsy and 54% (129/240) in the 2010–2015 cohort.

The numbers of B3 lesions in each category are shown in Fig 1. The total number of cases in the 10-year period was 67 (14%) cases of AIDEP, 47 (10%) ISLN, 102 (22%) FEA, 97 (21%) PL, 124 (27%) RS/CSL, five (1%) ML, 13 (3%) CFL, and nine (2%) cases classified as other. The cases categorised as "other" included atypical apocrine adenosis (n=6), possible DCIS on core biopsy but was insufficient to be graded as malignant and therefore required further sampling (n=2), and suspected spindle cell tumour (n=1) on initial vacuum biopsy, which was proven to be a malignant phylloides on final surgical pathology.

The number of cases of AIDEP decreased with an increase in the number of cases in FEA in the latter cohort, as shown in Fig 1. There was also an increase in the number of RS/CSL lesion with the remaining categories remaining fairly stable.

Lesion characteristics

The mammographic grade according to lesion type is shown in Fig 2. Three hundred and thirty-two (71.6%) of the lesions were classified as M3 (indeterminate), 97 (20.9%) as M4 (suspicious for malignancy) and 35 (7.5%) as M5 (malignant) with a similar distribution in both cohorts. Most M4 and M5 lesions were papillary lesions or RS/CSL. Documentation of the size of these lesions was only available in 52% of cases and was therefore not analysed further.

The distribution of mammographic signs was almost identical in the two cohorts apart from a minor non-significant increase in the proportion of isolated microcalcifications, which amounted to 45% (101/224) in 2005–2010 and 47% (110/240) in 2010–2015. The mammographic signs according to lesion type are shown in Fig 3.

The association between mammographic sign and B3 type with final histological outcome is shown in Table 1. There was a statistically significant increase in upgrade to malignancy for microcalcifications compared to all soft-tissue abnormalities (p=0.0177).

The presence or absence of epithelial atypia for PL and RS/CSL was not stated in the pathology report in 35 cases in the first cohort and 31 in the second cohort. There were four cases in the first cohort where no histology report could be retrieved and the data were collected from NBSS only.

Management outcomes

The potential outcomes following the initial B3 biopsy were open surgical biopsy/excision, further sampling with VAB/VAE, early recall, routine recall as shown in Table 2. Some cases underwent further sampling or surveillance outside the screening programme. There was a statistically significant reduction in the number of women that underwent a benign surgical biopsy (p=0.0016) and who were allocated to early recall (p=0.0341) between the two cohorts. There was also a significant increase in the use of VAB/VAE in the latter cohort for management of these lesions (p=0.0005).

The types of lesions that underwent second-line VAB/VAE are detailed in Table 3. In 2010–2015, there were two cases of AIDEP and four cases of FEA that underwent VAE, which was against NHS BSP guidance at the time. The first case of AIDEP demonstrated atypia in only one single duct on initial histology and the second case was of a fibroadenoma with AIDEP, which was small enough to completely

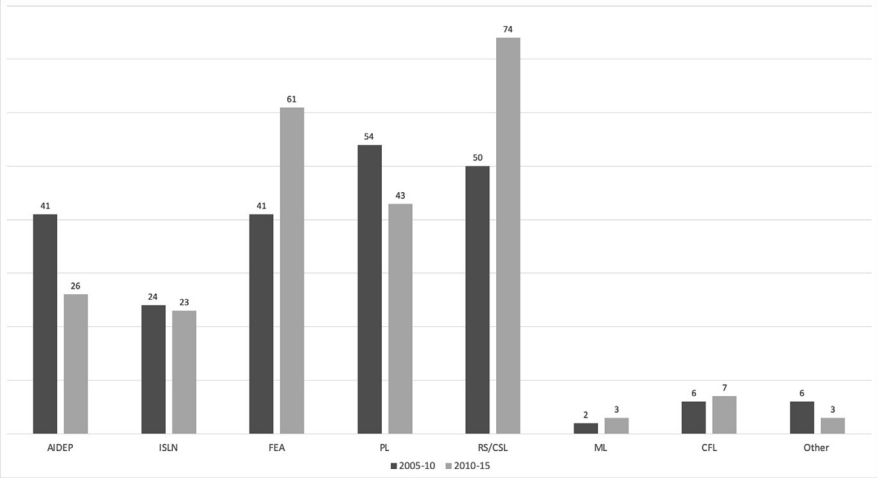

Figure 1 Number of B3 lesions in each cohort.

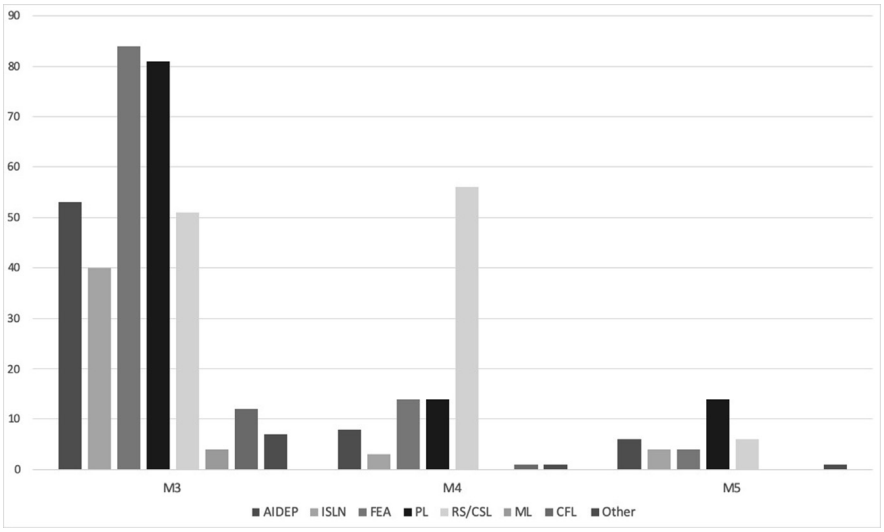

Figure 2 Mammographic score according to B3 category.

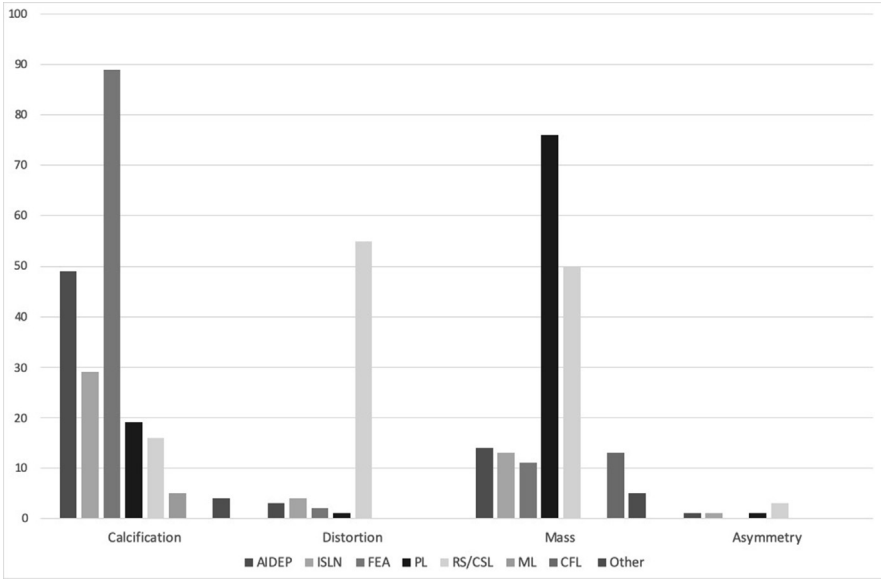

Figure 3 Mammographic sign according to B3 histology category.

excise with VAE. The four cases of FEA that underwent second-line VAB/VAE were all of microcalcification. Three of these cases had an initial VAB and the fourth case had an initial 14 G core biopsy the result of which was FEA with incidental RS. All the PL and RS/CSL that were managed with VAB/VAE had no atypia.

Table 1
Association between mammographic sign with final histological outcome 2005–2015.

Mammographic sign	*n* (%)	No further sampling[a]	Number of VAB or surgery	No upgrade	DCIS	Invasive disease	Upgrade rate
All soft-tissue abnormalities	253 (55)	38	215	183	21	11	15%
Distortion	65 (14)	17	48	42	5	1	12%
Mass	182 (39)	19	163	140	13	10	14%
Asymmetry	6 (1)	2	4	1	3	0	75%
Calcification	211 (45)	49	162	122	30	10	25%

VAB, vacuum-assisted biopsy; DCIS, ductal carcinoma in situ.
[a] No further sampling includes routine recall, non-screening surveillance, excision outside the NHS BSP and early recall.

Table 2
Management outcomes during each cohort.

	2005–2010		2010–2015		*p*-Value
	n	%	*n*	%	
RR[a]	20	8.9	42	17.5	0.0067
ER	17	7.6	7	2.9	0.0341
VAE	24	10.7	55	22.9	0.0005
Benign surgery	127	56.7	100	41.7	0.0016
Malignant surgery	36	16.1	36	15.0	0.7501
Total	224	100	240	100	

ER, early recall; VAE, vacuum-assisted excision.
[a] Routine recall, non-screening surveillance, excision outside the NHS BSP.

Table 3
Types of lesion that underwent second-line vacuum-assisted biopsy/excision in each 5-year cohort.

	2005–2010	2010–2015
AIDEP	0	2
ISLN	1	0
FEA	0	4
PL	13	24
RS/CSL	8	21
ML	0	2
CFL	2	1
Other	0	1
Total	24	55

AIDEP, atypical intraductal epithelial proliferation; ISLN, classical (not pleomorphic) in situ lobular neoplasia; FEA, flat epithelial hyperplasia; PL, papillary lesion; RS/CSL, radial scar/complex sclerosing lesion; ML, mucocoele-like lesion; CFL, cellular fibroepithelial lesion.

Upgrade rates

The upgrade rate to malignancy in the first cohort was 19.2% and in the latter cohort 18.9%. Over the 10-year period, there was an overall 6% upgrade to invasive malignancy and 13% upgrade to DCIS. No lesion that underwent further VAB/VAE was upgraded to malignancy. For all lesions that had an initial 14 G ultrasound guided core biopsy, there was a 17% upgrade to malignancy, and 21% upgrade to malignancy for those lesions that underwent initial 11 or 9 G VAB with no significant difference seen between the two cohorts.

There were four cases of AIDEP, four cases of FEA, and one papillary lesion, which were found to have ISLN on the final surgical pathology and have not been classified as upgraded to malignancy.

Table 4 shows the upgrade rates for each B3 category. There was a 53.8% (7/13) upgrade to malignancy for papillary lesions with atypia as opposed to 12.1% (8/66) upgrade to malignancy for papillary lesions without atypia. There was a 16.7% (2/12) upgrade to malignancy for RS/CSL with atypia as opposed to 7.9% (6/76) upgrade to malignancy for RS/CSL without atypia. The total number of cases of high-grade DCIS were 17, intermediate-grade DCIS 12, and low-grade DCIS 36. The total number of grade 1 cancers was 15, grade 2 cancers was eight, and there were no grade 3 cancers. Most B3 lesions were upgraded to low-grade invasive cancers or low-grade DCIS.

Discussion

B3 lesions comprise approximately 7–9% of screen-detected lesions with upgrade rates varying amongst the different histological subtypes.[15] The results of this audit are in line with the literature in terms of the proportion of B3 lesions in breast screening and upgrade rates to malignancy.[16,17] The results reflect change in guidance over time of the histological classification of B3 lesions and the modification in formal guidance on how these lesions should be managed.

Lesion characteristics

There was a non-significant increase in the B3 lesions detected as microcalcification alone, which may be due to the improved identification of low-suspicion microcalcification on digital mammography and an increased sensitivity of readers in the unit to recall microcalcification. Radial scars and complex sclerosing lesions accounted for the majority of M4 and M5 lesions as these presented as distortions or masses.

There was an increase in the number of cases of FEA in the latter cohort and a reduction in the number of cases of AIDEP by roughly a similar number. There has been a change in the terminology for columnar cell lesions with these lesions not being recognised as an entity for several decades.[14] Lesions with architectural atypia should be classified as AIDEP rather than FEA, and this clarification in the nomenclature may explain the differing data seen between the two cohorts.

During 2005–2010, the absence of atypia on the initial histology was not routinely documented in the histology report in 35 cases of PL and RS/CSL, highlighting the increased awareness of the significance of atypia on the malignant potential of these lesions.

Management

The proportion of B3 cases that had an initial VAB was not significantly different between the two cohorts. King's College Hospital was one of the first adopters of 11 or 9 G VAB for all mammography visible only lesions. Routine practice would be to perform VAB for all stereotactic biopsies as opposed to 14 G stereotactic biopsy, ensuring that more accurate and larger volume samples were obtained. Ultrasound-guided 14 G core biopsy is performed for all sonographically visible screen-detected soft-tissue abnormalities.

The significant reduction of benign surgical biopsies, reduction in the number of women on early recall, and increase in the use of VAE shown in this audit highlights the use of appropriate management strategies amidst growing concern regarding overdiagnosis and over-treatment in breast screening. Reduction in the number of cases put onto early recall is likely due to a change in policy for surveillance of ISLN. These cases were initially followed up in the NHS BSP as early recall but currently followed up in the symptomatic service with annual mammography for 5 years.

Table 4
Association between B3 categories with final histological outcome of B3 lesions 2005–2015.

	Total	No further sampling[a]	VAE	Benign surgery	Malignant surgery	DCIS	Grade	Invasive disease	Grade (G) and type	Upgrade rate
AIDEP	67	4	2	40	21	19	HG=5; IG=4 LG=10	2	G1=1; G2=1; Ductal=2	33.3%
ISLN	47	14	1	26	6	4	HG=1; IG=1; LG=2	2	G1=2; Ductal=1; Tubular=1	18.2%
FEA	102	10	4	68	20	12	HG=5; IG=3; LG=4	8	G1=4; G2=3, NS=1; Ductal=6; Lobular=2	21.7%
PL	97	18	37	27	15	11	HG=1; IG=2; LG=7; NS=1	4	G1=4; Ductal=3; Papillary=1	19.0%
PL with atypia	14	1	0	6	7	5	IG=2; LG=3	2	G1=2; Ductal=2	53.8%
PL without atypia	83	17	37	21	8	6	HG=1; LG=4; NS=1	2	G1=2; Ductal=1; Papillary=1	12.1%
RS/CSL	124	36	29	51	8	5	HG=2; LG=3	3	G2=2, NS=1; Ductal=2; Lobular=1	9.1%
RS/CSL with atypia	13	1	0	10	2	2	HG=1; LG=1	0	0	16.7%
RS/CSL without atypia	111	35	29	41	6	3	HG=1; LG=2	3	G2=2, NS=1; Ductal=2; Lobular=1	7.9%
ML	5	2	2	1	0	0		0		0.0%
CFL	13	0	3	9	1	0		1	Malignant phylloides=1	7.7%
Other	9	2	1	5	1	0		1	Malignant phylloides=1	14.3%

DCIS, ductal carcinoma in situ; VAE, vacuum-assisted excision; AIDEP, atypical intraductal epithelial proliferation; SLN, classical (not pleomorphic) in situ lobular neoplasia; FEA, flat epithelial hyperplasia; PL, papillary lesion; NS, not specified; RS/CSL, radial scar/complex sclerosing lesion; ML, mucocoele-like lesion; CFL, cellular fibroepithelial lesion.

[a] No further sampling includes routine recall, non-screening surveillance, excision outside the NHS BSP or early recall.

The increased use of VAE has been predominantly for PL and RS/CSL. In all of these cases no atypia was seen on first line biopsy. Case-by-case discussion at MDM was crucial in determining which lesions could be appropriately managed with this technique prior to current guidelines. During the latter cohort, if a distortion was considered likely to represent a RS/CSL radiologically then first-line 9 G VAB was performed by obtaining 18 cores. If the histology confirmed RS/CSL with no atypia, then the woman was returned to routine screening as the lesion was deemed to have been satisfactorily sampled. Following the introduction of new guidance, initial 9 G VAB is now performed by obtaining 12 cores only and then further sampling is undertaken with VAB/VAE by obtaining 18 cores.

The NHS BSP guidelines also recommend that B3 lesions with atypia should undergo VAE or further sampling with VAB, highlighting the importance of recognising atypia.[8,13,14] All cases of cytological and architectural atypia are followed up in the symptomatic service for 5 years with annual mammograms. More long-term follow-up of these lesions is required to determine their true malignant potential. The SLOANE project (a UK-wide prospective audit of screen-detected DCIS and atypical hyperplasia of the breast) aims to address this question and determine optimal treatment for DCIS and atypical hyperplasias.[18] Women with B3 lesions with higher malignant potential (e.g. AIDEP, ISLN, FEA) require pragmatic surveillance annually in the symptomatic service. Careful record keeping of the surveillance outcomes is paramount in ensuring that data are available when assessing outcomes and for the purposes of future audit and research.

Upgrades

The majority of lesions upgraded to malignancy were of low-grade neoplasia, which is known to exhibit indolent behaviour.[16] This audit has however showed that some B3 lesions could be upgraded to grade 2 invasive cancers also. Upgrade to malignancy was overall higher in the first cohort compared to the second, raising the possibility that more accurate initial diagnosis may have been due to larger tissue samples having been obtained. Limited information was available in this audit on the number of cores obtained at initial biopsy. The separate upgrade rates for lesions that underwent initial 14 G core biopsy versus VAB differ from the published literature. All 14 G core biopsies would have shown a lesion on ultrasound and therefore 14 G upgrade rates are low because invasive disease would have already been sampled. In addition, many of these soft-tissue lesions would be papillary lesions with a low upgrade rate in the absence of atypia. Review of all VAB performed in this period would be required to ascertain what the patterns of practice were.

The upgrade rates for papillary lesions with atypia within this audit are at the high end of those reported in the literature, which may be because of the small number of cases in the audit (n=13) compared to the literature.[14] Bianchi *et al.* reported upgrade rates of 47.8% and 13.2% in papillary lesion with atypia and without atypia, respectively, in a review of 114 cases.[19] New NHS BSP guidance acknowledges other studies that have also demonstrated this finding.[13] These guidelines recommend that papillary lesions with atypia should be surgically excised whole with clear margins (because of the need to microscopically

measure the extent of atypia for diagnosis). Similarly, cellular fibroepithelial lesions should be surgically excised with clear margins. The upgrade rate of RS/CSL with atypia is lower than that reported in the literature.[14] This may also be due to the small sample in this audit (n=13). Due to the low upgrade rate of RS/CSL with no atypia (7.9%), it may be safe to perform an initial VAB by obtaining 18 cores without the need for further sampling. A prospective audit of this would be of value to assess this further.

The management of ISLN has been shown to be variable in the literature a significant variation in the upgrade to malignancy for atypical lobular hyperplasia and lobular carcinoma in situ.[17,18] The development of evidence-based guidance will help establish the appropriate duration of mammographic surveillance of these lesions as they carry an increased risk of breast cancer in either breast.[4]

This audit details the management and upgrade rates of B3 lesions over a 10-year period from a national breast screening training centre where large gauge VAB was adopted early. There are, however, limitations to this audit in that further management carried out outside the screening programme was not always available. In addition, the size of the mammographic abnormalities was only available for 52% of cases. Lesion size is crucial in determining further management of a lesion that requires further sampling or excision.

In conclusion, the management of B3 lesions remains controversial. Careful and pragmatic implementation of the NHS BSP clinical guidance for breast cancer screening assessment is necessary for all screening units. Management of these complex cases should be determined following case-by-case discussion at a MDM. Adjustments in service provisions need to be made to allow for the increased number of VAE procedures that will need to be performed. Thorough data collection, audit, and robust follow-up of cases with a higher risk of malignant potential will aid in further improving both management and our understanding of these indeterminate lesions.

Conflict of interest

The authors declare no conflict of interest.

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