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Original article

Positive predictive value for malignancy on surgical excision of breast lesions of uncertain malignant potential (B3) diagnosed by stereotactic vacuum-assisted needle core biopsy (VANCB): A large multi-institutional study in Italy

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ABSTRACT

Percutaneous core biopsy (CB) has been introduced to increase the ability of accurately diagnosing breast malignancies without the need of resorting to surgery. Compared to conventional automated 14 gauge needle core biopsy (NCB), vacuum-assisted needle core biopsy (VANCB) allows obtaining larger specimens and has recognized advantages particularly when the radiological pattern is represented by microcalcifications. Regardless of technical improvements, a small percentage of percutaneous CBs performed to detect breast lesions are still classified, according to European and UK guidelines, in the borderline B3 category, including a group of heterogeneous lesions with uncertain malignant potential. We aimed to assess the prevalence and positive predictive values (PPV) on surgical excision (SE) of B3 category (overall and by sub-categories) in a large series of non-palpable breast lesions assessed through VANCB, also comparison with published data on CB. Overall, 26,165 consecutive stereotactic VANCB were identified in 22 Italian centres: 3107 (11.9%) were classified as B3, of which 1644 (54.2%) proceeded to SE to establish a definitive histological diagnosis of breast pathology. Due to a high proportion of microcalcifications as main radiological pattern, the overall PPV was 21.2% (range 10.6%–27.3% for different B3 subtypes), somewhat lower than the average value (24.5%) from published studies (range 9.9%–35.1%). Our study, to date the largest series of B3 with definitive histological assessment on SE, suggests that B3 lesions should be referred for SE even if VANCB is more accurate than NCB in the diagnostic process of non-palpable, sonographically invisible breast lesions.

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Introduction

The widespread implementation of mammographic breast cancer screening programmes in the last decades and the introduction of more sensitive radiological techniques such as digital mammography have led to the detection of more and more non-palpable breast abnormalities as microcalcifications. This has resulted in an increased frequency of non-operative diagnostic procedures performed for non-palpable breast lesions, in particular percutaneous core biopsies (CB).

Percutaneous CB has been introduced, particularly for non-palpable breast lesions, with the double purpose of maximizing, in comparison with fine needle aspiration cytology, the number of accurate and definitive preoperative diagnoses and avoiding a considerable number of open breast biopsies. A variety of different biopsy devices are available for this purpose. Conventional automated 14 gauge needle core biopsy (NCB) has recognized limitations especially in the assessment of microcalcifications due to not reliable sampling of the lesion.[1] Directional vacuum-assisted needle core biopsy (VANCB) was introduced in 1995 to remedy conventional NCB limitations.[2] VANCB employs vacuum assistance to draw the tissue into the needle, permits the use of larger needles (12 gauge to 8 gauge) thereby resulting in larger specimens, and has been unanimously considered to be more accurate than conventional NCB in the evaluation of microcalcifications.

According to the European guidelines,[3] for certain types of mammographic abnormalities (in particular, moderate to low level suspicion microcalcifications) a larger volume of tissue is required for accurate diagnosis, and this is possible using VANCB.

Although most percutaneous CB can be classified, according to the European[3] and UK[4] guidelines, as normal (B1) or benign (B2) on one hand, and suspicious or malignant (B4 and B5 respectively) on the other hand, a small proportion of lesions cannot fit in these categories with clear-cut indications (no surgical treatment vs surgical treatment) and have to be reported in the borderline category of B3 as lesions of uncertain malignant potential.[5] The B3 category thus includes a heterogeneous group of lesions that may provide benign histology on CB sampling but are recognized to show heterogeneity and may harbour malignancy elsewhere or have an increased risk of associated adjacent malignancy.

Although the B3 category represents a relatively small proportion of all CBs, in large series published so far its prevalence ranges between 5% and 10%[6,7]. Most B3 cases are referred for surgical excision (SE) to establish an accurate definitive histological diagnosis: B3 lesions in fact still represent a clinical dilemma as the only means of excluding malignancy associated or adjacent to a B3 CB is to excise and examine the entire lesion histologically. Thus the definitive histological diagnosis on SE is considered to be the "gold standard". For these reasons we have chosen to concentrate on B3 cases where subsequent surgical excision was performed.

The aim of this study was to evaluate the prevalence and the final outcome (overall and subtype-specific positive predictive values, PPVs) of the B3 category on routine breast screening practice in an Italian multi-institutional large series of non-palpable breast lesions assessed consecutively by stereotactic 11-gauge VANCB over a 11-year period.

Materials and methods

Pathologists of all Italian Pathology Departments diagnosing and reporting VANCBs according to the B classification as recommended by European[3] and UK[4] guidelines were contacted and invited to participate in the study: 22 out of 31 contacted institutions agreed, 14 from Northern Italy, 3 from Central Italy and 5 from Southern Italy. Breast radiologists from each participating institution were involved in the study.

Radiology Departments participating in the study were asked to provide from their computerised databases the total number of the stereotactic VANCBs performed, the time period and the mammographic patterns. Stereotactic VANCBs were performed in non-palpable breast lesions (such as architectural distorsion or irregular opacity) not detectable by ultrasound or for evaluation of microcalcifications. Stereotactic VANCBs were performed using a 11 gauge stereotactic vacuum-assisted device (Mammotome®, Ethicon Endo-Surgery, Breast Care, Norderstedt, Germany). The number of cores varied from 12 to 20. In case of microcalcifications as mammographic abnormality, cores were verified by radiography to confirm that microcalcifications had been retrieved. When microcalcifications were not evident at radiography of cores, cases were excluded from the study.

Cores from stereotactic VANCBs were fixed in formalin, embedded in paraffin and processed according to standard protocols. As part of our routine protocol, each paraffin block specimen was examined at a minimum of two levels and sections were stained with H&E. In all cases with problems in histological classification into one of the five "B categories" additional H&E levels and/or immunohistochemical examinations were routinely obtained.

The files of the participating Pathology Departments were searched for histology reports of all B3 stereotactic VANCB. In each participating institution only histology reports of B3 stereotactic VANCB were reviewed by the local pathologist; no histological slides were reviewed and no diagnosis originally made in the routine practice was altered in agreement with most mono- and multi-institutional studies reported in the literature.[6–12]

Because of the heterogeneity of B3 lesions and their different risk of associated malignancy, each centre was asked to provide also the subtype of each lesion according to the European and UK guidelines.[3,4] For the purpose of this study, the B3 category includes the following groups (based on the main pattern): a) atypical epithelial proliferation of ductal type (AEPDT) which included cases diagnosed as atypical ductal hyperplasia, apocrine atypia and sclerosing adenosis with atypia; b) flat epithelial atypia (FEA), which included columnar cell change/hyperplasia with atypia; c) lobular intraepithelial neoplasia (LIN), including both atypical lobular hyperplasia and lobular carcinoma in situ; d) radial scar (RS); e) papillary lesion (PL) and f) "other entities", including phillodes tumor, mucocele-like lesion, spindle cell lesion.

At each institution all stereotactic VANCB with a B3 diagnosis were discussed in a multidisciplinary meeting that included radiologists, pathologists and surgeons. Patients were referred for surgery or radiological follow-up depending on many factors: size, characteristics and BI-RADS category of mammographic abnormality, presence or absence of residual microcalcifications on post stereotactic VANCB radiograms, concordance between histological findings and mammography pattern.

Surgical specimens were extensively sampled and in case of microcalcifications totally embedded. Pathologists with experience in breast pathology and breast screening pathology evaluated stereotactic VANCB and SE specimens.

In each Pathology Department, histological reports of subsequent SE were searched for all B3 diagnoses on stereotactic VANCBs. Histological reports of subsequent SE were collected also for patients with B3 lesions who were known to be referred to other local breast services with the recommendation that the lesion was excised. In these cases radiologists collected histological reports of subsequent SE directly from patients.

Each local pathologist participating in the study reviewed all definitive histological reports of subsequent SE of B3 cases from his/

Table 1
Distribution of the original series of VANCB according to participating institutions and histological category.

Institution	Time period	VANCB (N)	Presence of microcalcifications (%)	B1 N (%)	B2 N (%)	B3 N (%)	B4 N (%)	B5 N (%)
1	Nov 98– May 09	4784	89.9	0 (0)	2963 (61.9)	402 (8.4)	0 (0)	1419 (29.7)
2	Feb 99–Jun 09	2457	83.5	22 (0.9)	1220 (49.7)	289 (11.8)	3 (0.1)	923 (37.6)
3	Jan 00–Dec 06	2122	NA	85 (4.0)	934 (44.0)	191 (9.0)	63 (3.0)	849 (40.0)
4	Apr 97–Dec 07	2068	79.3	23 (1.1)	1356 (65.6)	93 (4.5)	9 (0.4)	587 (28.4)
5	Nov 99–Jun 09	1968	85.3	321 (16.3)	827 (42.0)	271 (13.8)	380 (19.3)	169 (8.6)
6	May 99–Dec 08	1772	83.6	89 (5.0)	1031 (58.2)	253 (14.3)	14 (0.8)	385 (21.7)
7	Jan 04–Dec 08	1535	93.0	3 (0.2)	713 (46.4)	296 (19.3)	1 (0.0)	522 (34.0)
8	Apr 01–Mar 07	1393	50.5	5 (0.4)	981 (70.4)	142 (10.2)	0 (0)	265 (19.0)
9	Jan 03–Dec 08	1173	91.5	41 (3.5)	655 (55.8)	167 (14.2)	19 (1.6)	291 (24.8)
10	Jan 00–Dec 08	974	86.0	14 (1.4)	504 (51.8)	86 (8.8)	20 (2.1)	350 (35.9)
11	Jan 02–Dec 08	827	96.6	4 (0.5)	485 (58.6)	105 (12.7)	5 (0.6)	228 (27.6)
12	Jan 02–Dec 08	679	87.5	27 (4.0)	251 (37.0)	117 (17.2)	6 (0.9)	278 (40.9)
13	Jan 04–Dec 08	636	92.6	16 (2.5)	360 (56.6)	139 (21.9)	13 (2.0)	108 (17.0)
14	Mar 03–Feb 09	620	61.3	19 (3.1)	314 (50.6)	64 (10.3)	11 (1.8)	212 (34.2)
15	Nov 05–Aug 09	591	84.8	11 (1.9)	248 (42.0)	67 (11.3)	7 (1.2)	258 (43.6)
16	Jul 04–Jun 09	576	85.4	4 (0.7)	298 (51.7)	132 (22.9)	12 (2.1)	130 (22.6)
17	Jan 03–Jul 09	551	36.3	33 (6.0)	218 (39.6)	118 (21.4)	8 (1.4)	174 (31.6)
18	Jan 04–Dec 08	426	94.0	7 (1.6)	242 (56.8)	51 (12.0)	2 (0.5)	124 (29.1)
19	Oct 04–Jul 09	346	91.6	2 (0.6)	152 (43.9)	25 (7.2)	0 (0)	167 (48.3)
20	Jan 08–Jun 09	253	80.2	5 (2.0)	150 (59.3)	43 (17.0)	0 (0)	55 (21.7)
21	Apr 06–Apr 09	251	NA	8 (3.2)	163 (64.9)	23 (9.2)	0 (0)	57 (22.7)
22	Jan 08–Dec 08	163	98.7	0 (0)	74 (45.4)	33 (20.2)	7 (4.3)	49 (30.1)
	Total	26,165	83.4[a]	739 (2.8)	14,139 (54.0)	3107 (11.9)	580 (2.2)	7600 (29.1)
	Range %		36.3–98.7	0–16.3	37.0–70.4	4.5–22.9	0–19.3	8.6–48.3

[a] The overall percentage has been calculated excluding institutions 3 and 21.

her centre and reported them as (a) malignant lesions, including invasive carcinoma and ductal carcinoma in situ, or (b) benign-atypical lesions, including atypical ductal hyperplasia, atypical lobular hyperplasia and lobular carcinoma in situ. As for VANCBs also for SE specimens no histological slides were reviewed and no diagnosis made in routine practice was altered.

We calculated the percentages of B3 subtypes which were actually followed by SE ("referral rate") and the PPV for a subsequent malignancy, both overall and broken down by B3 category. Because of our choice of considering as "gold standard" the definitive histological diagnosis on SE, we calculated PPV including only patients with an actual histological report on SE available. PPVs, overall and for each specific subtype of lesion, were determined as follows: (number of malignant cases) × 100/(total number of B3 cases with SE). Spearman's ranks correlation coefficients were calculate to evaluate the associations between percentage of B3 cases overall cases, referral rate and PPV.

Results

Overall, 26,165 stereotactic VANCBs were identified between April 1997 and August 2009 (Table 1). A B3 diagnosis was reported in 3107 cases, corresponding to 11.9% of the entire series (range 4.5%–22.9%). The mammographic pattern leading to stereotactic VANCB was represented by microcalcifications in 83.4% of cases (range 36.3%–98.7% across institutions, median 85.7%).

SE referral rates varied substantially among subtypes, ranging between 35.7% for RS and 62.2% for AEPDT (Table 2). Overall, of the 3107 cases diagnosed as B3 on stereotactic VANCB, 1644 (54.2%) had a definitive histology report on SE available for review and were included in further analyses (Table 2). About one-fifth (PPV 21.2%) of all B3 diagnoses on stereotactic VANCB followed by SE proved to be malignant in this case series; however the PPV for each B3 subtype varied substantially (27.3%, 22.0%, 13.3%, 12.7% and 10.6% for AEPDT, LIN, PL, FEA and RS respectively). Type-specific PPVs and referral rates appeared to be strongly related and ranked in perfect agreement.

Table 3 summarises the distribution of our B3 diagnoses on stereotactic VANCB according to the subtypes of lesion in comparison with other published studies on percutaneous core biopsies[6–12]: the proportion of B3 diagnoses in our study (11.9%) was higher than the mean value of 5.8% (range 3.0–9.2%) reported by the other studies (p-value for proportion difference <0.0001). In our series AEPDT, LIN and FEA together represent 77.4% of the cases, probably due to the fact that microcalcifications are the most frequent mammographic abnormalities.

Overall, the PPV of B3 for malignancy at SE in our study (21.2%) was somewhat lower (p-value = 0.03) than that reported

Table 2
Lesions of uncertain malignant potential (B3) on stereotactic VANCB: surgical excision histology outcomes for different B3 entities and associated PPV for breast malignancy.

B3 category on VANCB with SE	Original series N (%)	Pts with SE N (%)	Referral Rate (%)	Non malignant on definitive/final surgical excision diagnosis	Malignant (invasive or ductal in situ carcinoma) on definitive/final surgical excision diagnosis	PPV (%)
AEPDT	1160 (38.3%)	721 (43.9%)	62.2%	524	197	27.3
FEA	556 (18.3%)	245 (14.9%)	44.1%	214	31	12.7
LIN	630 (20.8%)	377 (22.9%)	59.8%	294	83	22.0
RS	370 (12.2%)	132 (8.0%)	35.7%	118	14	10.6
PL	258 (8.5%)	135 (8.2%)	52.3%	117	18	13.3
Other entities	58 (1.9%)	34 (2.1%)	58.6%	28	6	17.6
All B3 entities	3032 (100%)[a]	1644 (100%)	54.2%	1295	349	21.2

[a] For institution 4, the type of lesion was available in 18 out of 93 cases, so the total number is 3032 instead of 3107.

Table 3
Distribution of B3 type of lesions and frequency of B3 category: review of the literature.

Type of lesion of B3 category	Lee AHS et al., 2003[8]		Houssami N et al., 2007[7]		Dillon MF et al., 2007[9]		El-Sayed ME et al., 2008[6,a]		Lieske B et al., 2008[10]		Hayes BD et al., 2009[11]		Noske A et al., 2010[12]		Present study, 2010[b]	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
AEPDT	33	28.4%[c]	172	46.3%[c]	54	25.6%[c]	188	36.0%[c]	90[d]	40.9%	25	17.7%	24	19.7%	1160	38.3%
FEA									1	0.5%	8	5.7%	43	35.2%	556	18.3%
LIN	14	12.1%	29	7.8%	12	5.7%	33	6.3%	25	11.4%	6	4.3%	10	8.2%	630	20.8%
RS	31	26.7%	63	16.9%	63	29.9%	156	29.8%	45	20.4%	57	40.4%	6	4.9%	370	12.2%
PL	24	20.7%	70	18.8%	34	16.1%	124	23.7%	35	15.9%	24	17.0%	26	21.3%	258	8.5%
Other entities	14	12.1%	38	10.2%	48	22.7%	22	4.2%	24	10.9%	21	14.9%	13	10.7%	58	1.9%
Proportion of B3 in the CB original series	3.0% (116/3822)		9.2% (372/4035)		5.7% (211/3729)		5.2% (705/13,452)		5.4% (220/4080)		7.7% (141/1829)		6.6% (122/1854)		11.9% (3107/26,165)	
B3 cases with surgical excision	82.8% (96/116)		75.0% (279/372)		83.9% (177/211)		80.4% (567/705)		90.5% (199/220)		100.0% (141/141)		66.4% (81/122)		54.2% (1644/3032)	

[a] The distribution of B3 categories according to the type of lesion is available only for 523 cases included in the final statistical analysis.
[b] For institution 4, the type of lesion was available in 18 out of 93 cases, so the total number in the distribution according the type of lesion the total number is 3032.
[c] In these series the number of cases is comprehensive of AEPDT and FEA.
[d] 57 cases of ADH + 33 cases of atypia not otherwise specified. Mammographic presentation of B3 lesions: microcalcifications 57.7%, mass 40.0%, other 2.3%.

in previously published studies[6–12] (overall PPV 24.5%, range 9.9%–35.1%, Table 4). Accordingly, subtype-specific PPVs were generally lower in our study than in the literature, with differences more evident for LIN (22.0% vs 42.3%) and RS (10.6% vs 14.9%).

Overall, a malignancy was diagnosed in 11.5% of all patients classified as B3 at VANCB, irrespective of referral to SE (349/3032). On the other hand, tumors detected at SE after B3 represent the 4.1% (349 out of 8529) of the total number of breast tumors emerged from the whole series of 26,165 VANCBs performed; almost 90% of all malignancies were classified as B5 (7600 out of 8529).

Referral rates and PPVs, overall and separately for the different combinations of participating institutions B3 entity-specific lesions, have been calculated (data shown in the on-line Appendix). A high degree of variation was found, especially concerning the distribution of B3 subtypes for different centres. Even considering only those institutions with a number of cases sufficiently high to draw conclusions, the estimates of referral rate among institutions varied substantially, while the range in PPV estimates was somehow narrower. The ranks correlation coefficients between percentage of B3 cases among total VANCBs and, respectively, referral rates and PPVs were −0.23 and −0.13, not statistically significant, thus allowing to exclude inter-institution differences in the prevalence of B3 cases, biopsy aggressiveness or ability to collect information.

Discussion

Our study represents to our knowledge the largest series of B3 lesions with surgical follow-up published to date and may offer some contributions to the quantification of referral rate and PPV of different B3 lesions as well as the opportunity of comparing the accuracy of conventional NCB and stereotactic VANCB by reviewing PPV of B3 series reported in the literature.

In our large B3 series, overall referral rate tended to be lower (54.2%) in comparison with values reported in the literature for B3

Table 4
Overall and lesion-specific PPV[a] of B3 category for breast malignancy based on surgical excision histology according to the type of core biopsy: NCB and VANCB.

Type of lesion of B3 category	Lee AHS et al., 2003[8,b]		Houssami N et al., 2007[7,c]		Dillon MF et al., 2007[9,d]		El-Sayed ME et al., 2008[6,e]		Lieske B et al., 2008[10,f]		Hayes BD et al., 2009[11,g]		Noske A et al., 2010[12,h]		Present study, 2010[i]	
	PPV	n/N	PPV	n/N	PPV	n/N	PPV	n/N	PPV	n/N	PPV	n/N	PPV	n/N	PPV	n/N
AEPDT	46.4%	(13/28)	44.7%	(63/141)	35.0%	(14/40)	32.4%	(61/188)	50.0%	(36/72)	32.0%	(8/25)	35.7%	(5/14)	27.3%	(197/721)
FEA									100.0%	(1/1)	12.5%	(1/8)	6.7%	(2/30)	12.7%	(31/245)
LIN	66.7%	(6/9)	60.9%	(14/23)	44.4%	(4/9)	29.6%	(8/27)	37.5%	(9/24)	50.0%	(3/6)	0.0%	(0/6)	22.0%	(83/377)
RS	20.0%	(5/25)	16.7%	(7/42)	16.6%	(9/54)	12.2%	(19/156)	9.3%	(4/43)	12.3%	(7/57)	0.0%	(0/5)	10.6%	(14/132)
PL	15.0%	(3/20)	22.7%	(10/44)	17.8%	(5/28)	10.5%	(13/124)	25.7%	(9/35)	8.3%	(2/24)	6.7%	(1/15)	13.3%	(18/135)
Other entities	14.3%	(2/14)	13.4%	(4/29)	10.4%	(5/46)	17.8%	(5/28)	33.3%	(8/24)	4.8%	(1/21)	0.0%	(0/11)	17.6%	(6/34)
Overall PPV	30.2%	(29/96)	35.1%	(98/279)	20.9%	(37/177)	20.3%	(106/523)	33.7%	(67/199)	15.6%	(22/141)	9.9%	(8/81)	21.2%	(349/1644)

PPV = Positive Predictive Value; n/N = number of breast malignancies/number of B3 biopsies with surgical excision.
[a] PPV values were calculated over the total of B3 cases with excision histology.
[b] NCB not otherwise specified, study period from July 1998 to June 2000, mono-institutional, histological reports reviewed, no histological slides reviewed.
[c] image guided core biopsy: ultrasound-guided NCB (14 gauge) when lesions were sonographically visible; stereotactic-guided VANCB (11 gauge) was preferentially used when lesions were sonographically invisible and/or microcalcifications, study period from January 1996 to March 2005, mono-institutional, histological reports reviewed, no histological slides reviewed.
[d] 262 cases of B3-B4 NCB: 55% ultrasound-guided NCB (14 gauge) when lesions were sonographically visible; 34% stereotactic-guided NCB (14 and occasionally 11 gauge) when lesions were sonographically invisible; 11% clinical-guided NCB (14 or 16 gauge), study period from January 1999 to July 2005, mono-institutional, histological reports reviewed, no histological slides reviewed.
[e] NCB not otherwise specified, study period from April 1999 to March 2006, multi-institutional, histological reports reviewed, no histological slides reviewed.
[f] image-guided core biopsy: 80% stereotactic-guided NCB (14 gauge), 17.7% ultrasound-guided NCB (14 gauge), 2.3% not specified, study period from April 1999 to March 2005, mono-institutional, histological reports reviewed, no histological slides reviewed.
[g] NCB not otherwise specified, study period from 2000 to 2008, mono-institutional, histological reports reviewed, no histological slides reviewed.
[h] image-guided core biopsy: ultrasound-guided NCB (14 gauge) when lesions were sonographically visible; stereotactic-guided VANCB (11 gauge) when lesions were sonographically invisible and/or microcalcifications, study period from January 2006 to December 2008, mono-institutional, histological reports reviewed, no histological slides reviewed.
[i] image-guided core biopsy: stereotactic-guided VANCB (11 gauge) in lesions sonographically invisible and/or microcalcifications, study period from November 1998 to August 2009, multi-institutional, histological reports reviewed, no histological slides reviewed.

category (range of referral rates: 66.4%–100%),[6–12] possibly because of several characteristics. First, our series is composed exclusively by stereotactic VANCBs that are recognized by a systematic literature review and meta-analysis to provide lower underestimation rates for clinically relevant diagnoses than does conventional stereotactic NCB.[13] Most reported studies[6–12] are series composed by conventional stereotactic and ultrasound-guided NCB and series in which conventional ultrasound-guided NCB and stereotactic VANCB are mixed; thus the comparison of our overall referral rate with those of other published series could be not appropriate. Secondly, a recent mono-institutional Italian study[14] focusing on stereotactic VANCBs in mammographic, non-palpable, ultrasound occult abnormalities over a period of five years (from February 2002 to February 2007) reported 102 cases of B3 lesions (102/530 with a B3 prevalence of 19.2%) with an overall referral rate of 51.9% (53/102), in close agreement with our results, probably reflecting the Italian routine practice in breast screening programmes in a specific period of time. Finally, the lack of standardised parameters that could help to identify subtypes of B3 category to be referred for surgery and those with a very low risk of carcinoma to be referred for clinical follow-up, and contrasting data on this subject resulting from literature, especially concerning B3 lesions diagnosed on VANCB, could in part explain the range of variability of referral rates among participating centres in our study.

A range from 4% to 22% for B3 prevalence among centres is high, and might suggest major differences in pathological criteria to report B3 cases and, subsequently, an inverse correlation between B3 prevalence and PPV. However, this correlation is quite modest, so that we can reasonably exclude that the variability of PPV values across participating institutions is attributable to differences in reporting B3 category. Previously reported studies,[6–12] including both non-palpable and palpable lesions, showed that the prevalence of B3 category varied from 3.0% to 9.2% (overall 5.8%), significantly lower than the value of 11.9% observed in our study. This difference is probably due to differences in the study series (non-palpable plus palpable lesions in published studies[6–12] versus non-palpable lesions, especially microcalcifications, in our study), in image guided devices used (ultrasound or stereotactic NCB plus stereotactic VANCB in published studies[6–12] versus stereotactic VANCB in our study) and in the histological criteria used for reporting B3 category among different studies. While diagnostic reproducibility for borderline proliferative breast lesions on surgical specimens among different pathologists is known to be modest, there are only few studies dealing with diagnostic reproducibility in reporting CB and one has been recently published by our group[15] confirming also in CB the sub-optimal inter-observer agreement when dealing with borderline proliferative breast lesions. On this basis we cannot exclude a certain degree of diagnostic variability among centres in our study, however we strongly feel that a certain degree of diagnostic variability has to be considered also for several published mono-institutional series.[7–12] Overall comparisons between different series should be always interpreted cautiously. A recent UK multi-institutional study[6] among 8 centres reported a range of B3 prevalence from 2.30% to 7.93% and a range of PPV value from 14.3% to 28.3% according to single institutions revealing a certain degree of diagnostic variability in reporting B3 category among different institutions. Nevertheless we think that our and UK study should be interpreted as a general picture of routine practice in a similar extended time frame in two different countries involved in breast screening programmes.

In our study, about one-fifth of B3 diagnoses followed by SE proved to be malignant (overall PPV 21.2%), while in previously published reports PPV ranged from 9.9% to 35.1% (overall PPV 24.5%).[6–12] This variation may be due to differences in the spectrum of assessed lesions (mass versus microcalcifications) and consequently to differences in the proportion of B3 subtypes[6–12]. In our study in fact lesions characterized by microcalcifications (i.e. AEPDT and FEA) or representing an incidental histological finding (i.e. LIN) constituted 77.4% of the whole series and 81.7% of B3 going to SE. Considering the high frequency of these lesions, an overall PPV of 21.2% has to be considered as suggesting that in sonographically invisible mammography patterns (especially microcalcifications) stereotactic VANCB has a higher accuracy if compared with stereotactic NCB. On the other hand, information on B3 patients who did not perform a subsequent SE was not available, thus we cannot exclude that the PPVs we have calculated might be affected by some bias. In particular, if we assume that the frequency of malignancies is lower among B3 patients not performing a SE, compared to those who followed the indication to SE, the PPVs we have reported might be to some degree overestimated, although they appear in agreement with most published studies.

One reason explaining why a malignant lesion might be classified as B3, especially by conventional NCB, is that pathological interpretation of specimens can be limited by small sample sizes. Stereotactic-guided NCB has limitations especially in the assessment of microcalcifications due to not reliable sampling of the lesion.[1,16] VANCB was introduced in 1995 to overcome conventional NCB limitations allowing a substantially larger total volume of breast tissue made available for greater diagnostic accuracy.[2,13]

A recent systematic review and meta-analysis suggested that stereotactic VANCB has an underestimation rate for malignancy lower than stereotactic-guided conventional NCB for non-palpable lesions and/or microcalcifications[13]: the main aim of replacing conventional stereotactic-guided NCB with stereotactic VANCB in the assessment of such patterns is therefore that of increasing the accuracy of non-operative breast diagnosis, thus avoiding unnecessary surgery.

Atypical epithelial proliferation of ductal type (AEPDT)

In agreement with the majority of previous studies on core biopsy,[6–12] AEPDT is the most frequent lesion in our B3 series (38.3%). Microcalcifications were the mammography pattern in 83.4% of the cases (median 85.7%), and it is well known that AEPDT is associated with microcalcifications: this explains the high frequency of AEDPT in our series. PPV of AEPDT is 27.3% which corresponds to other studies on VANCB reported in the literature,[1] while it is significantly lower when compared with studies reporting on conventional NCB or conventional NCB plus VANCB.[6–12] Several studies have noted the decreasing underestimation rates of AEPDT with the use of 11-gauge or 9-gauge needles (ranging from 10% to 39%) versus a 14 gauge device (ranging from 18% to 87%), based on the lower rate of malignancy on the subsequent SE.[17,18] However, the use of VANCB cannot sufficiently exclude the discordance between AEPDT found in VANCB and carcinoma found in subsequent SE to avoid open surgery. A recently published systematic literature review and meta-analysis on AEPDT diagnosed in VANCB reported a pooled PPV of 20.9% concluding that diagnosis of AEPDT in VANCB warrants surgical excision.[19]

Our results support the present standard clinical practice of performing SE for lesions yielding AEPDT on VANCB.

Lobular intraepithelial neoplasia (LIN)

LIN in our stereotactic VANCB series represents 20.8% of the B3 cases; 22.0% of patients with LIN were found to have a malignant lesion at SE.

In a recent review of the literature,[20] percentage of invasive carcinoma or DCIS on SE following a diagnosis of LIN on CB ranged

from 0% to 67%, thus supporting the practice of surgical excision. In a similar review, Hwang et al.[21] arrive at opposite conclusions suggesting that LIN on CB with concordant radiology and pathology can be appropriately managed with clinical follow-up without surgery.

A common drawback of all studies on outcome of LIN on CB is the relatively small number of cases that can be identified within a single institution. Brem et al.[22] reported on a multi-institutional study of 278 cases of LIN on CB. SE was performed in 164 cases and the overall underestimation rate was 23.2%. Higher underestimation rates were associated with the presence of a radiological mass or calcifications, a higher BI-RADS category and the use of a conventional NCB device. These authors recommended that all cases with LIN on CB should undergo SE because significant sampling error occur regardless the type of CB device.

In contrast Nagi et al.[23] reported a study on 45 cases of purely incidental LIN with SE diagnosed on conventional NCB or stereotactic VANCB, and in only three cases a malignancy was found corresponding to an underestimation rate of 6.7%. The authors concluded that LIN could be managed with clinical surveillance without the need for SE provided that careful radiological-pathological correlation is performed.

The management of LIN diagnosed on CB remains controversial especially in cases with radiological-pathological discordance and when the correlating radiological lesion is benign and would not by itself require SE.[24] At present, the majority of authors recommend SE for all cases of LIN diagnosed on CB.

Papillary lesion (PL)

PL in our series represents 8.5% of B3 cases, with a 13.3% value for PPV of malignancy after SE. Recent studies dealing with PL diagnosed by NCB have reported upgrade rates varying between 6% and 36%. The management of patients with papillary lesions diagnosed on NCB is at the moment somehow controversial.

Some recent studies emphasize the importance to differentiate papillary lesions on CB in uncomplicated benign papillary lesions and papillary lesions with atypia.[18] Most authors agree that a PL with atypia requires SE for definitive histological diagnosis, while the issue of whether to proceed to a SE for benign papilloma diagnosed at CB remains controversial due to the infrequent association with malignancy.[6]

It has been suggested that a complete removal by large gauge vacuum-assisted biopsy could be a safe alternative to SE for benign papilloma without atypia diagnosed on NCB.[25,26] Recently however, Bernik and colleagues[27] reported that percentage of upgrade was 54% and 11.8% in atypical and benign papilloma respectively, concluding that SE should be performed in all papillary lesions diagnosed by NCB.

Flat epithelial atypia (FEA)

FEA represents 18.3% of cases in our B3 series. This frequency is not comparable with other series because of FEA as separate entity of B3 category is reported only in more recent published studies, after the adoption of the morphologic classification scheme proposed in recent years.[28]

In our series, the PPV of FEA is 12.7%, in good agreement with values found in previous reports (from 0% to 21%).[29–32] It must be noted, however, that data on SE outcome after a diagnosis of FEA on NCB or VANCB have a limited value due to the small number of cases in all published series.

There is emerging evidence that FEA is the earliest morphologically identifiable non-obligate precursor of low grade breast cancer; besides, this type of lesion may coexist with entities such as DCIS, LCIS, lobular invasive cancer and low grade invasive cancer, so that further studies are required to clarify clinical behaviour and provide guidance regarding management of this type of lesion.[5]

Radial scar (RS)

RS represents 12.2% of our B3 cases series, and 10.6% of these patients were found to have a malignant lesion on SE. This is the lowest type-specific PPV.

The occurrence of invasive ductal carcinoma or DCIS involving or in close proximity to RS is well known, with upgrade rates to malignancy ranging from 0% to 34%[18], but values decrease to 0–12% for RS without atypia diagnosed on NCB.[25,33] In this latter group complete vacuum-assisted excision at stereotactic guidance could be considered an alternative to SE, providing that a pathologic-mammographic correlation exists.

In conclusion, the results of our study confirm findings from earlier reports demonstrating an improved accuracy of stereotactic VANCB compared to conventional NCB in the non-operative diagnostic procedure performed for non-palpable sonographically invisible breast lesions, especially microcalcifications.

Recently, vacuum-assisted excision has been proposed as an alternative strategy to SE in the treatment of B3 lesions without atypia, such as papillary lesions and radial scars, providing thorough multidisciplinary discussion has taken place before treatment is decided.[25]

All cases with a B3 diagnosis on CB should be discussed at a multidisciplinary meeting; the risk of associated malignancy at SE in our study varied according to different B3 categories. Our results suggest that, at the moment, the majority of B3 lesions, even if diagnosed at VANCB, should undergo SE in order to avoid missing a malignancy.

Additional studies, looking at radiological and morphological parameters may be useful for a better assessment of malignant potential of different B3 entities thus minimising unneeded surgery in the majority of patients with a B3 diagnosis on CB and a benign diagnosis on SE.

Ethical approval

Ethical approval was not required.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.breast.2010.12.003.

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