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On the diagnostic accuracy of stereotactic vacuum-assisted biopsy of nonpalpable breast abnormalities. Results in a consecutive series of 769 procedures performed at the Trento Department of Breast Diagnosis

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ABSTRACT

Aims and background. To assess the diagnostic accuracy of stereotactic vacuum-assisted biopsy of nonpalpable breast lesions.

Methods and study design. 769 consecutive vacuum-assisted biopsy procedures were retrospectively reviewed. Positive predictive value for carcinoma (B5) at vacuum-assisted biopsy was assessed on the overall series and by age, lesion morphology and size, degree of suspicion and calendar period. The accuracy of vacuum-assisted biopsy was based on surgical histology or follow-up (no change at 12 months was assumed as negative).

Results. Lesions were depicted as isolated microcalcifications, opacity + microcalcifications, or opacity in 716 (93.1%), 28 (3.6%), or 25 (3.2%) cases, respectively. Vacuum-assisted biopsy was negative (B1 = 63; B2 = 319) in 382 (49.7%), borderline (B3) in 142 (18.5%), suspicious (B4) in 2 (0.3%), and positive (B5) in 243 (31.6%) cases (*in situ* = 185, 24.1%), invasive = 58 (7.5%)), respectively. Age ($\chi^2_{df3} = 19.50$; $P < 0.002$), size ($\chi^2_{df4} = 51.02$; $P = 10^{-6}$) and degree of suspicion ($\chi^2_{df2} = 146.68$; $P = 10^{-6}$) were associated with a B5 outcome, no significant association was evident for morphology ($\chi^2_{df2} = 0,47$; $P < 0.78$), whereas calendar period had a moderate but significant inverse association ($\chi^2_{df2} = 6.12$; $P < 0.04$). The positive predictive value for surgically confirmed carcinoma (*in situ* or invasive) was 0% for B1, 0.7% for B2, 12.3% for B3, 100% for B4, 92.7% for *in situ* B5, and 94.6% for invasive B5. Conversion from *in situ* B5 to invasive was 12.3% and was insignificantly associated with size ($\chi^2_{df2} = 0.95$; $P = 0.62$) and histology grade ($\chi^2_{df2} = 3.64$; $P = 0.16$). Down-grading of vacuum-assisted biopsy lesions to a less severe histology occurred in 13 (7.2%) *in situ* and in 16 (28.6%) invasive carcinomas. B3 cases upgrading to more severe lesions was 0%, 4.5% or 16.0% in the presence of no, mild, or severe atypia.

Conclusions. The study confirmed a good performance of vacuum-assisted biopsy, possibly influenced by the local scenario (e.g., radiologist's and pathologist's interobserver variability and sampling modality). Conflicting results with the literature may have local explanations rather than being due to inadequate performance.

Introduction

Percutaneous core biopsy (core needle biopsy, commonly with 14 G probes) has become a common diagnostic procedure as a third-level test for the differential diagnosis of abnormalities with a suspicious report at palpation/imaging. It has a good performance[1-4] and is progressively replacing fine needle aspiration cytology for its higher accuracy[5] and lower inadequate sampling rate[3].

Key words: breast cancer, core biopsy, diagnosis, vacuum-assisted biopsy.

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Vacuum-assisted core-needle biopsy (VAB, commonly with 11 G probes), allowing for multiple and larger coaxial core sampling at 360° with a single skin insertion, has been introduced more recently and has partially replaced classic core-needle biopsy since it is more accurate and with a lower risk of underestimating lesion severity. VAB is particularly effective when the lesion to be sampled is not circumscribed (as for masses, which are commonly seen at ultrasonography and sampled with core-needle biopsy under ultrasound guidance) but is depicted as an area with ill-defined borders, typically a cluster of isolated microcalcifications (mostly occult at ultrasonography and requiring stereotactic guidance). Such abnormalities were the first for which fine needle aspiration cytology was abandoned, due to its poor accuracy[6].

Although VAB is commonly used, it is not free of limitations, particularly for the risk of carcinoma (either *in situ* or invasive) being reported at VAB as borderline (B3) or of invasive carcinoma being reported at VAB as *in situ*[1,3,4,7,8].

In the present study we considered a consecutive series of stereotactic VAB procedures performed at a breast diagnosis department on nonpalpable lesions occult at ultrasonography. The diagnostic accuracy and limitations of VAB are evaluated and compared with average literature figures.

Material and methods

The studied series was consecutively observed from January 2002 to December 2010. Lesions undergoing stereotactic VAB procedures had been diagnosed within the local district population-based mammography screening program or in subjects self-referring to the Breast Diagnosis Department clinics. All breast diagnosis activity in the Trento district is centralized at the Breast Diagnosis Department, where all necessary diagnostic procedures are available.

VAB samplings were performed using a stereotactic digital device (Diamond® Δ^{32} General Electric Medical System/Instrumentarium, Tuusula, Finlandia) equipped with a special lateral arm to support the VAB probe. The VAB probe used in all cases was a Mammotome® system (Ethicon Endo-Surgery, Cincinnati, Ohio, USA) with 11 G needles.

VAB procedures were mostly performed on the patient in the upright sitting position, using a dedicated chair (Diamond Stereotactic Chair, Instrumentarium), whereas in a limited number of cases, due to an anatomical situation and/or lesion site in the breast, the patient was positioned lying on her side on a self-blocking non-dedicated bed whose height was electronically controlled.

After a proper localization of the needle was controlled, a first core series was sampled in all cases (12 cores at 30° intervals on a 360° range), whereas a further series (6 to 12 cores) was sampled when microcalcifications were not identified on the X-ray check of the first sampled cores.

Several radiologists gave indications for sampling and/or performed the procedure during the study period. Between 2002 and 2005, two radiologists performed the VAB procedures, whereas after 2005 four other radiologists were involved. Presently, the whole team of six breast-dedicated radiologists is involved in giving indications for VAB, and VAB procedures are distributed among all operators with no selection.

Indication to surgery after VAB was essentially based on VAB histology outcome, although the morphology of the sampled lesion at imaging contributed to prompt surgery in the case of borderline histology and in a minority of cases with negative histology.

The following variables were considered for the study purposes: a) age; b) lesion morphology (calcifications, opacity, opacity + calcifications); c) size of sampled lesion (maximum diameter = largest distance between opposite margins, e.g., between the most distant microcalcifications); d) level of suspicion at imaging, according to three grades (R3-4-5), as recommended in the European Community Guidelines[9], for which predictivity estimates have already been reported[10]; e) date of VAB procedure; f) VAB histology report, according to B1-5 classification recommended by European Community Guidelines[11]; g) final histology report (WHO classification) for cases undergoing surgery; h) follow-up outcome for cases with no surgical confirmation (cases with negative histology report at VAB or refusing recommended surgery were assumed as negatives if no change was observed after at least one year).

VAB histology report distribution was first analyzed. We then determined the positive predictive value (PPV) for carcinoma (either *in situ* or invasive) as an indication to VAB on the whole series and according to age, morphology, lesion size, degree of pre-biopsy suspicion and calendar time. As regards the latter point, since a certain attribution of biopsy indication to a single reader was not possible (cases underwent double reading, arbitration of discordances was systematic, or the operator designed for the VAB procedure might refuse indication in a minority of cases), we limited our evaluation of a possible association of PPV with calendar period, knowing that from 2006 onwards indication to VAB was given by a broader panel of radiologists, including four with less experience. We then evaluated the association between VAB and surgical histology, particularly to asses the "conversion" rate to a more severe lesion of B3 lesions and *in situ* carcinomas. Observed results were compared to average findings in the literature. Observed differences within the study were checked by the chi-square test, statistical significance being set at $P < 0.05$.

Results

The study considered 769 subjects (average age, 54.3 years; range, 22-86) consecutively undergoing stereotactic VAB for a non-palpable suspicious lesion (isolated microcalcifications = 716 (93.1%); opacity + microcalcifications = 28 (3.6%); opacity = 25 (3.2%)). The VAB histology report was negative (B1 = 63; B2 = 319) in 382 (49.7%) cases, borderline (B3) in 142 (18.5%), suspicious (B4) in 2 (0.3%), and positive (B5) in 243 (31.6%) cases (*in situ* = 185 [24.1%], invasive = 58 [7.5%]).

Table 1 shows the association of several variables to VAB histology outcome. Age ($\chi^2_{df3} = 19.50$; $P < 0.002$), size ($\chi^2_{df4} = 51.02$; $P = 10^{-6}$) and degree of suspicion ($\chi^2_{df2} = 146.68$; $P = 10^{-6}$) showed a direct association with PPV for a B5 outcome, no significant association was evident for morphology ($\chi^2_{df2} = 0.47$; $P < 0.78$), whereas calendar period had a moderate but significant inverse association ($\chi^2_{df2} = 6.12$; $P < 0.04$). A temporal trend was evident also for the prevalence of B3 cases, which showed a significant increase over time, from 13.6% during 2002-2005 to 23.0% during 2009-2010 ($\chi^2_{\text{for trend}} = 7.36$; $P < 0.006$).

Table 2 shows the association of VAB histology report with final outcome. A minority of cases not undergoing surgery did not have a long enough follow-up according to study criteria (at least 12 months = 42 (5.4%)) or were lost to sight (refusing surgery or having surgery elsewhere = 9 [1.1%]). The PPV for histologically confirmed carcinoma (*in situ* or invasive) was 12.3% for B3, 100% for B4, 92.7% for *in situ* B5, and 94.6% for invasive B5. Conversion to invasive carcinoma among *in situ* B5 cases was 12.3%.

VAB was negative (B1-2) in 382 cases. However, 15 were sent for surgical biopsy due to suspicious morphology: 2 carcinomas (one *in situ*, one invasive) were detected (B1 PPV = 0%, B2 PPV = 0.7%). Thus far, no case not undergoing surgery has developed carcinoma within 12 months of follow-up.

VAB was borderline or suspicious (B3 o B4) in 144 cases. Of these, 116 accepted recommendation for surgery, which revealed carcinoma *in situ* in 10 and invasive in 6 (PPV = 11.2%). In 28 B3 cases, surgery was suspended in favor of early recall due to low suspicion at imaging and the absence of atypia or, in a few cases, due to the patient's refusal. None of these cases has yet shown a carcinoma within 12 months.

VAB was positive (B5) in 243 cases. VAB evidence of *in situ* carcinoma was confirmed in 143 of 178 cases with known surgical histology (80.3%), whereas surgical histology showed atypia or was negative in 2 and 11 cases, respectively. In 22 cases (12.2%), surgical histology showed invasive carcinoma. VAB evidence of invasive carcinoma was confirmed in 40 cases with known surgical histology (71.4%), whereas surgical histology showed *in situ* carcinoma or atypia in 13 and 3 cases, re-

Table 1 - Main features of studied cases and their association with VAB histology outcome

	VAB histology outcome			
Variable	Benign (B1-2)	Borderline/suspicious (B3-4)	Positive (B5) (%)	Total
Age, yr				
<40	21	5	8 (23.5)	34
40-49	109	45	50 (24.5)	204
50-59	137	73	85 (28.8)	295
>59	115	21	100 (42.3)	236
Lesion morphology				
Isolated calcifications	355	137	224 (31.2)	716
Opacity + calcifications	15	3	10 (35.7)	28
Opacity	12	4	9 (36.0)	25
Lesion size, mm				
0-5	78	31	22 (16.7)	131
6-15	172	74	88 (26.3)	334
15-30	88	22	75 (40.5)	185
31-50	28	7	32 (47.7)	67
>50	6	6	23 (65.7)	35
Missing	10	4	3	17
Level of pre-biopsy suspicion				
R3	308	107	90 (17.8)	505
R4	68	36	128 (55.1)	232
R5	3	0	25 (89.2)	28
Missing	3	1	0	4
Calendar period				
2000-2005	135	34	80 (32.1)	249
2006-2008	113	49	93 (36.5)	255
2009-2010	134	61	70 (26.4)	265
Total	382	144	243	769

VAB, vacuum-assisted core-needle biopsy.

Table 2 - Association of VAB histology to final outcome

	VAB histology						
Final outcome	B1	B2	B3	B4 *in situ*	B5 *in situ*	B5 invasive	Total
Surgical histology							
Benign	2	9	55	0	11	0	77
Atypia	1	1	45	0	2	3	52
Carcinoma *in situ*	0	1	8	2	143	13	167
Invasive carcinoma	0	1	6	0	22	40	69
Unchanged at follow-up	57	269	27	0	0	0	353
Insufficient follow-up[a]	3	38	1	0	0	0	42
Lost to sight[b]	0	0	0	0	7	2	9
Total	63	319	142	2	185	58	769

[a]Subjects with less than 12 months of follow-up. [b]Subjects who refused surgery, were operated elsewhere, and were lost to sight. VAB, vacuum-assisted core-needle biopsy.

spectively. Down-grading of VAB lesions to a less severe histology was most likely due to the fact that VAB had removed all the more severe lesion.

Table 3 shows the association of histology subtyping of B3 cases to carcinoma (*in situ* or invasive) at surgical histology. Overall, the PPV for carcinoma was 12.3%. No case of B3 without atypia showed carcinoma at surgical histology. Lesions with mild atypia (flat epithelial atypia or lobular intraepithelial neoplasia grade 1 or 2) showed one case of invasive carcinoma out of 22 cases (PPV = 4.5%), whereas cases with severe atypia (atypical ductal hyperplasia, grade 3 lobular intraepithelial neoplasia) showed 13 carcinomas out of 81 cases (PPV = 16.0%). The increase in B3 prevalence over time favored a higher prevalence of B3 with mild or without atypia, accounting for 20.0%, 27.0% or 49.4% of all B3 during 2002-2004, 2005-2007 or 2008-2010, respectively (χ^2_{df2} = 9.39; P = 0.009).

Table 4 shows surgical histology outcome in cases with VAB evidence of *in situ* carcinoma according to histology grade and lesion size. The probability of conversion to invasive carcinoma was directly associated with size (χ^2_{df2} = 0.95; P = 0.62) and with histology grade (χ^2_{df2} = 3.64; P = 0.16), though not at a statistically significant level.

Table 3 - Association of B3 histology subtyping and surgical biopsy outcome in 114 operated cases

	Surgical biopsy outcome			
B3 subtyping	Benign	Atypia	*In situ* carcinoma	Invasive carcinoma
Papillary lesion[a]	3	0	0	0
Radial scar[a]	5	1	0	0
Mucocele-like[a]	1	1	0	0
FEA	8	5	0	1
LIN1	1	2	0	0
LIN2	3	2	0	0
LIN3[b]	3	7	1	3
ADH	31	27	7	2

[a]Without atypia. [b]Includes cases reported as lobular carcinoma *in situ* for study purposes. FEA, flat epithelial atypia; LIN, lobular intraepithelial neoplasia grade 1 or 2; ADH, atypical ductal hyperplasia.

Discussion

The present series is sufficiently large enough to allow a reliable analysis of the diagnostic accuracy of VAB. It is noteworthy that the Trento District has a unique Breast Diagnosis and Pathology Department where all breast diagnosis referrals for both screening and clinical purpose are centralized. Considering also that the District has a limited "diagnostic" migration to other regions, the studied series accounts for a reliable sample of the whole resident population, as typical biases of areas with multiple concurrent diagnostic facilities may be excluded. A limited "therapeutic" migration to other regions and the existence of a local Cancer Registry allow for a complete follow-up of studied cases.

The PPV for carcinoma at VAB (B5) was directly associated to age, size and grade of suspicion, thus confirming previous reports on this aspect[3]. The observed lack of association with lesion morphology is most likely biased by the fact that VAB stereotactic series rarely include lesions depicted as masses, as most are easily identified at ultrasonography and thus undergo core-needle biopsy under ultrasound guidance. The reduction of PPV with time is probably due to the adoption of an increasingly lower threshold for suspicion. This may be explained by a greater confidence with the technique, which is thus more easily performed, or by an increasing fear of medical litigations for diagnostic delay in simply followed-up cases. It may also be explained by the inclusion in the team of radiologists with less experience, who may have favored the indication to VAB looking for higher sensitivity though with lower specificity. In fact, the rate of mild suspicious cases (R3) increased from 53% during 2002-2003 to 72% during 2009-2010 ($\chi^2_{\text{for trend}}$ = 13.21; P = 0.0002).

Table 4 - Surgical histology outcome in 180 cases of *in situ* carcinoma[a] (B4,B5) at VAB

	Surgical histology				
	Benign	Atypia	*In situ* carcinoma	Invasive carcinoma (%)	Total
Grading					
G1	5	0	13	0 (0)	18
G2	3	0	41	5 (10.2)	49
G3	3	2	83	16 (15.4)	104
Missing	0	0	8	1	9
Lesion size, mm					
0-10	9	0	47	6 (9.7)	62
11-20	1	2	36	5 (11.4)	44
>20	1	0	61	11 (15.1)	73
Missing	0	0	1	0	1
Total	11	2	145	22 (12.2)	180

[a]Two cases of B4 *in situ* carcinoma at VAB are included.

A negative VAB histology finding was highly reliable. All B1-2 cases undergoing surgery in the presence of high suspicion at imaging turned out to be benign. Such a good result may be explained by the large amount of routinely sampled tissue (12 cores at least) and by further sampling when microcalcifications were not evident at first sampled core X-ray checks, both conditions suggesting optimal lesion sampling. The completeness of lesion removal was also demonstrated by the relevant fraction of *in situ* (7.2%) and invasive (28.6%) carcinomas at VAB showing less severe or negative findings at surgical histology.

B3 lesions are relatively more prevalent (18.7%) compared to average literature findings[3,7,12]. This may depend on a greater attitude of pathologists to use such a diagnostic report, consistent with the low observed PPV (12.2%), definitely lower than reported in the literature[3,7,12]. The increase in B3 prevalence over time, mostly of B3 without or with mild atypia, may suggest a change of diagnostic criteria in the attribution of the B3 category. Still, a substantial difference in PPV is evident between B3 cases with severe atypia (16.0%) and those with minor atypias (4.5%) or with no atypia (0%). The finding suggests that the presence of severe atypia might be a reliable indicator to prompt surgery in B3 cases[13,14] and supports a choice favoring sole follow-up of B3 cases with mild or no atypia and low suspicion at imaging. This attitude was adopted in the present study, thus far with no carcinoma diagnostic delay.

Conversion from carcinoma *in situ* at VAB to invasive carcinoma at surgical histology was observed in 12.2% of the cases, a slightly lower frequency compared to the literature[3,7,15]. The finding may also be explained by the large and complete sampling of the lesions, which reduces the probability of missing limited infiltration foci. The study confirmed that both grade and size are associated with the probability of conversion to invasive carcinoma, but the finding did not reach statistical significance, probably for the limited examined sample size. In any case, it is worth noting that only a fraction of cases with conversion to invasive carcinoma at surgery might be predicted by a high grade (16 of 21) or by a large size (11 of 22). This is in line with other reports[3,7,14] and suggests that such a size- and grade-based prediction (commonly used by some centers, e.g. to select *in situ* carcinomas for the sentinel node procedure) is not highly reliable.

In conclusion, we observed a good performance of VAB in the study institution. It is also evident, in accord with literature findings, that several indicators of VAB performance may be strongly influenced by local variables: criteria to indicate VAB may affect carcinoma prevalence in VAB series; the amount of sampled tissue may affect the conversion rate to more severe lesions compared to those detected at VAB on one side, or negative findings rate at surgery on the other; criteria adopted by pathologists to report B3 and B4 may be more or less strict and thus affect prevalence and PPV of these lesions; completeness of surgical specimen examination may affect conversion rates to more severe lesions. All these conditions may contribute to the variability of VAB performance indicators observed in the literature and justify the difficulty in providing reliable reference standards and the need for local verification of diagnostic accuracy. When results are apparently different from the literature, local explanations should be looked for a, before VAB performance is considered to be inadequate.

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