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Accuracy Rates of US-guided Vacuum-assisted Breast Biopsy

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Abstract. *A prospective study designed to measure the accuracy of mammography (MRx), ultrasound (US), fine-needle aspiration cytology (FNAC) and one of the most recently introduced techniques, vacuum biopsy (VB), in the diagnosis of breast cancer is reported. A sample of 146 breast lesions on 135 patients were examined. The design of the study made it possible to compare MRx, US, FNAC and VB directly, because it excluded several confounding variables. Statistical indicators – sensitivity, specificity, predictive values (PPV and NPV), false-negative and false-positive rates (FN and FP), suspicious plus indeterminate rate and likelihood ratios (LR) – were calculated. Results: The NPV of MRx and US were remarkably high (92.4% and 97.9%, respectively), confirming previous reports. The complete sensitivity of FNAC was 80%, while specificity was 99.1% and LR of positive tests 88.8. The combined score of FNAC, US and MRx resulted in a good increase in complete sensitivity (97.1%), when compared with the results of the single diagnostic tests evaluated separately. The absolute sensitivity of VB was 97.1% and specificity was 100%. In conclusion, considered together, MRx, US and FNAC appear to be reliable diagnostic procedures and, when they are all negative, the possibility of a cancer is extremely low, although it cannot be completely ruled out. The VB test had the highest absolute sensitivity among all the methods compared. Therefore, this technique could be considered conclusive in diagnostically doubtful cases, avoiding open surgical biopsy.*

Breast cancer accounts for one-third of cancer diagnoses (more than 192,200 new cancer cases in 2001) and 15% of cancer deaths in U.S. women (1, 2) and is believed to be the most common cause of malignancy for women in most other Western countries, too. In Europe, breast cancer accounts for 34% of all prevalent cancers in females and in Italy over 33,000 new breast cancer cases were expected in 2002 (3).

Over the last 25 years, the diagnostic approaches and therapeutic strategies for breast cancer have changed dramatically and mortality rates have fallen by 21% as a result of earlier detection and improved treatment. The diagnostic tools have gradually become more diversified and sophisticated, with a consequent improvement in their resolution limits and accuracy, the tools referred to being digital mammography, ultrasound (US associated with colour doppler, power doppler, contrast agents), magnetic resonance, fine-needle aspiration biopsy (FNAC), core biopsy (CB), vacuum biopsy (VB) and advanced breast biopsy instrument (ABBI). A crucial role has been played by the introduction of national screening programmes (4).

At present, according to the European Quality Assurance Guidelines in Mammography screening (5) the "Triple Approach" is recommended: combined physical examination, mammography (MRx) and FNAC. By introducing mammography screening programmes, however, the size of detected breast lesions has become smaller and the diagnostic problems greater (6), so that it seems necessary to redefine the conditions and indications in the use of the new diagnostic tools recently developed.

The aim of this paper was to describe a prospective study, carried out in a well-defined clinical and experimental setting, in order to report the accuracy of certain well-established techniques, such as MRx, US and FNAC, in our sample of women, and to measure the accuracy of a recently introduced technique, VB, in the diagnosis of breast cancer.

Patients and Methods

The study comprised 135 patients selected for vacuum biopsy from among over 2,500 referred to the "P. Valdoni" Surgical Department of the University Hospital "Policlinico Umberto I" in Rome, Italy, from September 1998 to June 2000. All the patients' previous examinations and clinical data were thoroughly reviewed to select

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Table I. *Population characteristics.*

	Clinical exam		Family history[1]		Localization		Quadrant			Dimension (cm)		
Age (years)	Non-palpable	Palpable	Yes	No	Right	Left.	Superior	Inferior	Both	x≤1	1<x≤2	x>2
x≤40	11	13	3	19	12	12	15	3	6	4	12	7
40<x≤50	41	19	16	38	29	31	43	5	12	21	21	17
x>50	43	19	15	42	36	26	33	9	20	23	17	18
Total	95	51	34	99	77	69	91	17	38	48	50	42

[1]In two cases out of 135 subjects family history for breast cancer was not known.

cases in which second level examinations were absolutely necessary. The patients were included in the study according to the following clinical parameters: A) lesion with clinical/instrumental (MRx and US) controversial diagnosis, or B) ultrasound undetermined lesions without mammography (patients <40 years); and either of the following: lesions <1.5 cm in diameter; deep non-palpable lesions >1.5 cm in diameter, difficult to sample by core biopsy.

Since the cytological and histological specimens were taken under ultrasound guidance, all women included in the study had a lesion proven to be ultrasonographically evident. The total number of lesions was 146 on 135 patients, since 8 patients had two and one patient had four separate areas localized and sampled. One case, diagnosed as atypical hyperplasia, both ductal and lobular, was excluded, because the aim of the study was not to verify the diagnostic tests in borderline lesions. All the women were Caucasian and their clinical data are summarized in Table I. The average age was 49.4 years, ranging between 28 and 78. Two-thirds of the lesions were non-palpable (95/146). Five cases were areas of microcalcifications. In one case the dimension was not recorded. Forty-two lesions were larger than 2 cm in diameter. These lesions were sampled by VB instead of CB because of deep nodules suspected to be large carcinomas eligible for neo-adjuvant chemotherapy. Ninety-eight out of 140 of them were smaller than or equal to 2 cm in diameter and 48 of them had a maximum diameter of less than or equal to 1 cm. Most lesions were on the upper quadrants (91/146).

At the Breast Centre of the Surgical Department, US, FNAC and VB tests were performed during the same session by the same operator on all the women. MRx had been previously performed at some other institution on all but 13 women under 40 years of age. Before taking FNAC and VB, coagulation assays were carried out by standard methods and informed consent was obtained from the patients. US (7.5-10MHz CD-PD probe AU5 Esaote Biomedica, Italy) was used to detect lesions and as a guidance for both FNAC and VB (Ethicon Endo-Surgery, Somerville, NJ, USA). FNAC was performed by the standard technique with 3 or more passes, using a 21 to 23-gauge needle. No immediate adequacy assessment of the cytological sample was performed. The material was smeared on 2 to 6 glass slides and stained according to Papanicolaou. MRx and US-Doppler classical patterns (such as the presence of calcifications, echogenicity, shadow, vascularization, *etc.*) were recorded for all patients. An 11-gauge needle was used for VB: four to ten specimens were taken from each lesion and processed according to the standard procedures. All the specimens proved to be adequate both for routine stains and for immunhistochemical analysis of prognostic and predictive markers. Cytological smears were classified as follows: non-diagnostic (cases with few, less than six, normal looking cell clusters, in which no diagnostic conclusion could be reached (7)), benign, atypia probably benign, suspicious of malignancy, malignant (European Guidelines (5)). Ultrasound and mammographic examinations were classified by the Breast Centre operator according to the EUSOMA classification: normal/benign, benign lesion, indeterminate, suspicious of malignancy, malignant features. Histological specimens were classified as either benign or malignant.

After the tests, 45 women underwent surgery, 34 of them following a positive outcome of the biopsy and the remaining 11 because of a lasting suspicion of malignancy. The remaining women were checked every 6 months according to the standard. The follow-up ranged from 24 to 50 months (on average 39 months). No positive cases were detected during this time. The histological diagnosis on surgical specimen, when available (45 cases), was considered as the gold standard. In all the other cases, the negative clinical results of the follow-up were taken to be the true outcome.

Calculations of sensitivity, specificity, positive predictive value (PPV) of malignant, PPV of suspicious (including indeterminate), negative predictive value (NPV), false-negative rate (FNR) and false-positive rate (FPR) were carried out for MRx, US and FNAC according to the European Guidelines (5). These parameters were also calculated for the combined results (cumulative score = CS) of MRx, US and FNAC, obtained taking the "highest" score, as suggested by Westenend *et al*. (8). Sensitivity was calculated in two ways, the first including only cases with a diagnosis of malignancy (absolute sensitivity) and the second including cases with a diagnosis of malignant, suspicious or indeterminate (complete sensitivity). Other screening indicators computed were the likelihood ratios (LR) of positive and negative tests, which are defined as follows:

LR of positive test = Sensitivity/(1- Specificity)

LR of negative test = (1- Sensitivity)/Specificity

(see Sullivan (9) and references therein). Complete sensitivity was used in the calculations. Computation was provided by the EPI_PAK (9) and PEPI (10) packages.

Results

Tables II, III, IV and V show the comparisons between the outcomes of the single diagnostic tests and the definitive diagnosis. In Table VI, the cumulative score of the three diagnostic tools is reported. For each test, Table VII shows absolute and complete sensitivity, specificity, PPV for

Table II. *Mammography vs gold standard.*

	Gold standard		Total
Mammography	Benign	Malignant	
Normal/Benign	44	6	50
Benign lesion	41	1	42
Indeterminate	0	1	1
Suspicious	16	16	32
Malignant	0	10	10
Total	101	34	135

Table III. *Ultrasound vs gold standard.*

	Gold standard		Total
Ultrasound	Benign	Malignant	
Normal/Benign	0	0	0
Benign lesion	92	2	94
Indeterminate	4	3	7
Suspicious	15	16	31
Malignant	0	14	14
Total	111	35	146

Table IV. *FNAC vs gold standard.*

	Gold standard		Total
FNAC	Benign	Malignant	
Non diagnostic	27	2	29
Benign	83	5	88
Atypia/probably benign	0	0	0
Suspicious	1	1	2
Malignant	0	27	27
Total	111	35	146

malignant, PPV for suspicious and indeterminate, NPV, FN and FP rates, suspicious and indeterminate rates. LR for positive and negative tests are reported in Table VIII.

There were 7 false-negative MRx diagnoses (Table II): 5 infiltrating ductal carcinomas and 2 lobular carcinomas, one infiltrating and one *in situ* (CIS). In 6 cases no lesion could be detected, while in the last one a malignant lesion was misinterpreted as benign. All the lesions were in the upper quadrants and all but one (clearly malignant) were suspicious on ultrasound. In the six MRx imagings where no lesion was evident, the cytological examination was positive, while in the seventh case (an MRx benign-appearing lesion) a carcinoma was detected by VB. Out of the 33 cases classified as indeterminate or suspicious by MRx, 17 were histologically confirmed as malignant. All 10 cases with strong evidence of malignancy were confirmed at surgery. Eleven women under 40 years of age were not examined by MRx. One of these women was subjected to MRx only after diagnosis of malignancy: this case is not included in Table II.

Table V. *Mammotome vs gold standard.*

	Gold standard		Total
Mammotome	Benign	Malignant	
Benign	111	1	112
Malignant	0	34	34
Total	111	35	146

Table VI. *Combined score vs gold standard.*

	Gold standard		Total
Combined score	Benign	Malignant	
1 Normal/Non diagnostic	6	0	6
2 Benign lesion	78	1	79
3 Indeterminate	3	0	3
4 Suspicious	24	6	30
5 Malignant	0	28	28
Total	111	35	146

Table III shows the US results: 92 out of 94 US benign diagnoses were confirmed. Out of the 38 indeterminate or suspicious cases, 19 were histologically malignant. All the 14 cases considered malignant were confirmed.

Table IV, which shows the results of the FNAC, indicates that 2 of the 29 non-diagnostic cases and 5 of the 78 cases classified as benign were in fact malignant. Three were CIS and 4 were infiltrating carcinomas. The histotype was ductal not otherwise specified (NOS) in 5 cases and lobular in two. Only 2 cases were classified as suspicious: one of them was a carcinoma. All the 27 cytological specimens classified as malignant were histologically confirmed.

The results of VB are reported in Table V: 111 cases were negative and 34 positive. All the positive cases (2 *in situ* and 32 invasive) were confirmed on the surgical specimen. One negative biopsy proved to be malignant at surgery.

Table VI shows the results of the combined tests (MRx, US, FNAC): one case of cancer was not identified by any of the three methods; 28 out of the 35 cancer cases were detected as such by at least one of the three methods, 27 of which were identified by the cytological exam. However, the number of suspicious cases was noticeably greater as compared to FNAC, 6 of them proving to be malignant.

Table VII. *Diagnostic indicators for single procedures and for the Combined Score (CS). All the figures are percentages.*

	MRx (%)	Ultrasound (%)	FNAC (%)	CS (%)	VB (%)
Absolute sensitivity	29.4	40.0	77.1	80.0	97.1
Complete sensitivity	79.4	94.3	80.0	97.1	n.a.
Specificity	84.2	82.9	99.1	75.7	100
PPV malignant	100	100	100	100	100
PPV suspicious and indeterminate	51.5	50.0	50.0	18.2	not applicable
NPV	92.4	97.9	94.0	98.8	99.1
False-negative rate	20.6	5.7	20.0	2.9	2.9
False-positive rate	15.8	17.1	0.9	24.3	0
Suspicious and indeterminate rate	24.4	26.0	1.4	22.6	not applicable

Table VIII. *Likelihood ratios of positive and negative tests.*

	MRx	Ultrasound	FNAC	CS	VB
LR positive test	5.01	5.51	88.80	3.99	infinity
LR negative test	0.25	0.07	0.20	0.04	0.03

VB failed to diagnose one positive case; however this case was not the same one reported as negative by the cumulative score, so that no positive cases were lost in this study.

Statistical indicators of the performance of the different methods are reported in Tables VII and VIII. The LR-positive test of VB (Table VIII) could not be calculated, since no histological false-positive cases were present in our sample.

Lesions were stratified according to clinical data. Out of the 51 palpable lesions, 18 were invasive cancers. The non-palpable lesions were 95 and 17 of them were malignant. Non-palpable and/or less than one centimeter malignant lesions were more often underestimated by FNAC than palpable or larger ones (complete sensitivity 70 *vs* 89% and 67 *vs* 84%, respectively). Specificity was not affected by those clinical parameters. Similarly, dimension and palpability affected MRx results: small malignant lesions were more often classified as suspicious, sensitivity was lower (complete sensitivity 67 *vs* 83%). Quite the opposite, US sensitivity and specificity were scarcely influenced by lesion diameter.

Discussion

Modern diagnosis of breast disease is a multidisciplinary activity, requiring trained and experienced professionals using specialized equipment with up-to-date sampling and other diagnostic techniques. When imaging techniques (MRx and US) prove to be inconclusive for diagnosis, or even produce contradictory outcomes, it is mandatory to pursue the diagnostic itinerary with mini-invasive interventional procedures (cytological and/or histological). This motivated our prospective study.

First, some remarks on the methodology employed. Our sample is representative of a population of women with a breast lesion diagnostic dilemma; about two-thirds of them had non-palpable lesions. The design of the study made it possible to compare MRx, US, FNAC and VB directly, because it excludes several confounding variables. Most importantly, FNAC and VB were performed on the same lesion, by the same operator during the same session, using the same instrument, so that there were no differences in patient and lesion selection, and the operator dependence was thus standardized.

Secondly, a word of comment on the statistical indicators shown in Table VII. As already mentioned, sensitivity, specificity, predictive values, false-negative and false-positive rates, suspicious and indeterminate rates were calculated according to the European Guidelines (5). Note, however, that there is not a uniquely accepted definition of false-negative rate (FNR) and false-positive rate (FPR) in the literature (11, 12).

In this paper, we also calculated the likelihood ratios (LR). The LR positive test can be interpreted as the ratio of two conditional probabilities: the probability of having a positive (cancer) diagnosis from the examination *given* that the individual under study *has* cancer over the probability of having a positive diagnosis *given* that the individual *does not have* cancer. In the same way, the LR negative test is the ratio of the probability of a negative diagnosis *given* that the individual under study *does have* cancer over the probability of having a negative diagnosis from the examination *given* that the individual *does not have* cancer. These indicators have recently come into use (see for instance Chang (13) and references therein). The LR is the way to incorporate the sensitivity and specificity of a diagnostic test into a single measurement and, besides, it measures the power of a test to change the pre-test into post-test probability of the disease being present. It is particularly useful when combining two or more diagnostic tests (14). It is well-known that the prevalence of the disease always affects one of the indicators that we have mentioned, namely PPV, but not the LR.

Considering sensitivity (Table VII), the absolute sensitivities of the imaging methods (MRx and US) for the group of women under study were not very high (29.4% and 40% for MRx and US, respectively); on the other hand, if complete sensitivity is taken into account, then the US examination had the highest sensitivity (94%), as in other studies (15-17), but with higher specificity than previously reported (15, 16). Suspicious and indeterminate rates of the

two imaging methods were very similar (24% and 26% for MRx and US, respectively), but for both tests only half of such images in our sample corresponded to malignant tumours. Hence, morphological investigations are needed, since imaging techniques alone are not accurate enough for confirmatory purposes. The NPV of MRx and US were remarkably high, confirming previous reports (15, 18). Nevertheless, in general, this is not enough to exclude patients with a negative image test from surgery, and that is why inclusion of FNAC is recommended in the Triple Approach (5, 19). In our sample, the sensitivity of FNAC turned out to be a little lower than that reported by other authors in large studies of palpable (20-22) and non-palpable lesions (23-25), whereas the specificity (99.1%) and LR for positive test (88.8) were notably high. Clinical parameters do influence the FNAB specificity as previously reported (23-25). An erroneous or inadequate sampling could be suggested to explain false-negative cytological results in two inadequate cases and in another case that was negative both cytologically and histologically. In three other cytologically benign-looking samples, an *in situ* carcinoma (one ductal, one lobular and one both ductal and lobular) was detected on the surgical specimen. We would suggest that, in such cases, the few well-differentiated neoplastic cells were underestimated by the cytologist or that incomplete sampling was performed. An interpretation error was the cause of the other cytological false-negative case, namely a ductal carcinoma with several bipolar cells mimicking a fibroadenoma. From our experience, it seems that the cause of false-negatives FNAC is more often the difficulty in sampling and recognizing the few well-differentiated cells coming from small or *in situ* lesions, rather than a lobular histotype as suggested by other authors (26). Moreover, by FNAC it is not possible to define whether the lesion is *in situ* or invasive, while by tissue biopsy it is possible to detect the invasive component. Nevertheless, when only an *in situ* carcinoma is present on the small bioptical sample, invasiveness cannot by ruled out.

The cumulative score of FNAC, US and MRx resulted in an increase in absolute sensitivity and a decrease of specificity if compared with the results of the single diagnostic tests evaluated separately. Observe that the PPV of FNAC was 100%; this means that a pre-surgical biopsy would not have been necessary for the cytologically-positive cases. The results of our study show that MRx, US and FNAC, considered together, are reliable diagnostic procedures and, when they are all negative, the possibility of a cancer is extremely low (NPV=0.988 and LR for a negative test=0.04) although it cannot be completely ruled out. In fact, even benign triple test results do not entirely exclude the possibility of a carcinoma (27).

VB is a recently developed procedure that has some advantages over core biopsy, in that it does not necessitate multiple passages, and tissue specimens are larger and have greater consistency than those obtained by core biopsy, thus being easier to interpret; with this technique *in situ*/invasive lesions are more likely to be detected (28, 29). Moreover, the specimens allow the evaluation, by means of immuno-histochemical analysis, of prognostic and predictive markers such as Ki67, oestrogen and progesterone receptors, Herb-B2, *etc.* In our sample of women, VB had, obviously, the highest absolute sensitivity among all methods compared. Furthermore, the VB test was significantly more sensitive (p-value=0.041) than the combined score. Nevertheless, our study showed that even this test does not always have a 100% sensitivity, as already reported in the literature (30, 31). The only false-negative case was negative both by VB and FNAC, even if the US image showed the tip of the needles to be correctly positioned. A sampling error may have taken place: sampling had taken place either from a benign lesion in a patient with multiple lesions or the benign part of a lesion with multiple aspects (both benign and cancerous).

Recently, a number of borderline lesions that are notably out of the range provided by past clinical practice have come to the attention of the medical professionals who work in the field of breast cancer, with consequent risks of over- or under-diagnosis of malignancy. Increasingly imaging methods are not adequate to reach a definite conclusion. In this context, our results emphasize that FNAC is an important diagnostic tool for confirming a suspicious MRx or US, thus helping to program surgical procedures without delay, because of its extremely high predictive value, amply confirmed in this study. Furthermore, according to our results, when the score obtained by cumulating FNAC with US and MRx is ≤ 2, this may safely be used as a discriminant, safeguarding patients with benign pathology from a more aggressive and expensive diagnostic procedure, because of the high negative predictive value of the cumulative score.

On the other hand, when at least one test has an indeterminate or suspicious outcome (Combined score=3 or 4), our findings indicate that there is a non-neglectable possibility of a cancerous lesion and thus a VB should be performed. Benign and inadequate FNAC diagnoses must therefore be correlated with the clinical and imaging findings and, in discordant cases, patients should undergo biopsy. In those cases that cannot undergo CB, only VB or open biopsy can be used to solve the diagnostic dilemma. In conclusion, the new methodology recently introduced, VB, is complementary with respect to the triple test previously suggested. Its use may be conclusive, especially when diagnosis is difficult. In many instances it makes it possible to avoid open surgical biopsy, with a good cost/benefit ratio (31-33). The disadvantages of VB are mainly its invasiveness and its high cost when compared to FNAC or CB so, when possible, the latter should be performed instead of VB.

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