

PATHOLOGIC ASSESSMENT OF NON-PALPABLE PROBABLY BENIGN BREAST MASSES AT SONOGRAPHY: CAN INSTANT INTERVENTION BE AVOIDED AND IS FOLLOW-UP ADEQUATE?

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Aim of the study: To evaluate the pathologic results, determine the negative predictive value of non-palpable probably benign lesions at ultrasound and assess whether follow-up is adequate and immediate biopsy can be avoided.

Materials and methods: Four hundred and eight cases which were referred to our breast imaging unit between 2004 and 2008 for biopsy evaluation were enrolled into the study. Two hundred and thirteen probably benign solid masses are classified as BI-RADS 3 in 205 of the enrollees. All masses were sonographically detectable and were classified through the guidelines of BI-RADS lexicon for sonography before the final pathological examination. All pathologic results were evaluated and the negative predictive value, false negativity rate and 95% confidence interval were calculated.

Results: Of the 213 masses, fine needle aspiration cytology was performed in 120. US-guided wire localization and eventual surgery were carried out in the remaining 93 masses. Finally, 211 of the punctured lesions turned out to be benign and only two malignant lesions were detected. The resulting negative predictive value was found to be 99.1% while the false negative rate value was 0.9%.

Conclusion: With the results provided, we think that in the patients with sonographically detected probably benign breast lesions, short term follow-up seems to be a strong alternative to immediate biopsy with its reliable high negative predictivity as well as low false negativity.

Key-words: Breast, biopsy – Breast neoplasms, US.

Although mammography is the most widely used modality for early detection of breast cancer, with current advances in high-frequency transducers, US has become an important method for breast imaging. Traditionally, sonography has been used for solid-cystic differentiation as an adjunct to mammography, but today US can also be used to describe reliable signs to differentiate between benign and malignant masses. In addition, recent reports have pointed out that cancer can be obscured by dense breast tissue, and combination of both mammography and US may result in more malignant lesions being detected than with a single method alone (1-4).

The Breast Imaging Reporting and Data System (BI-RADS) developed by the American College of Radiology (ACR) in 1993 has mostly standardized the assessment and reporting of lesions on mammography. Both lesion description and patient management have become more consistent through the guidelines of BI-RADS for mammography. ACR also has developed a lexicon for breast masses for US to improve the efficacy of the modality and to standardize the lesion characterization

and reporting. The lexicon includes features such as shape, orientation, margin and posterior acoustic shadowing, and a solid mass is classified as probably benign (BI-RADS 3) with a circumscribed margin, oval shape and parallel orientation without posterior acoustic shadowing (5).

Although for probably benign masses that are visible on mammography, follow-up is mostly accepted as a standard method and supported by scientific data (6-10), there are limited information about the outcome of probably benign lesions that are classified only on US and it has not been proven whether the follow-up is the best strategy (11-14). The aim of our study was to evaluate the pathologic results of non-palpable probably benign masses (BI-RADS 3) that were classified only on US and to determine whether follow-up US is adequate and thus, immediate biopsy may be avoided.

Materials and methods

The study was approved by the ethics committee of the hospital. Four hundred and eight cases which were referred to our breast imaging unit between 2004 and 2008 for breast biopsy were classified. We

identified 213 probably benign solid masses classified as BI-RADS 3 went to pathologic evaluation in 205 patients and included in the study. The mean patient age was 44.2 years, with a range of 18-74 years.

As a routine protocol at our institution, either the patient is referred by the departments of our hospital or other centers for biopsy, US evaluation repeated on the admission day by one of the two radiologists who have more than 6 years of experience in breast imaging. All the masses are categorized based on the criteria of BI-RADS and noted on the biopsy procedure form of the patient. The sonographic evaluation was carried out using either GE Logiq S6 (GE Healthcare, Milwaukee, Wisc.) with a 7-12 MHz high frequency linear transducer or Toshiba, Powervision 6000 SSA-370A (Tokyo, Japan) with 6-11 MHz high frequency linear transducer.

The following US criteria were used to define a probably benign solid breast mass: shape (oval or macrolobulated fewer than four); circumscribed margins of the lesion; width greater than height (long axis parallel to the skin surface); echogenicity (isoechoic or mildly hypoechoic); and no posterior acoustic shadowing (Fig. 1) (Table I). To be included in the probably benign category, a mass needed to meet all the criteria regarding shape, margins, echogenicity, axis, and posterior acoustic shadowing

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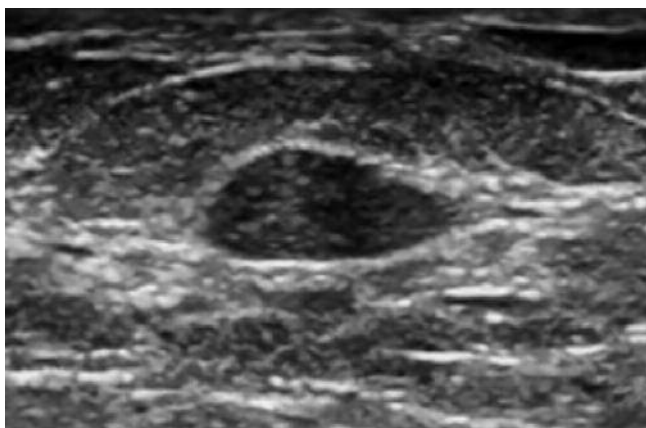


Fig. 1. — US shows an oval, circumscribed, hypoechoic typical probably benign mass in a 28 year-old woman classified as BI-RADS category 3 which was diagnosed as fibroadenoma after FNAC.

Table I. — Sonographic criteria for probably benign masses.

Shape	oval
Margin	circumscribed
Echogenicity	Iso-hypoechoic
Orientation	Parallel
Lesion boundary	Abrupt interface
Posterior echoes	Enhancement - no change (no shadowing)

mentioned above. Typically, benign masses (BI-RADS 2) such as cysts or intramammarian lymph nodes and suspicious malignant masses (BI-RADS 4-5) were excluded from the study.

The patients were informed about the probable malignancy risk of the masses that were assessed on US. Informed consent of all the patients was obtained. Biopsy was achieved not more than 3 days after the bleed-

ing parameters were checked. Indications for biopsy were either family history and/or patient anxiety. The technique used for pathologic evaluation was either fine-needle aspiration cytology (FNAC) or US-guided wire localization (USGWL) and surgical excision. Choice of the biopsy technique was based on the preference and experience of the radiologist, the surgeon, and the patient.

Cytology was considered negative for malignancy, when a definite benign diagnosis (fibroadenoma, papilloma, cyst content etc.) or a negative result such as benign cytology or no evidence of malignancy, was established. In the patients with indefinite result of FNAC or inadequate sample, the FNAC was repeated. The routine strategy at our breast unit for probably benign lesions without a definite diagnosis with benign cytology is short-interval follow up and we schedule a follow up protocol every 6 months for at least 2 years for these patients.

Statistical analysis

The false negative rate (FNR), the negative predictive value (NPV) and 95% confidence interval (CI) were calculated by using SPSS statistical program version 14.0 for Windows. To address the study hypothesis that fewer than 2% of the masses were malignant, frequencies were described using percentages and a corresponding 95% CI was calculated.

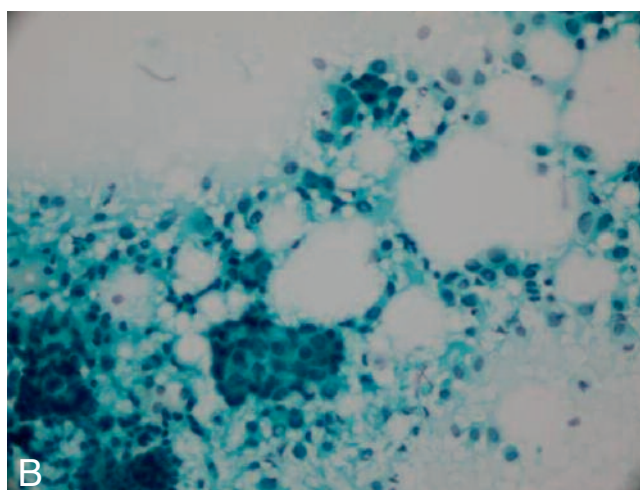


Fig. 2. — A. US demonstrates a circumscribed, well-defined, oval shaped solid mass with no posterior acoustic shadowing classified as probably benign in a 50-year-old woman. The needle is observed within the lesion during FNAC. B. Cytology of the lesion shows pleomorphic, hyperchromatic malignant cells in a disorganized architecture (pap x200).

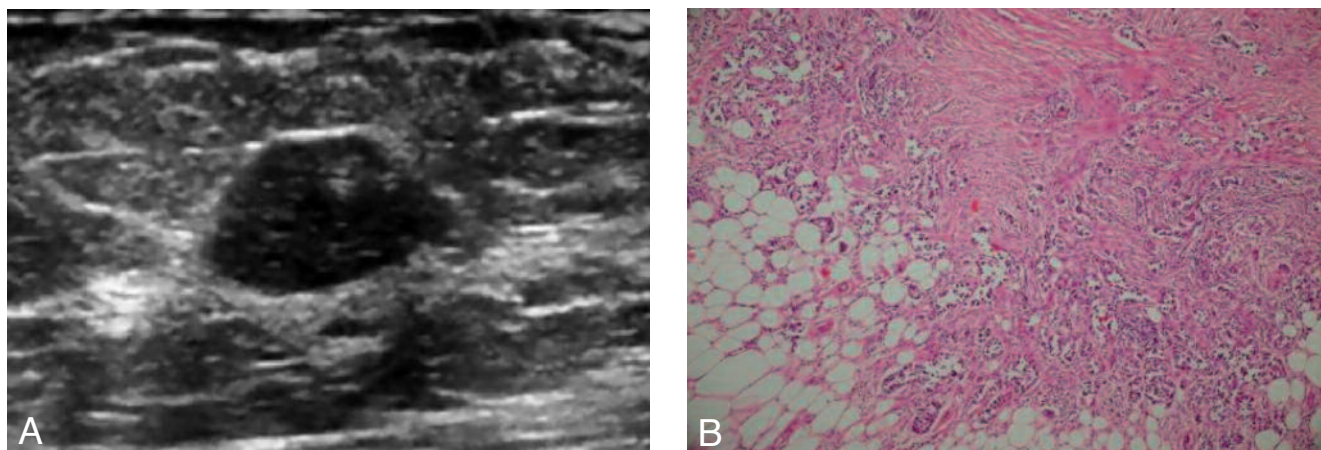


Fig. 3. – A. Non-palpable solid mass classified as probably benign in a 61-year-old woman. Note that the A-P diameter of the mass is minimal increased in the second look. After USGWL and surgery pathology revealed infiltrative ductal carcinoma. B. Low magnification of tumor shows haphazardly arranged tubules infiltrating adjacent adipose tissue (HE x 100).

Results

All the 213 masses classified as BI-RADS category 3 were visible on US. FNAC was performed in 120, and USGWL and excision carried out in the remaining 93 masses. The procedure was repeated in 11 masses that were reported as inadequate material or indefinite results in the first FNAC, and 8 fibroadenomas and 3 benign cytology were determined in the second intervention. Of the 205 patients with the 213 probably benign masses, 198 had a single lesion and the other 7 had multiple lesions.

Although some of the patients had mammography examinations and some of the masses were detectable on mammography, all the biopsy procedures were guided by US because all the masses were visible on sonography.

The pathological evaluation of 213 probably benign masses revealed 211 benign and two malignant lesions. One of the patients with a malignant mass was a 50-year-old woman whose malignancy was diagnosed with FNAC and whose histopathology was reported as infiltrative ductal carcinoma after surgery (Fig. 2A, B). The other patient with a malignant mass was a 61-year-old woman with infiltrative ductal carcinoma determined by USGWL and surgery (Fig. 3A, B). Both malignant masses were visible on mammography, but for the convenience of the patients, both procedures were achieved with the guidance of sonography. The FNR was calculated as 0.9% considering two malignant cases. The pathological evaluation revealed fibroadenomas in 99, fibrocystic changes in 37, fat

necrosis in 2, intraductal hyperplasia and papilloma in 1, adenosis in 5, and benign cytology in 67 of the remaining benign masses. The NPV was determined as 99.1%. The results of the pathological evaluation are summarized in Table II.

Of the 211 masses that were diagnosed as benign, 92 masses were completely removed by USGWL and surgical excision. In 52 of the 119 masses, the biopsy procedures of which was performed through FNAC, a definite benign diagnosis was obtained and in the remaining 67 masses, the pathological evaluation revealed benign cytology without a definite diagnosis. As it is a routine protocol at our breast imaging unit, for the group with benign cytology without a definite diagnosis a short-interval follow up was scheduled. However, only 41 of the 67 masses could be followed for a mean 16.6 months (range 6-36 months) and no morphological or dimensional changes and no late malignancy were determined during the follow-up period in this group.

Discussion

Although mammography is not the perfect tool of screening for breast cancer, it is the widely accepted modality for early detection of breast cancer. In addition, despite lack of scientific evidence that sonography can be used for breast cancer screening (15), US has nearly become a standard imaging procedure due to recent advances in ultrasound and transducer technology. Since it is known that US plays many different roles in breast imaging

such as solid-cystic differentiation or determination of the exact location of the masses, it is obvious that its major promising role is its ability of malignant versus benign discrimination and of characterization of the masses (2, 3).

BI-RADS classified the breast masses into different categories according to their morphologic characteristics, and BI-RADS category 3 is defined as morphologic features suggesting that a lesion is probably benign (5). It has been estimated that the probability of being malignant is below 2%, and it has been suggested that these lesions may be managed with periodic imaging, which should lead to reduction of biopsy rates. This strategy has been mostly agreed and supported by scientific data for mammography (6-10); however, for US, BI-RADS have a shorter history and this has not been proved yet.

To the best of our knowledge, there are few reports of the probably benign lesions determined on sonography. In the first of the two reports by Graf et al. on probably benign breast masses at US, 157 masses were classified as probably benign and in these 157 masses no cancer was diagnosed. In the second report, 448 probably benign masses were determined, and 445 probably benign masses were followed up. Of the 445 masses, 442 remained stable. Two masses that increased in size were fibroadenomas based on biopsy evaluation, and one mass became palpable and cancer was diagnosed. The FNR was 0.2% and NPV was 99.8% (11, 12). In another study, Mainero et al. categorized 148 masses as BI-RADS 3 and

Table II. – Pathologic evaluation in BI-RADS 3 masses.

	FNAC	USGWL	Total
Fibroadenoma	44	55	99
Fibrocytic changes	7	30	37
Benign cytology	67	–	67
Fat necrosis	1	1	2
Adenosis	–	5	5
Intraductal papilloma-hyperplasia	–	1	1
Malignancy	1	1	2
Total	120	93	213

FNAC: Fine-needle aspiration cytology
USGWL: US guided wire localization.

Table III. – Review of the literature regarding BI-RADS category 3 lesions at US.

	No of masses (BI-RADS 3)	No of malignancies	NPV (%)	FNR (%)
Graf et al. (1)	157	0	100	0
Graf et al. (2)	448	1	99.8	0.2
Mainero et al.	148	1	99.3	0.7
Park et al.	312	2	99.4	0.6
Present study	213	2	99.1	0.9

NPV: Negative predictive value
FNR: False negative rate.

also declared a high NPV with a rate of 99.3% (13). Likewise, in a recently published report on the same subject by Park et al., of the 312 probably benign masses, 2 malignancies were found, and the NPV and FNR were reported to be 99.4% and 0.6% respectively (14). Compared with the limited literature on the issue, the results of our study were similar. Of the 213 masses, two malignancies were found in the histopathologic examination, and the NPV and FNR were calculated as 99.1% and 0.9% respectively (Table III). In the previous and the present studies based on BI-RADS category 3 lesions at US, the probability of being malignant has been reported to be below 2%, which is the same rate for mammography reported in previous studies. Therefore, in the light of the results of the previous reports and the present study, it can be said that short-interval follow up seems an adequate strategy for probably benign masses.

The slight differences in statistical rates reported by similar studies are possibly due to the operator dependent nature of US and might be the interobserver variability in classifying the masses or various numbers

of masses included in the studies. The effect of inter and intraobserver variabilities was not calculated in the present study. However, considering the facts that two radiologists with more than 6-years of experience in breast imaging and the good intra and interobserver agreement stated in BI-RADS for US in the earlier reports (16, 17), observer related variability in this study may be disregarded.

Another point of criticism in our study may be the high rate of pathology diagnosed through FNAC and surgical excision rather than the core needle biopsy. Surgical excision is an alternative diagnostic technique in the management of breast lesions. Although using of excision for diagnostic purpose is expensive and invasive, it is reliable for diagnosing all types of breast lesions (including atypical hyperplasia, papillary lesions, mucinous lesion and phyllodes tumor). Another issue is that, whether surgical excision affects sentinel lymph node biopsy results. Although there are conflicting reports about the prior excisional biopsy affecting sentinel lymph node biopsy, the recent thought in the clinical literature is that excision-

al biopsies have no adverse impact on the process (18, 19).

It is known that core needle biopsy is increasingly being used as a faster, less invasive, and less expensive alternative to surgical biopsy for the histologic assessment of breast lesions (20). The reliability increases and in order to achieve a high diagnostic efficiency, minimum three cores per lesion is advisable (20, 21). Core needle biopsy has also some benefits such as being familiar to pathologists during histopathological assessment of the material (especially if experienced cytopathologists are not accessible), and the high ability to discriminate invasive cancer from in-situ carcinoma. However core needle biopsy may lead to histological changes in the main lesion including hemorrhage, granulation tissue formation, hemosiderin deposition, fibrosis, foreign-body reaction and infarction. Besides reduction of tumor size is another consequence of core needle biopsy (22).

There are many studies published on FNAC of the breast masses, especially in benign lesions that FNAC is sufficient and still maintain the validity (23-25). It is a reasonably rapid, less invasive and less expensive procedure. It is accepted to be very useful for evaluation of breast lesions by some authors especially for very small lesions, lesions located under the skin or close to the chest wall compared with core biopsy. On the other hand its ability to differentiate invasive cancer from in-situ carcinoma is limited and the tissue obtained may be inadequate to assess tumor grade and hormonal receptor status (26). Regarding the issues above, the patients with indefinite and inadequate results on FNAC underwent a second intervention, and the patients with benign cytology were scheduled for short-interval follow up for every 6 months in the present study. It is also clear that the selection of the biopsy procedure can be based on the personal experience or choice of the radiology-pathology team.

Although the possibility of malignancy for BI-RADS category 3 lesions is below 2%, follow up seems essential even in benign cytology without a definite diagnosis obtained with FNAC. While no standard interval and duration has been established for benignity of probably benign lesions, a minimum 2 years has been commonly established as the optimal time (11, 12, 14). We also perform and suggest that the follow-

up protocol must be scheduled at 6-month intervals for at least 2 years for patients with benign cytology without a definite diagnosis if FNAC was performed and for patients who do not undergo biopsy due to probably benign masses on US. Unfortunately, the mean follow-up period was under 2 years in the present study, and it was speculated that pathology results of the masses with benign cytology were explained to the patients by physicians as good-natured, which led to decrease in the number of control visits. We believe that the patients should be warned about the probability of malignancy and the importance of strict follow-up, especially if there was not a definite diagnosis.

In conclusion, the present study with a high NPV and a low FNR compatible with the limited literature confirmed that in circumscribed solid masses, which fulfill the criteria for BI-RADS category 3, short-term follow up is an adequate alternative strategy to immediate histopathologic examination. However, further studies with larger series and multicenter trials are needed to confirm efficacy of follow-up and to define the exact value of US in breast cancer.

References

- Baker J.A., Soo M.S.: Breast US: assessment of technical quality and image interpretation. *Radiology*, 2002, 223: 229-238.
- Stavros A.T., Thickman D., Rapp C.L., Dennis M.A., Parker S.H., Sisney G.A.: Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. *Radiology*, 1995, 196: 123-134.
- Rahbar G., Sie A.C., Hansen G.C., et al.: Benign versus malignant solid breast masses: US differentiation. *Radiology*, 1999, 213: 889-894.
- Crystal P., Strano S.D., Shcharynski S., Koretz M.J.: Using sonography to screen women with mammographically dense breasts. *AJR*, 2003, 181: 177-182.
- American College of Radiology: *Breast imaging reporting and data system, breast imaging atlas*. 4th ed. Reston, Va: American College of Radiology, 2003.
- Sickles E.A.: Periodic mammographic follow-up of probably benign lesions: results in 3,184 consecutive cases. *Radiology*, 1991, 179: 463-468.
- Varas X., Leborgne F., Leborgne J.H.: Nonpalpable, probably benign lesions: role of follow-up mammography. *Radiology*, 1992, 184: 409-414.
- Sickles E.A.: Probably benign breast lesions: when should follow-up be recommended and what is the optimal follow-up protocol? *Radiology*, 1999, 213: 11-14.
- Varas X., Leborgne J.H., Leborgne F., Mezzera J., Jaumandreu S., Leborgne F.: Revisiting the mammographic follow-up of BIRADS category 3 lesions. *AJR*, 2002, 179: 691-695.
- Vizcaino I., Gadea L., Andreo L., et al.: Short-term follow-up results in 795 nonpalpable probably benign lesions detected at screening mammography. *Radiology*, 2001, 219: 475-483.
- Graf O., Helbich T.H., Fuchsjaeger M.H., et al.: Follow-up of palpable circumscribed noncalcified solid breast masses at mammography and US: can biopsy be averted? *Radiology*, 2004, 233: 850-856.
- Graf O., Helbich T.H., Hopf G., Graf C., Sickles E.A.: Probably benign breast masses at US: is follow-up an acceptable alternative to biopsy? *Radiology*, 2007, 244: 87-93.
- Mainiero M.B., Goldkamp A., Lazarus E., et al.: Characterization of breast masses with sonography: can biopsy of some solid masses be deferred? *J Ultrasound Med*, 2005, 24: 161-167.
- Park Y.M., Kim E.K., Lee J.H., et al.: Palpable breast masses with probably benign morphology at sonography: can biopsy be deferred? *Acta Radiol*, 2008, 49: 1104-1111.
- Kopans D.B.: Sonography should not be used for breast cancer screening until its efficacy has been proven scientifically. *AJR*, 2004, 182: 489-491.
- Lazarus E., Mainiero M.B., Schepps B., Koelliker S.L., Livingston L.S.: BI-RADS lexicon for US and mammography: interobserver variability and positive predictive value. *Radiology*, 2006, 239: 385-391.
- Lee H.J., Kim E.K., Kim M.J., et al.: Observer variability of Breast Imaging Reporting and Data System (BI-RADS) for breast ultrasound. *Eur J Radiol*, 2008, 65: 293-298.
- Yararbas U., Argon A.M., Yeniay L., Kapkac M.: Problematic aspects of sentinel lymph node biopsy and its relation to previous excisional biopsy in breast cancer. *Clin Nucl Med*, 2009, 34: 854-858.
- Wong S.L., Edwards M.J., Chao C.: The effect of prior biopsy method and concurrent definitive breast procedure on success and accuracy of sentinel lymph node biopsy. *Ann Surg Oncol*, 2002, 9: 272-277.
- Youk J.H., Kim E.K., Kim M.J., Oh K.K.: Sonographically guided 14-gauge core needle biopsy of breast masses: a review of 2,420 cases with long-term follow-up. *AJR*, 2008, 190: 202-207.
- Bolívar A.V., Alonso-Bartolomé P., García E.O., Ayensa F.G.: Ultrasound-guided core needle biopsy of nonpalpable breast lesions: a prospective analysis in 204 cases. *Acta Radiol*, 2005, 46: 690-695.
- Chaiwuna B., Thorner P.: Fine needle aspiration for evaluation of breast masses. *Current Opinion in Obstetrics and Gynecology*, 2007, 19: 48-55.
- Boerner S., Fornage B.D., Singletary E., Sneige N.: Ultrasound-guided fine-needle aspiration (FNA) of nonpalpable breast lesions: a review of 1885 FNA cases using the National Cancer Institute-supported recommendations on the uniform approach to breast FNA. *Cancer*, 1999, 87: 19-24.
- Liao J., Davey D.D., Warren G., Davis J., Moore A.R., Samayoa L.M.: Ultrasound-guided fine-needle aspiration biopsy remains a valid approach in the evaluation of nonpalpable breast lesions. *Diagn Cytopathol*, 2004, 30: 325-331.
- Kocjan G., Bourgain C., Fassina A., et al.: The role of breast FNAC in diagnosis and clinical management: a survey of current practice. *Cytopathology*, 2008, 19: 271-278.
- Lieske B., Ravichandran D., Wright D.: Role of fine-needle aspiration cytology and core biopsy in the preoperative diagnosis of screen-detected breast carcinoma. *Br J Cancer*, 2006, 95: 62-66.