Diagnosis of non-palpable breast cancer: a review

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SUMMARY. The literature on several methods of diagnosing non-palpable breast carcinoma has been reviewed. Skin projection and dye are methods not frequently used. Several aspects of FNA biopsy/cytology, ultrasound-directed methods, frozen section and MRI localization procedures are highlighted and comparisons are made. Much attention is being payed to needle localization breast biopsy and stereotactic core needle breast biopsy.

The management of patients with mammographic abnormalities is shifting from needle localization to breast biopsy stereotactic core needle biopsy. Items of comparison between the two mentioned methods are accuracy, indications, complications and costs. The role of the ABBI system in the management of breast cancer has not yet been defined. A cooperative effort between the mammographer, surgeon and pathologist is critical to a successful image-guided breast biopsy programme. © 2002 Harcourt Publishers Ltd

INTRODUCTION

Since the 1980s, as mammography has improved, surgeons have a new entity to deal with: the non-palpable, usually asymptomatic, breast, lesion. Recent recommendations that all women over 40 years of age should consider annual screening mammograms will add to the growing number of impalpable lesions. At the same time the advances made in mammography, including its accuracy, safety and publicity, will lead to an increasing number of needle localization biopsies of the breast. In screening programmes approximately 15% of all lesions are found to be malignant. Screening mammography has increased the detection of non-palpable breast cancer, for invasive as well as pre-invasive lesions; at the same time it has resulted in improved long-term survival and cure rates for patients with breast cancer. As a result early detection can diminish the mortality rate by rates up to 20%. The best surgical management of non-palpable lesions is facilitated by: (i) confirmation of malignancy; (ii) histological assessment of invasion and grading; and (iii), oestrogen receptor assays.

HISTORY

In 1913 a German surgeon reported his experience with radiographs of a large number of excised breasts. A radiologist pioneered clinical mammography in the 1930s, and although mammography was introduced early in the 20th century, its use did not become widespread until the mid 1970s because of technical difficulties. The developing technology combined with greater public awareness increased the number of asymptomatic women undergoing ‘screening’. Published reports show that 9–24% of these non-palpable lesions are cancerous.

The introduction of localization techniques has dramatically increased the ability to find small cancers while improving cosmetic results. At the same time, most surgeons have changed from a one-stage procedure, with the use of frozen sections, to a two-stage procedure: first a fine needle aspirate or needle biopsy and, after complete diagnostic information is available, further decisions can be made. Interventional procedures are very important in clarifying non-palpable breast lesions. Traditionally the biopsy technique used
to evaluate non-palpable lesions has been needle-localized breast biopsy. Needle core biopsy has been added to the pre-operative assessment of mammographically identified non-palpable lesions with the aim of reducing the number of surgical biopsies for benign disease. An increase in diagnostic studies is associated with an increase in surgical activity as well as an increase in costs.

DIAGNOSTIC METHODS AND REVIEW OF THE LITERATURE

We will describe several diagnostic methods to assess non-palpable breast disease. Whichever method is used, the radiologist should ensure the shortest skin-to-lesion approach for the surgeon; at the same time the surgeon has to be informed about the localization procedure.

Skin projection

Pre-operative localization is of great importance in reducing the amount of excised tissue, thus minimizing the cosmetic damage while guaranteeing adequate excision. This method was described for non-palpable superficial lesions. An indelible marker is used. It is a simple, but inaccurate, method when the lesion is deep. Skin marking can be mammographically guided as well as being ultrasound guided.

Dye

The dye technique was first described by Egan. With the needle in place, 0.1–0.2 ml of iodinated contrast material and blue dye is injected. Methylene blue, as well as toluidine blue, Evans blue and isocyanide green have also been used, but their use has been criticized. A sterile charcoal suspension has also been used. Diffusion of the suspension can make localization difficult and the suspension can tattoo the needle tract and the skin.

Fine-needle aspiration biopsy/cytology

The use of needle aspiration (FNA) to obtain cellular material for pathological examination was introduced by Martin and Ellis in 1930. This method is most frequently used for palpable breast lesions as one part of modern ‘triple’ assessment. Using stereotaxic or sonographic guidance of the needle it is possible to use cytology for non-palpable breast lesions. The accuracy of this method is reported as being comparable to that reported for palpable masses. For this cytological procedure thin needles (20–22 gauge) are used. Ciatto et al. reported a sharp decrease in the benign/malignant ratio after routine FNA cytology (sonography-guided or stereotaxic) was introduced in 1986. Cangiarella et al. stated that it is a reliable and cost-effective method; however, mammographic follow-up is indicated because of the possibility of subsequent and independent cancers developing. In some studies it is suggested that FNA should be combined with core biopsy to obtain higher rates of detection to carcinoma in situ. Andreu et al. showed that large core (14-gauge) needle biopsy provides more accurate diagnosis than FNA biopsy in the management of non-palpable breast lesions. Also Britton et al. state that sensitivity and specificity are higher for core biopsy than for FNA biopsy; this is due largely to easier collection, preparation and pathological interpretation of specimens. FNA can also reduce the number of surgical biopsies; in patients with nodular densities of benign or indeterminate appearance, a negative fine needle aspirate is sufficient, according to some authors, for no further investigations to be required. By contrast in cases of stellate lesions, surgical excision is indicated. In patients with potentially malignant/suspicious microcalcifications, FNA is of limited value. Some authors state that this method disrupts breast tissue. It leads to inadequate samples in 6–47% of cases with a false-negative rate of up to 31%. Cytology provides no reliable information on grade and invasion; the reliability of cytological examination is generally more dependent on the cytologist than is histological examination of a core biopsy. FNA is also of limited value in distinguishing infiltrating carcinoma from carcinoma in situ.

Ultrasound directed methods (pre-operatively)

Fornage and colleagues and Weber et al. have reported on ultrasound-directed localization. In the literature ultrasound-guided wire localization and FNA are described. The European Group for breast cancer screening has considered the use of ultrasound. In a detailed review they describe the pros and cons of ultrasonography. Ultrasound of the breast is an important adjunct to mammography and clinical examination of both palpable and non-palpable breast lesions. Some authors believe that the use in screening programmes is associated with high rates of both false-positive and false-negative outcomes, suggesting little supporting evidence to use ultrasound. Other limitations are poor results in fatty breasts, the inability to depict microcalcifications and excessive scan and reviewing time. However, Caruso et al. state that this diagnostic procedure is simple, safe and accurate, so
they consider this method can be used for non-palpable lesions.\textsuperscript{55,56} Ultrasound guidance is probably preferable to other methods where feasible.

**Ultrasound directed methods (per-operatively)**

In some hospitals excisional/incisional biopsy under ultrasonographic guidance is performed.\textsuperscript{57} Some authors claim that with this technique adequate margins, i.e. performing the resection of nonpalpable breast lesions can be obtained.\textsuperscript{58,59} Another advantage is increased patient comfort, because the trauma of wire localization in the awake patient is avoided.\textsuperscript{60} So far, the literature and experience concerning this method are scarce.

**Frozen section**

Frozen section of a non-palpable lesion can be performed after pre-operative needle localization and subsequent biopsy.\textsuperscript{61–63} However, whether to use frozen section requires judgement. This is especially true when the gross lesion is small, i.e. \(<1\) cm in dimension. In this setting, a frozen section might not yield a definite diagnosis. Moreover, permanent sections from the frozen block might have sufficient freezing artefacts to render these sections sub-optimal or even useless for diagnosis.\textsuperscript{63–65} Another problem as reported by Cheng et al. is sampling error which leads to a false-negative diagnosis when frozen section is used to diagnose intraductal carcinoma.\textsuperscript{65,66} Last, but not least, patients do not know the exact diagnosis pre-operatively, so they cannot be adequately informed. Rothman et al. found that a fifth of the frozen sections in non-palpable breast lesions contributed nothing to the diagnosis.\textsuperscript{67} Bianchi et al. recommend frozen section as a feasible and reliable diagnostic procedure, particularly in cases where the lesion is excised because of a mammographic opacity that is identifiable on gross examination of the surgical specimen.\textsuperscript{62} As many mammographically detected breast lesions require examination of the whole specimen for an accurate diagnosis, frozen section is not applicable. As a negative margin status has become a pre-requisite for breast conserving therapy, it is a possible to evaluate the margins by frozen section but is not always accurate. It is concluded that intra-operative pathological assessment particularly of impalpable lesions should not be performed by frozen section.\textsuperscript{67}

**Needle localization breast biopsy**

This method involves surgical excision and has been the gold standard for the last three decades because the reliability is 99–100\%.\textsuperscript{68–70} Refinements in mammography have led to an increased number of needle-localized breast biopsies for impalpable breast lesions. The pre-operative localization of non-palpable breast lesions enables the surgeon to reliably locate and remove the lesion with a minimal volume of surrounding tissue, thereby keeping post-operative scarring or deformity to a minimum. Malignancy in non-palpable lesions biopsied with needle-localization techniques varies in most series from 14 to 30\%\textsuperscript{3,13,14,71–80} The technique for needle localization was first described by Dodd et al. in 1966 with other early reports by Threatt and Libshitz.\textsuperscript{81} Various techniques involve the positioning of a wire, needle, dye (as described previously), dye with wire or catheter or the use of a radioactive tracer. The use of a combination of needle and hooked wire was first described by Frank et al. in 1976.\textsuperscript{82} A needle containing a wire is inserted into the breast; after removing the needle the wire hooks onto breast tissue and anchors itself in place. A length of wire extends out beyond the skin and the surgeon can either dissect along the wire or find the wire within the breast and follow it to the lesion. The needle–wire combinations have been modified since the initial description. Placing the wire tip within 1–3 cm of the site to be biopsied results in failure rates 2–4\% for biopsies.\textsuperscript{32,74,83} Ideally the wire should pass within 1 mm of the lesion and be 1 cm part the area to be excised, and secured in breast tissue and not fat. The localization procedure is performed without pre-medication. As a general rule excision should be performed within 24 h of needle placement.\textsuperscript{84} Various ways of needle insertion have been described by Gisvold and Feig.\textsuperscript{32,85} Most radiologists prefer to enter the skin parallel to the chest wall, usually approaching the lesion from above.\textsuperscript{14,93,86} Specimen radiography is mandatory and it is important to orientate the specimen and ink the margins for the pathologist. Melanson et al. suggested fixing the specimen after excision to a square of cardboard; to improve the ability of the pathologist to locate any suspicious area within the specimen.\textsuperscript{87} For many years it was standard practice to perform an open surgical biopsy of all suspicious non-palpable breast lesions. However, biopsies for benign disease are unnecessary and undesirable and carry with them significant patient morbidity. Biopsy yield rate varies with mammographic features; Hasselgren et al. reported this rate to be highest for speculated masses (61\%), followed by suspicious calcifications (29\%).\textsuperscript{88} Careful attention to the technical details of the procedure and proper handling of the specimen are necessary. Wire localization as a diagnostic procedure has disadvantages including the use of general anesthesia, high costs and poor cosmesis.
with scar formation and distortion being a frequent problem.39 Sometimes a second (and even a third) operation may be necessary before an accurate diagnosis is reached.39,65 Arguments against this method include wire dislocation and general surgical complications such as wound infection and formation of haematoma.16,48,89,90 Other complications described are penetration of the pleural space or the wire retracting into the breast.91,92

Factors associated with unsuccessful needle localized breast biopsy include two lesions per breast, small lesions, small specimens and microcalcifications.89 Needle localization biopsies of non-palpable breast disease have a higher proportion of non-invasive lesions and early stage breast cancers than biopsies in palpable breast disease.5,67,93 Although primarily a diagnostic procedure, complete excision of small lesions is possible. Positive margins, and re-excision rates, are reported to be 55–83%.2,94–97

**Stereotactic-image guided-core needle biopsy**

Percutaneous core biopsy guided by digital stereotactic mammography is now the most common technique used in the investigation of non-palpable suspicious mammographic lesions.39 This method was described in 1990 by Parker et al.2,98,99 It is a radiologically guided method of localizing and obtaining a core sample of mammographically detected breast lesions. Azavedo et al. described this method as an alternative to FNA biopsy, although there could be some disadvantages such as being less acceptable for the patient.30 Prospective trials were carried out to define the precise role of this method; many advantages have been described in literature. With the use of larger needles (14-gauge), a more reliable diagnosis can be made. It shortens the time from detection of a lesion by mammography to diagnosis and therapy, it has significant cost savings compared with open biopsy, and is an accurate and less invasive method.2,39,65,95,96,100–102 There is a correlation with mammographic findings in 97% of biopsy specimens.102 A major advantage is that it allows a one-stage operative approach — a single operation as definitive therapy — with the result of better cosmetic outcomes.65,98 At least 5 or 6 cores are needed to give a 99% diagnostic accuracy particularly in women with mammographic microcalcifications of an equivocal nature.16,103,104 One theoretical concern is the possible implantation of tumour cells along the needle or core track.2,42,105 Some authors have described the phenomenon of epithelial displacement, although the biological significance has not yet been shown.65,69,106,107 In cases where core biopsy shows atypical hyperplasia or in situ carcinoma, it is recommended that an excisional biopsy is performed (+ pre-operative wire localization); nearly 20% of these patients have infiltrating carcinoma.65,69,98 The use of suction-assisted core biopsy systems allowing larger and continuous portions of tissue to be excised is a new and significant advance which reduces the number of patients found to have noninvasive disease on core and invasion after excision. Performing a one stage excision should increase the likelihood of obtaining complete excision with clear margins. Liberman et al. in contrast state that the likelihood of obtaining tumour-free margins at lumpectomy does not differ significantly for cancers diagnosed by either method.55,69 The false-negative rate varies between 0% and 18% for wire-localization and this rate is comparable to the 0.2% to 20% rate of core biopsy.39,89,95,100–111

Stereotactic core biopsy is a better alternative than excision biopsy.112 Additional studies with long-term follow-up are needed to prove that the false-negative rate is comparable with that obtained by diagnostic surgical biopsy.

**Magnetic resonance imaging localization procedure**

Magnetic resonance imaging (MRI) of the breast is a new method and a few reports have been published. In the past, disadvantages such as overlap in the MRI features of malignant and benign lesions, high costs and inability to resolve smaller masses and microcalcifications were described.113 Sittek et al. described 18 patients in whom the detection of breast lesions and wire localization of the lesion with MRI was efficient and reliable in non-palpable lesions only visible on MRI using a non-dedicated body coil.114

**Advanced breast biopsy instrumentation**

Advanced breast biopsy instrumentation (ABBI) is an alternative to large-core or suction-assisted stereotactic and open needle localized breast biopsies.115 This is a minimally invasive technique that uses digital stereotactic imaging to perform excisional biopsies of non-palpable breast lesions.115 The system, which can be performed by surgeons or radiologists, uses surgical cannulas up to 20 mm in diameter.116,117 ABBI can be used for microcalcifications, non-palpable noncystic nodular densities, architectural distortions or stellate lesions suspicious for cancer; indications for the technique are similar to those for traditional needle localization excisional breast biopsies.115,118,119 The method can be undertaken under local anaesthesia, it
has a low complication rate and appears cost-effective. Schwartzberg et al describe a sensitivity and specificity, for the diagnosis of carcinoma, of 100%. Matthews et al. (107 patients) state that the ABBI system might be able to excise small in situ or invasive breast cancers. The role of the ABBI system in the management of breast cancer has not yet been defined.

DISCUSSION

Screening mammography programmes appear to result in an overall decline in breast cancer mortality. Side effects, include the detection and biopsy of many non-palpable lesions that eventually prove to be benign, resulting in psychological distress to many women and a substantial contribution to the burden of costs on health care systems. As a consequence, adequate diagnostic procedures, with an optimal balance between a minimum rate of false-positive results and an acceptable rate of false-negative results, are mandatory.

Mammography remains the procedure of choice in screening asymptomatic women; however, other imaging methods, such as MRI, positron emission tomography and thallium-201 scintimammography could play an important role in detecting malignancies in the future. Several of these methods deserve further study as screening techniques.

Quality control is a significant concern in breast cancer screening and efforts should be made with regard to organization, quality assurance and research. Cooperation between surgeons, radiologists and pathologists and last, but not least, general practitioners is very important in the management of patients with mammographically detected lesions. When the management is suboptimal this results in inadequate or delayed care and so most of the benefits from the mammographic screening are lost. Bickell et al. conclude that the hospital where breast cancer surgery is performed should have a multidisciplinary approach as this is associated with a greater likelihood that women will receive effective local and systemic adjuvant treatments. Ultimately, improved quality of care should translate into morbidity and mortality reductions.

Several techniques for the diagnosis of non-palpable breast lesions have been developed. The choice of the technique depends on lesion characteristics particularly the site, breast configuration, equipment availability and cost considerations. As for screening programmes, quality control and quality assurance programmes should be instituted for the biopsy technique. External markers, mammographic mapping, needle dye injection and stainless steel needle localization have been replaced by the use of self-retaining wires. Utilizing carefully inserted wires, incomplete excision is seen in less than 5% of cases. However, needle localization is a semi-blind, invasive and costly procedure.

Stereotactic breast core biopsy is the natural progression in the diagnostic pathway and is replacing FNA and the placement of localization wires; it provides a histologic diagnosis while avoiding the deformity, much of the cost and trauma associated with surgical biopsy. It is accurate, less invasive, shorter time from detection to therapy, has a better patient acceptance and leads to fewer complications. Because the lumphatics are left intact there is a possibility of sentinel lymph node mapping and breast-conserving therapy rates are higher (one-step therapeutic procedure). Its precise role has to be defined; it must, and should, replace diagnostic needle-localized breast biopsy.

As experience with core biopsy diagnosis evolves, more patients will achieve definitive surgical therapy with a single procedure. Core biopsy has potential limitations: a false negative rate of 1.5 to 2% according to some authors so additional studies using the newer larger bore suction assisted core biopsy devices and long-term follow-up are needed. In case of a diagnosis of atypical ductal hyperplasia, over 50% of patients have invasive carcinoma at surgery. In these cases, needle localization breast biopsy is still recommended. For core biopsy a large needle at least 14-gauge or 11-gauge vacuum-assisted should be used and at least 5–6 biopsies should be taken, otherwise sampling errors occur.

Few papers have considered the combined use of core biopsy and FNA for screen-detected cancers. The combination leads to a higher detection rate of intraductal carcinoma. At the same time with the use of larger needles (14-gauge instead of 20 gauge), higher success rates are seen. If FNA is used alone, sensitivity and specificity are lower than for core biopsy alone; the difference is more marked for stereotactic-guided rather than ultrasound-guided biopsies. The difference in these results could be due in part to pathological interpretation. Cytology does not provide reliable information on grade and gives no information on tumour invasion but can be reported immediately. Needle localization is recommended if: (i) lumpectomy is the therapy of choice after core biopsy reveals malignancy, as a guide to the surgeon, even if a haematoma can be felt in the breast after core biopsy, because the centre of the haematoma might not be at the centre of the lesion; (ii) typical hyperplasia, in situ carcinoma or a radial scar is found on core biopsy as atypical hyperplasia is associated with a high
prevalence of invasive or in situ ductal carcinoma. In situ carcinoma most commonly presents as microcalcifications and lesions considered to be a radial scar require removal to allow the whole lesion to be considered to provide a definitive pathologic diagnosis; (iii) microcalcifications seen on mammography considered suspicious but not diagnosed in case of a suspicious mass on mammography where no histological diagnosis has been obtained – at least six samples are needed with core biopsy to give a 99% diagnostic accuracy.\(^{16,104}\) To investigate microcalcifications a greater number of samples are needed (up to 12). Calcifications can act as a mammographic marker for underlying in situ or invasive change;\(^{16,144}\) (iv) lesion \(<5\) mm treated by mastectomy without localization as small core-biopsy-diagnosed impalpable breast cancers may be missed in the mastectomy specimen;\(^{132,142,143}\) and (v), lesions are too close to the chest wall or the nipple complex.\(^{100}\)

For most non-palpable breast lesions frozen section should not be performed.\(^{63,69}\) Several studies have compared biopsies obtained with the ABBI system with ‘open’ excisional needle localized breast biopsy: the ABBI system is used with local anaesthesia, it allows for smaller biopsy specimens and higher patient acceptance and it is as efficacious as needle localization biopsy techniques in providing a diagnosis.\(^{119,144,145}\) Damascelli et al state that the quality of the biopsy specimen is identical to that of a surgical specimen, but with the advantage of stereotactic precision for localization of the lesion.\(^{117}\) The problem is that this procedure is rarely therapeutic and suction assisted large core biopsy is as accurate as the ABBI system with potentially less complications. Focal shadows and structural irregularity appear to be detected not as well by digital mammography and should be pre-operatively marked by using sonography.\(^{146}\) Rebner et al. even state that women with non-palpable breast lesions, who need a tissue diagnosis, are better treated by stereotactic or sonographically guided needle biopsy, either that core with an automated gun or a suction-assisted mammmotome biopsy.\(^{147}\) A multidisciplinary diagnostic strategy involving radiologists, surgeons, cytopathologists and pathologists is necessary to optimize the management of non-palpable mammographic lesions and reduce the number of unnecessary operations.\(^{47}\)

**CONCLUSIONS**

Stereotactic breast core biopsy is the natural progression in the diagnostic pathway in patients with mammographic abnormalities. Using the mammmotome, better biopsies are obtained than by using a standard core biopsy gun, and approximately 50% of lesions will be excised completely. It is clear that although needle localization breast biopsy is considered the ‘gold standard’ it is not perfect, and as stereotactic core biopsy will have a miss rate as low as 1–3%, it can replace needle localization biopsy in most cases with a metallic marker being left in place if the lesion is thought to have been removed by core biopsy as wide local excision could still be necessary. Dedicated stereotactic breast biopsy equipment is expensive, but set against the alternative of open surgical biopsy, it is cheaper and simpler.

With proper patient selection, the ABBI system is a safe, accurate and cost-effective method for performing breast biopsies; it belongs to the surgical armamentarium for the diagnosis of indeterminant non-palpable mammographic breast lesions.

Pre-operative diagnosis of a breast carcinoma is desirable allowing the specialist to plan a one-stage therapeutic operation; it also allows the patient time to ‘come to terms’ with the entirety of her management plan. Thirdly it reduces the costs of treatment.

Invasive cancers tend to be small, of low histologic grade and have a low incidence of lymph node involvement, with a high proportion of ductal carcinoma in situ and also a high proportion of lobular carcinoma.\(^{64,93}\)

Although existing breast cancer guidelines vary widely, they provide a good framework for quality-of-care evaluation. In reducing practice variations, clinical practice guidelines can improve the quality of care. Process measures of the quality of care are, for example, frequency and length of visits, costs of patients and to the health service.

A cooperative effort between the radiologist, surgeon and pathologist is critical to a successful image-guided breast biopsy programme, in order to achieve optimal results and eventually a mortality reduction. Specialist breast care nurses have become increasingly recognized as core members of the breast care team. The most helpful sources of information to patients are specialists, nurses and other cancer patients. Guidelines are only useful if they are utilized in a programme to improve quality, cost-effectiveness and outcomes. To accomplish this, they must include mechanisms for revision and evaluation.

**References**

Diagnosis of non-palpable breast cancer


20 The Breast


