State of the art of current modalities for the diagnosis of breast lesions

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Abstract. With the availability of numerous diagnostic techniques comes the possible risk of the unjustified use of such techniques and a lack of rational clinical application. Clearly, errors of this nature would affect the diagnostic accuracy and therefore reduce the possibilities for treatment. It is not uncommon for women and also for general practitioners to be misinformed about which is the most suitable technique or rather, which is the best combination of the various techniques. For this reason, inappropriate tests are often requested or, conversely, there is failure to request tests which would in fact make a useful contribution to safeguarding the patient's health. This work has the following aims: (a) to set out precisely the real diagnostic contribution of each method, both radiological and otherwise, and suggest methods of application and indications consistent with the state of the art, and (b) to suggest the most effective and rational combinations of the various techniques and organisation of diagnostic activities.

Keywords: Breast diseases – Mammography – Ultrasound – Magnetic resonance imaging – Needle sampling

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A critical analysis of the diagnostic methods in breast diseases

Breast self-examination

Women are still being advised to carry out periodic breast self-examination (BSE) although it has been well documented that this test does not provide early diagnosis (though it may anticipate the diagnosis) and that there is no evidence of a reduction in the mortality of women who practice BSE compared to those who do not [1, 2]. In informing women how to carry out BSE, general practitioners and specialists should ensure that both its advantages and its limitations are explained, so as to avoid both false reassurance and false alarms. Women should not be blamed for not wishing to carry out BSE. Since BSE may provide useful information in certain cases (when the lesion appeared, its volumetric development over time, etc.), the clinician would do well not to overlook findings reported by women who practice BSE.

From the methodological viewpoint, it is time to set aside commonplaces and teach women that BSE consists of two parts: an inspection to be carried out in front of the mirror, and palpation to be carried out in the supine position and not in the shower, as often happens. Because of the length of time it takes for the tumour to grow, it would be better to explain to women that almost monthly self-palpation not only creates anxiety but may actually delay the perception of nodes because the hand becomes accustomed to their slow growth. For this reason, it would be more logical to suggest that checks should be performed every 3 months during the fertile period, at the end of the menstrual stage.

Clinical examination

The clinical examination should only be performed by trained medical personnel in a suitable environment [3] and should be preceded by careful examination of the patient's case history, including the assessment of possible risk factors [4].

Signs and medical report

The most typical signs of cancer are the presence of a hard swelling with irregular or indistinct edges, skin involvement, fixation to the pectoral muscle or the chest wall, bloody discharge, axillary adenopathy (which is, however, non-specific if N2 cases are excluded) and the eczematous appearance of the nipple in Paget's disease.

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The relevant signs should be described in the concluding report. As regards nodular lesions, the report should always state the dimensions in centimetres, measured with callipers, and the site, with reference to the four quadrants and the areolar region. The conclusive diagnostic judgement (negative, benign or suspicious) should always be precisely indicated. In the case of suspicious signs, it is necessary to supply the data for the staging system or the TNM category directly.

Results

Sensitivity is relatively low for T1 forms (approximately 70%, but considerably lower for lesions of less than 1 cm) and therefore the clinical examination is of little use for the early diagnosis of tumours [5]. Its contribution is often limited to the perception of the existence of a pathology but it greatly facilitates the search for and recognition of lesions, preventing them from being overlooked. The specificity of this test is also somewhat limited; there would be a high bioptic cost if the decision on whether to perform a biopsy were to be based solely on the clinical examination.

It is obvious, therefore, that the clinical examination alone is not sufficient to exclude the presence of tumours and that any clinical signs, even if they are in the slightest way suspicious, should lead to the performance of other tests. Even today, a strong clinical suspicion of neoplasia constitutes good grounds for a biopsy, except in cases where mammography or other diagnostic techniques afford a sure diagnosis of benignity, as may occur in the presence of lipoma, calcific fibroadenoma, fat necrosis, etc.

It should be borne in mind that although the diagnostic contribution of the clinical examination is limited, its contribution in terms of giving accurate information to women, stimulating active involvement and renewing the relationship between doctor and patient is irreplaceable [6]. Under the pressure of economic problems, the human contribution which stems from the clinical examination is often overlooked. The effort to achieve lower mortality rates at an acceptable cost has made us forget that perhaps the greatest benefit of diagnostic activity lies not so much in the detection of disease as in the peace of mind that derives from a negative diagnosis [7].

Indications

As well as offering an opportunity to talk to the patient about the problem of breast cancer, the clinical examination provides a guide to the performance of instrumental diagnostic investigations and helps in their interpretation. It is still a fundamental and irreplaceable examination when a symptom is present. In such cases, the clinical examination should always precede instrumental investigations and should receive equal attention in the interpretative summary. For this reason, it is essential that the clinical examination is carried out by the physician who is to perform the instrumental investigation even if the patient has already been examined by other physicians.

Mammography

Mammography should be performed using the right equipment and methodology in order to acquire images which contain a wealth of information while delivering a limited radiation dose [8, 9, 10, 11]. In many diagnostic centres, digital technology is now widely used. The advantages of digital mammography include the possibility of obtaining high-quality images at lower doses than are required for analogue mammography, the capacity to compensate for errors in exposure and the broader dynamic range. However, while digital mammography provides images of a medium to high standard and facilitates perception of possible alterations [12, 13, 14, 15, 16], the spatial resolution of digital images is currently lower than that of analogue ones; this sometimes makes it more difficult to categorise a lesion. The availability of numerous second-level diagnostic tests minimises this drawback, since the chief requirement for a first-level test is its ability to detect the presence of a possible lesion. Indeed, the task of basic mammography, whether performed in the course of a screening programme or in a clinical context, is mainly that of selection. Attempting a diagnosis almost always comes later, on the basis of supplementary radiographs or further investigations.

The advantage of the easier perception of the signal afforded by digital mammography is increased by the possibility of using software (CAD: computer-aided detection) [17, 18, 19, 20, 21, 22] capable of evidencing with greater sensitivity small changes in density with morphological features suggestive of tumours. Such systems do not have a diagnostic task; their job is only to show items which might escape the radiologist's attention but which the radiologist must later interpret without being influenced by the results obtained using CAD.

The carcinogenic risk from mammography is similar to that which can be hypothesised for all other radiological investigations and should always be assessed on a cost/benefit basis [23, 24]. In the case of mammography, the danger of not recognising small carcinomas, in the highest risk age group, is vastly greater than the hypothetical risk posed by exposure to small doses of radiation. At our current state of knowledge, we can state that, while every effort should be made to keep radiation doses as low as possible or to reduce them still further [25, 26], the decision on whether or not to resort to mammography should be based above all on quantification of the

expected benefit rather than on the possible hypothetical risk. A special case is that of women with deleterious mutation BRCA1 since their breasts may be subject to greater sensitivity to ionising radiation [27]. The decision to use mammography on these patients, especially if they are young, should be made with care, and numerous trials are taking place to clarify whether magnetic resonance imaging may be used as a routine technique instead of mammography.

Signs and medical report

The most common signs of neoplasia are nodular opacities (64%), microcalcifications (19%) and structural distortions (17%) [28]. Other indirect signs of neoplasia, such as cutaneous inspissation and retraction, nipple retraction or an increase in vascularisation, are of little diagnostic importance since they are often associated with voluminous and clinically evident neoplasia.

Special cases are lobular carcinomas and inflammatory carcinomas. Owing to the preservation of the glandular architecture and the limited stromal reaction, lobular carcinomas frequently do not show particular features on mammography [29]. Inflammatory carcinomas almost always begin acutely with clinical signs, and it is often impossible to find even minor signs of them on previous radiographs. The mammography report should be drawn up according to the requirements for rationalisation and clarity of the informational content:

1. Less significant findings (benign calcifications, microcysts, intramammary lymph nodes, etc.) may be omitted since they are often a source of needless anxiety. It is better to indicate the presence and extension of the anatomical radiopaque structures that can mask the mass.
2. Noteworthy findings should be clearly reported, with precise indication of the site of the lesion, its dimensions, the possible presence of several lesions and lesion location(s). No indelible marks should be made on the original radiograph. In the presence of clinical signs, it should be specified whether or not there are corresponding changes on the mammogram.
3. The radiologist must clearly indicate both the diagnostic orientation and, especially in the case of small subclinical lesions, whether the finding requires further investigation or a biopsy. In such situations it is always best to specify which type of guide (ultrasound or stereotactic) is preferable for taking the cyto-/histological specimen.

In order to avoid distorted interpretations as regards both the diagnostic hypothesis and the possible continuation with tests for diagnosis, the radiologist must sum up the conclusions in a five-category classification ranging from negative (class 1) or certainly benign (the diagnostic strategy stops) to an ever-increasing possibility of pathology (BI-RADS classes) [30, 31, 32]:

1. In the presence of a lesion classified as benign (BI-RADS 2), no further tests are required and, if carried out, would only give rise to anxiety and false positives.
2. In the presence of a probably benign picture (BI-RADS 3), the radiologist should clearly indicate whether s/he feels it necessary to order other diagnostic tests or whether a short-interval follow-up is sufficient. In view of the consequences of a possible error of interpretation, the radiologist should keep track not only of the symptoms but also of the dimensions of the alterations found. In these cases the radiologist, wherever s/he may be operating (clinical diagnostics or screening), must never forget that s/he is the only person responsible for the successive choices since they are based on the radiological semeiotics. These choices should be clearly communicated to and shared with the patient and other specialists.
3. In the presence of a lesion classified as BI-RADS 4 (positive predictive value between 5% and 70%), further diagnostic tests should be carried out (ultrasound, fine-needle aspiration cytology). If these tests prove negative, the radiologist should re-examine the radiographs and write a new report leading to an "integrated conclusive summary".
4. In the presence of a lesion classified as BI-RADS 5, it is imperative to indicate surgical removal and therefore the histological diagnosis of the entire lesion. Other diagnostic tests may be useful only to assist in planning the surgical operation or to confirm the diagnosis in the case of non-surgical treatment.

In conclusion, in many cases the refined semeiotics of mammography permit diagnosis of the histological type, but the particular tasks of mammography are above all (a) the detection of possible lesions, (b) the search for "objective signs" of deviation from assumed normality (pathological semeiotics), and (c) the classification of the findings into one of the five categories mentioned above so that both the diagnostic hypothesis and the appropriate course of diagnostic and therapeutic action are clearly identified.

Results

Mammography has a sensitivity of more than 85%. However, the results are affected by the technical execution and the methodology used in the test. The accuracy is reduced if the adipose component is not well represented. In such cases it is very useful and sometimes indispensable to combine the test with a clinical examination or ultrasound [33]. Carrying out a clinical examination at the same time may also reveal the presence of

possible neoplasia in peripheral sites which might not be included in the standard routine projections.

Indications

Mammography enables exploration of the entire breast and offers the greatest sensitivity, in particular for tumours in the initial stage of development. For this reason it is the only test which can be used as the basic technique in a screening programme.

If the clinical examination produces evident findings, it is always appropriate to carry out mammography in patients older than 35–40 years. It enhances the diagnostic accuracy of the clinical signs, better defines the extension of possible suspicious lesions and enables the discovery of non-palpable contiguous or contralateral lesions.

Ultrasound

Ultrasound involves the use of high-frequency probes (greater than or equal to 10 MHz), linear or annular, and surface focussed. The recent introduction of machines with a digital platform has greatly improved the definition and detail of the ultrasound image, thanks in particular to the use of new multifrequency broad-band transducers, the possibility of recording the harmonic tissue frequencies, and the use of a wide field of view and compound scanning [34, 35, 36].

The examination should be performed carefully, exploring both breasts, in every quadrant, using different angles and exercising different pressure. Nowadays, the ultrasound scan may be enhanced by echo signal amplifiers, substances injected intravenously which increase the acoustic signal. Using special impulses, these substances generate harmonic frequencies which reveal both the macro-circulation and the micro-circulation and therefore give a more precise evaluation of vascularisation, if employed with the latest equipment with the appropriate software. The ability of this technique to detect the more homogeneous and regular vascularity of benign lesions as compared with carcinomas, where it is possible to reveal the presence of arteriovenous shunts, improves the accuracy of diagnostic differentiation between benign and malignant lesions [37, 38, 39, 40]. The use of echo signal amplifiers is, however, still at the stage of clinical validation. The current literature shows that the use of these substances improves sensitivity but leads to a considerable reduction in specificity.

Signs and medical report

Differential diagnosis is based on the morphology, structure, vascularisation and perilesional reaction. More specifically, the findings relevant to classification of nodules as suspicious or benign may be summarised as follows:

- Nodules of a suspicious nature: irregular morphology, poorly defined edges, inhomogeneous echo structure, posterior acoustic attenuation, hyperechogenicity of the surrounding fat, anarchic and plentiful vascularisation with more than one pole
- Benign type nodules: regular or oval morphology, well-defined edges, internal echoes absent (cysts) or weak and uniform, underlying echoes enhanced (cysts) or normal, surrounding echo structure preserved, vascularisation absent or peripheral and limited with only one pole.

The operator should describe the site of the lesions found, their nature (whether solid, liquid or mixed), their dimensions, their depth and possible involvement of the skin and the pectoral muscle. The description of the lesions as regards their physical acoustic features (anechoic, hyperechoic, hypoechoic etc.) is optional and of no great utility, whereas it is essential to include diagnostic conclusions. The conclusions drawn from the ultrasound scan are essential since they are the result of direct evaluation of the images on the monitor by the operator and cannot be deduced from photographic reproductions.

Where there are also clinical or mammographic lesions, the report should also state whether they correspond to the lesion identified by ultrasound.

Results

When used together with mammography, ultrasound improves diagnostic accuracy, increasing both the sensitivity (to as high as 90%) and the specificity (to as high as 98%) [41, 42, 43, 44, 45]. Despite the continuing technological development, ultrasound remains a complementary examination to mammography and cannot be used as a sole diagnostic test, except in certain specific situations [46].

The most obvious limitations of ultrasound lie in the identification and characterisation of preclinical tumour lesions. On the other hand, it possesses extremely high specificity in the diagnosis of cysts and may be considered a first-line technique for non-oncological situations as well, such as inflammation and trauma.

In screening programmes, there is no scientific justification for the use of ultrasound as the exclusive or preliminary diagnostic test [47].

The use of colour power Doppler provides additional, but still debatable information, in the differential diagnosis between benign and malignant pathologies. It is, however, of use in the diagnostic differentiation between fibrosis and relapse.

Indications

The indications for breast ultrasound suggested by the American College of Radiology in 1995, and updated in 1999 and 2001 [48], may be summed up as follows:

- Identification and characterisation of the lesions (whether palpable or not) and the further investigation of dubious clinical and/or mammographic findings.
- Guidance for interventional procedures (preoperative marking of lesions, cytological or histological sampling). One of the most recent indications is ultrasound-guided needle aspiration of axillary lymph nodes found to be suspicious on ultrasound, in order to prevent the excision of the sentinel lymph node if positive.
- Evaluation of breast implants.
- First-level investigation for evaluation of lesions in young women (under circa 30 years of age) and women who are breastfeeding or pregnant.

The use of ultrasound as a method of screening should at present be regarded as the exclusive province of clinical research.

Pneumocystography

Pneumocystography consists in obtaining radiographs after the emptying of a cyst and injection of air into it; the walls of the cyst can thus be studied and possible vegetation revealed. At present, pneumocystography should be performed only to resolve doubts which persist after the ultrasound scan.

Ductogalactography

Ductogalactography consists in the injection of a radiopaque hydrosoluble contrast medium into the secretion duct followed by radiography. It reveals defects in the filling of the duct due to vegetation within the duct, but cannot provide certain differential diagnosis between benign and malignant lesions. This test is indicated in cases of bloody, mixed serous and bloody, or transparent secretions, especially if unilateral and from a single duct and when occurring in the presence of suspicious cytology. It is not indicated when there are other types of secretion since the probability of otherwise hidden neoplasia in such cases is negligible.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) of the breast may only be performed with the appropriate equipment, including suitable hardware and software. The examination should be simple, fast and panoramic (a simultaneous bilateral study). It should guarantee high-quality images and provide a dynamic investigation with the possibility of subsequent processing of the images (subtraction, MIP, MPR, etc.) as well as measurement of the signal intensity-time (SI/T) curves.

The diagnostic accuracy of MRI depends on the technical and acquisitional features but also to a very great extent on the image processing. Processing should therefore be considered one of the main stages of the technique [49, 50].

Reparative processes lead to focal or diffuse inflammatory reactions, with hypervascular areas and a consequent enhancement effect which is sometimes difficult to distinguish from that due to malignant lesions. MRI should therefore generally be performed at least 6 months after surgery and 12 months after radiotherapy. If necessary, however, the examination may be carried out in the few days immediately following the operation, and it is useful when there is some doubt as to whether the lesion has been removed.

Hormone, physiological and pharmaceutical stimulation greatly affects the MR image. For this reason the examination should preferably be performed in the second or third week of the menstrual cycle, and, in menopausal patients, 1 or 2 months after possible replacement hormone treatment has been suspended. If this methodology is not observed, there is an increased risk of false positives. When MRI reveals lesions which did not appear on the conventional investigations, the matter can often be resolved by a second targeted ultrasound scan, guided by the MR images. When diagnostic doubt persists and cannot be resolved by second-look ultrasound (or mammography), it is advisable to repeat MRI 1 or 2 months later, in the suitable period for fertile women, before undertaking surgery [51].

It is also generally advisable for MRI to precede needle aspiration or needle biopsy since these manoeuvres may alter the behaviour of the precontrast signal and contrast enhancement. However, the methodological timing is still a matter of debate. It is believed to be best to take the specimen using the needle prior to MRI where there are unifocal lesions: if the specimen proves negative and the integrated negative diagnosis is deemed sufficiently accurate, normal follow-up with ordinary first-level tests may be considered sufficient. In contrast, where suspicious or clearly multifocal lesions exist, MRI should, if possible, precede needle aspiration.

Signs and medical report

Identification of lesions is based on visualisation of the areas of greatest vascularisation on images produced by subtraction. Once the possible lesions have been identified, the images are evaluated from the morphological viewpoint and the functional characteristics are assessed by means of SI/T curves.

Characterisation of breast lesions using MRI is based above all on contrast enhancement dynamics after the administration of paramagnetic contrast medium. The presence of enhancement is closely correlated with the dynamics of the contrast medium in the lesion, which appear to be determined by the volume and permeability of the vessels, as well as by the width of the interstitial space. Since these characteristics are intrinsic to the process of angiogenesis of malignant lesions, MRI of the breast may be assumed to be a suitable method for the discovery and quantification of the angiogenic process itself.

The parameters to consider are: morphology, edges, enhancement characteristics (homogeneous, inhomogeneous, centripetal, centrifugal), the intensity of the initial signal, and the course of the SI/T curve. As regards morphology, the criteria for malignancy are the same as for conventional techniques: irregular lesions with ill-defined edges. The functional aspect of malignant lesions is characterised by the enhancement features: inhomogeneous, with a centripetal, rapid and intense but brief course. A typical feature of malignant lesions is intense enhancement at the first measurement after injection of the contrast medium, with an increase in signal intensity of more than 70%–100% compared to the initial value; there is therefore an initially steep SI/T curve which decreases rapidly, giving an early wash-out, i.e. a fading out of the contrast medium. Benign lesions have a regular morphology and regular edges and show homogeneous enhancement with a slow and progressive course.

The report should state the presence of areas of enhancement, the lesion site, the lesion dimensions, the hypothesis as to its nature and the relation of the lesion to the surrounding tissue. Since MRI is often performed to resolve diagnostic doubts emerging from conventional methods, such tests should be referred to, a diagnostic conclusion should be expressed and specific suggestions should be made for further possible investigations.

It should be stressed that MRI cannot be proposed as the first diagnostic examination for breast pathologies and that the specific indications for this modality should be followed in order to prevent an excess of doubtful cases and false positives.

Results

MRI of the breast is characterised by very high sensitivity, of between 95% and 100% for infiltrating carcinomas and approximately 80% for in situ ductal carcinomas. The negative predictive value for infiltrating carcinomas approaches 100%. All authors agree on these values, but there is incomplete agreement on the specificity, which is approximately 80% using state of the art equipment.

Indications

Currently, breast MRI should be regarded as a technique to be used only in combination with mammography and ultrasound. There are a number of principal indications:

- The study of women with a genetic or high family risk of breast carcinoma. Owing to the ability of MRI to detect characteristics associated with the process of angiogenesis, use of MRI in conjunction with conventional techniques allows the identification of some tumours which would not otherwise be recognised (the contribution in this respect is particularly valuable in women with radiologically dense breasts) [52, 53, 54].
- The search for unknown primitive carcinomas when conventional methods are negative [55].
- Preoperative assessment or local staging in the case of breast carcinomas diagnosed using traditional techniques. MRI is the most accurate technique for correctly defining the relationship between surrounding tissue and the size and number of lesions, thus affording the identification of multifocality/multicentricity and contralateral lesions. The literature reports that multifocal/multicentric lesions not detected by conventional imaging techniques were identified using MRI in 16–37% of cases and that synchronous occult contralateral lesions were identified in 5–10% of the patients studied. In brief, MRI changed the therapeutic approach to the patient in between 11% and 51% of cases [56, 57].
- Monitoring of breast lesions treated with neoadjuvant presurgical chemotherapy (MRI permits more precise definition of the dimensions of the residual tumour and its differentiation from necrotic and fibrotic components) [58, 59, 60].
- Follow-up after breast-conserving surgery and/or radiotherapy, wherever conventional methods raise doubts regarding the differential diagnosis of fibrosis and relapses. The sensitivity of MRI in distinguishing between relapse and fibrosis ranges from 93% to 100%, and the specificity from 88% to 100% [61, 62].
- Evaluation of women with breast implants. MRI is the most effective technique for studying the state of the implant (integrity, fibrous capsule, dislocation, silicon migration); according to the literature, MRI has a 75% sensitivity and specificity in the recognition of ruptured implants. In addition, MRI allows assessment of the native breast and especially the regions hidden by the implant that are difficult to explore using mammography or ultrasound [63, 64, 65].
- Evaluation of breasts which are difficult to interpret using conventional techniques or for which different diagnostic approaches have yielded discrepant findings.
- As a guide for the taking of cyto-/histological specimens of lesions which can only be revealed by MRI.

Combined use of new stereotactic equipment and surface bobbins and non-magnetic needles now makes it possible to perform cytological and microhistological sampling pre-operative marking of lesions [66, 67, 68].

Contra-indications to MRI include inflammation, which is indistinguishable from malignant alterations, and all the other usual contra-indications (pacemakers, metallic plates etc.).

At our present state of knowledge, the most debated issue as regards the indications for MRI is whether or not it should be routinely used when a breast carcinoma has been diagnosed by conventional techniques and breast-conserving treatment proposed. The literature would appear to suggest that MRI should routinely be performed prior to conservative surgical interventions. However, it is clearly too early to impose such a protocol, both because it would be difficult to offer the test to every woman with a carcinoma in its initial phase and above all because we still do not have clear scientific evidence of the advantages in terms of survival. Until such evidence becomes available, each case should be carefully assessed and, before a decision is made on whether to use MRI, the patient should be made fully aware that if further foci are discovered, it will no longer be possible to avoid mastectomy, even though quadrantectomy and radiotherapy might offer the same results.

Needle sampling

Fine-needle aspiration for cytological analysis

Cytology is performed on: secretions from the nipple, the contents of cysts, material obtained from scarification of erosive lesions of the nipple, and aspiration samples of palpable or non-palpable solid tumefaction when it is not definitely benign. The slide should bear the data essential for identifying the patient, placed there prior to the test.

Fine-needle aspiration cytology (FNAC) may involve the use of a needle alone or a needle attached to a syringe, with the syringe mounted on a handle. Complications are typically negligible (infection, haemorrhage) and more serious complications (pneumothorax) are extremely rare if the methodology is appropriate. In theory, it is possible that dissemination of neoplastic cells might occur as a result of FNAC, but no such cases have been described in the literature on breast carcinoma.

Signs and medical report. A descriptive diagnosis is optional and, in this case, the cytopathological report should be clear and succinct. By contrast, the diagnostic conclusion is obligatory and should be codified into five classes:

- C1: findings insufficient for a diagnostic judgement
- C2: findings negative for tumour cells
- C3: findings dubious; lesions probably benign, but presence of atypia
- C4: suspicious findings, peremptory indications for surgical biopsy
- C5: positive findings for malignant tumour cells (an area of tumour cells unequivocally malignant, already recognisable when only slightly enlarged) with almost absolute positive prediction (>99%).

Results. The sensitivity of FNAC for breast cancer (suspicious + positive cases, excluding insufficient findings from consideration) is 90–95%, and it has a positive predictive value of more than 99%. The rate of insufficient findings in cases of cancer is less than 10%. When FNAC yields a positive finding, intra-operative histological confirmation may be omitted. When a suspicious finding is obtained (in the literature the predictive value of suspicious findings ranges between 40% and 80%), surgical biopsy is required, regardless of the clinical evidence. Given the possibility of false negative cytology, a negative cytological analysis is not sufficient to avoid a surgical biopsy if other diagnostic tests are either dubious or suspicious [69, 70, 71, 72].

If the sensitivity, specificity and predictive values achieved at a treatment centre are not comparable with the foregoing rates, it is necessary to critically review sampling, smear staining and interpretation and possibly to compare one's own practice with that at a more experienced centre.

Needle biopsy for histological analysis (percutaneous biopsy)

The specimen is taken using a wide-calibre needle and therefore special methodological precautions are required (informed consent, accurate anamnesis regarding coagulation disorders or allergy to anaesthetics, local anaesthesia and possible general sedation, cutaneous incision, subsequent manual compression for 10–15 min and radiography of specimens). In fact, not all of these precautions should always be carried out, but the methodology is undoubtedly more invasive than in FNAC. The average time for the procedure ranges from 15 to 60 min; a report is only available several days later.

Nowadays, various techniques are available for percutaneous biopsy, including multiple sampling with automatic or semi-automatic guillotine cutting needles with a 14- to 20-G calibre, the advanced breast biopsy instrumentation (ABBI) system, which allows removal of a core of breast tissue up to 2 cm in size, and the Mammotome breast biopsy system, allowing removal of samples with gentle suction.

Percutaneous biopsy allows histological analysis of the lesion, providing information on tumour invasiveness and certain parameters related to its aggressiveness; it yields a low number of insufficient findings. The expect-

ed results are influenced by the type of lesion (node or calcification), by the calibre of the needle and by the number of pieces taken. It should always be borne in mind, in the interests of correct programming of surgery and treatment, that in 10–30% of cases with a microhistological diagnosis of carcinoma in situ, subsequent surgical removal will reveal the presence of invasive carcinoma [73].

Indications for needle aspiration/biopsy and choice of method

Palpable lesions. Although FNAC almost always enables the diagnostic problem of palpable lesions to be resolved, it is preferable, except in certain specific cases, to use aspiration not as a sole clinical test but after evaluation of the mammogram (or at least the ultrasound scan). This ensures that FNAC is carried out only when necessary, at the right time and in the right place.

Non-palpable lesions. Needle aspiration should be performed with an ultrasound or a radiostereotactic guide. In some centres, it is possible to use an MRI guide. In all cases where the lesion, though discovered through mammography, can be recognised with a targeted ultrasound scan and where there is certainty that the lesion on the ultrasound image corresponds to that on mammography, ultrasound-guided aspiration is to be preferred because it is simpler, faster, more agreeable for the patient and less expensive.

The increasingly frequent findings of non-palpable lesions and their small size require that diagnostic procedures should be very strictly applied, that the recommendation for aspiration must be justified, and that the choice of method (FNAC versus percutaneous biopsy) must be rational [74, 75, 76, 77]. In the presence of lesions of a dubious nature, therefore, the radiologist should use second- and third-level examinations (targeted radiography, mammographic enlargement, possible ultrasound scan studies with a contrast medium, digital processing, MRI, etc.) to try to characterise the lesions as well as possible.

The following considerations may justify aspiration and help in selection of the method:

1. Needle aspiration should be deemed necessary if the expected findings might change the subsequent diagnostic approach or treatment (control or excision, interval between check-ups). It may also be recommended even when the mammogram is clearly suspicious or positive, in order to obtain a definitive preoperative diagnosis so that the patient can be better informed as to the type of surgical operation which will be performed or to avoid a two-stage operation (first, a diagnostic biopsy and then a radical intervention).
2. The choice among the various methods should be based both on the scientific evidence available (evaluation of the contributions they offer for diagnosis, knowledge of the prognostic factors and knowledge of the invasiveness of the carcinoma) and on personal experience.

It is always worth bearing in mind that, if a choice can or has to be made, it is best to employ the less invasive method in cases in which the results will tend to coincide or in which the particular information that may be obtained using the more invasive technique (e.g. tumour invasiveness or aggressiveness, histological type) is not indispensable or can be obtained during the surgical intervention without prejudicing it and the prognosis.

To sum up, the following guidelines may be suggested: given the grounds for needle aspiration, the method of choice to obtain further diagnostic information will in most cases be FNAC (less invasive, less costly), with percutaneous biopsy reserved for cases without a definitive diagnostic evaluation (cases that are classified as C1/C3, or which are the subject of disagreement between the radiologist and the pathologist) and cases in which information is required which cytology cannot provide (invasiveness, aggressiveness).

It should be stressed that the choice of method lies with the operators (the radiologist, pathologist and surgeon), who may prefer FNAC or percutaneous biopsy, according to their own experience. In many cases, moreover, the choice should be discussed and agreed upon on a case by case basis in the multidisciplinary unit.

Suggested diagnostic procedure for self-referrals

Women who are symptom-free

Under 40 years of age

There are no particular recommendations regarding the preventive control except to note that the women involved are at high risk and are part of a specific programme of diagnostic surveillance. Routine ultrasound scans are unjustified in the absence of objective signs.

Over 40 years of age

It is recommended that mammography should be performed at intervals of between 1 and 2 years. Mammography at 1-year intervals, in combination with routine breast and ultrasound examination, is justifiable for women with radiologically dense breasts owing to the greater difficulty in discovering a possible tumour and because the radiological density appears to be associated with a greater risk of tumour development [78, 79, 80, 81].

As regards the clinical and instrumental surveillance of the group of women with a genetic risk of breast carcinoma, there are as yet no recommendations grounded in hard scientific evidence. It is advisable for such women to attend centres where there are working groups devoted to the problem.

Given that mammography has limitations, especially in younger women, the usefulness of routinely combining MRI with ultrasound and mammography is currently being assessed. At present it is widespread practice to advise that check-up visits should begin at 30 or at the same age as the youngest family member affected. Currently, diversified diagnostic procedures and intervals according to the level of risk (e.g. genetic risk for breast cancer) are being evaluated. Periodic tests may also be advisable in males over the age of 50 when there is a family history of breast cancer.

Women with symptoms

Under 35 years of age

Due to the low incidence of breast carcinoma in patients aged less than 35 years, the clinical examination performed by the general practitioner may be sufficient to clear up any doubts and allay needless anxiety. In the presence of real focal pathology, which is not suspicious clinically, ultrasound and possible needle aspiration may be deemed sufficient. If the suspicion persists, the diagnostic evaluation should continue with mammography and other techniques if necessary.

Over 35 years of age

In patients aged over 35 years who have relevant symptoms, mammography in combination with clinical examination and, preferably, ultrasound will afford a correct diagnosis in most cases. The use of ultrasound has the advantage that it will avoid failure to diagnose carcinomas which cannot be revealed radiographically. Ultrasound is indispensable both when there is difficulty in exploring the breast radiographically (dense breasts) and when mammography or the clinical examination reveals nodules whose nature is unclear.

If the difficulty in classifying the images persists or if suspicious elements emerge, needle aspiration should be performed (percutaneous cytology or biopsy). It will be necessary to decide on a case by case basis whether or not needle aspiration should be preceded by MRI or breast scintigraphy.

Operational models (organisation of diagnostic procedures)

The organisation of the procedures used in diagnosing breast pathologies should take account of three objectives:

1. To diagnose most small tumours at an early stage so as to ensure a reduction in the mortality and a better quality of life
2. To achieve correct diagnosis of benign growths in order to avoid additional anxiety and unnecessary biopsies
3. To reassure healthy women and give them peace of mind

From the methodological point of view, two ways of proceeding can be considered:

– Creation of breast diagnostic units (BDUs)
– Implementation of mammographic screening programmes

Breast diagnostic units

Only the centralisation of diagnostic activity in a single site (a BDU), catering for both women who present spontaneously, with or without symptoms, and women selected through screening, enables administrators to optimise resources and to provide personalised procedures so that a definitive diagnosis can be obtained at low cost and with minimum inconvenience for the patient [82]. It is convenient to arrange for two sets of procedures: one set for women with symptoms and another for those without [83].

Patients with evident clinical symptoms are inducted into a set of procedures that includes a preliminary clinical examination, then mammography and, in rapid succession, any other tests (ultrasound, needle sampling) needed to reach a conclusive diagnosis. Communicating rooms need to be available.

Naturally, the sequence of the diagnostic procedures may require modification in accordance with the presumed pathology and the patient's age. The result is given to the patient at the end of the tests, except in cases in which it is necessary to take a sample with a needle (the analysis of which should also be carried out in the same centre).

In the event of a positive result, it is the radiologist who provides the first explanations and prepares the patient for the subsequent therapeutic procedures. The referring doctor is, of course, informed immediately (with the patient's consent) and is directly involved.

Women without clinical symptoms who spontaneously present with a view to prevention undergo the same set of diagnostic procedures on the first occasion as patients

with symptoms. In most cases, clinical examination and mammography are sufficient to conclude the diagnostic process in these women. The date of the next check-up and follow-up procedures are established when the results are given.

Women without symptoms who are found to be in a healthy state are offered one of two differing sets of subsequent procedures:

- Women with breasts that are more difficult to examine are invited to return for annual check-ups with mammography, clinical examination and ultrasound.
- Women with breasts that are mainly adipose can be monitored by mammography alone at 2-yearly intervals. In this case, interpretation of the radiographs is deferred and double reading is essential.

The diagnostic activity must be carefully monitored. The patient should come away from the BDU with a definitive diagnosis and not with a request for further diagnostic testing.

Mammographic screening

The purpose of mammographic screening is not diagnosis as such but the selection of women "probably affected by a tumour". The sole objective of the screening programme is to obtain a reduction in mortality at an acceptable cost; it is therefore to be undertaken only if its effectiveness has been demonstrated, if funds are available, if the cost is acceptable and if it is competitive in relation to other public health initiatives. For the same reasons, the programme is not directed at all women but only at those in the age band at greatest risk.

As far as breast cancer is concerned, screening programmes have now been operative for very many years and their effectiveness is proven; the cost per life saved would also appear to be acceptable [84, 85, 86, 87, 88]. Screening programmes can be credited with having demonstrated that prompt diagnosis results in a reduction in mortality and that good results can be obtained only if all steps of the programme are optimised and all results are periodically checked. Although the efficacy of mammographic screening has been proven over many years, it cannot be said that the population is adequately covered. However, it has to be borne in mind that is not possible, within a limited time, to fully implement a programme that requires broad participation among the population, growth of awareness, sufficient economic resources and an adequate number of well-trained professional figures (radiologists and radiographers) [89].

The negative aspects of a programme of mammographic screening are well known [90, 91, 92]: prolonged awareness of illness when therapy is not able to yield the desired results, over-diagnosis and over-treatment, false reassurance in the event of false-negative results, anxiety inducement in the event of false-positive results and the possible risk associated with radiation.

The operating methodology for a screening programme is today rigorously codified [93, 94, 95, 96]: exclusive mammography bi-annually, deferred reading, recall with further diagnostic testing of women with a doubtful diagnosis expressed even by only one of the two readers, and limitation to women aged between 50 and 69.

Some considerations with respect to current screening methodology

Mammography is offered as the sole test, at 2-yearly intervals and with deferred reading. This allows a reasonable number of examinations per hour to be completed and reduces the number of working hours required of radiologists, but it leads to less thorough and sensitive diagnostics, as well as to the need for follow-up in uncertain cases. The limited sensitivity of mammographic screening used as the sole test on a bi-annual basis is clearly attested to by the rather high rate of so-called interval cancers [97, 98, 99, 100]. It has been sufficiently documented that a good proportion of these cancers would be picked up if shorter intervals were used [101, 102, 103, 104, 105] and if the screening were combined with other tests [41, 42, 43, 44, 45]. It therefore seems reasonable to consider the possibility that, for women with breasts that are not amenable to X-ray scanning, the screening protocol should be modified to include routine ultrasound scans.

Very useful, but perhaps less feasible for reasons of cost and lack of personnel, would be the inclusion of the medical radiologist at the time of the first examination. The implementation of a concurrent clinical examination and ultrasound scan, when necessary, would lead to a 7–10% reduction in diagnostic errors [106, 107], and thus also the incidence of interval cancers [108, 109]. Furthermore, it would obviate the need to recall patients for second-level tests, which causes anxiety, and would offer the woman receiving the information the kind of human contribution that can only be ensured by the presence of the doctor.

As stated above, women aged 50–69 are prioritised as subjects for screening, but in view of the longer life expectancy of women in good health and past the age of 70, it may be advisable to continue actively screening women who attended previous tests up to the age of 74.

The decision as to whether the age at which the first "invitation to screening" is offered should be lowered to 45 can be left to the Health Authorities, taking into account available resources and working in collaboration with the Scientific Society. There is a general consensus that women should be given the opportunity to undergo periodic tests at this age since the results of recent studies, although not conclusive, have indicated the possible

effectiveness of early diagnosis in this age range as well. Naturally, the women concerned must be adequately informed of the possible benefits, but also of the possible negative effects (diagnostic overestimation of risk, anxiety) [110, 111].

Concluding considerations on procedures for timely diagnosis of breast cancer

Procedures for early diagnosis must be implemented in such a way that the entire geographic area in question is adequately covered, and women who undergo checkups, whether spontaneously or as directed by their own doctors, must be assured of good quality diagnosis. In order to obtain the greatest advantage from the diagnostic activities while containing the negative effects, every procedure aimed at achieving a timely diagnosis must take place within the context of a well-organised and supervised programme and must be supported by thorough training programmes for the operators. All the diagnostic programmes must therefore be backed up by adequate planning, and all the necessary resources, in terms of both professional support and institutional structures, must be guaranteed, including the health care functions subsequent to the diagnosis, namely therapy and follow-up to an appropriate standard.

Whenever the prerequisites for implementation of a high-quality screening programme within a limited period are lacking, it is essential that priority is given to measures aimed at reorganising and rationalising the diagnostic activities already available within that geographical area, reconstituting them into dedicated structures in the form of BDUs. It is necessary to create a network of BDUs evenly distributed across the territory since a network of this kind represents an indispensable preliminary phase in a programme that will extend to the population as a whole. The institution of a BDU network and the initiation of a screening programme may be perceived as a single project to be implemented at the regional level.

In view of the fact that the diagnosis of breast lesions is currently based on tests that rely largely or exclusively on the expertise of the radiologist, and given that the apparatus is costly and that its use must be supervised and carried out in an integrated fashion, it is appropriate for clinical and organisational responsibility for the diagnostic procedures to be entrusted to the radiologist, assisted by a physician or general practitioner and a pathologist. It is also necessary, when disease is found, for interdisciplinary expertise to be available so that the most suitable form of treatment can be identified more easily.

Possible non-standard modes of organisation should also be carefully evaluated [112, 113]; this lies within the remit of the respective technical committees. Similarly, the diagnostic protocol to be used can be modified with a view to increasing the sensitivity of screening [114].

Finally, it would be desirable for each region to set up an *interdisciplinary body of reference for quality assurance*. The function of such a body would be to ensure that work on breast pathology reaches a high level of quality, and that this level is maintained, throughout the region in question. Naturally, in order to guarantee the desired quality, it is necessary to allocate adequate resources and to ensure the availability of suitably qualified personnel.

One of the most urgent problems is to guarantee the quality of the procedures employed in breast pathology diagnostics, both in the clinical context and in screening. Attention needs to be paid specifically to the need to extend quality control to diagnostic centres that do not operate under the auspices of a screening programme, since today most women still undergo tests autonomously, outside the organised programmes. Some quality assurance activities can be undertaken as part of the activities of the health service, but others will require specific, targeted funding and will need to cover training activities, data collection and the compilation of proper annual reports to be presented at the regional level.

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