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Management of Non-palpable and Small Lesions Found in Mass Breast Screening

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INTRODUCTION

HIGH QUALITY mammographic screening programmes allow detection of a number of small, non-palpable abnormalities within the breast. Whether benign or malignant, these lesions present problems for radiologists, clinicians and pathologists of a different nature to those produced by the presentation of palpable breast lesions, resulting from consultations of women with symptomatic lesions. The balance and range of pathologies so found will be different from palpable lesions, and the various skills and decision-making processes required subsequently more complex.

This paper aims to outline as far as possible the necessary steps to be taken to maximise accuracy of diagnosis and treatment of such cases. We do not intend to give a dogmatic view of the management of small lesions but rather identify areas where a consensus has been reached, areas of controversy, and fields of research suitable for further investigations.

A diagnostic balance must be struck between the desire to recognise as many small tumours as possible, minimising the number of false negatives, while avoiding unnecessary examinations, investigations and biopsies resulting in high anxiety and cost for both the women and health services involved [1–3]. In order to maximise sensitivity and specificity, there are a number of quality measures that must be taken at both technical and professional level, with appropriate performance indicators. These are outlined in the European Guidelines for Quality Assurance and Quality Control in Mammographic Screening [4]. In summary, however, there are a number of specialised skills now required from hospital physicists and radiographers that allow the production of mammograms with high image quality and optimal positioning. Specific training and specialisation is required for screening radiologists in order to maximise small cancer detection rates and minimise the number of women recalled for further assessment. Double reading of mammograms may be useful in achieving this aim.

An extensive quality assurance programme is a prerequisite for effective screening and adequate assessment of suspicious lesions detected by mammography. Audit and comparison of results obtained from other screening programmes will encourage progressive improvement of the quality of the image and its interpretation [5].

Women with suspicious findings on mammography should be recalled to a specialist assessment centre for further investigations. These may include mammography with more refined projections, microfocus magnification, or ultrasound examination of the breast. Fine needle aspiration cytology may be undertaken, using either stereotactic or ultrasound guidance. This method requires some skill and experience, but will allow the reduction of unnecessary benign biopsies. Following such investigations, only a small percentage of women will require an open surgical biopsy for histological confirmation of the abnormality. The rate of benign biopsies should be no greater than that for malignancies. Experienced centres are able to achieve a malignant/benign ration of up to 10/1, according to the local conditions and the screening round [6–8].

Surgical management has also changed considerably. Mastectomy is now performed on a limited basis and tumorectomy is more often used. Precise localisation of non-palpable tumours using wires or marker dyes such as carbon particles should be provided to ensure that the margins of excision of tumorectomy are neither too large, for cosmetic reasons, nor too small, because of the risk of recurrence. Specimen radiography is essential to allow peroperative confirmation of surgical completeness of excision. Conversely, the amount of tissue excised for benign biopsies should be limited by surgical quality assurance meas-

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ures, such as placing a simple limit on the maximum weight of benign biopsies. Radiotherapy is usually performed on the whole breast after surgery for invasive lesions, with a boost to the tumour bed.

Prognosis of these small tumours is generally very good and adjuvant medical treatment (hormonotherapy in postmenopausal women, chemotherapy in premenopausal women) is indicated in the case of poor prognostic factors, e.g. histological grade, invasion of axillary nodes, etc. However, it should be noted that these prognostic factors are based upon studies carried out on larger tumours, and the usefulness of radiotherapy and adjuvant therapy for small invasive lesions should be further investigated.

The conclusion of the report emphasises the need for clinical research in this field, and of specific training for the key professional staff involved, radiologist, radiographer, cytopathologist, radiation oncologist and surgeon, in order to maximise the benefits and minimise disadvantages for women involved in a breast screening programme. Such benefits are substantial. However, it is only by rigorous attention to such training and quality assurance issues that the full benefits of a high quality screening programme will be delivered for the population.

DEFINITION OF THE PROBLEM

The chief aims of mammographic screening are to reduce the mortality from breast cancer in the group invited for screening, and to allow therapeutic intervention at an earlier stage in the natural evolution of breast cancer. Such aims can be achieved only when screen-detected abnormalities are properly managed. Prior to population screening programmes by mammography, experience with small tumours was limited. Although the prognosis of these small lesions has proved favourable, many diagnostic and therapeutic uncertainties remain. This report will be confined to mammographically detected intraductal and small invasive malignancies of 2 cm or less in diameter. Lobular carcinoma *in situ* will not be specifically considered as it is not directly related to mammographic screening, and its natural history is not clearly defined.

Optimal management of screen-detected lesions is a multidisciplinary effort. Screen-detected abnormalities which are clearly malignant on mammographic grounds may often be referred directly for biopsy, although the use of fine needle aspiration to allow definitive surgical planning pre-operatively is advantageous. A lesion whose significance is less clear requires discussion in a multidisciplinary setting, with results of specialised assessment and fine needle aspiration, in order to determine the need for surgical biopsy. The aim is to correctly identify those lesions requiring further investigation and, if necessary, biopsy while at the same time minimising the number of benign lesions called for additional evaluation. It is important to minimise the delay between screening process and the woman receiving her results, and any unnecessary delay in treatment should also be avoided.

The diagnostic work-up should provide sufficient information that, if an open surgical biopsy is planned, it can be a true therapeutic procedure, thereby avoiding a two-stage operation whenever possible. Surgical biopsy should allow optimal histopathological evaluation of the excised specimen. Most small *in situ* and invasive lesions can be adequately treated with conservative excision in combination with breast radiotherapy for the invasive tumours [9, 10]. However, in some cases, total mastectomy may be indicated for clinical or personal reasons [11, 12].

Diagnosis and treatment of non-palpable tumours represent a major challenge to all clinicians directly concerned with breast cancer. Results from the European pilot studies on breast screening indicate that management of these small lesions demands great skill and commitment from radiologists, pathologists, cytologists and surgeons. They should be specifically trained in the diagnosis and treatment of small lesions, and learn to collaborate with each other on a regular basis. By frequent multidisciplinary case conferences they will share the experience gained in the management of their patients. This has been shown to be one of the most important factors in the effectiveness of any successful breast cancer screening programme.

NATURAL HISTORY AND PROGNOSTIC FACTORS

The aim of early diagnosis and screening is to reduce the number of patients with distant metastases at initial treatment. It has been shown that there is a clear relationship between tumour volume and probability of distant dissemination. However, this probability is strongly influenced by several other interdependent variables [13–15], such as histological grade, proportion of proliferating cells (S phase fraction), presence or absence of hormonal receptors, molecular characteristics of the tumour such as cathepsin D, oncogenes, etc. During the growth of tumours, the number of involved axillary nodes increases with tumour size and, on average, the first involvement of an axillary node occurs at a much smaller volume than the one at metastatic dissemination [13]. However, involvement of axillary nodes is a good index of the propensity of a tumour to disseminate, and is, therefore, a valuable indicator of the tumour's biological aggressiveness, although it should not be the cause of the haematological spread, and should thus not be associated with it [13].

Data do not corroborate claims of some authors who consider that there are two types of breast cancer: (1) those which disseminate from the onset and are node positive. In this case, systemic therapy is required, regardless of the size of the tumour, (2) those with late dissemination. Conversely, the distribution of tumour size at dissemination appears to be unimodal from the tumour with very early dissemination to those with very late dissemination [13, 16, 17].

The tumours which are detected by screening are generally small, and the predictive value of axillary node involvement is limited. In a small but non-negligible proportion of these patients, distant dissemination has occurred prior to the involvement of the first lymph node, while dissemination has not yet occurred in a high proportion of patients with involved nodes. However, the natural history of small tumours, of less than 20 mm in diameter, is not well known since data are scarce, and there is no general agreement on the method used for measuring the volume [13–18].

One of the main aims of clinical and fundamental research is to identify the indicators which are of high predictive significance in patients with small tumours. A better understanding of the natural history of breast cancer could suggest the use of the most appropriate prognostic pointers and the ways to combine them for scoring the degree of virulence of small tumours [19]. However, these studies are difficult to perform for at least two reasons.

(1) While growing, the tumour progresses from "bad to worse". This progression is evidenced by the increase of the tumour grade over time: small tumours are often of low grade while

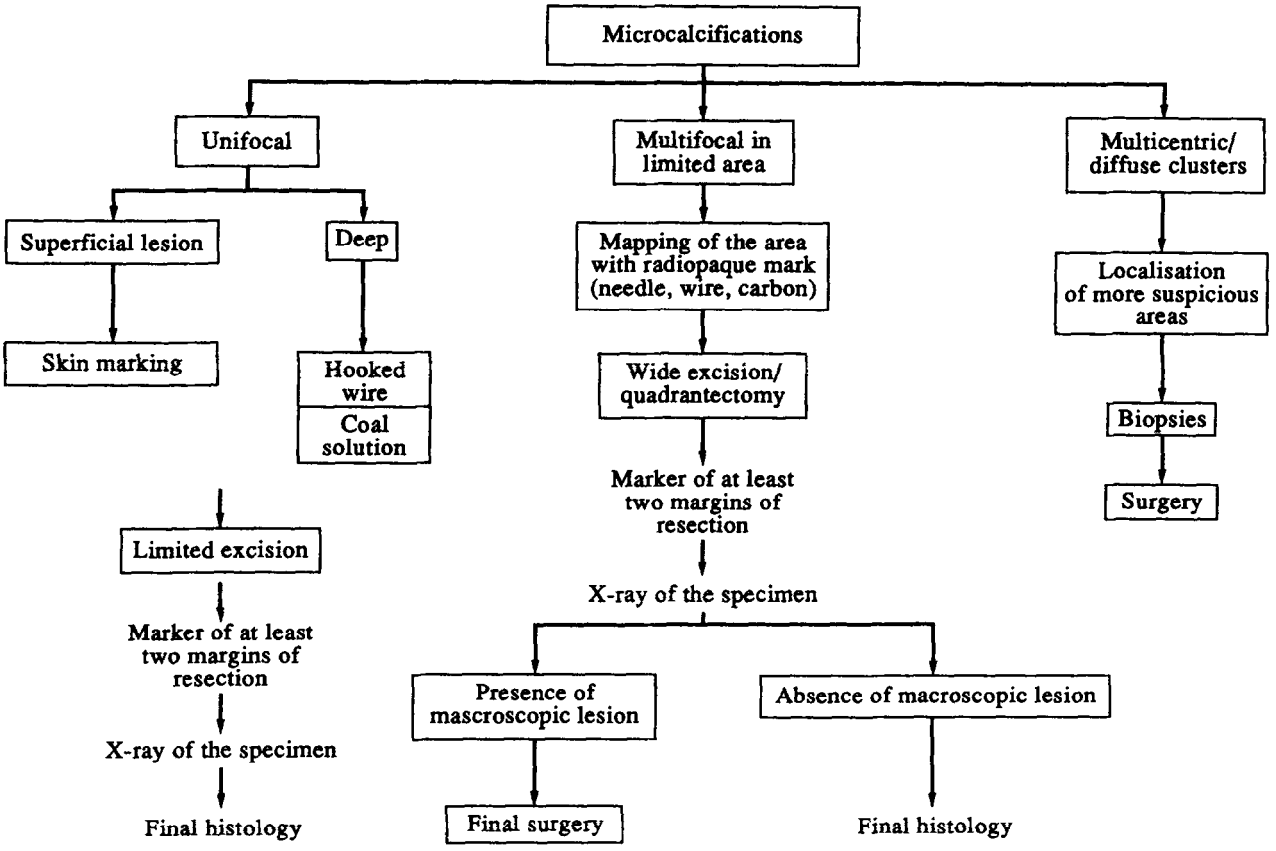

Fig. 1. Flowchart

most large tumours are of high grade [13, 16]. Moreover, conversely to what is observed in experimental tumours, the S phase fraction is slightly higher in large tumours than in small ones. Therefore, the significance of prognostic indicators may be different for small and large tumours. Early detection has also the advantage of avoiding, to a large extent, tumour progression.

(2) Biochemical data show that several types of molecular defects are observed in breast tumours. Therefore, it is unlikely that one or a few of these defects will be sufficient to determine prognosis.

As far as we presently know, size and histology are probably the two most valuable prognostic factors for cancers without nodal involvement, but they should be combined in the future with other indicators in a predictive index. For example, Rubens advocates combining size, histology and S-phase fraction [20].

The role of systemic therapy (adjuvant chemotherapy and/or hormonal treatment) for very small lesions is still controversial because its impact on long-term survival has not yet been conclusively evaluated by large, controlled clinical trials. The absolute benefits of such adjuvant treatment are certainly smaller than those demonstrated for larger tumours because the probability of distant dissemination is strongly related to tumour size [13, 17, 21]. Mass screening provides the opportunity to study both premalignant breast lesions as well as invasive breast cancers at the earliest stages of development. It is likely that research in this area will provide unique insights into the natural history of breast cancer, with important future implications for both prevention and treatment [17].

DIAGNOSIS

Breast screening

The key features at this stage are production of high quality mammographic images with high contrast and spatial resolution, using a dose of ionising radiation as low as reasonably practical. Experienced programmes achieve a mean glandular dose of less than 2 mSv per exposure, even with the use of a grid which allows higher resolution and marginal interpretation of small abnormalities. In order to achieve this, it is necessary to have mammographic equipment conforming to rigid specifications, and a dedicated processing system, usually using a longer processing time and a higher temperature than standard X-ray processing. Both the machine and processing equipment should be subject to regular control checks as laid out in the European Guidelines for Quality Assurance in Mammographic Screening [4].

It is vital that radiographers/technologists are specifically trained in the technique of positioning for mammographic screening, and should be the only group performing this function. Poor technique allows small abnormalities lying deep in the breast to be excluded from the film. It is important also to minimise discomfort for the woman as well as minimising the number of films (less than 3%) requiring repeat examination for technical reasons. A trained and fully experienced breast screening radiographer is most likely to achieve these aims, and will also be more conversant with quality control procedures.

The maximum benefits in mortality reduction from a breast screening programme will accrue when women regularly attend for their incident re-screens. Consequently, the entire screening

process must be as comfortable as possible, and it is undesirable to recall large numbers of women with benign abnormalities, i.e. false positives. This will have a detrimental effect on uptake in future rounds. In the first round of screening, a figure of 5–7% or less of screened women recalled for assessment is achievable. This should diminish in further rounds, figures of 3% or less are achieved by many experienced programmes. It is, therefore, another key feature of screening programmes to ensure that the mammograms are only interpreted by highly trained radiologists, subject to a minimum volume throughput, in order to maximise their skills. In the U.K., breast screening programme radiologists are recommended to spend three to four half days a week in the process of breast screening and should read a minimum of 5000 mammograms a year. Studies have shown that sensitivity and specificity increase with the experience of the radiologist [22].

Abnormalities such as irregular masses, suspicious microcalcification and architectural distortion will require recalling for assessment. Abnormalities such as benign breast change or clearly defined and well marginated masses may be returned to routine screening. The chances of a completely well defined mass of low density with no associated suspicious features being malignant are extremely low and statistically do not warrant recall for assessment. Double reading of all films has been shown to increase the sensitivity of a programme [23], but care must be taken to ensure that too many women are not consequently called for assessment. Particularly in an office-based programme where first reading is provided by the local radiologist, it is essential that second reading be provided by a fully experienced screening radiologist. Cases of discordant opinion between radiologists reading a screen-detected abnormality may be solved either by a system of third reading or by a consensus decision.

Screening mammography requires a different skill and outlook than symptomatic mammographic interpretation for radiologists [24]. Skill and experience in the latter do not necessarily equate with a satisfactory performance in the former. Ideally, the two should be combined to maximise radiological skill and interpretation. The recall of a symptomatic patient with a dubious abnormality for further films in 3 or 6 months time is not a practice to be encouraged in screening.

Mammographic screening may be satisfactorily performed using a high quality single mediolateral oblique projection (single view). However, two-view mammography, incorporating a cranio-caudal projection, is also performed in certain screening programmes. This practice is certainly advisable during the early learning curve of any screening programme. Experience shows that the cancer detection rate may increase slightly with two views, and the recall rate for assessment should be considerably diminished. The extra films will, of course, result in additional exposure to ionising radiation for the woman. However, if two views are only performed on the woman's prevalent screen, and incident screens are restricted to a single view, the additional exposure over the women's screening lifetime will be low.

Assessment of screen-detected abnormalities

Varying health systems have different methods of providing breast assessment, e.g. office or hospital based. What is clear, however, is the necessity for the highest quality equipment including the ability to perform spot compression, microfocus magnification mammography and specialised additional projections, if required. Sonographic assessment must be available to accurately identify solid from cystic lesions, and as far as possible predict diagnostic features. Skill and experience in assessment will, combined with the use of fine needle aspiration cytology (FNAC), result in the minimum number of unnecessary benign biopsies. A multidisciplinary team setting including a radiologist, cytopathologist, surgeon and oncologist is highly advantageous in maximising the exchange of information and learning between the group as well as allowing discussion of individual cases at case conferences. Before a woman undergoes a biopsy, it is recommended that her case be discussed at such a conference.

It is essential that the radiologist who has taken overall responsibility for the reading of the screening mammograms be involved in the assessment process. This allows greater feedback and maximises both reading and assesment skills. Classification of radiological findings into a graded system as follows is of benefit as such a practice will tend to introduce more consistency and cross disciplinary, interpretational ability.

R1 Normal or generalised benign changes.
R2 A discrete abnormality having benign characteristics mammographically.
R3 An abnormality present which is indeterminate and requires further assessment.
R4 An abnormality is present which is suspicious for malignancy.
R5 Radiological features suggestive of malignancy.

A similar grading system can be applied to both cytological and clinical findings, further aiding management decisions during case conferences. It is advisable for all women recalled for breast assessment from a screening programme to undergo a physical examination.

Two of the key performance indicators used to assess the success of a breast screening programme are the cancer detection rate and the rate of small invasive cancers equal to or less than 10 mm detected. The majority of established high quality screening programmes in the northern part of Europe detect between five and seven cancers per 1000 women screened on the prevalence round according to the underlying national incidence. Up to 50% of these will be non-palpable. Fifteen to twenty per cent will be ductal carcinoma *in situ*. Somewhere in the region of 75% can be expected to be lymph node negative. Analysis of the numbers of small invasive cancers detected can be regarded as an indicator of sensitivity in terms of image quality and radiological acuity. In the U.K. screening programme, an ideal figure is set of 16 or more of these small invasive cancers to be detected per 10 000 women undergoing screening.

It is possible to achieve satisfactory results across a national breast screening programme. The U.K. figures for 1991–1992, where over 1 million women were screened, demonstrated the following results:

No. of women screened:	1 059 703
Uptake rate:	71.3%
Recall rate for assessment:	6.2%
Biopsy rate:	0.89%
Cancer detection rate:	6.2 per 1000
Benign/malignant ratio:	2.3/1

Fine needle aspiration cytology

Fine needle aspiration cytology (FNAC) permits the study of cells from an area of mammographic uncertainty, allowing facilitation of management decisions. FNAC, in combination with increasing radiological expertise can lead to malignant/

benign biopsy ratios in specialist centres of between 3/1 and 10/1, especially on the incident screening rounds. It, therefore, minimises the number of unnecessary benign biopsies, is highly advantageous in cost and reduces anxiety for the woman as well as in cost and bed utilisation by the health system [18, 25]. It is a relatively simple and cost-effective method which, nevertheless, requires a great deal of skill and training in both technique and interpretation [26, 27].

Not only is FNAC useful for predicting management requirements of uncertain abnormalities in the breast, it is also useful in confirmation of malignancy in order to allow definitive one stage surgery. Lesions having a high or relatively high degree of suspicion, such as spiculated or poorly defined masses, focal architectural distortion and microcalcification having certain suspicious features, should undergo aspiration prior to biopsy. Other lesions, such as indeterminate microcalcification, relatively well defined but solid masses as demonstrated on ultrasound, and areas of marked focal asymmetry, may be subjected to FNAC with a view to returning to normal screening having had a benign diagnosis confirmed. It is not generally necessary to aspirate or drain cysts unless ultrasound demonstrates any complex features, the cyst is in some way symptomatic or the patient specifically requests it.

The predictive value of FNAC will vary according to the experience of the teams involved. It is generally not possible to differentiate *in situ* from invasive malignancies on cytological grounds. It is important to ensure accurate placement of the needle tip in the lesion, and this may be done with ultrasound, stereotactic or perforated plate guidance [28, 29]. It is not always possible to obtain epithelial cells from an abnormality, e.g. if the lesion is purely fibrotic. However, with skill and experience, it is possible to achieve only a 5–15% inadequate result rate. The best results have been published in studies in which a very limited number of people perform the aspirates and specialist cytologists read the results [30]. In general, the person best suited for aspiration of these small impalpable lesions will be a radiologist. A number of passes may need to be made in order to obtain satisfactory results. Confirmation of cellularity is advisable and to this end it is useful to have some form of on the spot staining (Diff Quik), and such a function can be performed by a technician. Ideally, if a trained cytologist can be present, this allows not only confirmation of cellularity but also prediction of the final result, even though a full Pap stain will be required. The key issue here is to ensure that the result of FNAC is appropriate to the radiological findings. If not, it allows an instant decision to be made to switch imaging modalities, e.g. from ultrasound to stereotactic or *vice versa*, in order to maximise the predictive value. Such a facility also allows the minimum number of passes through the breast lesion for the women. It allows a number of women to be discharged immediately from the assessment clinic on the basis of a radiological abnormality which does not carry a high degree of suspicion combined with a benign cytology.

A cytological grading system similar to that used in radiology is in use in the U.K., and is listed below:

C1	Insufficient epithelial cells for diagnosis
C2	Benign epithelial cells
C3	Indeterminate, possibly with features of atypia
C4	Suspicious of malignancy
C5	Malignant on cytological ground

Core biopsy

This procedure yields a tissue sample for histological examination. Core biopsy is obtained with a biopsy needle of 14–18 gauge similar to those used for renal or prostatic biopsies. The core of tissue obtained is about 1 mm in diameter and 10–12 mm in length. It is usually suitable for a detailed histological examination.

As with FNAC, it is crucial to accurately target the lesion in order to obtain representative material. This can be done either by ultrasound, perforated plate or stereotactic techniques.

Core biopsy may differentiate between *in situ* and invasive malignancy, and it may also be able to identify the well differentiated cancers. However, both these factors are very dependent upon the exact site from which the sample is obtained. This method is more expensive than FNAC, complete histological laboratory facilities should be available, and there will be some delay in reporting. There is a greater probability of causing a haematoma and some discomfort for the woman.

In summary, FNAC should currently remain the first choice method of assessing the nature of a lesion if mammographic and sonographic criteria are not sufficient. Core biopsy may be reserved for lesions where there has been an insufficient or indeterminate result from FNAC, and a management decision is still unable to be reached on other grounds.

Interval cancers

An interval cancer is a cancer arising in a woman who has had a "normal" screen. The number of such cancers diagnosed during the 12 months following the screening procedure should be limited to less than six per 10 000 women screened. However, an accurate determination of the number of interval cancers depends much upon an accurate cancer registry. Interval cancers may arise from sub-optimal positioning radiographically, misinterpretation of a lesion mammographically thought to be benign, or may genuinely not have been visible on the screening mammogram. It is not possible to avoid interval cancers in a screening programme. What is necessary, however, is to minimise the number of women recalled for assessment and those undergoing biopsy, while at the same time not allowing the interval cancer rate to rise above that expected. The knowledge and study of such interval cancers is a valuable learning experience for the team.

Pre-operative localisation of non-palpable lesions

A number of pre-operative localisation marker methods may be provided in order to most accurately guide the surgeon for excision of non-palpable abnormalities in the breast. These have been described elsewhere [31–33].

Accuracy of localisation is essential both for completeness of excision and postoperative cosmesis. A number of techniques are available but the most commonly used are those involving the insertion of a hooked guide wire or other marker, e.g. carbon particles. Whichever method is used, the radiologist should ensure the shortest skin to lesion approach for the surgeon, and should make certain that a report on the localisation procedure or the radiologists' instructions to the surgeon accompany the woman to the operating theatre so that there can be no doubt in the surgeon's mind as to the procedure that has been undergone, and the relationship of the marking device to the lesion. Most commonly, a perforated plate device is used for the localisation approach, sometimes a stereotactic device is used although there is an inherent problem with Z axis (depth) if this technique is used for direct wire placement. If the lesion is sonographically visible and has been confirmed as malignant, then surface skin marking with an indelible marker accompanied by a report

stating the size and depth of the lesion in relation to the skin mark provides sufficient accuracy as there will be a wide margin of excision anyway. This also provides the shortest possible skin to lesion approach for the surgeon, as the ultrasound technique generally employs the same anterior oblique position as required for operative surgery. Ultrasound guidance may also be used for wire placement.

Handling of biopsies

An adequate pathological evaluation requires proper orientation of the specimen and handling by the pathologists. In order to achieve this, the surgeon should lable the specimen at two points, e.g. at the closest point to the nipple and at 12 o'clock. The entire surface of the specimen may be coated with Indian ink in order to facilitate microscopic recognition of surgical edges. Subsequently, specimen radiography should be performed to ensure completeness of excision.

Specimen slice (4–5) radiography following initial handling in the pathology laboratory may also be valuable to concentrate attention on the abnormal area. Adequate orientation of the specimen, initially, will allow more accurate surgical re-excision if the margins of the initial biopsy specimen are not clear of malignancy.

A small tumour may be snap frozen for oestrogen receptor/progesterone receptor assessment and for other prognostic parameters, providing this does not compromise conventional pathological examination. Frozen section is not a reliable technique for the small non-palpable lesions typically detected by screening.

The pathological report should include:

—the size of the tumour (consensus opinion is that this should be measured on the fixed specimen) and any involvement of axillary nodes. Whether a predominately intra-ductal malignancy has small foci of microinvasion. The histological grade of the tumour according to the WHO grading (first edition: 1968),

—a statement regarding the potential presence of an extensive intra-ductal component defined as 10 or more foci of ductual carcinoma *in situ* beyond the edges of the invasive mass,

—a statement regarding the involvement or otherwise of the surgical margins (either free, close or involved) and the closest distance between the tumour edge and the margin of the specimen in millimetres.

TREATMENT

Surgical management of non-palpable breast lesions

General approach to open biopsy. Before the operation, the surgeon should make his/her final assessment on the localisation of the lesion and also consider the course of the localisation device from the skin to the lesion as well as the relationship of the lesion to the tip of the needle, wire or dye deposition. In some cases, cutaneous radiopaque markers may accompany the wire to assist in delineating the extent of microcalcifications. Multiple needles or wires may also be used to bracket the lesion.

When the localisation procedure has been performed using a stereotactic device, the surgeon should realise that the point of entrance of the wire, or the carbon tattoo, may be in a different quadrant with respect to the lesion. In general, however, the radiologist should make every effort to accurately position the guide from the closest skin surface to the lesion.

Open biopsy can be performed in an out-patient clinic with local anaesthesia, when the risk of malignancy is considered low and the lesion is not too deep. If a wire guide is used the surgeon should follow the wire while avoiding transection of the wire or contact with the lesion. The use of wires with thickened segments just proximal to the hook may facilitate the ability of the surgeon to anticipate the hooked portion of the wire and the location of the lesion. Traction of the wire may cause it to be moved or dislodged, however, during the resection, a gentle pull on the wire may aid in determining the direction of its course. The specimen should be removed in one block in order to facilitate orientation for the radiologist and pathologist and to ensure that the margin is continuous. The preoperative location with carbon particles offers certain advantages over the wire guide in that it does not require immediate surgery. It can also be used for identification of the right area of the specimen by the pathologists who should state on the pathologist's report that carbon has been found on the slide. Conversely, the carbon marking can be less reliable if the surgeon should transect the pathological area to find the trace of carbon particles. Breast incision is the usual approach unless the lesion is located in the deeper portions of the breast in which case some have used an inframammary incision, undermining the gland above the pectoralis major, and removing the lesion through the resection of the deeper breast parenchyma. The specimen should be marked with two different radiopaque markers on the two borders corresponding to two resection margins. Subsequently, radiography of the specimen is performed to verify the total removal of the lesion. The surgeon should then decide whether the margin of the nearest border should be re-excised or not in order to decrease the probability of positive margins at the final histological report. The specimen should be moderately compressed for the specimen radiograph but not overly compressed so as to avoid damage of the tissue potentially complicating the pathological evaluation. Frozen sections are not recommended for lesions less than 1 cm in diameter since they may compromise analysis of the permanent sections. In general, a frozen section is not recommended whenever the lesion is not palpable, and localised only due to the microcalcifications.

The closure of the tumorectomy must be performed with special attention to the cosmetic result, especially in the case of wide glandular resection. In the lower mid-part of the breast, it is recommended to close the defect with glandular flaps and sutures. In contrast, in the upper mid-part, no glandular closure is required because the risk of secondary glandular retraction is very low. Drainage is usually useful, unless the tumour bed is perfectly dry. The edges of the skin must be carefully approximated by two layers of continuous intradermic sutures.

Treatment options for non-palpable carcinoma. Treatment of mammographically detected cancers can be divided into the treatment of infiltrating carcinomas, and ductal carcinoma *in situ* [40–49].

Infiltrating carcinoma (IC). The treatment of non-palpable IC is similar to palpable carcinoma. However, approximately 50% of IC are smaller than 1 cm and the infiltrating component is often small [34–36]. Conservative therapy is the treatment of choice, and consists of a wide excision with a 1 cm zone of normal tissue to a free margin (microscopically) around the tumour. The surgeon may have difficulties in achieving free margins because he/she has to carry out resection without feeling the tumour in the breast parenchyma. Although there are no scientific grounds to assume that resection of the margins

decreases the risk of positive margins, it has been proved [37, 38] that the probability of finding tumour foci around the primary tumour decrease, and in this case, further resection of the nearest margin can be advised. It is recommended that the resection should provide tumour-free margins. Despite the small size of these cancers, axillary dissection is recommended for infiltrating carcinoma because the rate of lymph node involvement is between 5 and 30% according to the literature (see Table 1).

Ductal carcinoma in situ(DCIS). Different options are proposed for the treatment of DCIS, depending upon the extent of multicentricity and multifocality in this type of lesion. More recent studies suggest that multifocality (extensive DCIS in a duct network) is common [37, 38], while the concept of multicentricity appears to be less important than in the past. Multifocality means neoplastic foci located around the main tumour, and the aim of the surgical treatment should be the complete removal of all the foci. Multifocality is probably of monoclonal origin which means that all the neoplastic cells are the progeny of the same cancerous cell. Multicentricity on the other hand evokes the presence of several clones of neoplastic cells.

On the basis of these premises, conservative surgery may be proposed in non-extensive DCIS [42–44].

As regards conservative treatment, it is not easy to set a limit on the dimension of the tumour, but a 2–3 cm lesion may be treated while preserving the breast, if its volume gives a satisfactory cosmetic result. An EORTC protocol considers lesions up to 5 cm for conservative treatment of DCIS. Definitive results are needed before advising conservative surgery in such a large tumour.

The second criterion to decide the extent of the surgical treatment (conservative surgery versus mastectomy) is generally based on the histological prognostic factors such as comedo or non-comedo carcinoma and the type of cells. A more extensive conservative surgery with 2 cm free margins (quadrantectomy or segmentectomy) may decrease the probability of residual tumour foci [38], and may be an alternative to mastectomy. If the final histological report does not show free tumour margins, further resection or mastectomy should be considered.

Post-operative mammography is advised in cases where microcalcifications are associated with tumour to assess the likelihood of residual disease. Further resection or mastectomy may be appropriate in the case of residual microcalcifications indicating residual tumour.

If mastectomy is employed, immediate or delayed breast reconstruction are viable alternatives. Axillary dissection is not indicated due to the absence of axillary node involvement in DCIS [45].

Table 1. Nodal involvement with mammographically detected non-palpable infiltrating carcinoma

Author	Number	Percentage
Tabar [18]	272	5
Schwartz [39]	167	33
Luini [40]	116	20
Tinnemans [41]	81	21
Papatestas [8]	67	22

Radiation therapy

The principal role of radiotherapy in the treatment of screen-detected cancers is irradiation of the preserved breast. Treatment of lymph node areas will be uncommon with these early lesions. In breast cancers treated by complete local excision, local recurrence rates are reduced by a factor of four to five due to the administration of megavoltage radiation therapy [46–49]. Since breast preservation represents a major treatment objective, whole breast irradiation is recommended after breast-conserving surgery for invasive carcinomas, regardless of size, pathological features, or status of resection margins. For ductal carcinoma *in situ*, the role of radiation therapy is more controversial. However, for those limited intraductal lesions considered for conservative excision, there is evidence that the effectiveness of radiotherapy is similar to that already demonstrated in the treatment of invasive cancers [43].

Radiation treatment generally uses photons from a 4–6 MV linear accelerator or a telecobalt machine, with two opposed beams directed tangentially along the chest wall to minimise lung irradiation. A total dose of 45–50 Gy in 1.8–2 Gy fractions over 5 weeks is generally recommended [35, 47, 48]. Since most local failures occur in the vicinity of the primary tumour, supplementary localised irradiation of the tumour bed area ("boost") is usually given, most commonly 10–20 Gy using an external electron beam or interstitial Iridium-192 implant [48]. Localisation of the tumour bed for boost treatment can be based on clinical information and preoperative mammogrammes, but intraoperative marking of the primary tumour area using radiopaque clips is recommended. The technical aspects of radiation therapy for early breast cancer are described in a European consensus report [61].

Systemic adjuvant therapy

It has been shown that adjuvant multichemotherapy as well as tamoxifen therapy can prolong the disease-free interval and improve overall survival of breast cancer [50–55].

Polychemotherapy for 6 months after primary local therapy is more efficacious in premenopausal women, while adjuvant tamoxifen treatment for more than 1 year is more efficacious in postmenopausal women. The effect on the disease-free interval has generally been better than the effect on overall survival. On patients with node-positive cancers and/or with tumours larger than 3 cm, most oncologists agree that adjuvant chemotherapy has a positive effect. Adjuvant therapy for small, node-negative cancers is more controversial. The smaller the risk of relapse, as judged by tumour size, pathological grade and lymph node involvement, the smaller will be the absolute benefit and cost-effectiveness of adjuvant therapy, and the greater would be the significance of the toxic side-effects of that treatment. Since most breast screening programmes include women aged 50 and over (i.e. postmenopausal women), a major question is whether or not tamoxifen should be used for small, node-negative cancers. The absolute benefit in terms of increased survival might be questioned, but tamoxifen can reduce the risk for local recurrence and also reduce the risk for a new primary cancer in the contralateral breast. It might also have positive effects on the risk for cardiovascular disease. The prognostic significance of the proliferative indices, oncogene expression, growth factor receptors and ER receptor status is not totally understood. The understanding of their role as prognostic markers might lead to a better selection of women for treatment in the future [55].

If tamoxifen is chosen as adjuvant systemic therapy for small, node-negative cancers, the most important overall recommen-

dation that can be made is to encourage women to participate in clinical trials. Examples of such trials could be to study duration and dose of tamoxifen treatment. Other important studies include the role of LHRH agonists in the treatment of small breast cancers and the benefit of adding polychemotherapy to tamoxifen for high risk patients.

The value of adjuvant tamoxifen for node-negative cancers less than 1 cm and the value of chemoprevention with tamoxifen in high risk groups are both areas which should be investigated, as well as the role of systemic adjuvant therapy for non-palpable and small breast cancers [56].

AREAS FOR RESEARCH

Surgery

Studies are in progress to define prognostic discriminators for local recurrence in women with DCIS [36, 57]. The treatment at the present time may be influenced by some of the available prognostic discriminators that appear to reliably predict patients with DCIS who are at high risk for development of recurrent disease:

Poor prognostic discriminator (mastectomy)	Good prognostic discriminator (conservative)
Tumour size >2.5 cm	Tumour size <2.5 cm
Comedo carcinoma large cell	Cribriform or micropapillary small cell
Positive resection margins*	Clear margins
Residual microcalcifications	Negative mammogram

*Recently quadrantectomy (a larger operation than lumpectomy) has been introduced as a treatment option after lumpectomy in cases where the margins are positive or after a post-operative mammogram had suggested residual disease. Other trials are starting with the purposes of establishing the possible role of tamoxifen in patients with DCIS.

The effect of positive margins both in DCIS and infiltrating carcinoma should be discussed with regard to the need for surgical management: re-excision, mastectomy or follow-up.

Studies using mammographic criteria for breast conservative surgery are ongoing. Wide excision of non-palpable tumours is considered as one of the major criteria to enhance the chance of cure. At the same time, cosmetic result should be excellent to avoid any psychological morbidity. Therefore, the use of plastic surgery techniques should be considered as an area of surgical research for the treatment of screen-detected lesions.

Pathology

In pathology, an agreement on terminology is required as well as common objective criteria for grading and classification. For small tumours, the methods used for assessing the size of the tumours differ widely from hospital to hospital. For prognostic studies, a common methodology should be recommended. Similarly, the criteria used for assessing axillary lymph node involvement should be better defined and standardised (number of nodes examined, number of slices per node, etc.).

Radiotherapy

Although radiotherapy that is limited to the breast is generally well tolerated, its inconvenience and potentially adverse effects on the cosmetic results in a minority of patients cannot be denied. In addition, as most patients with screen-detected cancer have long survival expectancies, concern has been expressed about the possibility of contralateral breast cancers and other secondary malignancies in irradiated patients [58], but this fear is not supported by available data [59]. Continued evaluation of the associated benefits and risks is justified, particularly with regard to screen-detected lesions [58–70].

However, it should be noted that some data suggest that the incidence of contralateral breast cancer is lower in irradiated patients [58, 59], suggesting that at least some of these may be due to the migration of neoplastic cells from one breast to the other. It has been reported that long-term survival of irradiated patients is hampered by cardiac complications [60]. These should be avoided by carefully planning dosimetry and limitations of the dose received by the heart. Nonetheless, long-term follow-up is required for checking the absence of toxic effects.

The use of brachytherapy alone, without external irradiation has been explored by some groups [20]. This is a research technique which cannot be used routinely since it is difficult to achieve a homogeneous dose distribution.

Another research problem is related to the timing of radiotherapy and chemotherapy when both are indicated. Delaying the delivery of radiotherapy increases the risk of local recurrence due to tumour repopulation. Recent data suggest that the recurrence and mortality rates are higher when, after surgery, chemotherapy is given first followed by radiotherapy, than when the reverse timing is used [68]. However, delay in the onset of chemotherapy may lower the effectiveness of adjuvant chemotherapy due to cell proliferation in distant metastases. This is why concomitant or alternating regimens deserve to be investigated.

Irradiation of the internal mammary chain is another controversial topic in axillary node-positive patients. Several data suggest its effectiveness, at least for tumours located in the inner quadrants [61, 62]. However, most of these data were obtained in patients with relatively large tumours, so the question remains open for patients with small tumours.

Finally, the main research issue involving radiotherapy concerns the selection of patients suitable for treatment by conservative surgery alone [63, 64]. In this regard, the main uncertainty is whether or not local recurrence has an impact on long-term survival. Data are conflicting [61, 64, 65, 66, 70]. It has been demonstrated that about 40% of early invasive breast cancers are truly unifocal, having no extensions 1 cm from the edge of the primary tumour. Criteria need to be established to identify such unifocal lesions by careful histopathological study of the excision specimen, or by other means. Relevant information should be provided by prospective trials based principally on screen-detected cancer, including those restricted to intraductal carcinomas.

In patients treated with breast irradiation, volume, dose and fractionation can be optimised. The precise benefits of boost therapy in patients receiving whole breast irradiation are currently under study, as is the possibility of limiting radiation treatment to the tumour bed area [48].

Given the burden of breast cancer patients on busy radiotherapy departments, and the high incidence of this disease in the elderly, research on fractionation schedules is primarily intended to reduce the number of radiation treatment sessions. However, doses per fraction higher than 2 Gy should hamper the cosmetic results and may increase the incidence of late effects.

Total mastectomy is the standard surgical treatment for operable local recurrence in the conservatively operated breast. However, a second local excision may be efficacious in selected patients [67]. For patients who had been treated with conserva-

tive surgery without breast irradiation, it is unknown whether they could retain their breasts and be treated with radiation therapy at the time of recurrence (in view of local failure) [48, 68].

The role of systemic treatments at the time of local failure deserves further investigation. Prospective clinical trials with proper stratification according to the main prognostic indicators should be carried out [69].

CONCLUSION

The management of non-palpable lesions discovered by mammographic screening raises several clinical problems. When management is incorrect, most of the benefits expected from such a screening programme are lost. It is the responsibility of regional and national authorities to ensure a quality assurance programme aiming at improving the management and operation of their breast screening programme. One of the key means of achieving this is for the various professional groups involved to undergo specific training with regard to assessment of screen-detected abnormalities and any subsequent treatment. In particular, specific courses should be organised at national or European level for the key professional staff involved, i.e. radiologists, radiographers, hospital physicists, cytopathologists, radiation oncologists and surgeons. National and European training centres of excellence should be set up and should assist the creation of multidisciplinary teams working in specialist centres.

Efforts should be made in the following three areas:

(1) Organisation

Screening should be considered in its entirety and every step in the chain should be monitored and well performed. Women should be subject to a regular call/recall system. Abnormalities detected on screening should be speedily referred to a specialised assessment centre with the minimum delay of any subsequent treatment. This requires a well trained and extensive administrative network. There should be failsafe mechanisms to ensure women are all followed-up following an abnormal mammogramme. Liaison with local health authorities and general practitioners is essential.

(2) Quality assurance

The screening unit is responsible for the quality of the screening process and should guarantee it for the population it serves. A quality control programme and constant evaluation are thus essential. Quality assurance is a process by which minimum standards must be set and improvement on these standards constantly attempted. Every team member must constantly evaluate his/her own performance and aim to improve it. The European Guidelines on Quality Assurance in Mammography Screening should be widely circulated and taken as a basis for regional or national regulations.

(3) Research

Particular attention should be paid to research with the objective of standardising nomenclature and investigations, introducing quantitative criteria and finding new diagnostic methods and treatment modalities. A better knowledge of the natural history of small tumours and their prognostic factors is required in order to define the therapeutic indications more accurately.

The benefits of breast screening in the reduction of breast cancer mortality and an increase in the patients quality of life after treatment [3] are accepted. To achieve this ambitious goal requires much effort from clinicians, national and European organisations in order that poor quality and variation of accepted techniques do not diminish the achievable benefits for the screened population.

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