Approach to the diagnosis of a breast lump

A breast lump raises the fear of breast cancer in all women.

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Patient complaints of breast lumps or lumpiness are common, ranging from 40% to 70% in women seeking advice. A breast lump, either self detected, screen detected or clinician detected, raises the fear of breast cancer in any woman, irrespective of age.[1,2] Fortunately, the vast majority of breast lumps are benign, but this does not negate the need for evaluation of any palpable breast lesion. Failure to diagnose breast cancer accounts for the most frequent and expensive claims brought against physicians.

Public education about breast cancer has heightened awareness regarding breast health, and it is anticipated that an increasing number of women will present for the evaluation of breast masses.

Aetiology of breast lumps[3]

There are many causes for breast lumps. The differential diagnosis of a dominant breast mass includes a macrocyst (clinically palpable cyst, accounting for approximately 25% of breast lesions), a fibroadenoma, fat necrosis and cancer.

The mode of presentation, age of the patient, reproductive history, history of trauma, constitutional symptoms and previous breast pathology are helpful in elucidating the possible cause. For example, in women <30 years of age, a single lump is most commonly a fibroadenoma. With increasing age, macrocysts, fat necrosis and carcinomas are common.

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Approach[2,4,5]

Goal of evaluation

Breast lumps cause anxiety in most patients. The goal of the diagnostic evaluation of a patient with a breast mass is to rule out cancer and address the presenting symptom. The extent of the evaluation depends on the age and risk status of the patient as well as the type of breast lesion.

Generally, the older the woman, the greater the degree of suspicion and the more aggressive the evaluation.
It is challenging to achieve this while minimising unnecessary excision biopsies, pain, emotional trauma, invasiveness of a procedure and cost.

An expedient evaluation is important, although it should be remembered that diagnosing breast cancer is not a medical emergency.

Confirming the presence of a mass

When patients present with a history of a breast lump, the first crucial step is to determine whether a discrete mass is indeed present. Discrete masses are three-dimensional, measureable (with definable borders), distinct from surrounding tissues, and generally asymmetrical when compared with the other breast.

The following may be mistaken for a mass, e.g. normal structures (prominent rib or costochondral junction, particularly in thin patients), an illusive mass (created by improper examination by pinching of the tissues), and nodularity.

Nodularity versus a discrete mass

Normal breast tissue may vary in consistency, depending on the age of the patient and the menstrual cycle. In young patients the breast glandular tissue is generally lumpy (nodular) and more pronounced in the upper outer region of the breast and inframammary ridge. Nodularity is considered to be a physiological process. Compared with a persistent, discrete lump not palpated in the contralateral breast, nodularity is ill defined, often bilateral, and tends to fluctuate with the menstrual cycle.

Method of assessing a breast mass

The triple assessment is a diagnostic procedure that combines a clinical examination, imaging and a tissue biopsy. It is currently the gold standard for the assessment of all patients presenting with symptomatic breast disease.

Individually, each has an appreciable false-negative rate, and none of the components of the triple assessment has been found to be 100% sensitive or specific.

When adequately performed – with the three components producing concordant results – the diagnostic accuracy of the triple assessment approaches 100%. It is generally accepted that >95% of palpable malignant breast lesions can be diagnosed in this way. When all aspects of a triple assessment suggest benign disease, most large series report a false-negative rate of 0.1 - 0.7%. The false-positive rate is around 0.4%.

Diagnosis

Clinical assessment[2-4]

The initial step is to take a history and perform a physical examination.

History

A complete history of the presenting complaint is vital. In addition, the following need to be documented:

Age is important. The younger the woman, the greater the probability that a breast lump will be benign. The chance that a breast mass in a woman under 25 years of age is cancerous falls between 1 in 229 and 1 in 700.

However, with increasing age (>40 years) benign breast problems are less frequent and all clinical abnormalities should be regarded as possible cancers until documented as benign. By the age of 70 more than three-quarters of masses evaluated by biopsy are malignant.

A personal history of breast cancer is a risk factor for recurrence or a contralateral new primary tumour. In women treated with breast-conserving surgery, the incidence is 1% and 2% per annum above the lifetime risk for invasive duct and lobular carcinomas, respectively.
A past history of a **breast biopsy showing atypical hyperplasia, a family history of breast cancer, and other risk factors for breast cancer** should be sought.

Recent trauma to the breast, pregnancy, lactation, and the presence of concurrent **constitutional symptoms** are also important considerations when trying to elucidate the cause of the lesion.

Clinical breast examination (CBE)
The accuracy of palpation in evaluating a breast mass is limited. Nevertheless, digital palpation of the breast is effective in detecting masses and may assist in determining whether a mass is possibly benign or malignant. CBE can detect up to 44% of cancers, of which up to 29% would have been missed by mammography.

Generally, benign masses do not cause skin change, are smooth and mobile, are soft to firm to palpation and have well-defined margins. Malignant masses, in contrast, are generally hard and immobile, may be fixed to surrounding structures, and have poorly defined or irregular margins. There is a caveat: some mobile masses can be cancerous, and not all fixed masses are cancer.

Infections, such as mastitis, are characterised by signs of inflammation; however, similar symptoms may be present in patients with inflammatory breast cancer. Caution should prevail when assessing patients with suspected breast infections.

CBE alone is inadequate for the assessment of a breast mass and the definitive diagnosis of breast cancer. Cysts cannot be distinguished from solid masses and signs of cancer are not distinctive. Even among experienced examiners there is a surprising lack of agreement about physical findings. It has been estimated that the diagnostic accuracy of physical examination is 60 - 85%.

Imaging[5-8]

Palpable lesions are always imaged before a biopsy is done. The extent of imaging for the evaluation of a mass depends on the age and risk status of the patient and the degree of clinical suspicion. Generally, mammography is performed in women aged 35 or over and ultrasonography is the preferred modality for women under 35 years of age. Other imaging modalities such as MRI are used selectively.

In the case of a potential malignancy, imaging studies are useful to define the extent of the malignancy and to identify non-palpable masses elsewhere in the breast or on the contralateral side. These findings may alter the therapeutic approach, especially the choice of local therapy.

Ultrasound
Ultrasound has become a valuable tool in assessing breast masses, as it is widely available, quick to perform, non-invasive and less expensive than other imaging modalities. Its main advantage is that it can accurately differentiate a solid mass from a cystic one. The specificity of ultrasound in detecting cystic lesions is 98%, and cysts ≥2 mm can be detected.

Ultrasound has a higher sensitivity than mammography in detecting lesions in women with dense breast tissue. In this setting, its use as an adjunct to mammography may increase the accuracy by up to 7.4%. With regard to clinically palpable solid lesions, the specificity of ultrasound is superior to mammography: 97% versus 87%. It is furthermore a complementary modality to an equivocal CBE and a normal mammogram in determining whether a mass is present. Further uses include the evaluation of non-palpable lesions detected on screening mammography, image-guided biopsy of lesions and follow-up of benign lesions such as fibroadenomas. However, it is an operator-dependent technique with a lower sensitivity than mammography.

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Mammography
Mammography is an essential component in the assessment of a palpable breast mass. It serves to characterise and determine the extent of the mass, and to evaluate the breasts for clinically occult lesions. In the case of malignancy, multiple (multifocal/multicentric) cancers are not unusual. Bilateral synchronous cancers are reported in 3% of cases; approximately 65% of these are detected only by mammography.

Diagnostic mammography requires that a radio-opaque marker is placed over the area of concern to ensure that any mammographic abnormality corresponds with the clinical finding. Each breast is imaged separately in the craniocaudal (CC), mediolateral oblique (MLO) and mediolateral (ML) views. Additional views, tailored to a specific problem, are occasionally required to adequately visualise the lesion.

The sensitivity of diagnostic mammography is around 90%, and the specificity up to 88%. The known false-negative rate of mammography is between 8% and 10%. Approximately 1 - 3% of women with a clinically suspicious abnormality and negative imaging (normal mammogram and ultrasound) may have breast cancer. Therefore, in the case of a negative mammogram further investigation is necessary if a lump is detected on clinical examination.

The sensitivity of mammography is decreased by dense breast tissue obscuring a lesion. False-negative results arise with poor technique and inadequate views that do not include the mass, or when the findings are misinterpreted by the radiologist, notably when there is overlap in the mammographic features of benign and malignant masses.

In women younger than 35 years, if the results of the initial evaluation (triple assessment) suggest malignancy, mammography is indicated for assessment of the extent of the disease.

Digital mammography
This mammographic technique allows images to be enhanced and transmitted electronically. The ability to alter the contrast and brightness permits the identification of features that are diagnostic of benign and malignant disease. The overall cancer detection rate is similar to that of standard film mammography.

Advantages of digital mammography include better image quality, fewer artefacts, fewer patient recalls and telemammography.

Magnetic resonance imaging (MRI)
High-resolution contrast-enhanced MRI has recently emerged as a sensitive imaging modality for the detection of breast cancer.

The high sensitivity, which approaches 98%, makes MRI useful in specific clinical situations, such as evaluating patients with breast implants, detecting local recurrence after breast-conserving therapy, and detecting multifocal/multicentric disease. However, the moderately low specificity of 47 - 67% requires MRI-guided biopsy of lesions not seen on other imaging modalities, many of which are later found to be benign.

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MRI avoids exposure to radiation, has a sensitivity superior to that of mammography and is more accurate than both mammography and ultrasonography in determining the size of a breast cancer mass. However, the technique is cumbersome and expensive, not readily available, does not detect microcalcifications, is inferior to mammography in detecting non-invasive cancers and requires a special coil to obtain a biopsy of occult lesions. Furthermore, there are concerns that MRI findings may result in increased mastectomy rates in patients with early breast cancer, and it remains unclear

whether alterations in management based on MRI findings actually benefit patients.

Computed tomography (CT) scanning
This modality has no established place in the evaluation of palpable breast masses. In select cases it may be useful to provide information about the extent of tumour invasion into muscle and skin.

Tissue biopsy[5,9-12]

The decision to perform a biopsy is based on the clinical appreciation of a palpable mass, irrespective of the findings of imaging studies, all of which have appreciable false-negative rates. Experts are divided on whether *all* solid masses require a histological diagnosis: some are in favour of this approach, while others suggest clinical follow-up for young women with lumps of low suspicion on CBE and imaging.

Open surgical biopsy remains the gold standard for establishing the histopathological nature of any breast abnormality. However, before scheduling the patient for surgical excision in the operating room, every attempt should be made to determine, via percutaneous biopsy techniques (fine-needle aspiration cytology or core needle biopsy), whether the breast lesion is benign or malignant. These non-invasive biopsy techniques can frequently be facilitated by image guidance (stereotaxis or ultrasound). A stereotactic biopsy uses mammography to pinpoint an abnormal area demonstrated on a breast-imaging test. The technique uses stereo images, i.e. of the same area obtained from different angles, to locate the area of concern, which may be palpable or impalpable, thus permitting the radiologist to perform a core needle biopsy.

Not all benign lesions require excision, and in patients diagnosed with a breast malignancy the consequences of a diagnostic excisional biopsy may impact on subsequent management options for breast cancer treatment.

However, when a percutaneous needle biopsy yields a benign result discordant with the clinical and/or radiological impression, it is incumbent on the health care provider to pursue the situation with a different diagnostic manoeuvre. Performing all biopsies under image guidance (sonographic or stereotactic) significantly reduces the frequency of false-negative results. If the initial biopsy was performed as a freehand procedure, then repeating it with image guidance is appropriate.

Fine-needle aspiration cytology (FNAC)
FNAC is a simple, quick and relatively painless procedure, where cells are aspirated using a 10ml syringe attached to a 23-gauge needle and the application of negative pressure. It is suitable for women of all ages, does not require local anaesthesia, and can be performed either freehand or using ultrasound to guide the needle into the lesion.

When performed by trained physicians (cytopathologist or clinician), it is associated with a high rate of accurate diagnosis, with the frequency of satisfactory specimens ranging from 89% to 98%. Studies have demonstrated a sensitivity of 87% and a specificity of 99.5%. In expert hands, the sensitivity of FNAC ranges from 96% to 98%.

A specific advantage of FNAC is the immediate evaluation of specimen adequacy for cytodiagnosis in one-stop clinics, thereby reducing non-diagnostic rates due to inadequate sampling as the procedure is repeatable. FNAC sampling is also useful in the case of lesions at sites inaccessible or unsafe for core needle biopsy, and it is therapeutic in the management of palpable cystic masses.

On the downside, the procedure is highly operator dependent, requires special training by a pathologist and is associated with an appreciable false-negative rate of 9.6%. Inherent limitations of the technique include the inability to distinguish invasive from non-invasive carcinomas and to accurately diagnose lobular carcinomas. Cytology in the evaluation of a palpable mass during pregnancy is of low sensitivity, as atypical cytomorphological findings are encountered during gestation and lactation.

The sensitivity of diagnostic mammography is around 90%, and the specificity up to 88%.

When is FNAC indicated?
- Its primary use is rapid diagnosis in palpable masses, although it may be insufficient to base treatment on. This form of biopsy is generally reserved for lesions thought to be benign on clinical assessment, e.g. a fibroadenoma, where it provides an immediate definitive diagnosis. The technique can be used to triage patients for conservative treatment or surgery. Observation may be appropriate once the benign nature of the lesion is confirmed, generally by correct and specific typing on core needle biopsy. It is diagnostic and therapeutic in the case of simple breast cysts.
- It is also useful for diagnosing abnormal axillary lymph nodes in patients with known breast cancer. The overall reported sensitivity rate is >95% for metastatic malignancies.

Core needle biopsy (CNB)
This allows for the histological diagnosis of a solid lesion by providing cores of tissue using a 14-gauge manual or automated core biopsy needle. The procedure is associated with a specificity of 85 - 100% and a sensitivity of 80 - 95%. The sensitivity increases when the procedure is performed under image guidance (99% in palpable lesions and 93% in impalpable lesions), and multiple cores are taken. A minimum of 4 - 5 cores are advised to achieve greater accuracy: the first core from the centre of the lesion and the remainder at the quadrants thereof. This improves the sensitivity from around 81% (2 cores) to 95 - 100%.

CNB potentially overcomes several shortcomings of FNAC. CNB leads to improved diagnostic accuracy as a result of its superior sensitivity and specificity. With regard to breast cancer, it permits correct histological categorisation of lesions and confirmation of invasion, and provides the necessary prognostic and predictive marker information. On the downside, it requires more time and training than FNAC, the administration of local anaesthesia, and the results are not immediately available.

When is a CNB indicated?
- For the primary diagnosis of a suspicious mass, as it provides enough tissue to confirm the diagnosis and perform all other necessary tests (tissue architecture, IHC staining, receptor status, HER2 status).
- In palpable lesions of an indeterminate nature, to provide a definitive histological diagnosis and additional prognostic factors essential for planning future management.
- In impalpable radiologically detected lesions, guided CNB is preferred.

Excision biopsy
Also known as a lumpectomy, this refers to the removal of the entire lesion with a margin of normal tissue for diagnostic or therapeutic purposes. It is performed in the operating room under local or general anaesthesia, and is indicated in patients with a discordant triple assessment. With the availability of more sophisticated diagnostic manoeuvres, the need for a diagnostic excision biopsy has declined.

Incision biopsy
This refers to the removal of a portion of the lesion for tissue diagnosis, and is currently seldom required. The typical scenario would be a large tumour where at least two CNBs, one of which was performed under image guidance, are non-diagnostic, and the lesion is too large for an excision biopsy with an acceptable cosmetic result.

Management[4,13]

Cyst

Cysts are aspirated to dryness and the area is palpated for a residual mass. If the fluid is not bloody and the mass disappears, the fluid is not submitted for cytological examination

because of the low likelihood of cancer. Furthermore, the finding of atypical cells in cyst fluid cytology is not uncommon, resulting in a clinical dilemma when the cyst resolves with aspiration and imaging is normal but the cytology report indicates the need for a biopsy.

No positive cysts were found in a large study that routinely assessed non-bloody specimens, yet atypical cells were found on cytological examination in almost 25% of these cyst fluid aspirates. Routine cytological examination of cyst fluid is not cost-effective, often results in unnecessary surgical biopsies and does not obviate the need for clinical follow-up.

A bloody cyst aspirate, non-resolution of the palpable abnormality after fluid aspiration, and a cyst that recurs within 4 - 6 weeks all point to a pathological cause for the cyst. This can either be due to a benign lesion (large intraductal papilloma) or a malignancy (intracystic or partially cystic carcinoma). Irrespective of this, these cases warrant surgical excision of the cyst.

Solid mass

The management of a solid mass depends on the degree of clinical suspicion and the age of the patient.

If a benign lesion is diagnosed after a triple assessment, the options include surgical excision or follow-up of the lesion. It is not necessary to excise all benign solid breast masses, and a selective policy is recommended based on the nature of the lesion and patient preference. In the event of a conservative approach being preferred, there must be a defined follow-up plan to facilitate the early detection of a missed cancer. The patient is examined every 3 - 4 months for one year to ensure stability of the mass. The mass is measured at each visit and compared with the size at initial presentation. This approach should only be undertaken by a physician experienced in the evaluation of breast masses.

If the breast lump is found to be cancerous, staging investigations follow and the patient is managed in a multidisciplinary team.

Early detection affords the best chance for successful treatment.

References available at www.cmej.org.za

In a nutshell

- A palpable mass in a woman's breast represents a potentially serious lesion.
- All palpable lesions require evaluation.
- The triple assessment is an effective strategy in the management of breast lumps.
- The first step is to confirm the presence of a discrete mass.
- The next objective is to distinguish simple cysts from solid lesions.
- Simple cysts are aspirated to dryness and require no further treatment if they do not recur.
- Pathological cysts require surgical excision.
- A solid lesion requires a firm diagnosis, necessitating histological examination.
- Benign solid lesions may be managed expectantly, provided regular follow-up is undertaken.
- Malignant solid lesions are referred to a multidisciplinary team for further management.

Single suture

A weak spot in infant leukaemia

Hundreds of infants who die each year from an aggressive form of leukaemia could be saved, thanks to the discovery of the disease's weak spot.

Mixed-lineage leukaemia (MLL) accounts for 70% of leukaemia in infants under 2, half of whom will die within 2 years. Eric So of King's College, London, and colleagues have discovered a protein that both drives the development MLL and makes it resistant to treatment.

The guilty protein is beta-catenin, a transcription factor, which activates other genes. In experiments on normal and MLL cells from mice and humans, the researchers demonstrated that beta-catenin is activated in cancer stem cells that prompt leukaemic blood cells to multiply. When the team used fragments of interfering RNA to sabotage the production of beta-catenin in these stem cells, the blood cells returned to an early leukaemic state. The cells stopped multiplying and became vulnerable to treatment with drugs.

Next the team hopes to test drugs that block the function of beta-catenin, which is also implicated in the development of skin and colorectal cancers.

New Scientist, 18 December 2010.