DOI: 10.2478/cipms-2022-0001 Curr. Issues Pharm. Med. Sci., Vol. 35, No. 1, Pages 1-5

Current Issues in Pharmacy and Medical Sciences
Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: http://www.curipms.umlub.pl/

Modern breast cancer diagnostic methods

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ARTICLE INFO

Received 12 December 2020
Accepted 23 February 2022

Keywords:
breast cancer,
diagnostic procedures,
mammography,
ultrasonography,
biopsy.

ABSTRACT

World wide, breast cancer is the most common malignancy in women. Despite an increased incidence of this cancer, the mortality rates have been maintained at the same level. This is due to the continuous development of therapeutic, as well as diagnostic methods because appropriate, effective treatment is dependent on accurate diagnosis. At the same time, the success is that more and more patients undergo breast- and axillary lymph nodes-sparing surgeries, therefore, determining the initial advancement stage of breast cancer is absolutely essential for ensuring proper therapy. This is a review of current guidelines for both early and advanced stages of breast cancer diagnostics. The principles described are largely based on the work of the European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO). The review includes the rule of imaging studies, especially mammography screening and histopathological evaluation with molecular classification of breast cancer.

INTRODUCTION

In today's world, breast cancer is the most common malignant tumour amongst women (23%), and it is the main cause of malignant tumour-related deaths (14%). According to the WHO, this type of neoplasm is annually diagnosed in 1.7 million women, and causes 500,000 deaths each year [1]. Over the last three years, the European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO) have devised specific diagnostic and therapeutic algorithms that can be applied in patients suffering from both early and advanced stages of breast cancer. Exact procedures for patients with the BRCA gene mutation have been defined as well. Specific indications have been set for each procedure and their clinical relevance has been rated [2].

Imaging studies

Despite many negative opinions on the effects of mammographic screening, the ESO and ESMO consensus emphasizes the necessity of performing mammograms in women within the age range of 50-69 years. It also recommended that they should be carried out in accordance with the current guidelines, i.e. every 1-2 years. The results of scientific analyses based on the Scandinavian countries, according to which mammographic screening may lower the breast cancer mortality rate by 30 - 40%, have been cited for many years and have not been questioned so far [3].

Even though studies carried out by Gøtzsche show that screening mammography performed in female patients of ages 40-49 and 70-74 has little effect on lowering the breast cancer mortality rate [4], regular mammographic screenings still seem to be justified in these age groups. The International Agency for Research on Cancer is of the same opinion. On the other hand, the guidelines of the American Cancer Society (ACS) contradict the ESMO guidelines and propose that the targeted age of mammography screenings should be limited to 40 years and the intervals should be reduced to 12 months. It is estimated that at present, mammography is the most effective method of detecting the subclinical form of breast cancer, therefore, it is imperative that all the European Union countries carry out the screening programmes [5].

Currently used mammography (MMG) has been enhanced by tomosynthesis, which guarantees higher diagnostic sensitivity of the procedure. It is regarded as the leading method enabling early diagnostics of the preclinical stages of a neoplasm, which results in an increased percentage of patients who qualify for the breast-preserving treatment. Advances in traditional imaging technologies have brought modifications to classical mammography practices and bettered it by introduction of spectral mammography. The essence of this type of procedure is intravenous infusion

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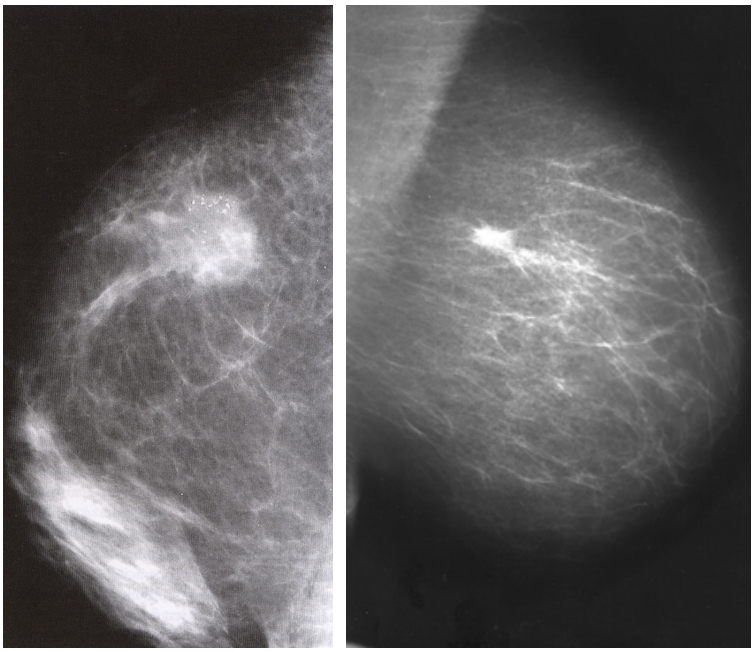

Figure 1. Breast cancer in mammography evaluation (authors' own documentation)

of a contrast agent, which allows imaging of tumour blood vessels. It is exceptionally useful in young patients whose mammary glands are of a higher density. That specific type of MMG is slowly becoming a major diagnostic standard – an alternative to breast magnetic resonance imaging (MRI) [6].

Popularisation of breast MRI has made it a more common examination in breast cancer diagnostics. At present, it is a recommended qualifying test for breast-preserving treatment in patients with suspected multifocal carcinoma. It is mainly performed in the patients after neoadjuvant therapy in order to evaluate their response to the treatment and the current size of the tumour. An MRI examination is recommended in the case of discrepancies in mammographic, ultrasound and clinical examination results, as well as in women with breast implants who underwent reconstructive surgery, and also in the case of occult breast cancer (i.e., with metastases to the axillary mammary glands with no visible primary outbreak in the breast). Breast MRI shows high sensitivity (up to 95%) but low specificity, therefore, diagnosing a high-grade malignant tumour using MRI might prove difficult. It is recommended that the BRCA gene carriers and patients with family history of breast cancer should undergo annual breast magnetic resonance and mammography alternately (every 6 months). A diagnostic scheme combining different kinds of diagnostic tests enables detection of a pathology in lower grade of clinical development, in comparison to a single-diagnostic type scheme (probability of diagnosing cancer is higher by 70%). It should be emphasised that imaging diagnostics in this group should start 10 years prior to the age of the youngest family member diagnosed with breast cancer [2,7,8].

In order to ensure high quality of screening tests, they should be carried out by specialised research centres, under supervision of certified radiologists and in cooperation with Breast Unit experts. Average sensitivity of mammography is 85%. The standard MMG description is a seven-grade BI-RADS grading system (Breast Imaging-Reporting and Data System) devised by the American College of Radiology (ACR) in order to standardise test description [9]. The grading categories are: BI-RADS 0 – incomplete classification, necessity of repetition of either MMG or USG; BI-RADS 1 – image normal, 0% chance of malignancy; BI-RADS 2 – image normal, but benign changes are present; BI-RADS 3 – visible changes are most likely benign, chances of malignancy lower than 2%; BI-RADS 4 – changes visible, additional biopsy required in order to define a specific type; BI-RADS 5 – changes found are specific for carcinoma, more than 95% chance of malignancy; BI-RADS 6 – breast cancer diagnosed and confirmed using histopathological examination [10].

Breast ultrasonography (USG) is a preventive examination performed in women younger than 35 years with a high density of the breast tissue. It is also used as a routine test, supplementary to mammography, in breast cancer patients. Both sensitivity and specificity of ultrasonography are lower than in the case of mammography (Fig. 2) [2]. However, the possibility of differentiating between the cystic and solid changes, as well as the possibility of evaluation of the size of the tumour and its location are the main advantages of ultrasonography. USG of the axillary region is a preoperative standard in the assessment of the axillary lymph nodes, mainly in patients qualified for a surgery without lymph node removal (sentinel lymph node biopsy) [2].

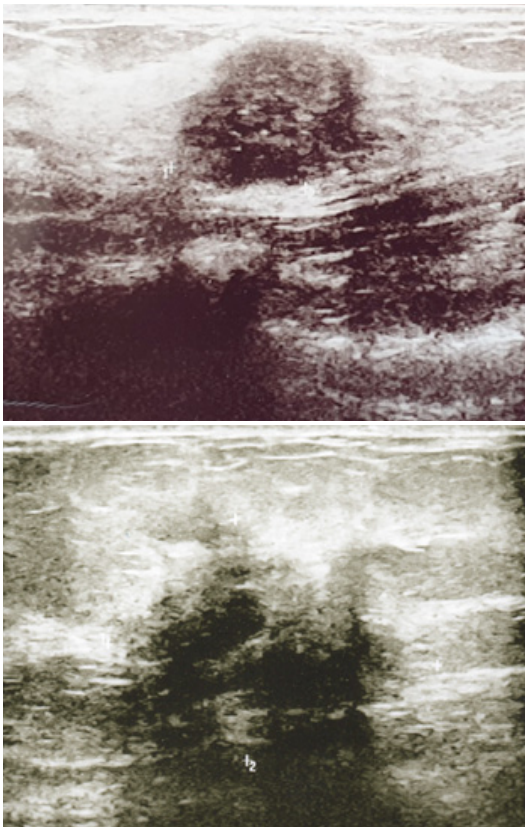

Figure 2. Breast cancer in USG evaluation (authors' own documentation)

Skeletal scintigraphy is generally performed before initiating systemic treatment in patients with advanced breast cancer so that bone metastases can be ruled out, it is also performed while monitoring post-operative patients when they reveal bone ailments and/or a significant increase in the level of the CA15.3 marker.

Positron emission tomography–computed tomography (PET-CT) is becoming a more and more popular diagnostic procedure in breast cancer patients since its availability to the patient has been much easier in recent years. Distant metastases with unknown primary origin and post-treatment evaluation are the main recommendations for PET-CT [11].

Algorithms for diagnostic procedures in breast cancer

Easier availability of imaging techniques of mammary glands has resulted in detection of most breast cancers with the use of MMG and USG, however, approximately 30% of all female patients still discover a tumour by themselves during breast self-examination. A tumour or a pathology detected by either MMG or USG prompts patients to visit their general practitioner who will refer them to an oncological surgery specialist. Highly specialized surgeons in Breast Units of comprehensive cancer centres perform a thorough assessment of the clinical stage of both the neoplasm and the patient's general condition. In recent years, the diagnostic algorithm for breast cancer patients has undergone significant changes, mainly due to the introduction of targeted therapy and modern preoperative chemotherapy and immunotherapy. Evidence of better efficacy of personalised treatment and treatment complexity proves that team decision-making at the time of diagnosis is mandatory [12].

The current schematic diagram of diagnostic procedure includes assessment of the patient`s general condition, local assessment, i.e., primary tumour evaluation, assessment of the regional lymph nodes and examination for the presence of metastatic lesions.

Determination of the patient`s general condition includes an interview, physical examination and defining the patient`s menopausal status, which often determines the choice of the type of treatment. A total blood count, liver and kidney function tests, as well as an assessment of the heart condition are all essential components of the appraisal of a patient`s general physical condition. Additionally, the serum alkaline phosphatase and calcium levels should be marked [2]. Primary tumour evaluation is carried out by performing physical examination, mammography, breast USG and, in some of the patients, breast MRI.

The currently recommended diagnostic method in the initial phase is extraction of the tissue material for histopathological evaluation of the molecular subtype and grade of the malignancy of the tumour. A sample is obtained via a core needle biopsy or mammotome biopsy and, in exceptional cases, an open biopsy.

Assessment of the regional lymph nodes is performed by physical and ultrasound examination, and in the case of clinical enlargement of the lymph nodes, the presence of neoplastic cells, evaluation is based on an ultrasound-guided, fine-needle biopsy or, exceptionally, ultrasound-guided core needle biopsy [13].

Distant metastases rarely occur in the early stages of breast cancer, but in clinical practice, their presence is most often ruled out by performing: a chest radiograph (metastases to the lungs), abdominal USG (metastatic changes in the liver) and skeletal scintigraphy (metastases to the skeletal system). Additional diagnostic parameters include concentration of CA15.3, alkaline phosphatase, phosphate and total serum calcium levels. Symptoms reported by the patient need to be taken into account. In patients with cancer subtypes of poorer prognosis (HER2+, triple-negative) who are to receive neoadjuvant treatment, a chest and abdominal tomography is performed instead of USG and radiograph [2].

Histopathological evaluation

Invasive tests are an integral part of the initial breast cancer diagnosis since they provide the tissue material for microscopic evaluation and defining cancer receptor status. A core needle biopsy is performed with the use of an approx. 2.0mm-diameter needle, usually equipped with a mechanism enabling ejection of the blade ("shot"). The obtained cylindrical tissue "rolls" represent the actual structure of the tumour to a better degree, compared to a fine-needle aspiration biopsy (FNA), the extracted material also allows for histopathological evaluation. A core needle stereotactic biopsy is performed under mammographic, ultrasonographic or magnetic resonance guidance. It is currently recommended as early as the initial diagnostic phase in all patients with suspected breast cancer.

A mammotome biopsy, also called a 'vacuum-assisted biopsy' (VAB), can be either a diagnostic procedure (tissue sample collection) or it can be regarded as a minimally invasive surgery performed in order to excise benign breast lesions (e.g., fibroadenoma). The purpose of the operation is a good aesthetic effect. In the case of a diagnostic biopsy, the sample collection site needs to be marked with a permanent or absorptive marker.

The development of minimally invasive methods has significantly diminished the role of a surgical biopsy as a diagnostic procedure. At present, it is exceptionally used in the diagnostics of cancerous ulcers or as an open biopsy in diagnostically difficult cases of breast cancer in when both a core biopsy and a mammotome biopsy are inefficient.

An open biopsy with an intraoperative histopathological examination allows avoiding a multistage surgery and accelerates the therapy. It is still successfully performed in certain clinical cases, i.e., when there are discrepancies in the clinical, radiological and histopathological examinations. An open biopsy is a valuable method fast-tracking the treatment of small tumours subjected to multiple non-diagnostic oligobiopsies [2,12,13].

The histopathological evaluation standard includes determination of the histopathological type and degree of histological malignancy; it also involves immunohistochemical evaluation of the expression of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2). If the HER2 status (test 2+) is ambiguous in this method, the test is repeated using fluorescence in situ hybridization (FISH). Proliferation marker Ki67 is routinely assessed. Final histopathological diagnosis should be made in accordance with the WHO (World

Health Organisation) classification and the 8th version of the Tumour Node Metastasis (TNM) system of American Joint Committee on Cancer (AJCC). The currently developed evaluation system includes separate clinical (cTNM), pathological (pTNM) and post-neoadjuvant (ypTNM) classifications. It is worth mentioning that lobular carcinoma in situ (LCIS) is classified as benign and has been removed from the current version [14].

On the basis of the obtained receptor status and level of Ki67 proliferation marker, the tumour is qualified as a specific molecular subtype (Tab. 1). Individual subtypes vary in prognosis and show different responses to various systemic treatment regimens. The development of a new classification of breast cancer was a breakthrough in the systemic treatment of this disease. The research conducted at the turn of the 20th and 21st centuries gave grounds for defining specific biological features of breast cancer and stratifying the risk of recurrence of the disease and death. A correlation between the course of disease and the molecular subtype of the cancer was discovered. GEP (Global Gene Expression Profiling) study made it possible to propose gene expression patterns for particular types of breast cancer. On the basis of molecular differences in the breast cancer cells, the following subtypes were identified: Luminal A, Luminal B, Luminal B HER2 positive, HER 2 positive non-luminal and triple-negative (basal-like/TNBC) [8] (Tab. 1).

Table 1. Molecular classification of breast cancer based on the ESMO Clinical Practice Guidelines [8]

	Luminal A	Luminal B HER2-neg.	Luminal B HER2-pos.	Non-luminal HER2-pos.	Basal-like (TNBC)
Occurrence	40%	30-40%		10-15%	10-15%
ER	+	+	+	–	–
PgR	+(≥20%0	±(<20%)	All	–	–
HER2	–	–	+	+	–
Ki67	<14% (<20-30%)	≥14% (≥20-30%)	All	all	all

Molecular subtype, clinical advancement of the carcinoma and the presence of gene mutations are all elements that determine the type and sequence of treatment that needs to be carried out, i.e. a surgery, systemic treatment and radiotherapy which also determines the type of surgery.

Expressions of the ER, PgR and HER2 receptors are the most significant predictors in breast cancer patients. Overexpression of the ER and PgR receptors correlates with a good response to the hormone treatment (HTH), a weaker response to chemotherapy (CHTH) and a better prognosis. On the other hand, the HER2 overexpression and amplification are negative prognostic factors and they are indicative of the need for applying anti-HER2 therapy (trastuzumab, pertuzumab) [15].

In order to modify the primary treatment scheme after the surgery has been performed, the risk factors are reassessed on the basis of the postoperative histopathological examination (pTNM). Additional prognostic factors obtained following the operation include: the actual size of the tumour, its relation to the chest wall and the skin, possibility of the cancer being multifocal, number of affected axillary lymph nodes and the presence of blood vessels and lymphatic infiltrations [13,14].

CONCLUSION

Breast cancer diagnosis is becoming more and more difficult. Neoplastic outbreaks most frequently detected with the use of imaging technology are often minuscule and, in many cases, they cannot be detected on palpation. Collecting diagnostic material for histopathological examination requires from the surgeons better and better precision and manual prowess. Routinely, a biopsy is guided with USG, MMG or MRI, which requires good technical knowledge about these diagnostic tools and skilful physical operation of these devices. At the same time, more and more patients undergo breast- and axillary lymph nodes-sparing surgeries, therefore, determining the initial advancement stage of breast cancer is absolutely essential for ensuring proper therapy. Reconstructive surgeries (including simultaneous reconstruction), which are becoming a standard practice in Breast Units, are another challenge. Balancing between the quality of oncological treatment and the aesthetic effect of reconstructive surgeries proves to be increasingly difficult for surgeons, radiotherapists and clinical oncologists.

In conclusion, it is worth emphasizing that in recent years, despite an increased incidence of breast cancer, the breast cancer mortality rates have been maintained at the same level. The fact that the number of performed breast-sparing and reconstructive surgeries is increasing also seems to be another success.

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