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Mini Review

Breast cancer: an up-date review

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Abstract

Breast cancer is the second most common cancer in the world and the most common cancer among women. The most common presenting symptoms are a painless subareolar lump, nipple retraction, and bleeding from the nipple. Last advances in screening and therapy have reduced morbidity and mortality. The purpose of this work is to make a revision about the recent scientific literature on breast cancer.

Epidemiological Data

Prevalence and incidence

Breast cancer (BC) is the second most common cancer in the world and the most common cancer among women. Its prevalence is estimated to reach 3.2 million by 2050 and it is higher in developed countries [1].

Lifetime risk of developing BC in every woman is 12.4%. Its incidence is higher in developed countries (more developed regions, 74.1/100,000; less developed regions, 31.3/100,000) and varies greatly with ethnicity (Northern America, Europe and Australia/New Zealand, 85.0-92.0/100,000; Asia, 27.5/100,000) [2].

Mortality and survival

BC is the fifth leading cause of cancer death in worldwide: it is the most common cause of death in less developed countries and it is the second cause of death in developed countries after lung cancer. Higher mortality rates are observed in less developed regions [3].

Due to better access to screening and therapeutic programs, the survival rate of BC is increasing, and the 5-year survival rate was 89% between 2005 and 2011. The 1-year survival rate of BC in European countries varies from 94.1% in Scotland to 97.1% in Italy. Because of the delay in seeking diagnosis of and treatment for BC among African women, survival rate is low among them [4].

Risk factors

The risk of developing BC increases with age, with the probability of developing BC being 2.3% up to 49 years (1 in 43 women), 5.4% in the 50-69 age group (1 in 18 women), and 4.5% in the 70-84 age group (1 in 22 women). The incidence curve increases exponentially until the age of menopause (around 50-55 years), and then slows down reaching a plateau after menopause, to subsequently increase again after 60 years of age [5,6]. Major risk factors are:

- reproductive factors: a long fertile period, nullity, first full-term pregnancy after 30, no breastfeeding [7,8]
- hormonal factors: increased risk in women taking hormone replacement therapy during menopause, especially if based on synthetic estrogen-progestin with androgenic activity; increased risk in women taking oral contraceptives [7,8]

- dietary and metabolic factors: high consumption of alcohol and animal fats and low consumption of vegetable fibers seem to be associated with an increased risk of BC [7,8]
- prior radiotherapy and prior breast dysplasia or neoplasm [8]
- familiarity and heredity: although most BCs are sporadic forms, 5%-7% are linked to hereditary factors, 1/4 of which are determined by the mutation of two genes: BRCA-1 and BRCA-2 [8]

Screening

Screening is a periodic secondary prevention activity aimed at asymptomatic women in order to detect BC at an early stage with potential to reduce morbidity and mortality. Mammography is still considered the most effective screening test [9].

Mammography has variable relevance and efficacy according to age [10]:

- 50-69 years, it is recommended every two years [10]
- 40-49 years, it should be performed by considering known risk factors [10]
- 70 years and over: consider extending the screening program to women aged 70-74 [10]

The question of the age until which to continue screening mammography is a difficult one, even in view of the continuing trend of increasing life expectancy. In this context, the American Cancer Society, which correlates the indication to mammography screening to life expectancy, suggesting that mammography should be continued as long as the woman is in good health and has a life expectancy of 10 years or more [11,12].

In women at high risk because of family history of BC or BRCA1 and/or BRCA2 mutation, instrumental examinations should start at the age of 25, or 10 years before the age of tumor onset in the youngest family member [13].

The reduction in mortality for women aged 50-69 was estimated by the IARC working group to be 23% for all invited women (adherents and non-adherents) and 40% for women participating in the screening program [14].

Diagnosis

The most common presenting symptoms in male BC patients are a painless subareolar lump, nipple retraction, and bleeding from the nipple. Usually the primary consideration in the differential diagnosis is gynecomastia, which affects approximately 30% of healthy men. Mammography can be helpful in differentiating gynecomastia from malignant breast disease. Malignant breast tumors are more often eccentric and have irregular spiculated edges. Ultrasonography can also be a useful adjunct and provide information regarding nodal involvement. After appropriate local imaging, any suspicious mass needs to be biopsied to confirm the diagnosis [15].

The indications for breast MRI are [16]:

- preoperative staging of newly diagnosed BC (ipsilateral and contralateral): MRI is more sensitive than conventional imaging (mammography and ultrasound) in the local staging of BC (size of index lesion, multifocality, multicentricity, contralateral malignant lesions)
- evaluation of the effect of neoadjuvant chemotherapy
- differential diagnosis of lesions around a surgical scar
- CUP syndrome: detection of occult BC with axillary lymph node metastases and negative mammography and ultrasound
- equivocal results of mammography/ultrasound if biopsy is not possible
- evaluation of women with breast implants
- Pathologic characteristics
- In 2012, WHO describes different histopathological classifications of BC [17].
- According to molecular biology testing, the immunophenotypic groups of clinical relevance and with important therapeutic implications are [18-20]:
- "Luminal A": neoplasms with marked hormone receptor expression, HER2 negative with low proliferative activity, favorable prognosis
- "Luminal B/HER2 negative": hormone-receptor positive, HER2 negative and high proliferative activity
- "Luminal B/HER2 positive": hormone-receptor positive, over-expressed or amplified HER2, any value of proliferative activity
- "HER2 positive (non-luminal)": overexpressed (3+ score of immunohistochemical reactions) or amplified (FISH or other methods) HER2 and hormone receptors both negative
- Triple-negative: no hormone receptor expression and HER2 negative

Staging

The TNM staging system follows the American Joint Commitment classification [21].

The stage of disease is fundamental for the management of patients with primary BC in local-regional and distant staging. Particularly in patients with stage I and II BC, the risk of detecting asymptomatic distant metastases by bone scintigraphy, liver ultrasound and chest X-ray is so low that local-regional staging alone is indicated [22].

Chest CT, ultrasound or abdominal CT and bone scintigraphy are indicated in patients at higher risk of asymptomatic metastatic disease at onset: clinically positive axillary lymph nodes, large tumors (larger than 5 cm) and aggressive tumor biology. The same indications are valid for patients who are symptomatic or present clinical or laboratory signs suggesting the presence of metastases. CA-PET/CT is only indicated as a diagnostic examination in cases where the conventional methods described above are inconclusive [23].

Prognostic and predictive factors

Prognostic factors are related to the patient's prognosis, while predictive factors are related to the potential effectiveness of an anticancer treatment. Some prognostic factors that have been shown to be important and useful in the selection of the type of treatment, such as [24-28]:

- Tumor size: it is difficult to define a threshold value below or above which the tumor can be considered as having a poor or good prognosis, except for very small tumors.
- Axillary lymph node status: the impact of the presence of isolated cancer cells or micrometastases in the sentinel lymph node on the prognosis does not appear to be significant.
- Histological grade: a high histological grade (G3) is considered an unfavorable prognostic factor. The evaluation of an intermediate histological grade (G2) is more difficult.
- Proliferative activity: proliferative activity as measured by the Ki67 labeling index is a recognized prognostic factor.
- Histological type: tubular, medullary, adenoid cystic and apocrine histotypes have a favorable prognosis.
- Vascular invasion: vascular invasion is not universally accepted as a prognostic factor.
- HER2 status: HER-2 overexpression by immunohistochemistry or HER2 gene amplification, present in approximately 13%-15% of BCs, is a well-established prognostic factor and predictive factor for response to HER2 drugs and likely for hormone therapy resistance.
- Status of hormone receptors (ER and PgR): it is important to define the status of both estrogen and progestin receptors and report the percentage of positive cells, which must be evaluated as a continuous quantitative variable.
- Multifocality: refers to the presence of several cancer foci separated by healthy parenchyma. "Satellite nodes" of the primary node are defined as lesions located less than >5 mm from it and separated by healthy parenchyma.
- Intratumoral lymphocytes: a pronounced intratumoral stromal lymphocytic infiltrate has a better prognosis than carcinomas with lymphocytic depletion.

Treatment

Breast-conserving therapy and adjuvant radiation in breast-conserving therapy

BCT involves excision of the tumor (lumpectomy) followed by adjuvant whole breast irradiation (WBI). In order to perform BCT, it must be possible to excise the tumor to negative margins with an acceptable cosmetic outcome, the patient must be able to receive radiotherapy, and the breast must be suitable for follow-up to allow prompt detection of local recurrence. The contraindications to BCT arise logically from these requirements. Contraindications to BCT include the presence of diffuse suspicious or malignant appearing calcifications, disease that cannot be resected to negative margins with a satisfactory cosmetic result, and the presence of contraindications to delivery of radiation such as prior treatment of the breast field or active scleroderma. In women with large tumors relative to breast size, neoadjuvant chemotherapy (NAC) can be used to downstage the tumor. It is important to determine preoperatively whether or not the patient is a candidate for adjuvant radiation. Prior chest wall irradiation, pregnancy at the time of diagnosis, and the presence of a connective tissue/collagen vascular disorder may be contraindications to radiation treatment. Patients with a history of mantle radiation delivered for Hodgkin's lymphoma may be ineligible for adjuvant radiation if the radiation threshold dose has been exceeded during prior therapy [29].

Mastectomy

In patients undergoing mastectomy, total mastectomy (simple mastectomy), skin-sparing mastectomy, and nipple areolar-sparing mastectomy are options for the majority of patients. Total mastectomy removes the breast parenchyma, nipple areolar complex, and excess skin from the chest wall, leaving only enough skin to close the incision. It is generally used when the patient will not undergo immediate reconstruction. The skin-sparing mastectomy was developed to facilitate immediate reconstruction, and removes the breast parenchyma and nipple areolar complex, leaving the skin as a natural envelope for placement of the tissue expander/implant or autologous flap.

Postmastectomy radiation (PMRT) is a well-established component of BC treatment in patients with advanced disease. PMRT is indicated with four or more positive axillary lymph nodes and tumor size ≥ 5 cm [30,31].

Neoadjuvant chemotherapy

NAC was initially utilized as a way of rendering locally advanced, inoperable BC, resectable. More recently, NAC has been used in operable tumors to downstage disease in the breast and axilla with the intention of facilitating breast conservation. Accurate evaluation of response to therapy. MRI is more accurate than mammography or ultrasound in predicting the extent of residual disease, but a normal MRI does not exclude the presence of scattered foci of viable carcinoma that may preclude BCT. Mammography is complimentary to MRI in evaluating suitability for BCT post-NAC as calcifications present at diagnosis infrequently resolve with NAC [32,33].

Adjuvant medical therapy

Adjuvant systemic therapy has the goal of eradicating clinically and radiographically occult micrometastatic disease. Selection of adjuvant systemic therapies is based on risk stratification of the patient. Two factors affect risk: disease burden (number of lymph nodes, size of the primary tumor) and disease biology as determined by HR and HER2 status, and genomic assays.

In high-risk patients, systemic chemotherapy is generally recommended. There are several standard chemotherapy options, typically containing both an anthracycline and a taxane.

Patients with HER2 positive BC are given HER2 targeted therapy in combination with a chemotherapy backbone. The availability of HER2 targeted agents has dramatically changed the prognosis of patients with HER2 positive BCs.

Endocrine therapy is recommended for most patients with HR positive disease. Patients may be treated with endocrine therapy for 5-10 years, and possibly longer. Five years of adjuvant tamoxifen reduces risk of recurrence by nearly 50% during years 0-4, with continued risk reduction of over 30% in years 5-9. Tamoxifen is used in premenopausal and postmenopausal women; aromatase inhibitors (anastrozole, letrozole, and exemestane) are only used in postmenopausal women and are generally preferred over tamoxifen as adjuvant therapy but may also be prescribed sequentially with tamoxifen [34].

Surveillance

Surveillance after therapy is comprised primarily of history, physical exam, and annual mammography. Routine computed tomography or positron emission tomography imaging in the absence of symptoms has not been shown to improve survival. Serum tumor markers (CA 15-3 and CEA) are non-specific and may prompt unnecessary imaging and procedures; they have no role in post-adjuvant therapy surveillance in an asymptomatic patient. After a BC diagnosis, patients should be encouraged to make lifestyle modifications that can decrease their likelihood of recurrence, including maintaining a normal body mass index [35].

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