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Breast cancer: carcinogenesis, diagnosing and treatment

Marta de Souza Albernaz[1], Fagner Santos do Carmo[2], Edward Helal-Neto[2], Sofia dos Santos Nascimento[2], Ralph Santos-Oliveira[2,3]

[1] Clementino Fraga Filho University Hospital, Federal Universityof Rio de Janeiro, Brazil; [2] Brazilian Nuclear Energy Commission, Nuclear Engineering Institute, Brazil; [3] Brazilian Association of Radiopharmacy, Presidency, Brazil

Summary. Breast cancer is the most common and deadly type of cancer that affects women worldwide. A good anamnesis, allied with a highly accurate diagnosis and a correct interpretation of the data acquired relies the best chance for the patient to receive the best treatment and, in this direction, improve the chance of cure and/or better prognosis. In all the cases, a good theoretical basis is fundamental. Thus, this update review intend to be a primary source on Breast Cancer, paving and consolidating knowledge in the field of breast cancer and helping physicians in their daily difficult task to deal with this disease.

Key words: oncology, education, cancer, female, disease

Cancer

Cancer is generally defined by an uncontrolled, usually rapid cellular proliferation, and therefore does not respond to the common mechanisms of cell cycle control. It is a highly complex, heterogeneous, and multifactorial disease. In several types of tumors, some malignant cells migrate to new sites (metastasis) forming secondary tumors that generally have a large impact on patient's survival. This process of invasion and metastasis begins by a local invasion, extravasation of tumor cells into blood or lymphatic vessels, dissemination, intravasion to distant organs, formation of small tumor cells nodules (micrometastasis) and, growth of macroscopic tumors.

Although there are numerous barriers to the development of cancer, a tumor cell can acquire characteristics that allow it to grow and spread such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Moreover, tumors are surrounded by a repertoire of "normal cells" that contributes to the acquisition of these characteristics, creating a tumor microenvironment. Therefore, tumor growths rely on the intrinsic contribution of intracellular signaling pathways and the complex interaction between components of the tumor microenvironment (1, 2).

Tumors can be divided into benign and malignant according to their biological behavior. Benign tumors do not invade adjacent tissues and grow locally resembling their original tissue. They are rarely life threatening. Malignant tumors, on the other hand, are those rapidly dividing that invade neighboring structures and give rise to metastasis (3).

Breast cancer is the most common cancer among women worldwide. A number of recognized risk factors contribute to the development of breast cancer, including hormone reproduction, age, obesity, alcohol, radiation, benign breast disease and lack of exercise. According to Lv et al (2016), more than 240,000 women developed breast cancer and ~ 40,000 died of the disease in the United States in 2016. Overall, about 1.7 million women were diagnosed in 2012, emphasizing the urgent need for effective and safe therapeutic approaches. Although most breast cancers are slow-growing or indolent, a subgroup acquires an aggressive phenotype for a variety of reasons. Molecular,

genotypic and phenotypic studies clearly demonstrate the heterogeneity of breast cancer with multiple subtypes and classifications (3, 4).

Carcinogenesis

Carcinogenesis is a multistep process characterized by genetic alterations that affect key cellular pathways involved in growth and development (5, 6). Oncogenes refer to genes whose alteration cause gain-of-function effects. Activated oncogenes, for example, can cause cells designated for apoptosis to survive and proliferate instead. Most oncogenes began as proto-oncogenes, normal genes involved in cell growth and proliferation or inhibition of apoptosis. When subjected to a genetic mutation, proto-oncogenes are up-regulated and can predispose cells to become cancerous. These genes are thus termed oncogenes (7, 8). On the other hand, tumor suppressor genes cause loss-of-function effects that contribute to a malignant phenotype. For example, a tumor suppressor gene can protect a cell from one step to the path to cancer. When this gene is altered it causes a loss or a reduction in its function, allowing the cell to progress to cancer. The effects of these alterations are very complex because of the high number of changes needed for a cell to become cancerous and the interaction of the biological pathways involved.

Carcinogenesis can be conceptually divided into four stages: tumor initiation, tumor promotion, malignant conversion and tumor progression. The activation of oncogenes and inactivation of tumor suppressor genes are mutational events that result from permanent DNA damage caused for example, by chemical exposures. The accumulation of mutations, and not necessarily the order in which they occur, constitutes multistage carcinogenesis (5, 9).

Tumor initiation is the first stage in which the initial modifications are irreversible genetic damage caused by carcinogens. A chemical carcinogen causes a genetic error, modifying the molecular structure of deoxyribonucleic acid (DNA) that can lead to a mutation during DNA synthesis. These irreversible changes can lead to the activation of oncogenes or inactivation of tumor suppressor genes (7, 10).

Tumor promotion involves the selective clonal expansion of mutated cells. These cells are non-mutagenic, requiring a metabolic activator (oncopromoters) to mediate their biological effects (7, 11].

Malignant conversion is the transformation of the pre-neoplastic cell into one expressing malignant phenotype. The promotion of the tumor contributes to the process of carcinogenesis by the expansion of a population of initiated cells that converge to malignancy. The conversion of a fraction of these cells to malignancy will be accelerated in proportion to the rate of cell division and the amount of dividing cells in the benign tumor or pre-neoplastic lesion. Some components of the diet and prolonged and excessive exposure to hormones are examples of factors that promote the transformation of cells started into malignant ones. The p53 gene located on chromosome 17p13.1 is the most common target of genetic changes in human tumors, being altered in just over 50% of the cases. The homozygous loss of this gene is notable because it can occur in virtually all types of cancer, partly explained by its functional activities, which involve cell cycle arrest and the onset of apoptosis in response to DNA damage (9, 10, 12).

Tumor progression comprises expression of the malignant phenotype and the tendency of malignant cells to acquire more aggressive characteristics over time. In addition, metastasis may involve the ability of tumor cells to secrete proteases that allow invasion beyond the site of the immediate primary tumor (13). At this stage, the cancer is already established, evolving the appearance of the first clinical manifestations of the disease (1, 6, 11, 14].

In all this process, other genetic changes may occur, including activation of oncogenes and functional loss of tumor suppressor genes. Proto-oncogenes can be activated by two major mechanisms: for example, in the RAS gene family, point mutations are found in highly specific regions of the gene and the *MYC*, *RAF*, HER2 and *JUN* genes may be overexpressed, sometimes involving amplification of chromosomal segments containing these genes. The loss of tumor suppressor gene function normally occurs in a bimodal fashion, and more often involves point mutations in one allele and loss of the second allele by a deletion, recombination event, or non-chromosomal disjunction (1, 15, 16).

The uncontrolled proliferation of cancer cells may lead to the formation of, new blood vessels (angiogenesis), required to the adequate supply of oxygen and nutrients to proliferating tumor cells. The formation of such new blood vessels is important not only in supporting tumor growth, but also provide an opportunity to cancer cells to invade neighboring tissues, enter the circulatory system and begin the metastatic process. When present in the lymphatic and blood vessels, tumor cells can then reach distant organs and proliferate in a secondary place completing the metastasis process (6, 16-18).

Cancer initiation and progression is considered as a multistep process which lately drives malignant transformation of normal cells. However, nowadays, several evidences have suggested that cancer stem cells (CSCs) contribute to the metastatic dissemination of solid tumors. These cells, cancer stem cells (CSCs), are a small cell subpopulation with embryonic characteristics such as self-renewal, high proliferation rate, and the ability to generate heterogenic lineages of cancer cells, are key contributors to the development and progression of the disease (19).

Different theories have been proposed about the origin of CSCs and several hypotheses have been described. One of them states that CSCs arise from stem cells. In fact, stem cells can divide to produce copies of themselves, or self-renew and, are pluripotent (able to differentiate into most mature cell types). Therefore, an unsuitable mutation may lead to transformation of dormant normal stem cells to cancer stem cells (CSCs) (20, 21). According to another, CSCs may arise from progenitor cells. Indeed, the differentiation pathway from a stem cell to a differentiated cell usually involves intermediate cells types, called progenitor cells that are more abundant in adult tissue than are stem cells. Progenitor cells usually divide to produce mature cells and retain a partial capacity for self-renewal. Thus, this property has led to the theory that mutations in progenitor cells could lead to a source of CSCs (22, 23).

Some researchers have suggested that CSCs could arise from mature, fully differentiated cells. In this theory, a adult somatic cell could undergo several mutations and de-differentiate to become in a more stem-like state. The genetic mutations would need to drive not only the de-differentiation process, but also the self-renewal of proliferating cells (24, 25).

Because most deaths from cancer patients are from metastasis, a better understanding of the mechanisms of tumor metastasis is important for developing more effective therapeutic strategies

Breast cancer

Breast cancer is the most common cancer among women worldwide (both in developing and developed countries). In 2012, about 1.67 million new cases breast cancer were detected worldwide, accounting for approximately 25% of all cancers diagnosed in women. Still in 2012, 522,000 deaths from breast cancer were recorded in women worldwide. These deaths account for 15% of all cancer deaths in women. Breast cancer is the second leading cause of cancer death in developed countries (198,000 deaths) behind only lung cancer (26, 27). Women with breast cancers can be successfully treated if diagnosed in an early stage of the disease.

Histological classification of breast tumors

Breast cancers usually are epithelial tumors of ductal or lobular origin and are classified as follows: Ductal carcinoma in situ (DCIS), Lobular carcinoma in situ, Invasive ductal carcinoma (ductal breast cancer), Invasive lobular carcinoma, Medullary carcinoma, Mucinous (colloid) carcinoma, Tubular carcinoma, Papillary carcinoma, Metaplastic breast cancer (MBC), Phyllodes tumors, Mammary Paget disease (MPD), Inflammatory breast cancer.

Invasive ductal carcinoma

Most breast tumors originate in the ductal epithelium (about 80%) and are known as invasive ductal carcinoma. The “invasive ductal carcinoma” refers to cancer that has broken through the wall of the milk duct and begun to invade the adipose tissue of the breast. Over time, invasive ductal carcinoma can spread to the lymph nodes and possibly to other areas of the body. The diagnosis of invasive ductal carcinoma is made

by the exclusion of recognized specific breast cancer. When the lesion does not fulfill the diagnostic criteria for any other special types of mammary carcinoma, tumor has been classified as invasive ductal carcinoma without other specification. The tumor is formed by the proliferation of epithelial elements with relatively high cytological atypia, which is characterized by the presence of many epithelial cells in the cytoplasm with a variable tendency to form pseudo-glandular or duct-like structures, and with variable mitotic activity (28, 29). The cytological characteristics vary widely and can be found from small cells with homogeneous nuclei to large cells with irregular and hyperchromatic nuclei. On the margins of the tumor mass, neoplastic cells infiltrate into the stroma and fibro-adiposal tissue, and there is often an invasion of the perivascular and perineural spaces, as well as of the blood and lymphatic vessels (30, 31).

Lobular carcinoma

Lobular carcinoma, often called, invasive lobular carcinoma, is the second most common type of breast cancer after invasive ductal carcinoma. It occurs in the breast lobules of the mammary gland, and can broke through the wall of the lobes and invade the tissue of the breast (10% of the cases).This type of cancer has a good prognosis, with a 10-years overall survival in 80-90% of the women. It is characterized by a risk of bilaterality and high rate of late systemic recurrence. They are often distinguished by their molecular physiology, since they often have E-cadherin loss and are typically positive for estrogen and progesterone receptors. In addition, several distinctive genomic alterations were observed in lobular tumors, including 1q gain and chromosome 16q20. A large study of lobular characteristics also categorized several mutations in the PTEN, TBX3 and FOXA1 genes that typify lobular carcinomas (31, 32).

Tubular carcinomas

Tubular adenomas are rare benign neoplasms, representing 0.13-1.7% of benign breast lesions. Tubular adenomas are circumscribed, unencapsulated, slow-growing, firm, movable, and small to medium-sized female breast lesions consisting of densely packed regular round tubules. Young women of reproductive age (15-49 years) are commonly affected. The upper and outer quadrant of the breast is the most preferred site. Recurrence or increased risk of cancer is not reported from cases of tubular adenoma (33).

Mucinosis carcinoma

This type of cancer represents 1-4% of all cases of breast cancers. It usually manifests in postmenopausal women, has a good prognosis, with a 10-year survival rate in 80% to 90% of cases, often associated with mutations in the BRCA1 gene (34).

Marrow carcinoma

This type represents less than 5% of all invasive breast cancers. It is more common in young women and is associated with abnormalities in the BRCA1 gene. It has a better prognosis than ductal carcinomas (12).

Micropapillary carcinoma

It is a distinct form of mammary carcinoma characterized by the proliferation of malignant cells in micropapillary arrays within cystic spaces in the breast stroma, without epithelial or endothelial lining, with frequent metastasis in the diagnostic phase (35). The incidence of IMPC ranges from 3 to 6 % of all primary breast cancers. It is an important subtype due to its unique features such as high proclivity to lymphovascular invasion, lymph node metastasis, local recurrence, and distant metastasis, thus exhibiting a more aggressive behavior with a poorer prognosis than invasive ductal carcinoma (36, 37).

Carcinoma papillaryis

With an incidence ranging from 1.1% to 1.7% of all malignant tumors of the breast, is considered a rare type. In most cases, these types of tumors are diagnosed in older women who have already been through menopause. Histopathological features include low grade cellular atypia, intracellular or extracellular mu-

cin deposition, and solid papillary growth pattern, as well as neuroendocrine differentiation (38, 39).

Metaplastic carcinoma

Due to the great heterogeneity and the different evolutionary profile, this group was sub classified. The fibromatosis-simile subtype presents a differential diagnosis with lesions and benign fusocellular tumors, especially in needle biopsies with limited samples or when they occur associated with sclerosing lesions, radial scars or papillomas. Immunohistochemically study for cytokeratins (CK), especially those of high molecular weight (34β E-12, CK-5 or CK-5/6), and p63 aids in the differential diagnosis and positively affects tumor spindle cells. Differential diagnoses include benign fusocellular lesions (fibromatosis, nodular fasciitis, myofibroblastoma and needle biopsies after needle biopsy) and low-grade fusocellular sarcomas (40, 41).

The spread of mammary carcinomas is by local invasion (skin, nipple, muscle or chest wall), lymphatic or hematogenous. In 30% to 50% of the cases there is axillary lymph node involvement at the time of diagnosis, and regional metastases indicate distant and systemic metastatic potential. Women with 1-3 compromised lymph nodes have 60% survival at 10 years; this rate reduces to 20% in women who had 3-4 or more lymph nodes with metastases at the time of diagnosis. Systemic metastases generally occur in the lungs, bones, liver, adrenal glands, ovaries, and the central nervous system. About 30% of women without axillary metastases develop systemic metastasis later, indicating that a large proportion of breast carcinomas are already systemic diseases at the time of diagnosis (32, 42).

Molecular classification of breast tumors

There are 6 intrinsic subtypes according to their gene expression pattern: luminal A, luminal B, HER-2, basal-like, normal-like, and claudin-low overexpression tumors.

Luminal

Approximately 75% of breast cancers are positive for Estrogen receptor (ER) and/or Progesterone receptor (PR). This type of tumor encodes typical proteins of luminal epithelial cells so they are termed the luminal group. The luminal tumor cells look the most like cells of breast cancers that start in the inner (luminal) cells lining the mammary ducts. Two main luminal-like subclasses corresponding to Luminal A and Luminal B have been described so far (3, 8, 43).

Luminal A

About 30-70 percent of breast cancers are luminal A tumors. These tumors frequently have low histological grade, low degree of nuclear pleomorphism, low mitotic activity and include special histological types (i.e., tubular, invasive cribriform, mucinous and lobular) with good prognosis. They areoriginatedin epithelial cells differentiated from ducto-lobular lumens, presenting overexpression of estrogen receptor (ER) and progesterone (PR), and genes that are activated by hormonal binding, such as the BCL2 gene, which regulates apoptosis, and the GATA-3 transcription factor, and absence of HER2. The Ki67 evaluation shows a low proliferation rate (<14%). Because luminal A tumors tend to be ER-positive, treatment for these tumors often includes hormone therapy. Patients with luminal-A breast cancer have a good prognosis and the relapse rate is significantly lower than the other subtypes (3, 43).

Luminal B

Luminal-B tumors comprise 15%-20% of breast cancers and have a more aggressive phenotype in comparison to Luminal A. They present higher histological grade, proliferative index and a worse prognosis. Luminal B tumors have a higher recurrence rate and lower survival rates after relapse compared to luminal-A subtype. Luminal B tumors tend to be ER-positive. They may be HER2-negative or HER2-positive. Approximately 30% of HER2-positive tumors defined by immunohistochemistry are assigned to the luminal-B subtype. This tumor is also sensitive to hormone therapy, although to a lesser extent, and Trastuzumab (TZB) can be used successfully if it is HER2 positive (3, 43).

HER2

The human epidermal growth factor receptor-2 is a member of the family of four membrane tyrosine kinases. The HER2 receptor is encoded by the HER2 gene, which is a proto-oncogene mapped in chromosome 17q21. HER-2 is amplified in 15-20% of breast carcinomas. Its overexpression is associated with a more aggressive tumor phenotype, but more responsive to monoclonal targeted therapy (Herceptin). HER2 positivity confers a more aggressive biological and clinical behavior. Morphologically, these tumors are highly proliferative, 75% have a high histological and nuclear grade and more than 40% have p53 mutations. Nearly half of HER2-positive breast cancers are positive for ER but they generally express lower ER levels (44-46).

Basal-Like

The basal-like subtype is highly aggressive and, therefore, of particular clinical relevance (3, 43). Basal-like breast cancers are more likely to occur in younger women, and are associated with mutations in the breast cancer susceptibility gene (BRCA1). They are characterized by high tumor rate, proliferation rate, frequency of recurrence and the presence of p53 mutations. Morphologically, it is characterized by a high histological grade, by a high mitotic index, by the presence of central necrotic areas and by the prominent lymphocytic infiltrate (8). It is estimated that 15 to 20% of breast carcinomas are basal-like. They are undifferentiated or undifferentiated lesions with high proliferation rates. For the most part (70-80%), they are triple-negative tumors by immunohistochemically reaction, with negativity of ER, PR and HER2.

It is important to notice that despite the similarity, basal-like and triple-negative breast cancer terms are not synonymous: the first one is defined by gene expression in DNA microarrays, and the second one, by immunohistochemically criteria. The panel of markers proposed for the classification of the basal-like type would be the absence of expression of RE, PR and HER2, expression of high molecular weight/basal cytokeratin's, CK5/6, 14 or 17, and expression of EGFR (HER1). Triple negative breast cancer with basal-like features lack expression of the biomarkers ER, PR, and HER2, but commonly express high molecular-weight 'basal' cytokeratin (CK5/6, CK14, and CK17) epidermal growth factor receptor (EGFR), vimentin, p-cadherin, αB-crystallin, fascin, and caveolins 1 and 2 (47).

Basal-like tumors, despite being more aggressive, are more responsive to neoadjuvant chemotherapy (8, 48). BRCA1 dysfunction, seems to represent a mechanism that generates basal-like and triple-negative tumors; Thus, it may be inferred that at least a part of these are incompetent in the DNA repair mechanism involved in the homologous recombination pathway; this makes these cells more dependent on repair pathways by the enzymes of poly ADP-ribose polymerase (PARP) (3, 43).

Normal-like

The existence of the normal-like subtype is controversial. The term was used because the genes expressed therein are usually shared with normal epithelial tissue. However, it is not clear whether this subtype even exists or whether its determination was simply due to contamination with normal tissue samples (49, 50).

Claudin-low

Recognized in 2007, they are also triple-negative tumors, with low expression of claudin genes 3, 4 and 7, and loss of E-cadherin. Its frequency is estimated to be 5% of all breast carcinomas and its origin is linked to cells very close to the primitive stem-mammary cells (49, 51). Claudins are transmembrane proteins involved in adhesion between cells, and the regulation of some of them is associated with breast cancer, apparently by epigenetic silencing, facilitating cell migration and tissue invasion (50, 51).

In claudin-low carcinomas there are no markers of luminal differentiation; on the contrary, these forms are rich in markers of stem cells, cancer initiating cells, epithelial-mesenchymal transition, and genes associated with the immune response. It is the tumor whose cells most resemble stem cells (49, 52). They have a high histological grade, little differentiation and show a marked lymphocytic infiltration (52).

Risk factors

Breast cancer is a type of cancer considered multifactorial, involving biological-endocrine factors, reproductive life, behavior and lifestyle, aging, factors related to women's reproductive life, family history, high density of breast tissue (ratio between glandular tissue and adipose tissue of the breast) are the most well-known risk factors for the development of breast cancer. In addition, alcohol consumption, excess weight (due to IGF-1 genes, such as IGF-1, as well as changes in serum levels of hormones such as insulin and leptin), sedentary lifestyle, and exposure to ionizing radiation are also considered as potential agents for the development of this cancer (53).

However, breast cancer observed in young women has very different clinical and epidemiological characteristics than those seen in older women. They are generally more aggressive, have a high rate of BRCA1 and BRCA2 gene mutations, and overexpress the human epidermal growth factor receptor 2 (HER2) genes (54-56).

Changes in genes, such as the BRCA family, increase the risk of developing breast cancer (57, 58). Factors related to women's reproductive life are also linked to the risk of developing this type of neoplasia. Early menarche (age at first menstruation less than 12 years), late menopause (after age 55), nulliparity, and having the first child after the age of 30 contribute to an increased risk of breast cancer. On the other hand, breastfeeding is associated with a lower risk of developing this type of cancer (57).

The practice of physical activity and healthy eating with maintenance of body weight are associated with an approximately 30% reduction in the risk of developing breast cancer. Postmenopausal obesity is also considered a risk factor, but this risk decreases with the practice of regular physical activity (59-61).

Early detection aims to identify cancer in the early stages, in which the disease may have a better prognosis. Is important to notice that early detection of breast cancer do not reduce incidence but may reduce the mortality (62, 63). To solve this problem, different non-invasive imaging technologies are researched for both early diagnosis and to monitor the onset of metastasis. These techniques include, Positron Emission Tomography (PET) or Single-Photon Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI), Mammography, Ultrasonography (US), Computerized Tomography (CT), and Optical Imaging (bioluminescence and/or fluorescence imaging) (62, 64-67).

Mammography

Mammography is considered the standard method of early detection of breast cancer and diagnosis, but it has limitations, such as low sensitivity in dense breasts. Breast cancer is a heterogeneous disease, with variation of biological behavior, different growth rates and different metastatic potential (62). Slow-growing tumors are more easily detected in the tracing, but there may be no benefit in their early detection. In more aggressive cancers, early detection with mammography, in addition to being more difficult, may not be effective due the rapid growth rate and the potential to generate metastases in a short time, even when the primary tumors are still small (64-66, 68).

Ultrasonography

Ultrasonography is, alongside mammography, the most important imaging method in the diagnostic investigation of suspected mammary alterations, and the two methods are seen as complementary in the approach of different clinical situations. Ultrasonography is used to detect, characterize and guide the biopsy of breast lesions. It presents two important advantages on mammography: the absence of the use of ionizing radiation and the fact that its diagnostic acuity does not depend on the mammary density (66. 69). The US has known limitations that compromise its potential as a screening method for breast cancer. Among these limitations, there is the dependence on the presence and experience of the attending physician, the greater difficulty in standardizing examination techniques and interpretation criteria, and the difficulty in detecting micro-calcifications (70).

Magnetic Resonance

Magnetic resonance imaging is effective for the screening of dense breasts and identification of addi-

tional occult lesions in the ipsilateral or contralateral region of the breast. It may also help to determine if lumpectomy or mastectomy (unilateral or bilateral) is the best treatment. Although MRI is highly sensitive (94% to 100%), specificity is low (37% to 97%). It is suggest that the combination of MRI and mammography screening could improve the chances of early detection of breast cancer. However, magnetic resonance imaging is not routinely used in screening due the price of the exam (63, 66, 71).

Nuclear Medicine

Nuclear Medicine has been used in the last 40 years as in diagnostic imaging, decision-making regarding the treatment or monitoring the response to treatment. Imaging radiopharmaceutical could evaluate organ physiology, distinguishing between normal and neoplastic tissue (62, 66).

The most commonly used radiopharmaceutical breast imaging is 99mTc-sestamibi. This radiopharmaceutical enters the cell by passive diffusion of the extracellular compartment into the cytoplasm and accumulates into the mitochondria, considering that most of the malignant cells have a higher mitochondrial intracellular, it accumulation indicates the tumor presence (66, 72-75). Studies on the sensitivity and specificity of MIBI for detection of breast cancer demonstrated a sensitivity of 96% in detection, but showed a moderate specificity (59%) (66, 76).

Treatment

Surgery

Surgery is a common treatment for breast cancer, and its main purpose is to remove as much of the cancer as possible. There are two main types of surgery to remove breast cancer. In the breast-conserving surgery (also called a lumpectomy, quadrantectomy, partial mastectomy, or segmental mastectomy) only the part of the breast containing the cancer is removed. The aim of this type of surgery is to remove the cancer as well as some surrounding normal tissue. How much of the breast is removed depends on the size and location of the tumor and other factors. The mastectomy on the other hand, is a kind of surgery where the entire breast is removed, including all of the breast tissue and sometimes other nearby tissues. There are several different types of mastectomies. Some women may also get a double mastectomy, in which both breasts are removed (77, 78).

Radiotherapy

Radiation after BCS (Breast Conserving Surgery) for early as well as locally advanced tumor after neoadjuvant chemotherapy (NACT) is now considered as an integral part of BCT (Breast Conserving Therapy) whereas post mastectomy radiation (PMRT) to chest wall and or regional area is considered beneficial for a select group of high risk patients (79).

Radiation therapy is a treatment with high-energy rays (such as x-rays) or particles that will kill tumor cells. Two main types of radiation therapy are conventionally used to treat breast cancer: the external beam radiation (a type of radiation coming from a machine outside the body), and brachytherapy (a radioactive source put inside the body). The external beam radiation is the most common type of radiation therapy to treat breast cancer. The radiation beam is usually generated by a linear accelerator capable of producing high-energy X-rays and electrons. Different types of external beam therapy are used for specific types of cancer. For example, Three-Dimensional Conformal Radiation Therapy (3D-CRT) is used when tumors are not regular (different shapes and sizes) and uses special imaging techniques to show the size, shape and location of the tumor. This technique precisely tailors the radiation beams to the size and shape of the tumor allowing nearby normal tissue to receive less radiation. The Intensity Modulated Radiation Therapy (IMRT) is a specialized form of 3D-CRT in which the beam can be broken up into many "beamlets" and the intensity of each beamlet can be adjusted individually. This allows the radiation to be more exactly shaped to fit the tumor and limits the amount of radiation that is received by healthy tissue near the tumor. The Proton Beam Therapy uses protons rather than X-rays to treat cancer and more effectively reduces the radiation dose to nearby healthy tissue. In the Neutron Beam Therapy, a neutron beam is often used to treat cancers radioresistants to the conventional X-ray radia-

tion therapy. The Image Guided Radiation Therapy uses imaging techniques (CT, ultrasound or X-rays) to increase the delivery of radiation to the tumor site in cases were tumors can move between treatments because of differences in organ filling or movements while breathing. Still, which areas need radiation depends on whether mastectomy or breast-conserving surgery (BCS) was done and whether the cancer has reached nearby lymph nodes (81, 82).

Although radiation provides significant benefit to many women with breast cancer, it is also associated with risks of toxicity, including cardiac and pulmonary toxicity, lymphedema, and secondary malignancy.

Chemotherapy

Chemotherapy is a type of cancer treatment that uses one or more anti-cancer drugs (chemotherapeutic agents) as part of a standardized chemotherapy regimen. Chemotherapy may be given before surgery, after surgery or for the main treatment of advanced breast cancers. The main purpose of the neoadjuvant therapy, also referred to as preoperative or primary chemotherapy, is to reduce the size of the primary tumor, eventually allowing radical or more conservative surgical interventions. The adjuvant chemotherapy (after surgery) on the other hand is used after surgery to try to kill any cancer cells that may have been left behind or spread but can't be seen, even on imaging tests. Chemotherapy can also be used as the main treatment for metastatic breast cancer and cannot be surgically removed (83-86).

The most commonly used drugs for adjuvant and neoadjuvant chemotherapy include: Anthracyclines such as doxorubicin (Adriamycin) and epirubicin (Ellence); Taxanes, such as paclitaxel (Taxol) and docetaxel (Taxotere); 5-fluorouracil (5-FU); Cyclophosphamide (Cytoxan) and; Carboplatin (Paraplatin).

Most often combinations of two or three of these drugs are used. For advanced breast cancer on the other hand, a single combination is usually utilized and chemotherapeutic drugs include: Docetaxel, Paclitaxel, Platinum agents (cisplatin, carboplatin), Vinorelbine (Navelbine), Capecitabine (Xeloda), Liposomal doxorubicin (Doxil), Gemcitabine (Gemzar), Mitoxantrone (Novantrone), Ixabepilone (Ixempra), Albumin-bound paclitaxel (nab-paclitaxel or Abraxane) or Eribulin (Halaven) (83-86).

Hormone therapy

Hormone therapy, such as anti-estrogen therapy and estrogen ablation, is the treatment of choice for patients with breast cancer expressing estrogen receptors (ER) and/or progesterone receptors (PR). The clinical usefulness of hormone therapy has been proven in the prevention and used after surgery (as adjuvant therapy) and sometimes before surgery (as neoadjuvant therapy) as well (87).

The ER and PR were the first predictive biomarkers recommended for routine clinical use in breast cancer. They are used to distinguish patients who have little or no chance of benefiting from hormone therapy from those who do have some reasonable chance. Once a tumor has been defined as having ER and/or PR expression, a number of potential strategies to target the hormonal pathway can be used. For example, tamoxifen acts as an antagonist of the ER (by interrupting the transcription of estrogen-regulated genes) and disrupts the proliferative effects of estrogen in the breast. The fulvestrant, similarly acts at the level of the estrogen receptor, but in contrast to tamoxifen only has antagonist activities because it leads to the degradation of the ER protein with loss of ER and subsequent PR expression. Several strategies to produce estrogen deprivation are also used to treat breast cancer such as suppression of ovarian estrogen production in premenopausal women or the use of aromatase inhibitors in postmenopausal women. Moreover, high dose steroids (including estrogen or progesterone) can paradoxically also has an anti-breast cancer effect. Therefore, the selection of hormonal therapy is typically based on several factors including menopausal status and side effect profile (88, 89).

Targeted therapies

Clinical trials investigating new drugs and therapeutic combinations have led to promising advances in breast cancer therapy.

The epidermal growth factor receptor 2 (ErbB2, HER2), a member of the growth factor receptor family (HER1/2/3/4), has been one of the most success-

ful targets discovered in breast cancer. HER2-targeted therapy using the humanized monoclonal antibody trastuzumab has significantly improved disease-free and overall survival in early stage HER2-positive breast cancer. Nowadays, trastuzumab is considered a first-line treatment for advanced HER2-positive breast cancers (90).

In addition to hormone and HER2-targeted therapies recent preclinical studies have shown several targetable pathways that overcome resistance and are currently being used in the clinical setting. The mTOR inhibitor everolimus and the CDK4/6 inhibitor palbociclib have been approved in HER2-positive metastatic breast cancer and improved disease-free survival. The combination of pertuzumab with Trastuzumab and taxanes further improved disease free survival in HER2-positive breast cancer. However, patient selection and predictive biomarker development remains a big challenge for targeted therapy development in breast cancer (91-93).

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Address: Dr Ralph Santos-Oliveira
Laboratory of Radiopharmacy and Nanoradiopharmaceuticals
E-mail: presidenciaradiofarmacia@gmail.com