Mexican consensus on breast cancer diagnosis and treatment

I. Introduction

The first National Consensus on Diagnosis and Treatment of Breast Cancer was carried out in Colima in 1994; its conclusions were widely diffused[1] and have been useful as a guide for oncologists and other general practitioners and physicians of related specialties. Since then, nine periodical revision meetings have taken place, where available knowledge and information have been updated, and participation was extended to other subspecialties and disciplines related to the diagnosis and treatment of this disease. The conclusions were published in specialized journals[2-9] and are available online at the Consensus page (www.consensocancermamario.com) and other institutions and oncology societies' websites.

Since these publications have been widely diffused and constantly updated, practically all oncologists of the country are aware of the Consensus conclusions and use them as a tool to support decision-making in their daily oncology practice. In addition, they are part of several oncology institutions guidelines and of the documentation the Mexican Official Standard on the subject is based on.[10]

On this occasion, we met, now virtually, on January 29 and 30, 2021, with the purpose to review recent advances in the field of breast cancer prevention, diagnosis and treatment. Nearly 105 nation-wide renowned physicians from all institutions and specialties related to this disease were convoked and, in working groups, they analyzed the updated information of each area with the purpose to present it at plenary sessions for approval. This time, the subject "Covid and breast cancer" was added, owing to the pandemic caused by this disease and the impact it has had on patient care.

It should be mentioned that 1,570 participants registered to electronically witness the consensus, out of whom 25 % were residents, 60 % from localities other than Mexico City and more than 200 participants were from Central and South America.

We hope that the conclusions of this ninth revision serve as a guide for the medical community in general and for oncologists in particular, in order for them to offer patients with this disease an accurate diagnosis and an optimal and updated treatment.

II. Epidemiology of breast cancer in Mexico

1. Introduction

Breast cancer is the most common tumor in women worldwide and the leading cause of cancer-related death. Around 1.7 million new cases are estimated every year and 552,000 women die from this disease. Approximately 45 % of cases occur in low- or middle-income countries (765,000), and 55% of all breast cancer deaths occur in these countries (287,100). Global mortality rate is 13.2 x 100,000, ranging from 8.8 in Asia to 19.7 in Western Europe.[1] In Latin America, since 2000, the World Health Organization (WHO) reported that the main trend was towards an increase in breast cancer. In 2008, the Pan American Health Organization (PAHO) reported that 320,000 cases were diagnosed in this area and an increase of 60 % was estimated for 2030.[2,3]

In Mexico, breast cancer has had a constant increase, both in incidence and mortality, over the last three decades. According to the Ministry of Health Epidemiology Department report, the incidence increased

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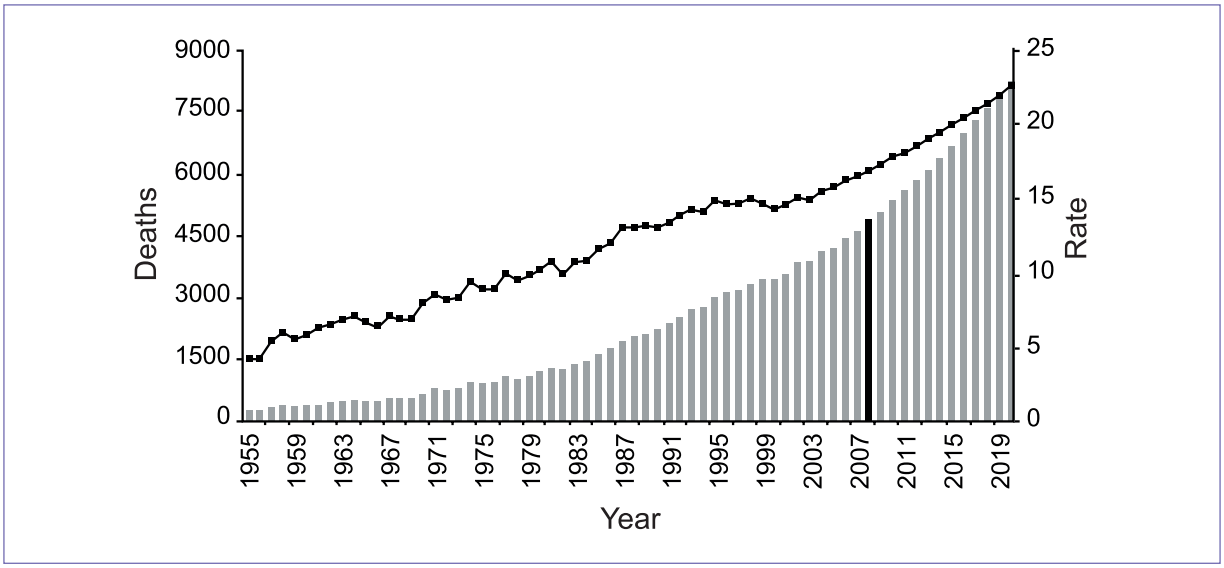


Figure 1. Mortality tendency and number of breast cancer cases in Mexico, 1955 - 2007 and 2008 - 2020 projection
*Crude rate per 100,000 women aged 25 years and older.
Source: WHO, INEGI, SSA Databases. 1955-2007.

between 2000 and 2013, from 10.76 cases per 100,000 population to 26.1 per 100,000 women older than 25 years of age, with 23,873 new cases being estimated in 2013.[4] The increase is evident, but obviously there must have been an underreporting that explains such a substantial difference (Figure 1). This has been influenced by factors such as population aging, lifestyle "westernization", deficient education and information regarding the disease, lack of a national program for timely detection, care delay in public institutions, as well as insufficiency of human, material and technical resources for treatment, together with the lack of specialized breast units.

In Mexico, there has been a constant increase in life expectancy since the 1970s, with women reaching a mean of 77 years of age, and men 75 years. This has led to population aging, with a significant number of women being incorporated to the risk age (> 40 years) each year, and estimations indicating that by 2020 there will be around 30 million women in this group[5] (Figure 2).

Despite the fact that breast cancer in Mexico is diagnosed at a mean age of 52.5 years, one decade lower than in the population of North America and Western Europe,[6,7] its incidence grows proportionally to age increase, which makes us foresee that, only considering population aging, there will be also a substantial increase in the number of breast cancer cases in the coming years. Furthermore, in our population, breast cancer in women younger than 40 years is more common (13.3 %) than in the North American or European population.[6]

2. Economic impact of the disease

Economic impact is not only driven by the high cost of diagnostic procedures and treatments, but also because it affects women at productive stages of life. The cost of treatment is much higher at locally advanced and metastatic stages, which are the stages that predominate in our country.[1] The National Institute of Public Health calculated that each woman that dies from breast cancer is equivalent to 21 years of healthy life lost (YHLL), which represents a huge economic cost for the country, in addition to the familiar and social impact of the lack of a mother, with children usually adolescents or young people.[8]

There are important differences in the incidence and mortality of the disease between the northern and central states of the Mexican Republic and the southeastern states, with a higher percentage of indigenous population.

This is due, among other reasons, to the change in the lifestyle of the population, which has adopted the Western model, where women in general have a higher level of education and work outside the home, with a

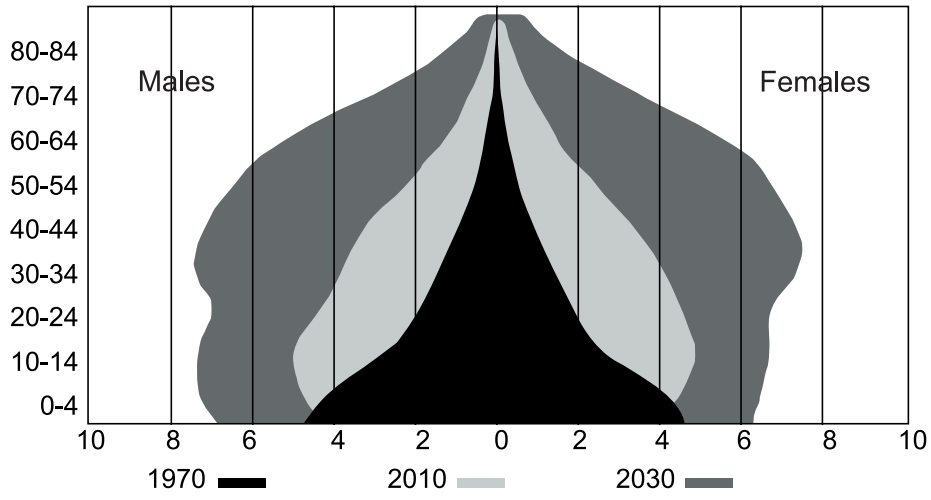


Figure 2. 1970-2030 population pyramid.

higher consumption of animal fats, tobacco and alcohol, sedentary lifestyle and overweight, delay in reproduction initiation, with a late first pregnancy (> 30 years) and absence of breastfeeding, in addition to the use of hormonal agents at menopause. This causes for breast cancer to increase its incidence in areas where women have these characteristics, while less developed states, where women continue with usual household chores, where they do not have the resources for eating animal fats and physically work in the countryside, have children at an early age and breastfeed them for long periods, the disease is less common, but, paradoxically, when it occurs, low education, lack of economic resources and health services coverage, causes for mortality to be higher (Figure 3).

As of 2007, the extinct *Seguro Popular* incorporated breast cancer into the "Catastrophic Expenses" program, which guaranteed free access to comprehensive treatment of this disease to patients that were not social security beneficiaries. However, in our country, the disease is diagnosed at locally advanced stages (IIb-III) in 55.9 %, and in 10.5 % at metastatic stage (IV) (Figure 4), to conclude that, although universal access to treatment is efficient, we have not yet managed to improve early detection. In this regard, the Mexican Institute of Social Security (IMSS – *Instituto Mexicano del Seguro Social*) has recently created several Breast Cancer Diagnosis centers, and the Ministry of Health has implemented units called "DEDICAM" in several states of the republic, without their impact yet being known. We must direct the greatest effort to try to detect breast cancer at the earliest stage of the disease.[8-10]

III. Information and risk factors

1. Introduction

The incidence of breast cancer varies around the world, and there are various risk factors that must be addressed from the perspective of health prevention and promotion.[1] The sustainable development global goals, proposed by the World Health Organization (WHO), aim to ensure a healthy life by promoting well-being for all people of all ages, with gender equality.[2] In the specific subject of breast cancer, community-based interventions aimed at adult people have been established to be able to impact on early detection and primary prevention.[3]

Prevention activities include educational communication for awareness on risk factors and promotion of healthy lifestyles, since the lack of physical activity and obesity increase the possibility of sporadically developing breast cancer. We recommend for education on breast cancer to be aimed at sensitizing women on the importance of knowing their breasts' normal characteristics, seeking timely medical attention if they discover any abnormality, and periodically attending the doctor for clinical and radiological evaluation (see Chapter V. Screening studies).[4,5]

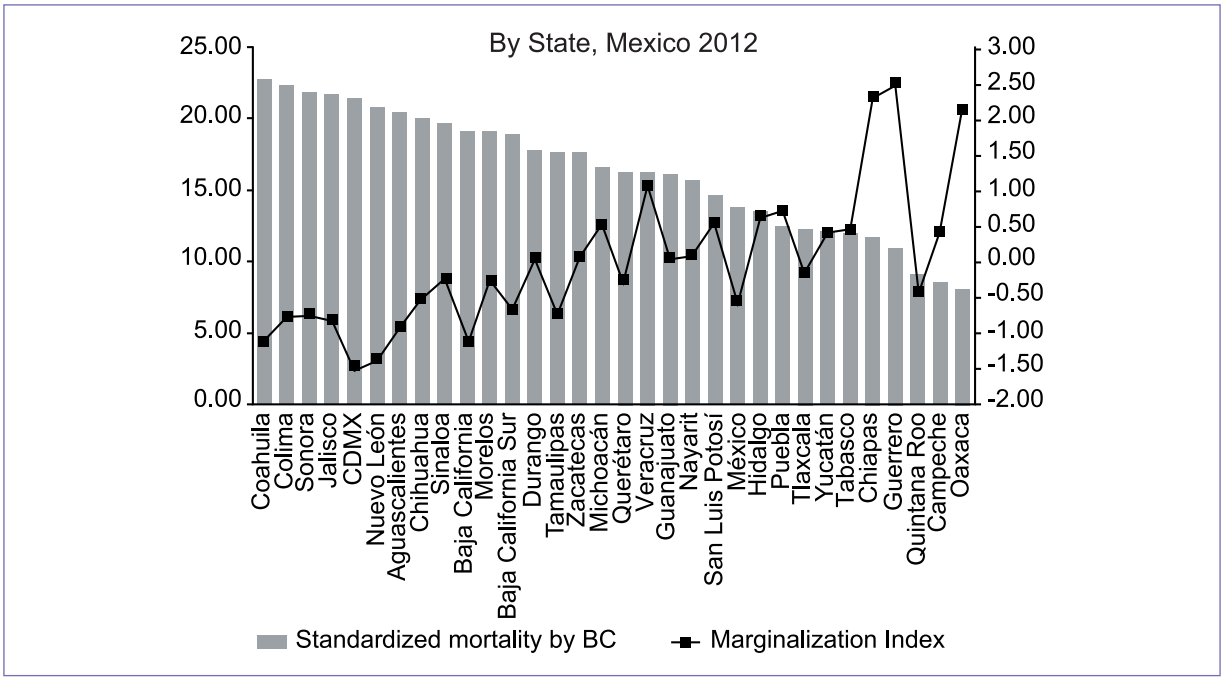


Figure 3. Breast cancer. Mortality and marginalization index in women aged 25 years or older, by State. Mexico 2004-2012.
Standardized mortality by BC Marginalization Index.
Source: Ventura-Alfaro CE. Salud Pública de México. 2016;58(2):194.

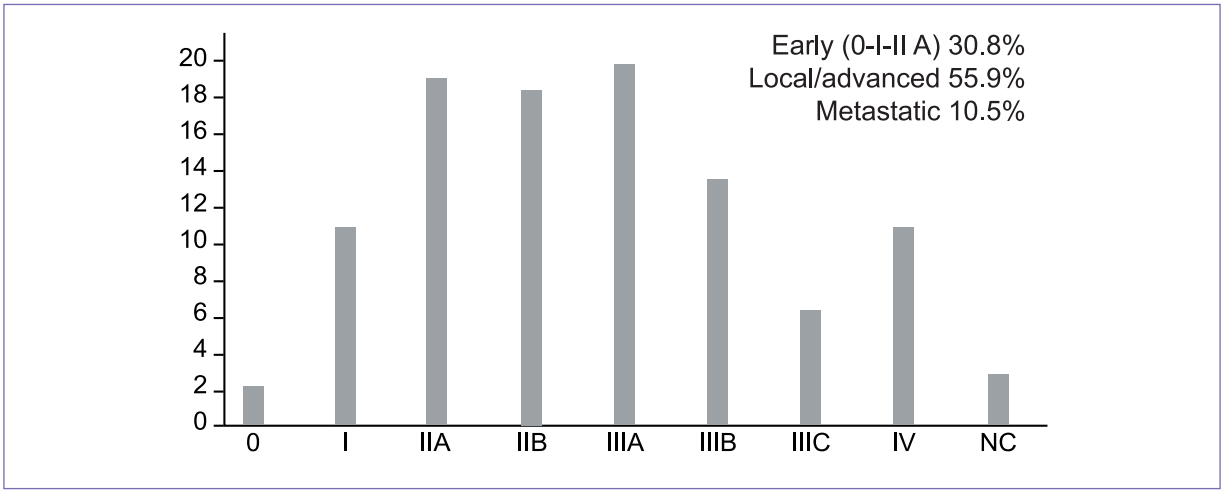


Figure 4. Stages at diagnosis at *Seguro Popular.*
Source: *Secretaría de Salud México. Seguro Popular. Informe sobre cáncer de mama,* 2015.

In addition, to promote primary prevention and timely detection, it is essential to include community leaders (government officers, teachers) in the programs, as well as training of first-contact doctors. Educational interventions can be implemented in community settings, including workplaces, primary care clinics, and schools.[5,6] Including the subject of oncology in the programs of medical faculties, and training medical students on breast cancer early detection is also suggested.

Inequalities in access to medical care for breast cancer are reflected on statistics about life years lost due to premature death and quality of life loss of due to disability, which is why specific and systematized actions should be implemented for risk factors identification, detection, early diagnosis and timely referral.[7]

2. Risk factors

Known risk factors for the development of breast cancer are the following:[3,7,8]

2.1 Biological

- Female gender.
- Advanced age.
- Personal or family history of breast cancer (in first-degree relatives).
- History of atypical ductal hyperplasia, radial or star image and lobular carcinoma in situ.
- Menstrual life longer than 40 years (menarche before 12 years and menopause after 52 years of age).
- Breast density.
- Being a carrier of mutations in breast cancer susceptibility genes.

2.2 Associated with the treatment of previous diseases

- Exposure to therapeutic ionizing radiation to the chest, mainly during development or growth.

2.3 Reproductive

- Nulligravida.
- No breastfeeding.
- First full-term pregnancy after 30 years of age.
- Hormonal therapy with combined estrogen and progesterone at perimenopause or postmenopause for more than five years.

2.4 Lifestyle-related

- Obesity.
- Sedentary lifestyle.
- Alcohol consumption.
- Smoking.[9-11]

The most important lifestyle-related risk factor is obesity and, given that in Mexico this condition is present in a very high percentage of the population, it represents a serious public health problem with high impact on society. Obese postmenopausal women are at higher risk for the development of breast cancer in comparison with non-obese women, which appears to be due to high levels of circulating estrogen. In addition, breast cancer survivors who develop obesity have a higher risk of recurrence or second primary tumors.[12-15]

A waist circumference larger than 80 centimeters is associated with an increased risk of breast cancer; on the other hand, menarche at an early age associated with states of morbid obesity is another important factor in the genesis of this pathology. Care of the obese patient should include dietary modifications, promotion of physical activity, components of behavioral change and long-term follow-up.[15]

3. General recommendations regarding physical activity

United States CDCs indicate:

- 150 minutes/week of moderate-intensity aerobic exercise (walking or bicycle riding)
- 75 minutes/week of vigorous-intensity aerobic activity (running, jogging, jumping, swimming)

Motivation is essential for achieving adequate treatment adherence and maintaining its effects in the long-term. Inclusion of physical activities in the community helps to prevent chronic diseases in general, and such activities are protective against breast cancer and, for this reason, their importance should be diffused via mass media (including social networks) to the entire population, with particular emphasis on high-risk populations.

IV. Breast cancer primary prevention

1. Risk-reduction therapy

The criteria applied in studies to consider high-risk women as candidates for chemoprevention include:[1]

- Age > 60 years.
- Age 35 to 59 years with 5-year risk ≥ 1.66 % in the Gail model for breast cancer.
- Age ≥ 35 years with a previous history of lobular or ductal carcinoma in situ, ductal or lobular atypical hyperplasia.
- BRCA-1 or BRCA-2 mutation carriers without prophylactic mastectomy.[2]

2. Pharmacological intervention

In women at high risk,[1,2] the use of the following agents is recommended:

- Tamoxifen at a dosage of 20 mg/day in pre- and postmenopausal women or raloxifene at a dose of 60 mg/day in postmenopausal women for a 5 year-period, based on the P-1 (NSABP), RUTH 4, MORE 4, CORE, STAR 2 and IBIS-I trials. Their use was shown to reduce the risk of invasive ductal carcinoma and they were approved for this purpose.[1,3-10] There are no randomized studies for patients younger than 35 years of age.
- Low-dose tamoxifen (5 mg every 24 hours for 3 years) in symptomatic patients with the 20-mg standard dose may be an option.[11]
- Aromatase inhibitors (AI) in postmenopausal patients. Exemestane (MAP-33 trial) and anastrozole (IBIS-II6) showed a reduction in the risk for invasive breast cancer.[12,13] These agents have not yet been approved by regulatory agencies for this indication.

To decide on the use of risk-reducing drugs, other factors that might contraindicate them should be taken into account; for tamoxifen, a previous history of thromboembolic events or atypical endometrial hyperplasia, and for an aromatase inhibitor, significant osteopenia or osteoporosis.

Surgical intervention: See Chapter X. Risk-Reducing Mastectomy (RMR).

V. Early diagnosis. breast assessment by imaging

1. Screening studies

General recommendations

- Monthly breast self-exam from 18 years of age on (7 days after menstruation conclusion).
- Annual breast clinical examination from 25 of age on.
- Annual screening mammography in asymptomatic women from 40 years of age on.[1]
- Breast ultrasound (US) is the initial study of choice in women younger than 35 years with breast pathology.
- The use of screening mammography in women with dense breasts combined with ultrasound increases sensitivity to 87 %.[2]

2. Imaging studies

The use of imaging studies such as mammography, ultrasound (US), magnetic resonance imaging (MRI) and, more recently, molecular studies, allows to detect, characterize and evaluate the disease and its extension, as well as breast lesions follow-up.

Histopathological study is the gold standard for breast cancer diagnosis. Percutaneous biopsies with core needle and aspiration systems with stereotactic or US guidance are the methods of choice for non-palpable and palpable lesions with suspected malignancy. In cases where the lesions are visible only by MRI or molecular studies, the biopsy will be carried out using these methods.

2.1 Mammography

Mammography is the only imaging method that has shown a 21 % reduction in breast cancer mortality; in high-income countries, organized, population-based screening has been observed to reduce mortality by more than 30 %.[3]

Mammography has a diagnostic sensitivity of 77 % to 95 %, and specificity of 94 % to 97 %, both being dependent on breast density.[4]

Although these data are significant, the decision to start and/or maintain a breast cancer program requires an evaluation of screening cost-effectiveness; mammography favors early diagnosis and the use of effective therapies against breast cancer, improves patient overall survival, and reduces the economic impact of life-years lost.

It is important to consider that screening mammography may cause over-diagnosis and unnecessary treatments (20 %), anxiety in women, and radiation-induced cancer (one in thousand screened women).[5]

Currently, there are different acquisition techniques in mammography:

- Conventional acquisition. The mammography device is analog and image acquisition is carried out with the screen-film system, which also includes an equipment for automatic development.
- Digital acquisition. Through detectors integrated to the mammography device itself (digital) or external detectors (digitized, CR); the study is printed with a high-resolution laser equipment.

2.1.1 Digital mammography

It uses a digital detector. Image acquisition, processing and visualization are handled independently, which represents a greater advantage with regard to the analog system; in addition, the percentage of repetitions due to constant image quality control is reduced, which results in higher productivity and lower ionizing radiation dose.

From the clinical point of view, digital mammography increases breast cancer detection in patients with dense breasts, which are a recognized risk factor for breast cancer, and can improve microcalcification visualization.[6]

Digital mammography has the capacity for advanced applications, such as:

- Telemammography. It is a tool that allows images to be sent for remote interpretation or consultation.
- Tomosynthesis or three-dimensional (3D) mammography. Multiple images are obtained from different angles; it improves breast cancer detection by 27 % and reduces the number of recalls in screening programs by 17.2 %.[7,8]
- Synthesized mammography. It is a technique that involves obtaining three-dimensional images and, based on them, obtaining two-dimensional reconstructions, whereby the radiation dose is reduced by 39 %. One of the advantages of synthesized mammography is that it improves the visualization of architectural distortions, masses and microcalcifications.[9]
- Stereotactic biopsy with tomosynthesis. When an architectural distortion is found, without ultrasound translation, the biopsy should be guided with a cutting-aspiration system and stereotaxy integrated with tomosynthesis, since these distortions generally correspond to invasive carcinomas.
- Computer aided detection (CAD) system. In general, these are systems that guide the detection of tumors in a medical image by acting as a second reader. In mammography, various methods for segmentation or extraction of the characteristics of mammary tumors have been designed. Evaluation of CAD systems performance in mammography indicates that their sensitivity is high, but also the number of false positives, which reduces their specificity.[10]
- Contrast-enhanced mammography. Functional study that combines conventional mammography with intravenous administration of contrast medium. There are two modalities: temporary and dual. Its purpose is to detect small-sized tumors, which allows the visualization of findings with contrast medium uptake on normal glandular tissue that shows no enhancement, which is highly useful in dense breasts and in patients with contraindications for magnetic resonance, or as an alternative to it with similar results.[11]

Regardless of the type of mammographic technique used, there should be a quality assurance program involving the physical area, the equipment and the personnel. The performance of breast studies should be carried out by trained radiological technical personnel and the interpretation be made by certified radiologists with experience in this area.

The mammography should be interpreted and the conclusion expressed using the BI-RADS system (Table 1).[9,12]

2.1.2 Diagnostic mammography

It is performed in case of a mammography with any detected anomaly and in the following situations:[14]

- Dense breast.
- Breast lesions detected with other imaging modality and that clinically require this study.
- Palpable mass or tumor.
- Blood-stained secretion from the nipple.
- Changes in nipple or areola skin.
- Focal, persistent pain.
- BI-RADS 3 follow-up.

2.1.3 Special indications for mammography

- Young woman with clinical suspicion of breast cancer, regardless of their age.
- Family history of breast cancer at early ages. Annual mammography will be indicated from 30 years of age on, or 10 years before the age of the youngest relative with cancer (not prior to 25 years of age). Annual contrasted MRI should be considered alternating with mammogram.
- Previous history of breast biopsy with histological report consistent with high-risk lesions.[15]

2.2 Breast ultrasound

Breast ultrasound (US) is a valuable tool, complementary to diagnostic mammography. It requires high-resolution devices, in addition to experience and knowledge on the anatomy and pathology of the mammary gland and its assessment by US. US should be performed with a high-frequency, broadband and variable focal zone (ideally between 10 and 23 MHz) linear transducer.[16]

Targeted US is the complement of diagnostic mammography owing to its usefulness to differentiate cystic from solid nodules, and out of these, benign from malignant lesions, vascularity status and elasticity of a tumor. It is useful in breast cancer initial staging, as it evaluates multi-finality, multi-centricity, extension or intraductal component, lymph node status of both the

Table 1. BI-RADS system[13]

Category		Recommendations
0	Insufficient for diagnosis. There is 13 % possibility of malignancy.	Evaluation with additional mammographic images or other studies (US) is required, as well as comparison with previous examination. This category should not be used as an indication for magnetic resonance imaging.
1	Negative No findings to report.	Annual mammography in women from 40 years of age on.
2	Benign findings	Annual mammography in women from 40 years of age on.
3	Probably benign findings. Less than 2 % likelihood of malignancy.	Unilateral imaging follow-up of the side with suspicious findings required at 6 months and subsequently annual bilateral for 2 years; this category is recommended only in diagnostic mammography.
4	Findings suspicious of malignancy. It is subdivided into: 4a - Low suspicion for malignancy 4b - Moderate suspicion for malignancy 4c - High suspicion for malignancy	4 (>2 - <95 %) 4a (>2 - ≤10 %) 4b (>10 - ≤ 50 %) 4c (>50 % - ≤ 95 %) Requires biopsy
5	Highly suggestive of malignancy	Requires biopsy. PPV > 95 %
6	With histological diagnosis of malignancy	Awaiting definitive treatment or treatment response evaluation

Source: American College of Radiology. Mammography, 5th ed., 2013.

axilla and supra- and infra-clavicular and parasternal regions, which can determine treatment changes by up to 28 %.[17]

Screening US is indicated in patients with dense breasts and negative mammography.[17,18]

Clinical indications for breast ultrasound

- Assessment of palpable anomalies and those detected by mammography and MRI.
- Evaluation of breast implants.
- Guide for interventional procedures.
- Radiotherapy treatment planning.
- Assessment of axillary lymph nodes.

In women with dense breast tissue, screening US can detect mammographically occult carcinomas (1.9 to 4.2 additional cancers per 1,000 examined women).[19,20] Numerous studies have shown that, in these cases, US additionally demonstrates two to five occult carcinomas per 1,000 women. Usually, tumors that are occult in mammograms and are detected by US are invasive and lymph node-negative. Breast density is an important factor in the detection and diagnosis of breast carcinoma, since it decreases its sensitivity; in addition, it represents a significant increase in the risk for developing this pathology (4.7 times higher than in women with fatty breasts). Some MRI-detected lesions are mammographically occult, but can be found by targeted US (second deliberate examination); this recommendation is also valid for molecular studies.

Breast US extended vision modality is useful for measuring large lesions and assessing multifocality.

The role of the radiologist in breast cancer staging is to demonstrate, before a surgical procedure, the presence of axillary metastases with a positive predictive value that is high enough to allow the surgeon to decide when to perform axillary dissection. The presence of axillary metastases and the size of the primary tumor are two prognostic factors for evaluating patients with invasive breast cancer and determine the use of systemic chemotherapy and radiotherapy. In patients with T1 and T2 and negative lymph nodes, sentinel lymph node procedures should be performed.[21]

US is the basic tool for evaluating axillary lymph nodes; it has a moderate sensitivity, but can be highly specific, especially when morphological criteria suggest compromise.

Findings such as fatty hilum loss and peripheral vascularity are more important criteria than lymph node size for identifying metastases. Focal or diffuse cortical thickening is considered the earliest sign to identify them, but it is a difficult-to-apply criterion that has a low predictive value because it is not specific. It can be subjectively or specifically evaluated by measuring cortical thickness, which should be thinner than 3 mm.[22]

Lymph nodes with suspicious morphology on imaging should undergo fine-needle aspiration biopsy (FNAB) or core needle biopsy to avoid anesthetic risk, surgical time, and increased cost. FNAB has a reported diagnostic sensitivity of 25 % to 87 %; core needle biopsy, from 90 % to 94 %.[23]

2.3 Magnetic resonance

Complementary method to mammography and ultrasound. It does not use ionizing radiation and provides morphological and functional information, through intravenous administration of paramagnetic contrast medium (gadolinium); it requires a scanner of at least 1.5 tesla and a special antenna for the mammary gland.

Magnetic resonance imaging has a sensitivity of 90 % and a specificity of 89 %.

Multiparametric evaluation must be carried out: it includes perfusion curves, spectroscopy and diffusion, which increases specificity of the method.[24]

Kinetic evaluation (perfusion curves) of the observed lesions measures contrast uptake, within the lesion, over a period of time. Signal intensity (SI) increases after contrast administration (SI Post); it is measured in comparison with pre-contrast level (SI Pre); by relating the signal time and intensity, curves are generated that provide information about the vascular properties of the lesion. Three types of curves are generated that consist of two stages; the initial one, which can be slow, moderate or fast, and the delayed stage that can be continuous (type I), which is considered in more than 90 % of benign lesions, plateau (type II), considered indeterminate, or washout (type III), which is the most common in malignant lesions.[15]

MRI has a higher number of false negatives in tumors smaller than 3 mm, as well as in low-grade carcinoma in situ and in lobular carcinoma, and, therefore, for an accurate diagnosis, integration of morphological and functional characteristics together with mammography and US findings is essential.

Specificity of this method is increased with the spectroscopy technique (virtual biopsy), which allows the quantification of choline, a cell-proliferation tissue marker that provides biochemical information of tissues. Another technique is diffusion, which is based on the movement of water molecules within the tissue and is useful in the differentiation of benign and malignant lesions. The use of gadolinium in pregnant women is contraindicated.

The conclusion and recommendations should be expressed using the BI-RADS system.

Indications for contrasted magnetic resonance imaging:

- Breast cancer staging.
- Assessment of margins after primary tumor excision.
- Local recurrence (with an interval of 6 months after surgical management and one year post-RT).
- Treatment response.
- Search for occult primary tumor with axillary metastases.
- Screening in patients with high risk and dense breasts, alternating with mammography and US. This study is also indicated in patients with genetic risk of hereditary breast cancer, since sensitivity and specificity for this group is 91 % and 97 %, respectively; an abbreviated protocol is recommended, which reduces costs and acquisition time, with a high predictive positive value.
- Guide for biopsies of lesions that are visible only with this method and not corroborated in a second US deliberate examination.
- Routine preoperative use of MRI to evaluate disease extension is not recommended because it has not shown to improve overall survival or to decrease re-excision rates or reduce costs.
- Non-contrasted MRI is indicated in breast implants integrity evaluation, particularly with suspected intracapsular rupture or other complications.[25,26]

2.4 Molecular studies of the breast (PET and PEM)

Positron-emission tomography (PET) and positron-emission mammography (PEM) are imaging studies that are not only morphological but functional, which evaluate malignant tumors molecular activity by intravenously injecting a radiotracer, generally 18-fluorodeoxyglucose, although there are increasingly more tracers available on the market, with an increase in specificity.

PET-CT combines computed tomography (CT) and nuclear medicine, with precise localization of the primary tumor, as well as distant metastases, treatment response evaluation, follow-up and re-staging; it has a spatial resolution of 1.7 mm, and semi-quantitative uptake units are referred to as SUV and should not exceed 2.5; qualitative comparison is also carried out by comparing the uptake with other organs.

PEM uses a compact device, where the detectors are above and below the mammary gland, which is why it has great spatial resolution, which in turn allows

detecting lesions as small as 1.2 mm; it provides images in projections similar to mammography, after intravenous injection of half the dose of radiotracer that is used in PET-CT. It has similar sensitivity to contrast MRI, but higher specificity; its main indication is breast cancer locoregional staging, as well as if breast-conserving surgery is planned, for axillary evaluation, treatment response, and detection of recurrences, and it is useful in augmentation mammoplasty and suspected CA. This imaging method is not affected by breast density and is not limited by recent post-surgical changes.

There may be false negatives in small carcinomas with poor metabolic activity, low nuclear grade, cancer in situ, and infiltrating lobular cancer, similar to MRI.

Both studies (PET and PEM) can be simultaneously performed with the PET-CT dose; it is highly useful in endocrine tumors such as endometrium, thyroid, colon, and ovary tumors, where they can be associated with breast cancer (double primary tumor).[27,28]

VI. Image-guided interventional procedures (breast and lymph node chains)

1. Introduction

Until a few years ago, excisional biopsy, after marking with percutaneous needle, was the only diagnostic tool in clinically non-palpable lesions. Currently, core needle biopsy has become a diagnostic evaluation tool in non-palpable breast lesions that avoids excisional biopsies in benign cases, brings down costs and reduces risks for the patient, with minimal changes of breast tissue that might alter follow-up in subsequent mammograms.

In cases of malignant neoplasms, it allows the surgeon to plan therapeutic alternatives together with the patient. A guiding method whereby the lesion is best visualized should be selected: microcalcifications by mammography with a stereotactic system and, recently, with tomosynthesis, which is highly useful in architectural distortions; the mass or nodule mainly by US guidance and less frequently in cases in which the suspected lesions are only visualized on MRI or positron emission mammography (PEM). Image-guided biopsy increases diagnostic accuracy, including cases of palpable tumor.[1]

2. Indications for biopsy

Suspicious lesions categorized as BI-RADS 4 and 5:
- Suspicious microcalcifications.
- Focal asymmetry.
- Asymmetry development or changes in a previously-existing lesion detected on mammographic follow-up.
- Architectural distortion, a radiological sign that is best characterized by tomosynthesis and that represents invasive cancer in most cases.

Placing a marker at the biopsy site is recommended.

Corroboration of microcalcifications extraction is carried out with mammographic control of the fragments, prior to referral for histopathological study.

2.1 Aspiration biopsy (cytology)

It is performed with percutaneous sampling of suspicious lesions, with a fine needle of 22 to 25G gauge for cytological diagnosis; it is low-cost, in addition to having adequate sensitivity and specificity; it is limited by the need for experience of both the radiologist who performs it and the cytologist who interprets it. Currently, the use of cytology, mainly in the evaluation of axillary lymph nodes with morphology changes, contributes to decision-making in the multidisciplinary management of patients.

FNAB sensitivity for axillary lymph node metastases varies depending on the suspicion prior to the procedure:
- 11 % for morphologically normal lymph nodes (< 3 mm uniform cortex).
- 44 % in indeterminate lymph nodes (> 3 or < 3 mm uniform cortex with focal thickening).
- 93 % for suspicious lymph nodes (focal thickening and > 3 mm cortex and/or fatty hilum loss).
- Global sensitivity ranges from 25 % to 86.4 %, specificity from 81 % to 100 %, false negative (FN) rate from 3.7 % to 19 % and false positive rate is 0.68 %. Positive predictive value (PPV) ranges from 64 % to 100 %, and negative predictive value (NPV), from 59 % to 80 %.
- Marking of cytologically-reported metastatic lymph nodes provides a better evaluation of the pathological response after neoadjuvant chemotherapy, to find out if there is residual disease.

2.2 Core needle biopsy (histological)

It is the ideal method for non-palpable lesions diagnosis; it is performed under local anesthesia, and is a well-tolerated, ambulatory procedure with minimal complications.

In lesions categorized as BIRADS 4 and 5, either nodules or microcalcifications, there is the alternative of stereotactic or US-guided biopsy with vacuum-assisted cutting systems; the latter is essential for microcalcifications.

Microcalcifications extraction is corroborated with mammographic control of the fragments, prior to histopathological examination.

Surgical biopsy is required for diagnostic and therapeutic purposes when in the core needle biopsy and/or vacuum-assisted core biopsy histopathological result there is no correlation between imaging and pathology or when histopathological study considers excision.

Radiological control of the operated breast is necessary in a 6-month period.

In all cases, the correlation between imaging and pathology results should guide treatment; breast cancer management multidisciplinary groups shall have a systematic working method that enables clinician, radiologist and pathologist correlation.

Placing a marker at the biopsy site at the end of the procedure is recommended.

The use of neoadjuvant CT in lymph node-positive (N1) breast cancer diagnosed by percutaneous biopsy reduces axillary disease by 55 %, which is why leaving a marker in the lymph node is recommended.[2,3]

VII. Histopathological study

1. Recommendations for conservative surgery specimen handling and report

1.1 Intraoperative indications

- Surgical margins status.
- Sentinel lymph node.

1.2 Specimen handling

- The specimen should be referred with radiological study.
- Margins (6) referred with silk suture, beads or staining (ideally stained by the surgeon).
- The surgical specimen should be received intact (without any type of manipulation or section).
- The specimen should only be sectioned by the pathologist (Table 2).
- Surgical margins perpendicular sections (for ductal carcinoma in situ, a surgical margin is regarded as negative when it is ≥ 2 mm apart).[1] If it is less than this distance, it should be specified in the report.
- Serial sections of the specimen with a thickness of 3 to 5 mm.
- Include the sections in a serial and ordered manner. If the specimen has a wire marker, refer the number of capsules where the marked lesion is located.
- Including the totality of tissue marked by the wire plus 1 cm of its periphery is recommended, as well as representative samples of the remaining tissue.
- Indicate the list of sections in the gross description.

2. Recommendations for infiltrating breast carcinoma histopathological report

This Consensus recommends the AJCC 2018 protocol (eighth edition) for examination of breast cancer patients' specimens.[2] The diagnostic parameters we consider to be essential in the histopathology report are:

2.1 Type of specimen and anatomical location

2.1.1 Macroscopic parameters

- Specimen weight and size.
- Tumor size on its three dimensions.
- Type of margins: infiltrating and non-infiltrating.
- Tumor distance from margins and surgical bed (the margins should be referred by the surgeon preferably with colored stains).[3]

2.1.2 Microscopic parameters

Histological type

Histological type diagnosis should adhere to the criteria of the WHO Classification of Breast Tumors, 5th edition.[4]

In case different patterns are observed, specify the percentage of each one of them.

Medullary carcinoma, oncocytic, rich in lipids, rich in glycogen, with clear cells, sebaceous differentiation, neuroendocrine differentiation, carcinoma with giant cells of the osteoclast type, pleomorphic, with achoriocarcinoma differentiation and with a melanocytic pattern cease to be histological variants and become morphological patterns of non-special-type (NST) invasive carcinoma.[4]

Two subtypes are added: mucinous cystadenocarcinoma and tall cell carcinoma with reverse polarity.[4]

Neuroendocrine neoplasms are divided into neuroendocrine tumors and neuroendocrine carcinoma.[4]

Table 2. Criteria for the selection of the type of biopsy

Type of biopsy	Type of lesion	Needle caliber
FNAB	– Cysts. – Axillary lymph nodes. – Not recommended in breast primary tumor.	– 22-25 G
Core needle biopsy	– Solid lesions.	– 11 and 14 G are the most widely used
Automated vacuum-assisted stereotactic or ultrasound-guided core needle biopsy	– Suspicious calcifications, stereotactic biopsy – Focal asymmetries and architectural distortions only visible in tomosynthesis with negative US, biopsy with integrated stereotaxy and tomosynthesis is suggested. – Complex nodule, ultrasound guidance	– 8 to 14 G – Al least 8 samples; this number will depend on lesion type and size
Surgical biopsy	· Lesions that cannot be percutaneously biopsied (technical limitation), discordant previous core needle biopsies	

Histological grade

Variants should be graded with the Scarff-Bloom-Richardson (SBR) grading system, as described below:

– Tubule formation
  - Score of 1: 75 % or more of the tumor composed of tubules.
  - Score of 2: 10 % to 75 % of the tumor composed of tubules.
  - Score of 3: less than 10 % of the tumor composed of tubules.

– Nuclear grade
  - Score of 1: small, uniform nucleus, dense chromatin.
  - Score of 2: nucleus with moderate variation in size and shape; pootly apparent nucleolus can be observed.
  - Score of 3: nucleus with marked increase in size, irregular shape and contour, 2 or more prominent nucleoli, thick chromatin.

– Mitotic count
  - Score of 1: ≤ 12 mitoses per 10 HPF.
  - Score of 2: 13 to 24 mitoses per 10 HPF.
  - Score of 3: ≥ 25 mitoses per 10 HPF.

The mitotic parameter herein referred is given for a field diameter of 0.65 to 40X in 10 fields, for another diameter, consult the objective conversion table in reference 4.[4]

The three above-mentioned parameters and the final score shall be reported separately to determine the histological grade, which will be as follows:

– Grade I: 3 to 5 points.
– Grade II: 6 to 7 points.
– Grade III: 8 to 9 points.

In the presence of canalicular carcinoma in situ or lobular carcinoma in situ, mention the type and percentage.

Lymphovascular permeation is assessed in peritumoral tissue.

Infiltration to the skin, nipple and areola (papillary, reticular, ulcerated dermis) and muscle.

Tumor-infiltrating lymphocytes (TILs) assessment will be carried out following the International TILs Working Group 2014 recommendations.[5,6] This parameter is of mandatory reporting in triple-negative carcinoma and in the HER-2 neu group, since currently it is considered a strong prognostic and predictive factor.[7]

2.2 Definitions and general concepts

It is well known that malignant neoplasms are antigenic and can cause an immune response, due to the altered protein products they produce and that can be recognized by our immune system as foreign elements. The elements that are released due to the immune response have a prognostic and predictive role in many solid neoplasms.

Lymphocytes that infiltrate tumors, known in the universal literature as TILs (tumor-infiltrating lymphocytes), have acquired great importance as biomarkers, which may indicate the use of immunotherapy treatments in cancer. Therefore, using them routinely in certain neoplasms is advised.

Currently, several guidelines or recommendations are available for the correct evaluation of TILs, which will be described in this consensus.[8]

2.3 Host immune response

The protein products generated by cancer cells, due to the genetic mutations they undergo, act as neo-antigens and become "foreign" cells. In addition, the hypoxic and necrotic microenvironment of neoplasms send signals of harm to the immune system.

Immune cells that infiltrate neoplasms can promote their growth and progression, but also can create an immunosuppressive environment where the neoplasm develops. CD8+ cytotoxic T-cells, interferon-γ-producing T-helper cells, and natural killer cells are generally associated with favorable antitumor immune responses, along with macrophages with the M1 phenotype and dendritic cells (Table 3).

Table 3. Immune cells present in tumor microenvironment

Tumor suppression	Tumor progression
M1	T-regulatory cells
NK cells	M2
NK T-cells	Type 2 dendritic cells
N1 cells	N2 cells
CD8+ T-cells	Th2 cells
Type 1 dendritic cells	Myeloid cells
Th1 cells	
Tfh cells	

2.4 TILs evaluation in invasive carcinoma of the mammary gland

Most breast carcinomas show some amount of lymphoid infiltrate, there are even carcinomas that are rich in this infiltrate, which are neoplasms occupied by TILs in an area > 50 % or 60 %. The breast carcinomas that generally show the aforementioned characteristic correspond to the group of triple-negative (20 %) and HER-2+ carcinomas (16 %). Only 6 % of luminal carcinomas show this characteristic.

Several meta-analyses have confirmed that high levels of TILs are associated with better disease-free survival and overall survival, only in the triple-negative and HER-2+ subtypes.

Table 4. Guidelines for TILs evaluation in invasive breast cancer

Stromal compartment TILs should be evaluated separately from the tumor compartment and each item reported appart.
Exclude TILs that are outside the invasion margin (adjacent stroma, perilobular stroma, etc.).
Areas that show artifacts, necrosis or tumor regression areas (hyaline areas) should not be taken into account.
The count should take lymphocytes and plasma cells into account, but not polymorphonuclear cells.
With one section (4-5µ, magnification: x200 to 400), if necessary, several sections can be evaluated, e.g., in cases of intratumor heterogeneity
Tumor sections are preferred, instead of core needle biopsies.
Evaluate the entire tumor area (central and infiltrating margins), avoid sites where a higher number of lymphocytes are concentrated ("hot spot")
TILs should be evaluated as a continuous variable; this provides more relevant biological information (%).
To evaluate the percentages of lymphocytes, their growth pattern separately or in small groups, the fact that the % of stromal TILs is a semi-quantitative parameter should be taken into account, e.g., 80 % of stromal TILs means that 80 % of the stromal area shows a dense mononuclear infiltrate.

2.5 Interpretation of TILs present in breast carcinoma

To evaluate TILs, we must know some concepts:

TILs or lymphocytes that infiltrate carcinomas are located in the area that separates the tumor margins from host tissue, in an extension of 1 mm. Thus, there are two compartments: the central portion of the tumor and the invasion margin.

The guidelines that shall be taken into account for TILs interpretation in invasive carcinoma are shown in Table 4.

2.6 Intra-tumor lymphocytes (TILs) evaluation in intraductal carcinoma

In comparison with invasive carcinoma, less information is available regarding the lymphoid infiltrate associated with intraductal carcinoma (IDC). Some studies suggest that IDC-associated TILs are related to certain clinical-pathological characteristics and disease progression, but have no prognostic significance. Pruneri et al.[9] reported, in a series with numerous cases, the association between stromal TILs with intraductal carcinoma grade, patient age and presence of comedo-necrosis. The already-mentioned characteristics were

observed more often in HER-2+ intraductal carcinomas. No relationship was observed with the percentage of recurrence. In this study, the method that was used was similar to that already described for invasive carcinoma, with specific modifications for intraductal carcinoma.

The methodology used by some authors is the following:

- Touching TILs: the thickness of a lymphocyte that is in contact with the duct's basement membrane is taken into account, 20 ducts are counted and divided into the following groups: < 5 lymphocytes per duct: negative; scant (6 to 20 lymphocytes per duct) and dense (> 20 lymphocytes per duct).
- Stromal TILs: periductal stromal area around the duct in two fields at higher magnification and relative to the margin. Low: < 5 TILs; and high: > 5 TILs.
- Circumferential or nearly circumferential (> 75 % of circumference): ducts surrounded by lymphocytes and plasma cells, at least three layers thick. Classification: present or absent.

2.7 Links for tutorials

- TILs and Breast Cancer. International Immuno-Oncology Working Group
- Supplemental Digital Content 1, http://links.lww.com/PAP/A13
- Supplemental Digital Content 2, http://links.lww.com/PAP/A14
- Supplemental Digital Content 3, http://links.lww.com/PAP/A15
- Supplemental Digital Content 4, http://links.lww.com/PAP/A16

2.8 Microcalcifications

- Report the presence of microcalcifications and the entity they are associated with in core needle biopsies, stereotactic biopsies and breast-conserving surgery specimens.

2.9 Other associated entities

- Hyperplasia, columnar cells, microglandular adenosis, etc.

2.10 Axillary dissection

- Specify total number of dissected lymph nodes.
- Number of lymph nodes with metastasis.
- Size of dissected lymph nodes.
- Capsular rupture and periganglionar soft tissue infiltration by neoplastic cells.

3. Recommendations for post-treatment specimens report

To perform a complete evaluation and guide post-treatment specimen sampling, the pathologist should have the following information (Table 5).[10,11]

The microscopic findings that can be observed in breast tissue and lymph nodes are summarized in Table 6.

4. Histopathological report of high-grade precursor lesions and breast carcinoma in situ

4.1 Recommendations

For intracystic papillary carcinoma and related papillary neoplasms histopathological report, the following should be taken into account:[12]

- Diagnostic criteria (Table 7).
- When there are invasion foci in intracystic papillary carcinoma, only the size of the infiltrating component should be reported for staging purposes.
- Establishing papillary neoplasms definitive diagnoses with intraoperative core needle biopsy and aspiration biopsy is contraindicated.

4.2 Lobular carcinoma in situ

It can be associated with tubular carcinoma, infiltrating lobular carcinoma, and columnar cell lesions, usually flat epithelial atypia (Rosen triad).[13]

The diagnosis of columnar cells as a precursor lesion can be performed following the flow chart shown in Figure 5.[1,14]

- Columnar cell lesions
  - TDLU: Acini with variable dilatation
  - Lined by columnar epithelial cells

4.3 Triple-negative carcinoma and association with microglandular adenosis

Microglandular adenosis (MGA) is considered a benign ductal proliferation, but in 27 % of cases there is a significant risk for the development of basal-type invasive or in situ carcinoma (triple-negative). Therefore, MGA detection and certainty diagnosis are important and include the following IHC panel: S-100 positive, ER

Table 5. Handling of surgical specimen with neoadjuvant treatment

	Breast-conserving surgeries < 5 cm or < 30 g specimens	**Breast-conserving surgeries < 5 cm or > 30 g and mastectomy specimens**	
	Specify if neoadjuvant treatment has been received, used regimen, duration. Initial TNM staging with an emphasis on clinical or radiological size, specify multifocality.		
Clinical data in the request	Data from initial biopsy report (histological grade, subtype, molecular profile, cellularity) Specify whether or not there is marking at previous biopsy site and location Clinical or radiological suspicion of pathological complete response It is recommended for the radiologist and surgeon to place a metal clip before treatment, in order to ensure tumor bed identification.		
Fixation	Usual, preferably receiving fresh to make sections, 10% buffered formalin. Maximum 24 hours		
Sections	After borders' staining, on medial-lateral direction, perform 3-mm-thick sequential sections.	After margins' staining. On medial-lateral direction, perform 1-mm-thick sequential sections.	
Schematization	List of sections specified by macrophotography, drawing, photocopy, radiographic plate.		
Sections	Usual surgical technique	Include representative borders in perpendicular direction	Inclusion of borders as usual, in perpendicular direction
	Second stage margin enlargement surgical technique	Include borders in perpendicular direction. Assess whether representative are included or comprehensively	
Inclusion of sections	With visible macroscopic tumor Without visible macroscopic tumor	Include comprehensively with residual tumor emphasis Include comprehensively	Include residual neoplasm, at least 5 blocks, and the rest in alternating sections (2 for each section) with a maximum of 25 blocks Include 2 blocks for each section, aligned with emphasis on areas of hemorrhage and fibrosis, with a maximum of 25 blocks
In case of clinical or radiological suspicion of complete pathologic response	Total inclusion	Include two cuts for each section alternately, up to a maximum of 25 blocks and individualize if full inclusion is required.	

negative and p63 negative, type IV collagen to visualize the basement membrane.[15,16]

4.4 Recommendations for ductal carcinoma in situ report

- Anatomical-radiological correlation
  - Mammography of the specimen (microcalcifications, density alteration).
- Tumor size
  - Multiply the number of tissue slides with tumor by 4 mm (thickness of the section for inclusion).
  - Measure the largest diameter in the tissue slide, when it is a single focus.
  - The size of the tumor will be taken as the largest of the two previous measurements.[17,18]
- Grade
  - Nuclear grade
    - Grade 1
      - Monotonous nuclei.
      - 1.5 to 2 times the size of an erythrocyte or the nucleus of an epithelial cell.
      - Diffuse chromatin.
      - Occasional nucleoli and mitosis.

Table 6. Post-chemotherapy histological changes in breast tissue and lymph nodes

Histopathological findings	Recommended report
Stromal changes: architectural partial obliteration, fibrosis and histiocytic infiltrate. Nuclear changes: nucleomegaly, nuclear irregularity, multinucleation, chromatin vacuolization, occasionally decrease in nuclear grade. Cytoplasmic changes: abundant, vacuolated, eosinophilic, or gray bluish cytoplasms. Residual tumor can be observed as: isolated tumor cells, tumor groups or as small well-defined glands with nuclei without atypia.	Total number of lymph nodes. Number of lymph nodes with treatment-related changes without viable carcinoma. Number of lymph nodes with metastasis. Larger diameter of the metastatic focus (classification of micro, macro or isolated group of cells should not be used). Extracapsular extension: present (longest diameter), absent, indeterminate. Complete response: Absence of viable carcinoma cells, fibrosis, and foamy macrophage clusters. In some cases, the use of IHC is recommended to identify residual neoplastic cells.

Table 7. Recommendations for papillary neoplasms histopathological report

	CK 5/6
Papillary carcinoma Encapsulated or intracystic	Negative
Solid papillary carcinoma – In situ – Invasive	Negative
Intraductal papilloma – Atypical (area of atypia ≤ 3 mm, focus ≥ 3 mm is considered DCIS-associated papilloma) – With DCIS – With LCIS	Positive (mosaic pattern) Negative in carcinoma areas
ER	**p63, AML or calponin**
Intense positive	Absent in tumor periphery and center
Intense positive	Absent in tumor periphery and center Present in lesion periphery and center
Weak and focal positive	Present in lesion periphery and center Negative in carcinoma areas

CDIS: carcinoma ductal *in situ;* CLIS: carcinoma lobulillar *in situ*; RE: receptores de estrógeno; AML: actina de músculo liso.

- Cell polarization.
- Grade 2
  - Moderate pleomorphism.
  - 2 to 2.5 times the size of an erythrocyte or the nucleus of an epithelial cell.
  - Fine to coarse chromatin.
  - Evident nucleolus and scant mitoses.
- Grade 3
  - Marked pleomorphism.
  - More than 2.5 times the size of an erythrocyte or the nucleus of an epithelial cell.
  - Prominent nucleoli.
  - Abundant mitoses.
  - Absent or present necrosis.

– Architectural patterns
- Comedo.
- Cribriform.
- Papillary.
- Micropapillary.
- Solid.

– Rare variants
- Apocrine cells.
- Hypersecretory cystic.
- Mucocele type.
- Signet ring cells.
- Small cells.
- Squamous type.
- Spindle cells.

– Papillary lesions
- Complex or atypical papilloma.
- Papilloma complicated with carcinoma in situ.

– Surgical margins
- Specify the distance between the closest ductal carcinoma in situ (DCIS) focus and the stained margin. If positive, report whether they are focal or diffuse (a surgical margin is considered negative for ductal carcinoma in situ when it is > 2 mm away).[1]

– Microcalcifications
- Associated with carcinoma in situ.
- Adjacent to the area of carcinoma in situ.

– Other parameters

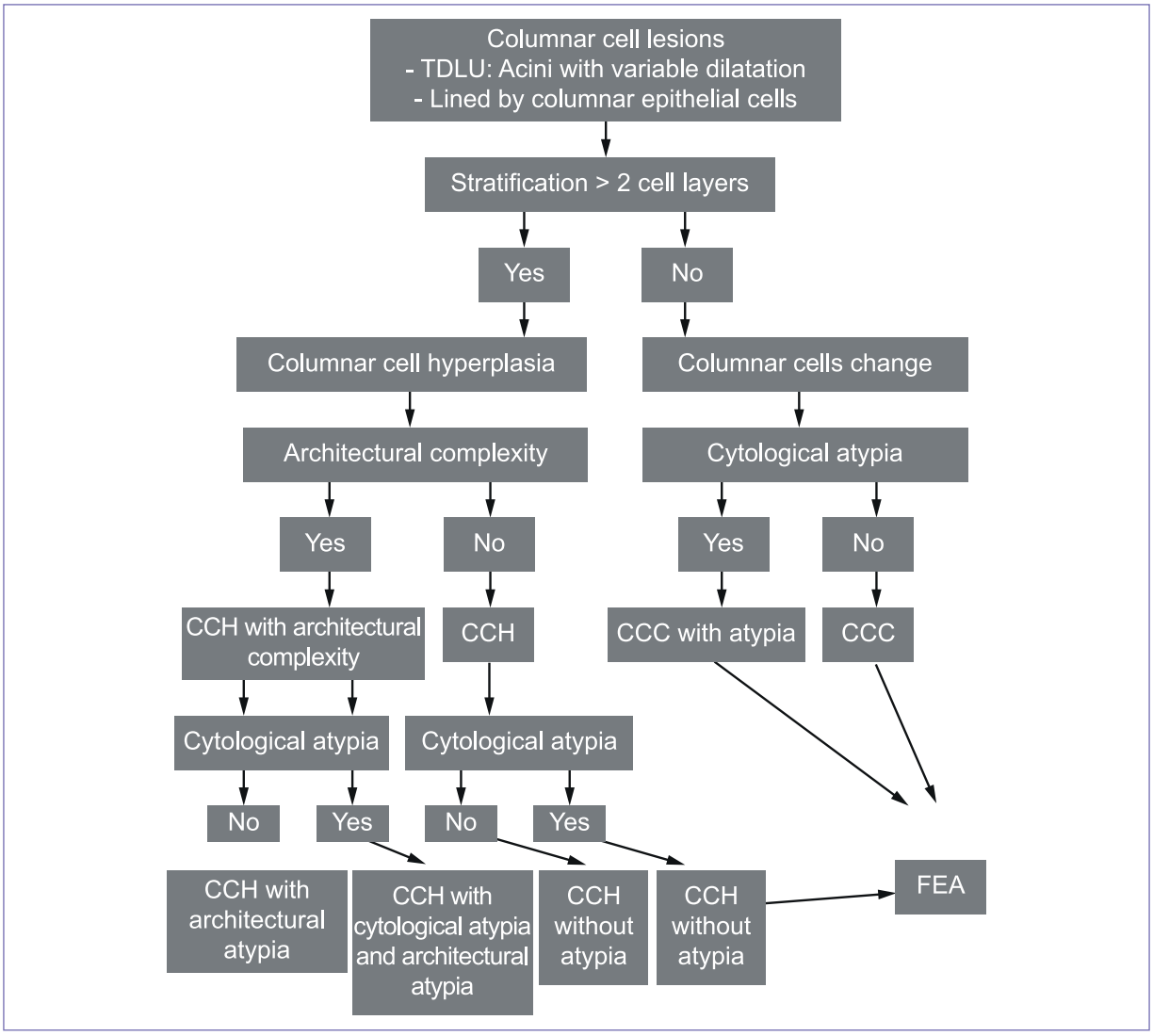


Figure 5. Diagnostic algorithm for columnar cell papillary lesions.
CCH: columnar cell lesions; TDLU: acini with variable dilatation; Lined by columnar epithelial cells.

- Determination of hormone receptors with a report that must include the percentage of positive neoplastic cells. In the consensus, HER-2 neu determination was not considered relevant for ductal carcinoma in situ; however, it can be carried out for research purposes.

– Microinvasive carcinoma

- The term "microinvasive carcinoma" refers to the presence of DCIS, in which there is rupture of the basement membrane, in one or more foci, of up to 1 mm. It is generally associated with high-grade intraductal carcinoma and much less frequently with lobular carcinoma in situ.

5. Recommendations for sentinel lymph node histopathological report

Sentinel lymph node (SLN) evaluation includes:

– Intraoperative procedure:[19,20]

- Lymph node serial longitudinal sections with a thickness of 2 mm.
- Cytological evaluation by apposition or imprinting of each side.

Ten definitive, serial paraffin-embedded sections, with an interval of 200 microns[21] and IHC (cytokeratins AE1/AE3), in section number 5, only in selected cases or with lobular carcinoma.

– Histopathological report

Table 8. Buffered formalin formula (pH ~6.8)

Pure formalin	1 liter
Distilled water	9 liters
Monobasic sodium phosphate	40 grams
Dibasic sodium phosphate	65 grams

- Lymph node negative for metastases by hematoxylin-eosin (H-E) and IHC.
- Positive lymph node with macrometastasis (metastases larger than 2 mm).
- Positive lymph node with micrometastases of 0.2 mm to 2 mm in largest dimension. Report if they were detected by H-E or IHC.
- In case of several metastatic foci, the largest should be taken into account.
- Positive lymph node with isolated tumor cells (single cells or small nests not larger than 0.2 mm). Report if they were detected by H-E or IHC.[22]
- Report capsular rupture and adipose tissue extension size.[22]
- Up to six dissected lymph nodes are considered sentinel.

6. Recommendations for breast tumor fine needle aspiration biopsy (FNAB) report

The Consensus does not recommend making therapeutic decisions based on primary tumor cytopathological diagnosis.

7. Recommendations for axillary lymph node with possible metastasis FNAB report

– Positive for metastasis.
– Negative for metastasis.
– Insufficient for diagnosis.

8. Recommendations for the report of prognostic-predictive factors by immunohistochemistry

Hormone receptors (estrogen and progesterone) and HER-2 oncoprotein and ki67 overexpression are essential prognostic and predictive factors in breast cancer, which is why these markers should be determined in all patients with this diagnosis.[23,27,28]

8.1 Tissue handling

10% buffered formalin should be used as fixative (Table 8).

The tissue should be placed as quickly as possible in the fixative, less than 15 minutes after obtaining it.

Tissue should be sectioned in 2- to 5-mm thick sections for inclusion, and in the case of core needle biopsy, including two cylinders per capsule is recommended owing to breast cancer recognized heterogeneity.

The ratio of sample volume to fixative should be 20 to 1.

A minimum fixation of 6 hours and a maximum of 48 hours is recommended. To avoid prolonged fixation, switching to buffer solution before 48 hours have elapsed is desirable.

Accelerating the histological processing technique using heat (stove, microwave oven, etc.) is not recommended.

Intra-tumor heterogeneity is related to tumor genetic instability and to the development of different clones within the tumor,[24] which is why the immunohistochemical study should be repeated in the following situations:

– In case initial biopsy tissue is scarce
– Carcinomas with histological grade variation and/or morphological disparity between initial biopsy and surgical specimen
– In case of multicentricity/multifocality with different histology
– High histological grade carcinomas
– Bilateral tumors, with different histology
– In metastases and recurrences
– In mastectomy-dissected tumors that showed no response to neoadjuvant treatment, with unexpected evolution or that were triple-negative at onset.
– When HER-2 evaluation is not possible in the initial biopsy due to poor fixation artifacts, it should be repeated in the surgical specimen.
– When staining in the core needle biopsy is heterogeneous and shows strong positivity foci in <10 % of the invasive carcinoma area

Preferably, initial biopsy result should be reassessed together with the mastectomy in order to compare immunomarking expression and report it in the diagnosis.

8.2 Interpretation criteria

The following guidelines decrease the likelihood of misinterpretations:[25]

– Validated antibody clones should be used.
  • Clones for estrogen receptors: 1D5, 6F11, SP1, 1D5+ER.2.123.
  • Clones for progesterone receptors: 1A6, 1294, 312.
  • Clones for HER-2: 4D5, CB11, A085.[25]
  • Positive and negative controls should always be checked. There should be no nonspecific staining in the control or in the problem case (e.g., HER-2 neu-positive healthy tissue).
  • Collate positive and negative internal control
  • Interpret each stain only in samples with more than 60 % of well-preserved tissue.
– Estrogen (ER) and progesterone (RP) receptors are positive when expressed as nuclear staining. The H-score and Allred systems are suggested,[23,24] specifying the percentage of positive cells.
  • H-score system
  • Percentage of positive cells × 3 (intense nuclear staining), plus
  • Percentage of positive cells × 2 (moderate nuclear staining), plus
  • Percentage of positive cells × 1 (weak nuclear staining).

  The result is the H-score index, which ranges from 0 to 300.
  • Allred system

  Positive area with higher staining intensity calculated as follows:
  • 0: No positive cells.
  • 1: < 1 % positive cells.
  • 2: 1 % to 10 % positive cells
  • 3: 11 % to 33 % positive cells.
  • 4: 34 % to 66 % positive cells.
  • 5: 67 % or more positive cells.

  Staining intensity: 1 = weak, 2 = moderate and 3 = intense. The result is the Allred index, which ranges from 0 to 8.

  Currently, it is valid to report only the percentage of positive cells for both estrogen and progesterone receptors. Both ER and PR are considered positive with a percentage of 1 % positive neoplastic cells.[25]
– HER-2 overexpression[26,27]
  • Positive (3+): intense and uniform membrane staining in > 10 % of neoplastic cells.
  • Indeterminate (2+): weak and complete membrane staining in > 10 % of neoplastic cells.
  • Negative (0-1+): staining is not identified or is weak and incomplete in at least 10 % of neoplastic cells.

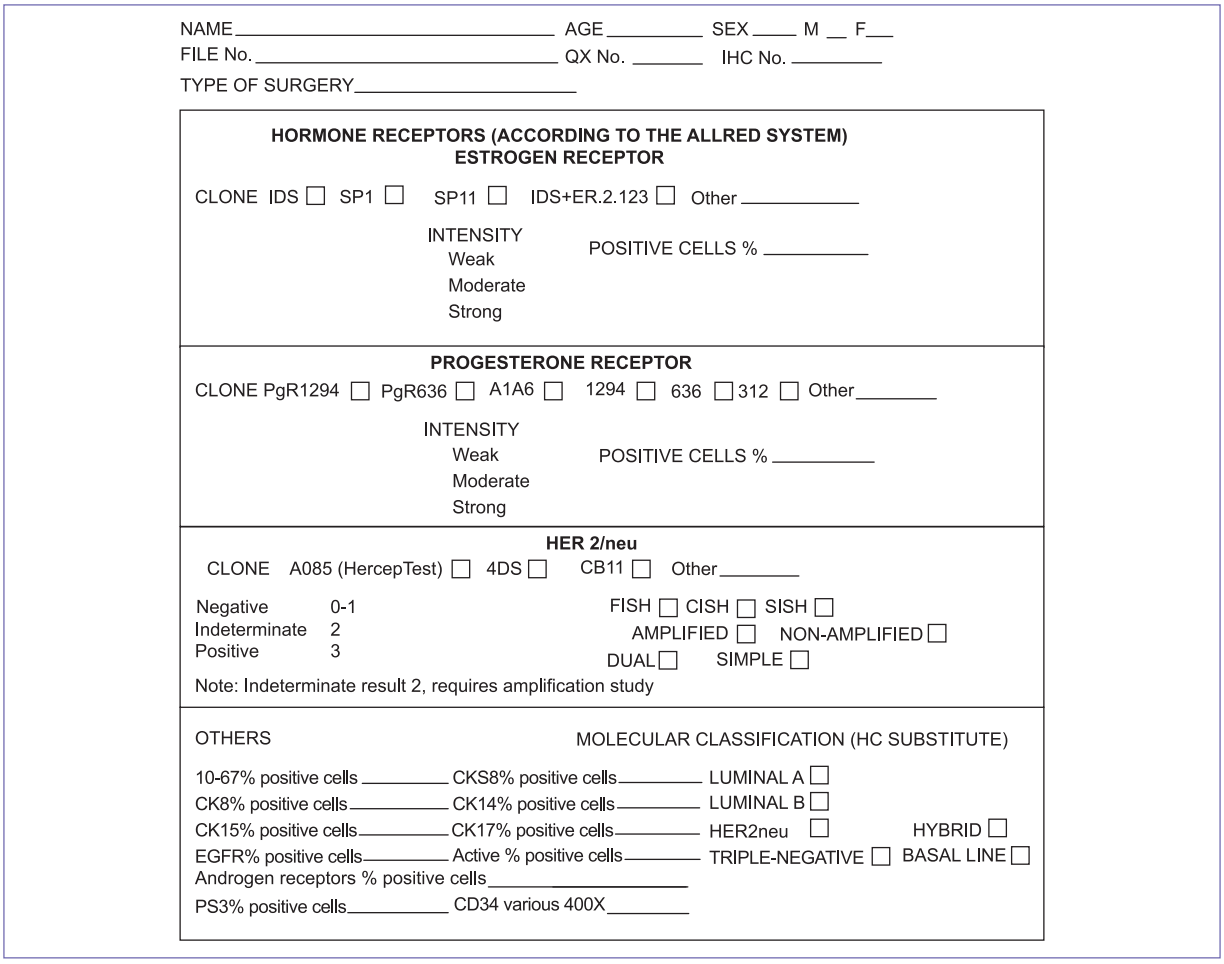
  In HER-2, the classification only applies to invasive carcinoma, not to carcinoma in situ. Cases with HER-2 positivity in normal ducts and lobules are not assessable and should be repeated.
– Recommendations for reporting Ki67 are the following:[28-30]
  • Preanalytical
  • The Ki-67 index can be determined on tru-cut biopsies and/or complete tumors in wide excisions.
  • Ki-67 index in tissue microarrays should only be used in clinical or epidemiological trials.
  • Analytical
  • Known positive and negative controls should be included on electrocharged tissue slides.
  • Nuclear staining is only considered positive.
  • The MIB-1 antibody is the one that is currently accepted.
– Interpretation
  • In tumor panoramic view, choose at least three high-power fields (400×) that represent the entire tumor staining spectrum. Evaluation is carried out in at least 500 neoplastic cells, with 1000 cells being most recommendable.
  • In studies for assessing prognosis, evaluating the invasive margin of the tumor is recommended.
  • In pharmacokinetic studies comparing tru-cut biopsies and wide excisions, evaluating the entire tumor is recommended.
  • A “hot spot” is defined as the area where the staining is particularly higher, relative to other adjacent areas. If there are several “hot spots”, the one with the highest rank should be chosen.

  Using is two methods recommended:
  • Average. It consists of manually counting the number of positive cells on three previously-selected fields and calculating the average.
  • Hot spot. It consists of manually counting the number of positive cells in the highest ranking hot spot, and calculating the average.
– Report
  • The Ki67 index that is reported is the percentage of positive neoplastic cells among total counted cells.
  • We recommend reporting the index obtained by the two above-described methods: “hot spot” and “average”.
  • The cutoff point recommended by this Consensus is 20 %.

8.3 Report form

The IHC report should be linked to pathology main report in order to ensure that the results are incorporated into the final diagnosis.

In order to ensure for the results to be reproducible, the report must include the antibody clone and brand, status (positive or negative), as well as the


NAME _____ AGE _____ SEX ____ M __ F___
FILE No. _____ QX No. _____ IHC No. _____
TYPE OF SURGERY _____

HORMONE RECEPTORS (ACCORDING TO THE ALLRED SYSTEM)
ESTROGEN RECEPTOR

CLONE IDS ☐ SP1 ☐ SP11 ☐ IDS+ER.2.123 ☐ Other _____

INTENSITY
Weak
Moderate
Strong

POSITIVE CELLS % _____

PROGESTERONE RECEPTOR

CLONE PgR1294 ☐ PgR636 ☐ A1A6 ☐ 1294 ☐ 636 ☐ 312 ☐ Other _____

INTENSITY
Weak
Moderate
Strong

POSITIVE CELLS % _____

HER 2/neu

CLONE A085 (HercepTest) ☐ 4DS ☐ CB11 ☐ Other _____

Negative 0-1
Indeterminate 2
Positive 3

FISH ☐ CISH ☐ SISH ☐
AMPLIFIED ☐ NON-AMPLIFIED ☐
DUAL ☐ SIMPLE ☐

Note: Indeterminate result 2, requires amplification study

OTHERS

10-67% positive cells _____ CKS8% positive cells _____
CK8% positive cells _____ CK14% positive cells _____
CK15% positive cells _____ CK17% positive cells _____
EGFR% positive cells _____ Active % positive cells _____
Androgen receptors % positive cells _____
PS3% positive cells _____ CD34 various 400X _____

MOLECULAR CLASSIFICATION (HC SUBSTITUTE)

LUMINAL A ☐
LUMINAL B ☐
HER2neu ☐ HYBRID ☐
TRIPLE-NEGATIVE ☐ BASAL LINE ☐

Figure 6. Pathology report. Breast prognostic and predictive markers.

used criteria and system. This Consensus recommends the following form for the report of these markers (Fig. 6).

8.4 Routine quality control

Routine quality control is essential for IHC reaction success.

Positive and negative controls should be included on the same tissue slide where the problem tissue is analyzed. If these controls are in a separate slide, it has to be ensured that they undergo simultaneous and identical procedures than the problem specimen.

Controls must be identically fixed and processed than the examined tissue, and undergo the same antigenic retrieval and immunostaining protocol.

Controls with three staining levels (negative, weak/moderate, intense) should be used in order to obtain an adequate staining.

Histological sections for immunohistochemistry testing should be stored at room temperature for a period no longer than 14 days, after which the results are questionable.[31]

8.5 External quality control

Pathology laboratories that perform IHC testing should participate in an external quality control program.

For an adequate IHC quality control, it is considered that the laboratory should process the samples of at least 200 cases per year.[28,32]

9. Recommendations for molecular biology

9.1 HER-2 amplification

Currently, there are different techniques to identify HER-2 gene amplification. Fluorescent in situ hybridization (FISH) is considered the gold standard. Other variants of the technique are chromogenic in situ hybridization (CISH) and silver in situ hybridization (SISH), which can be simple (based only on HER-2 detection) or dual (based on the HER-2/chromosome 17 centromere ratio).[32]

HER-2 amplification should be sought in indeterminate cases (2+ positive) by IHC.

CISH or SISH techniques can be used as long as a validation process has been carried out in parallel with the FISH technique and concordance of at least 95 % has been demonstrated between FISH and the other methodology.

9.2 HER-2 hybridization reactions interpretation criteria

The following guidelines reduce the probability of interpretation errors:

- The area of invasive carcinoma should be selected in the H-E-stained tumor section; the test will not be carried out in areas with carcinoma in situ.
- The control is initially assessed; if inadequate, the test should be repeated.
- Global evaluation of the case should be made and have at least 20 neoplastic cells for SISH or CISH and 40 for FISH, in at least two different invasive carcinoma fields. In case there are areas with and without amplification, they should be separately counted. It should be reported as amplified with a note specifying that there are areas without amplification.[26,27]

9.3 Cutoff points for FISH and dual SISH

- Positive: HER-2/CEP 17 ratio > 2.0.
- HER-2/CEP 17 < 2, but with HER-2 absolute count per nucleus > 6.
- Indeterminate: HER-2/CEP 17 ratio < 2 and absolute HER-2 count per nucleus ≥ 4 and < 6.
- Negative: HER-2/CEP 17 ratio < 2 and absolute count < 4.

9.4 Cutoff points for simple CISH

- Positive: > 6 copies/nucleus.
- Indeterminate: 4 to 6 copies/nucleus (in two counts).
- Negative: < 4 copies/nucleus.

  Using preferably dual systems is recommended.
- In the following unusual situations,[28] in single probe reactions, if the signal count is > 4 but < 6, repeating the study with dual probes is recommended.
- In dual probe reactions, in the situations listed below, IHC testing in the same tissue is suggested. If the laboratory that performed the hybridization was not the same that performed the IHC testing, based on IHC repetition, positive (3+) or negative (0 or 1+) status of the case is reported; but if it confirms to be 2+, a new, blinded interpretation is made by another observer. It is also justified to perform IHC or hybridization in additional blocks of the case. If the new evaluation yields any of these unusual situations again, it should be reported as follows:
  - HER-2/> CHR 17 ratio < 2.0, but HER-2 signals average ≥ 6: Positive
  - HER-2/> CHR 17 ratio < 2.0, but HER-2 signals average ≥ 4 and < 6: Negative
  - HER-2/> CHR 17 ratio ≥ 2.0, but HER-2 signals average < 4: Negative

  In all cases, a comment is made on the limited evidence in this type of situations.

9.5 Molecular classification of breast carcinoma and its approach with immunohistochemistry

Translational medicine works on breast cancer four molecular phenotypes (luminal, with HER-2 overexpression, basal phenotype and normal breast-like), which initially were defined by genomics,[34] have enabled approaching this classification using more accessible methodologies, such as IHC, emplouing routine markers such as ER, PR and HER-2.[35-38]

In the Mexican population, mean frequency of subgroups defined by these markers is as follows: hormone receptor-positive 60 %, HER-2-positive 20.4 % and triple-negative 23.1 %.[39,40]

Table 9 shows breast cancer molecular subtypes and their approach by IHC, according to this Consensus.[41-43]

9.6 Triple-negative breast cancer

Triple-negative breast cancer (TNBC) and the basal phenotype should not be considered synonymous, since only 49 % to 71 % of TNBCs are basal phenotype and 77 % of basal phenotypes are triple-negative.[44,45] TNBCs have been sub-classified by gene expression

Table 9. Breast cancer molecular subtypes and their approach by IHC according to this consensus

Subtype according to 2021 Colima Consensus	Approach by immunohistochemistry
Luminal A	ER +, PR > 20 %, Ki67 < 20 % HG* 1 or 2 and HER2-
Luminal B	(HER-2 negative) ER +, HER-2 –, PR < 20 %, or Ki67 > 20 % HG* 3
	(HER-2 positive) ER +, HER-2 +, PR and Ki 67 any value
HER-2	HER2 +, ER – and PR –
Triple-negative	ER –, PR – and HER2 –

*HG, histological grade.

in different ways: a) HER-2 neu-enriched, basal phenotype and claudin-low,[40] b) basal 1, basal 2 (BL1 and BL2), mesenchymal (M) and mesenchymal stem cell-type (MSL), immunomodulatory (IM) and androgen-associated luminal type (LAR).[46,47]

The following IHC panel is recommended for TNBC in order to favor biomarkers and patient subgroups identification:

- Basal cytokeratins (ck5/6, ck14 and ck17).
- EGFR.
- P53.
- Androgen receptors.
- PDL-1 (only in triple-negative metastatic tumors).

9.6.1 Classification of triple-negative tumors

- Low histological grade
  - Adenoid cystic carcinoma
  - Secretory carcinoma
  - Fibromatosis-type metaplastic carcinoma
  - Mucoepidermoid carcinoma
- Intermediate histological grade
  - Acinar cell carcinoma
- High histological grade
  - Metaplastic variant squamous cell (epidermoid) carcinoma
  - Spindle cell variant metaplastic carcinoma
  - Metaplastic carcinoma with heterologous components
  - Mucoepidermoid carcinoma
  - **Carcinoma with medullary pattern**

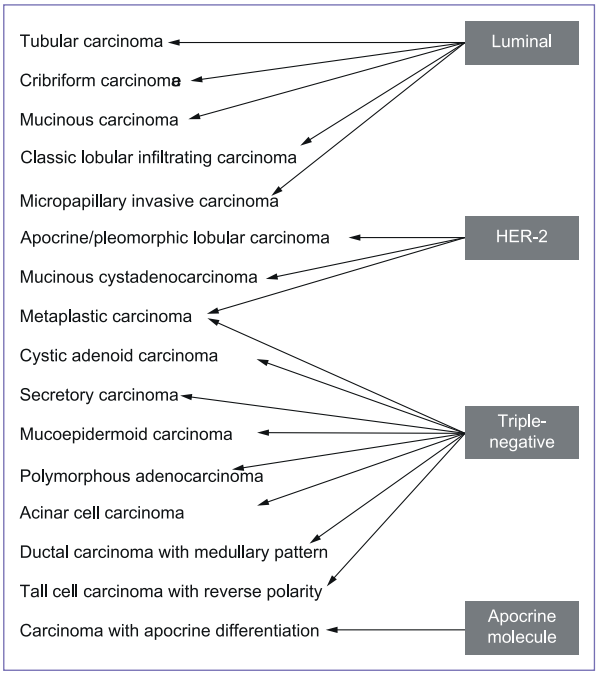


Figure 7. Special types and molecular subtypes.

9.7 Special types

Group of carcinomas with morphological characteristics, biological behavior and clinical evolution that are different from infiltrating ductal carcinoma NST, which also accounts for 25 % of all breast carcinomas.[47,48] Special types are shown in Figure 7 and Table 10 in correlation with the molecular subtype. In secretory carcinoma and adenoid cystic carcinoma, characteristic genetic alterations have been identified and, currently, it is desirable demonstrating them in order to have a certainty diagnosis for these entities.

Secretory carcinoma must have the t(12;15)(p13;q25) translocation with the ETV6-NTRK3 fusion gene.[44]

Adenoid-cystic carcinoma must have the t(6; 9)(q22-23;p23-24) translocation, with the MYB-NFIB fusion gene.

In cases of lobular carcinoma that are difficult to diagnose, use e-cadherin, β-catenin and p120.[49]

9.8 Participation of the pathologist in genomic signature studies

Currently, genomic signature determination is carried out in a centralized manner at specialized laboratories. Participation of the pathologist is highly important for proper selection of the material required for the tests,

Table 10. Breast cancer molecular subtypes characteristics and special histological types assignment

Molecular subtype	ER, PR, HER-2	Additional marker
Basal phenotype	ER – PR – HER-2 –	CK5/6 + EGFR +
HER/ER	ER – PR – HER-2 -	CK5/6 +/– EGFR +/–
Normal breast-like	ER – PR unknown HER-	CK5/6 EGFR +
Luminal	ER + (–) PR +/– HER – (+)	
Molecular apocrine	ER – PR – HER2 +/–	AR + CK5/6 +/– EGFR +/–
Claudin-low	ER – PR – HER-2 –	CLDN-low/– CDH1-low/– CK5/6 +/–
Interferon-related	ER –/+ PR unknown HER-2–	STAT1
Proliferation micro-arrangements	Special histological type	
High	Cystic adenoid Acinar cells Medullary Metaplastic Lobular pleomorphic Secretory	

(Continues)

Table 10. Breast cancer molecular subtypes characteristics and special histological types assignment *(continued)*

Molecular subtype	ER, PR, HER-2	Additional marker
High	Apocrine Lobular Micropapillary Lobular pleomorphic	
Low	Medullary Metaplastic	
Low/high	Apocrine Osteoclastic ductal carcinoma Lobular Micropapillary Mucinous Neuroendocrine Lobular pleomorphic Tubular	
High	Apocrine Lobular pleomorphic	
High	Metaplastic Medullary (?)	
High	Medullary (?)	

AR: Androgen receptor; CDH1: E-cadherin; CDLN: Claudin; CK: Cytokeratin; EGFR: Epidermal growth factor receptor; ER: Estrogen receptor; PR: Progesterone receptor; STAT1: Signal transductor and transcription activator 1; –: Negative; +: Positive; +/–: Occasional positive; –/+: Rarely positive

and observing the following points is therefore recommended.

- Use only samples that in their processing have been fixed in 10% buffered formalin.
- Attach complete and adequate diagnosis, including immunohistochemistry markers according to the signature to be assessed.
- Mammaprint requires at least 3 mm of invasive carcinoma. Oncotype requires 5 mm to 10 mm of invasive carcinoma. Endopredict requires tissue slides or blocks containing more than 30 % of tumor.
- Avoid selecting blocks that contain large areas of necrosis or hemorrhage.
- Select blocks less than 5 years' old.

10. Anaplastic large cell lymphoma associated with implant use

This entity has been recently recognized, which is why currently there is no standardized management; definitive diagnosis will be established on the cytological study of the fluid obtained from the seroma, or in capsulectomy specimens; performing the procedures described in Table 11 is suggested.

VIII. Breast cancer tnm staging

1. Introduction

The American Joint Committee on Cancer (AJCC) breast cancer staging system provides important prognostic information.

Breast cancer behavior has been understood both by clinical stage and by identification and validation of prognostic biological markers that are determinant for treatment.

Table 11. Recommendations for the handling and report of capsulectomies in patients with suspected anaplastic large cell lymphoma associated with implants[51,52]

Indications	Late seroma (time of appearance longer than 1 year after implant placement)	Positive or suspected cytology for anaplastic large cell lymphoma
Fixation methods and time	– 96º alcohol in a 1 to 1 ratio – Fixation for no more than 48 hours	– 10% formalin – Complete capsule (referred intact and with the implant within), oriented by the surgeon – 6-48 hours of fixation
Procedure description	– 10 to 50 mL (at least) – Standard or liquid-based cytology – Centrifuge, perform stained smears with the preferred technique – Cell block with sediment (if there is material) – If possible, determine IHC markers (at least CD30 and ALK)	– Gross examination (measure, color, consistency, thickness) – Stain the identified specimen on six faces (upper, lower, lateral, medial, anterior and posterior) – Section the specimen at the upper face in the shape of a cross. – Description of surfaces (smooth, granular, nodular, fibrinoid, hemorrhagic, fleshy appearance) – If any of these characteristics is identified or a tumor is present, extensive sampling of these areas should be carried out. – If there are no apparent alterations, including for each face of the specimen (six faces) two tissue fragments per cassette measuring at least 2 cm in length each is suggested, i.e., a total of 12 cassettes. – H-E routine sections – IHC: CD30 and ALK 1 (at least)
Microscopic findings	– Large, disc-adhesive cells with nuclei of irregular contours, vesicular chromatin, nucleolus, ample cytoplasm – Cells with horseshoe-shaped or kidney-shaped nuclei – CD30 + and ALK -	– It is common to observe necrotic areas with lymphoid cell phantoms and karyorrhexis, alternating with fewer viable neoplastic cells and inflammatory infiltrate – There may be extensive areas of fibrosis/ sclerosis – Positive CD30 in neoplastic cells in addition to preserving immunoreactivity in areas of necrosis – Negative ALK 1 (excludes systemic LCAL)
Others	– Flow cytometry – Molecular studies	– IHC markers: granzyme B +, perforin +, CD 3 +, CD43 +, EMA +/-, CD 68 –, CK AE1 / AE3 –, CD 20 –, CD 31 –, melan - A – – Molecular studies
Report	– It should be described as suspicious in case of having only the morphological evaluation, without confirmation by IHC and/or flow cytometry. – In addition to recommending clinical-radiological correlation	– For staging purposes, whether it is localized disease should be reported (cells present only in the effusion, internal face of the capsule, thickness of the capsule without exceeding it) which has a better prognosis and only increases capsulectomy. – Infiltration beyond the capsule, and/or to adjacent soft tissues, and/or tumor formation (worse prognosis and may be candidates for adjuvant CT)

Changes in AJCC guidelines 8th edition include lobular carcinoma in situ elimination, since it does not correspond to a malignant lesion and is merely a risk marker. On the other hand, biological markers are included in order to determine a "Clinical and Pathologic Prognostic Stage".

Based on the classic tumor (T), lymph node status (N) and metastasis (M) parameters, it is possible to determine the clinical and pathologic anatomic stage as in previous classification; in this 8th Edition, to the above, tumor grade, estrogen and progesterone receptors, HER-2 neu and, if available, the recurrence score calculated with Oncotype DX are added in order for a clinical and pathologic prognostic stage to be established with all this information.

To calculate these stages, this consensus recommends the use of electronic platforms such as:

– https://itunes.apple.com/gb/app/breast-cancer-staging-nm-8/id1218852568?mt = 8
– https://play. google. com/store/apps/details?id=com. wesley. TNMBreast&hl=en_US

These apps can be downloaded to smart phones and other electronic devices for reference.

There are three criteria for staging:

– Anatomic stage. It is based exclusively on the anatomic extent of the disease, defined by the T, N and M categories.
– Clinical prognostic stage. Where in addition to the stage determined by T, N and M based on physical examination and imaging studies, the tumor grade,

and estrogen receptors, progesterone receptors and human epidermal growth factor receptor (HER-2) status should be included.
- Pathologic prognostic stage. It is used to assign the stage in patients who have undergone surgery as primary treatment or after neoadjuvant treatment.

This staging system should not be used for all malignant breast tumors histology types. There is a specific staging system for some histological varieties, such as:
- Sarcomas of the breast
- Phyllodes tumors
- Breast lymphomas

2. Extent of disease evaluation for initial staging

Strictly, it is not necessary for a patient to have radiological evaluation of distant sites to be classified as M0. Extent of disease evaluation should be mainly focused on the signs and symptoms of each patient. In the absence of specific symptoms or abnormalities in general blood tests, for stages I and IIB, no extent of disease evaluation study is required. For locally advanced breast cancer, the following imaging studies could be considered:
- Abdominal computed tomography (CT) or magnetic resonance imaging (MRI) in cases of elevated liver function tests or alkaline phosphatase, or abdominal symptoms or abnormalities on physical examination (may be substituted for abdominal ultrasound in the absence of CT or MRI) (NCCN Category 2A).
- Chest CT scan in case of pulmonary symptoms (NCCN Category 2A)
- Bone scan in case of localized bone pain or elevated alkaline phosphatase (NCCN Category 2B).
- PET/CT for stage IIIA and onwards (NCCN Category 2B).

IX. Carcinoma *in situ*

1. Ductal carcinoma in situ (DCIS)

This is a heterogeneous group of neoplasms, characterized by the presence of malignant epithelial cells that grow within the mammary ducts, without surpassing the basement membrane, and are identified by optical microscopy. It adopts different intraductal growth architectural patterns and exhibits variable cytological and necrotizing characteristics; it can be unifocal or multifocal. It is also known as intraductal carcinoma.

These carcinomas are suspected by an abnormal mammographic finding (microcalcifications, a mass or dense asymmetric area) or by the existence of a palpable lump or discharge from the nipple; a rare form of presentation can be Paget's disease (DCIS involvement, confined exclusively to the areola-nipple complex).

Histological diagnosis and extent of disease determination (size) are essential for the selection of adequate therapeutics. It is important to emphasize that, on occasions, intraductal carcinoma grows within the ducts in a discontinuous form and that the extent is often greater than visualized on mammogram or clinically estimated.

1.1 Local and regional treatment recommendation

DCIS surgical resection is the treatment of choice. Surgical options include breast-conserving surgery, total mastectomy with or without immediate reconstruction, and oncoplasic breast surgery. In case of clinical suspicion of invasion, it is advisable to add sentinel lymph node biopsy.

In breast-conserving surgery, surgical specimen X-ray is a useful method to verify complete excision of the lesion. The resected surgical specimen should always be oriented in order to accurately know each one of the surgical margins (superior, inferior, internal, external, superficial and deep), with reference to at least three of the margins with silk, metal staples or preferably by means of the staining of the specimen by the surgeon. In breast-conserving surgery, it is important for a radiopaque mark to be placed on the surgical bed, to guide the radiation oncologist in case the patient is candidate for adjuvant radiotherapy.

Excision final pathological margin is considered close when it is < 2 mm and optimal when it is ≥ 2 mm.[1] In case of a surgical bed with fascia, it is considered optimal when reported as negative.

Recommendations for re-excision (breast-conserving or oncoplastic surgery):
- Margin smaller than 2 mm. It should be noted that additional routine surgery may not be justified in patients with margins < 2 mm who will receive adjuvant radiotherapy.
- Residual microcalcifications.

In cases treated with breast-conserving surgery, radiotherapy will be administered only to the breast.

All patients with breast-conserving surgery do benefit from postoperative radiotherapy, particularly those with high risk of local recurrence: < 50 years of age, > 15 mm tumor, multifocal disease, intermediate or high nuclear grade, central necrosis, comedo histology or radial surgical margin <10 mm.[2-4]

Moderate hypofractionation with schemes of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions is not inferior in local control and cosmetic results to the conventional scheme of 50 Gy in 25 fractions, and thus it can be used.

Accelerated partial breast irradiation with external-beam radiotherapy is an option for patients with DCIS (of low risk), if this technique is available at the hospital center.[5-9] Boost in patients with DCIS is controversial. Based on current evidence, it could be offered in patients younger than 50 years of age or with margins < 2 mm.[10]

Recommendations for total mastectomy

- Multicentric disease
- Unfavorable breast-tumor ratio
- Impossibility to obtain negative margins (absence of tumor in ink marks)
- Patient wish
- Impossibility to administer radiotherapy.

The state of the surgical margins and a high grade may increase the risk of recurrence after surgery. Patients in whom microinvasion or invasion is identified in the definitive histological examination will be treated according to invasive carcinoma guidelines.

In specialized centers, a multidisciplinary team will be able to evaluate, in special situations, the proposal of prophylactic contralateral mastectomy, which has demonstrated to be safe and efficacious by reducing the likelihood of cancer in the future in high-risk asymptomatic women.[11]

In patients with good prognostic factors (mentioned in the staging criteria), disease-free survival for management with surgical resection without radiotherapy is higher than 94 %.[12,13]

1.2 Sentinel lymph node in carcinoma in situ

In general, axillary or sentinel lymph node dissection is not recommended; however, in those patients who will require total mastectomy for their management, or in whom there is suspicion of invasion, sentinel lymph node localization and histological evaluation and action as a consequence of the results may be considered; this will avoid unnecessary lymph node dissections in the future if microinvasion or invasion is found in the surgical specimen. When sentinel lymph node biopsy is considered and the procedure is unsuccessful, radical axillary dissection is not recommended. Figure 8 presents the corresponding algorithm.

1.3 Treatment with tamoxifen and aromatase inhibitors

Risk-reduction therapy with tamoxifen is recommended for 5 years in patients with breast-conserving surgery and positive hormone receptors. In postmenopausal women, treatment with an aromatase inhibitor for 5 years may be considered.[14]

In case of mastectomy, see Chapter XXI. Chemoprevention.

1.4 Follow-up

Mammary gland evaluation in cases of DCIS treated with breast-conserving surgery should include a mammogram 6 months after the conclusion of local tretment. Subsequently, annual mammography + ultrasound shall be performed.

2. Lobular carcinoma in situ LCIS (lobular neoplasm in situ)

It is a rare lesion, in which histological and differential diagnosis with atypical hyperplasia requires the intervention of expert pathologists. Generally, it is not associated with a palpable mass or specific mammographic changes. This lesion is regarded as a risk marker and not a cancer that evolves directly into the invasive form. About 10 % to 15 % of patients will develop an invasive carcinoma in either breast sometime in their lifetime, generally of the infiltrating ductal type. The risk for invasive breast cancer appearance is close to 0.5 % per follow-up year (cumulative), and when associated with first-degree genetic makeup, the risk increases to 1 % per year.

The classic variant does not require surgical management. There is evidence to support that the presence of aggressive variants, such as the pleomorphic subtype or association with necrosis or signet ring cells, have a higher potential for developing invasive carcinoma than the classic variant, which is why the treatment of choice in these cases is complete excision of the lesion with negative margins (Figure 9).[15]

All patients with LCIS should be included in a program of close monitoring and surveillance, in addition to counseling regarding chemoprevention or prophylactic bilateral mastectomy. Due to the low percentage of progression to invasive disease, LCIS does not require management with radiotherapy.

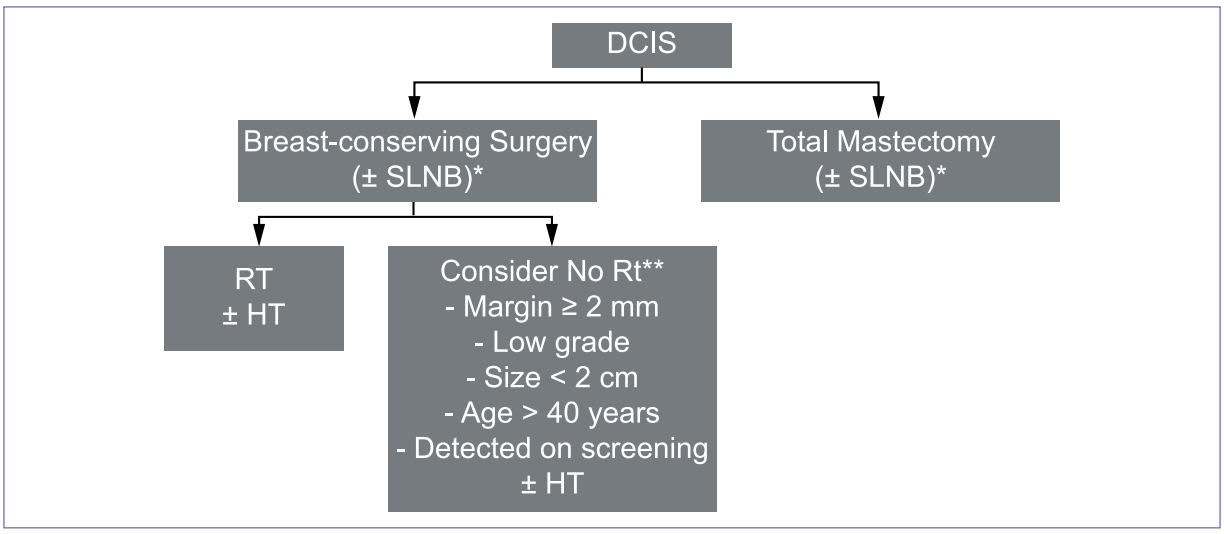


Figure 8. Ductal carcinoma surgical management algorithm.
*In case of clinical suspicion of invasion.
**Must meet ALL.
Abbreviations: DCIS; Ductal carcinoma in situ; SLNB: Sentinel lymph node biopsy; Rt: Radiotherapy; HT: Hormonal therapy.

X. Early breast cancer management

1. Breast cancer primary surgical management

Primary surgical management is indicated for those patients with early breast cancer. It can be with breast-conserving surgery or total mastectomy, regardless of axillary surgical management. It should be followed by adjuvant therapies, as indicated. As in other clinical scenarios, evaluation of the case by multidisciplinary teams is recommended. The strategy of performing excisional biopsies with intraoperative study of a breast lesion, suspicious by clinical and imaging examination, and in case of malignancy, performing modified radical mastectomy, should be abandoned. Currently, it is necessary for all patients to have histological confirmation prior to surgery.

1.1 Breast-conserving surgery

Breast-conserving surgery is the complete excision of the primary tumor with a negative pathological margin. Most cases should be complemented with adjuvant radiotherapy, and it is the standard treatment at early stages.[1] Breast-conserving surgery and adjuvant radiotherapy have shown similar results in terms of locoregional recurrence and overall survival in comparison with radical surgery.[2-5]

– Selection criteria and indications
  - Favorable breast-tumor ratio, which allows anticipating a good esthetic result.
  - Desire of the patient.
– Contraindications
  - Inflammatory carcinoma.
  - Unfavorable breast-tumor ratio, even with the use of oncoplastic techniques.
  - Impossibility to receive adjuvant radiotherapy.
  - Impossibility for negative margins to be obtained (multicentricity).

Although multicentricity as a contraindication for breast-conserving surgery has been questioned in prospective studies by showing satisfactory esthetic results, its oncological safety and long-term results have not been reported.[6]

The goal is to obtain negative margins in the pathology examination with a satisfactory esthetic result, which can be achieved by simple resections or using oncoplastic techniques. The surgical specimen should always be oriented and marked for recognition by the pathologist. Standardization in hospital centers is recommended for reference of the surgical specimen. In

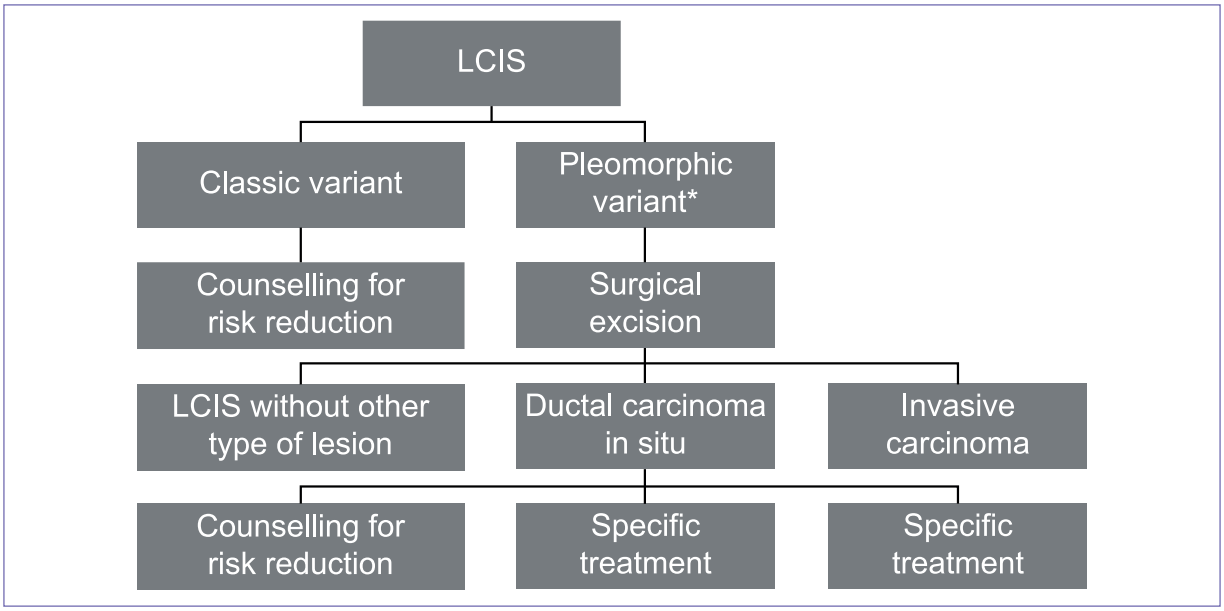


Figure 9. Lobular carcinoma in situ management algorithm.
*Also consider signet ring cell variants or presence of comedonecrosis.
Abbreviation: LCIS: Lobular carcinoma in situ.

case of positive margins, it must be expanded. The surgical bed should be marked with radiopaque clips for future localization (radiotherapy and surveillance).

Current oncoplastic techniques allow mobilization of a larger proportion of breast tissue and thus obtain a better esthetic result, without conferring a higher risk of conversion to mastectomy in case of requiring re-excisions.[7]

1.2 Mastectomy

- Types of mastectomy
  - Simple or total.
  - Skin-preserving.
  - Areola-nipple complex-preserving.
  - Modified radical.
  - Radical.

It is important for patients to be informed about the techniques and possibilities of breast reconstruction, as well as the timing they can be carried out in (see Chapter X. Reconstruction).

- Indications for mastectomy
  - Patient preference. Multicentric disease with no possibility of free margins.
  - Breast-tumor ratio, unfavorable for a good esthetic result.
  - Difficulty for adequate follow-up.[8-11]

1.3 Oncoplastic surgery

Oncoplastic surgery is a series of surgical techniques that allows proportionally larger resections to be carried out, with a satisfactory esthetic result. It is based on the integration of plastic surgery techniques for the repositioning of healthy breast tissue after complete resection of the tumor with negative margins.[12]

There are three factors to be considered when selecting the surgical technique:

- Breast-tumor ratio.
- Localization of the lesion.
- Breast density.

Clough et al. propose to classify oncoplastic techniques in two groups:

- Resected volume of less than 20 %. These techniques can be carried out by a surgical oncologist, without specific training in oncoplastic surgery.
- Volume to be resected from 20 % to 50 %. These procedures require residual skin excision for remodeling of the breast. They are based on mammoplasty reduction techniques and require specific training, and simultaneous (preferable) or delayed symmetrization of the contralateral breast.

Oncoplastic surgery has enabled for the indications for breast-conserving treatment to be broadened.[13-17] Optimal results are obtained with a good selection of candidate patients, in the context of multidisciplinary

teams that include surgical oncologists with training and experience in oncoplasic surgery.[18-20]

In oncoplastic surgery, establishment of an intraoperative adequate margin acquires more relevance, since with the large tissue mobilization that is performed, it can be difficult to locate the exact site for extension in case of positive margins, which is why we recommend relying on methods to ensure said margin (margin inking, intraoperative ultrasound and X-ray, etc.). The tumor bed should be marked with staples after resection and prior to tissue repositioning in order to allow the radiation oncologist higher precision for identifying the area that is to receive additional doses.[19-21]

1.4 Surgical treatment of the axilla

In invasive cancer, axillary evaluation is an essential part of its management; the primary goal is prognostic information provided by lymph node status.

In initial staging, systematic clinical examination and imaging studies should be considered to guide evaluation/management decisions; complete evaluation of axillary regions with ultrasonography is recommended in all patients.[22-25]

The decision of surgical treatment should take into account possible scenarios:

- Disease status.
- Negative lymph nodes (cN0).
- Positive lymph nodes (cN+).
- Timing of surgery.
- Primary surgery.
- Post-neoadjuvant treatment surgery.
- Response/negativization.
- Persistence.
- Extent of the surgery that will provide the necessary information.
- Sentinel lymph node (SLN).
- Radical axillary dissection (RDA).

Possible scenarios are summarized and combined in Figures 10 to 13.

1.4.1 Sentinel lymph node

In clinically negative axilla (cN0), sentinel lymph node biopsy (SLNB) is the standard for surgical staging, aimed at knowing the histopathological status, based on randomized studies that have demonstrated the oncological safety of the procedure and a lower morbidity (lymphedema, pain and sensory alterations of upper limb and shoulder), with regard to the effects of radical axillary dissection.[25-28]

The sentinel node (SLN) procedure recommendation primarily includes the surgeon's experience, who must demonstrate mastery of the mapping technique. Regarding SLN identification, it is independent of the dye or radioisotope application site (peritumoral vs. periareolar).

Although high localization rates have been demonstrated with a single technique, regardless of which one is used, the recommendation is to do it with both (dye and radioisotope) if a nuclear medicine department is available. As a specific recommendation, if the necessary conditions are not available, i.e., mastery of the technique, surgical devices, tracers, or a pathology team familiar with the management of lymph nodes, referral of patients to centers specialized in the procedure should be considered (currently, performing an axillary dissection in case of cN0 and primary surgery is considered oncologically incorrect).[29,30]

Omission of radical axillary dissection in case of positive SLN

Prospective studies such as ACOSOG Z00117, NSABP-32,[29] IBCSG 23-01[31] and AMAROS,[32] support the recommendation to omit radical axillary dissection in selected cases, as well as the use of radiotherapy, for adequate regional control in some cases with positive lymph nodes and with less morbidity in comparison with axillary dissection.

It is possible for radical axillary dissection to be omitted in:

- Patients with T1-T2, with SLN positive for micrometastasis.
- Patients with T1-T2 tumors, treated with breast-conserving surgery and SLN.
- If the result is 1 or 2 SLNs positive for macrometastasis, and patients will undergo adjuvant treatment with radiotherapy and systemic treatment.

Patients undergoing post-neoadjuvant treatment surgery who were initially N+ corroborated by biopsy and who were considered cN1 (< 4 lymph nodes initially involved), preferably with radiopaque marker placement prior to treatment, with complete response in the subsequent clinical evaluation, with the following to be complied with:[33,34]

- Double mapping technique.
- Dissection of at least 3 lymph nodes.
- Marked lymph node dissection.

1.4.2 Radical axillary dissection (RAD)

Since the results of the NSABP B-04 trial,[26] which establishes the separation of the concepts of

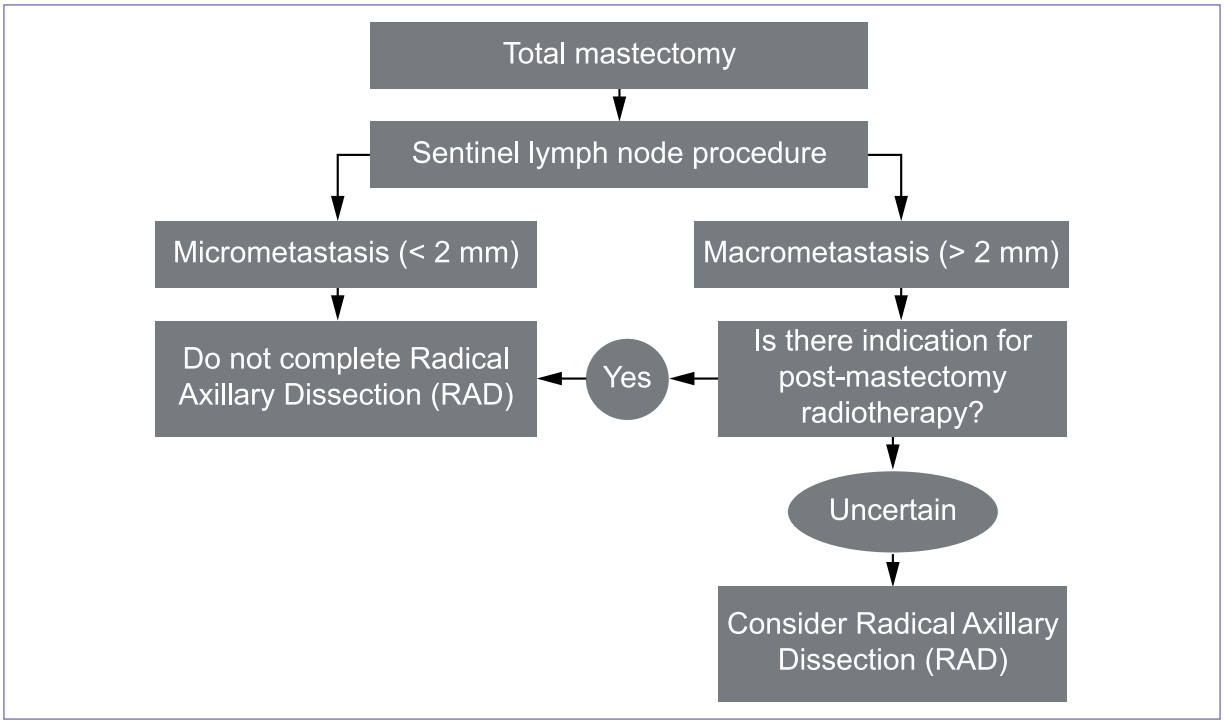


Figure 10. Primary surgical treatment.
Clinically negative lymph nodes (cN0)

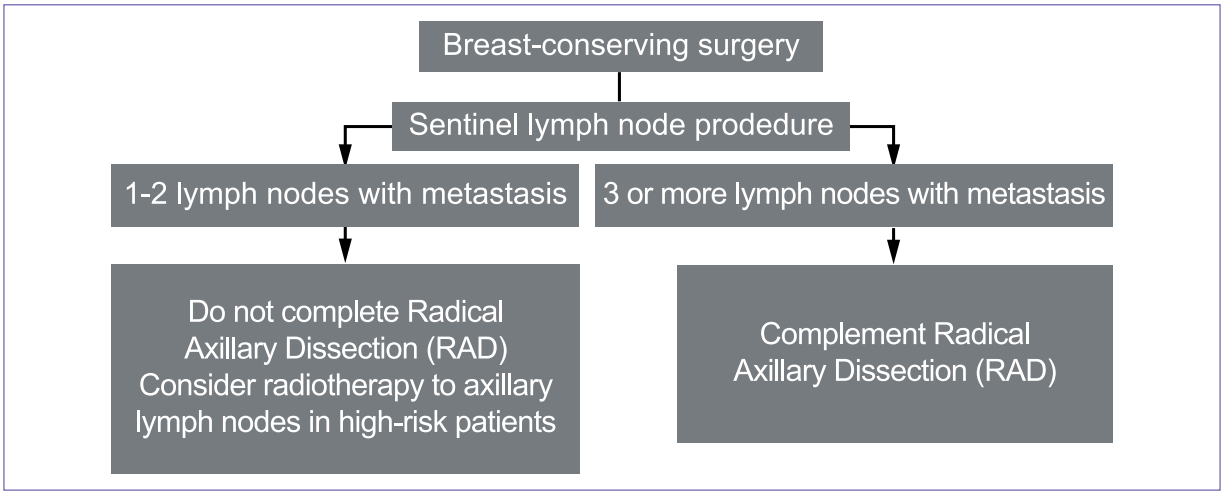


Figure 11. Primary surgical treatment.
Clinically negative lymph nodes (cN0)

management of the breast and the axilla, the conventional procedure is considered in patients who will undergo primary/post-neoadjuvant treatment surgical management, who have initial lymph node involvement (preferably corroborated by biopsy) or persistent disease.

Anatomical extension of the procedure must contain Levels I and II, with Level III being reserved for those cases in which macroscopic clinical involvement is found during the surgical procedure. Regarding the extent in the number of lymph nodes, the recommendation considers a lymph node harvest of at least 10 nodes

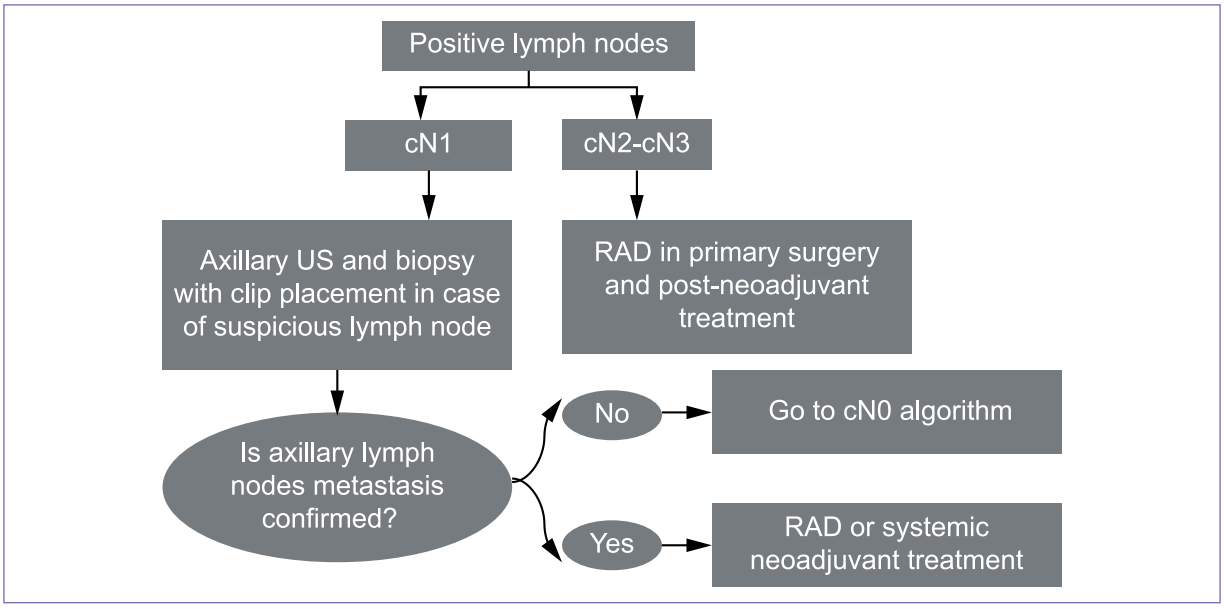


Figure 12. Patient with clinically positive lymph nodes (N+)

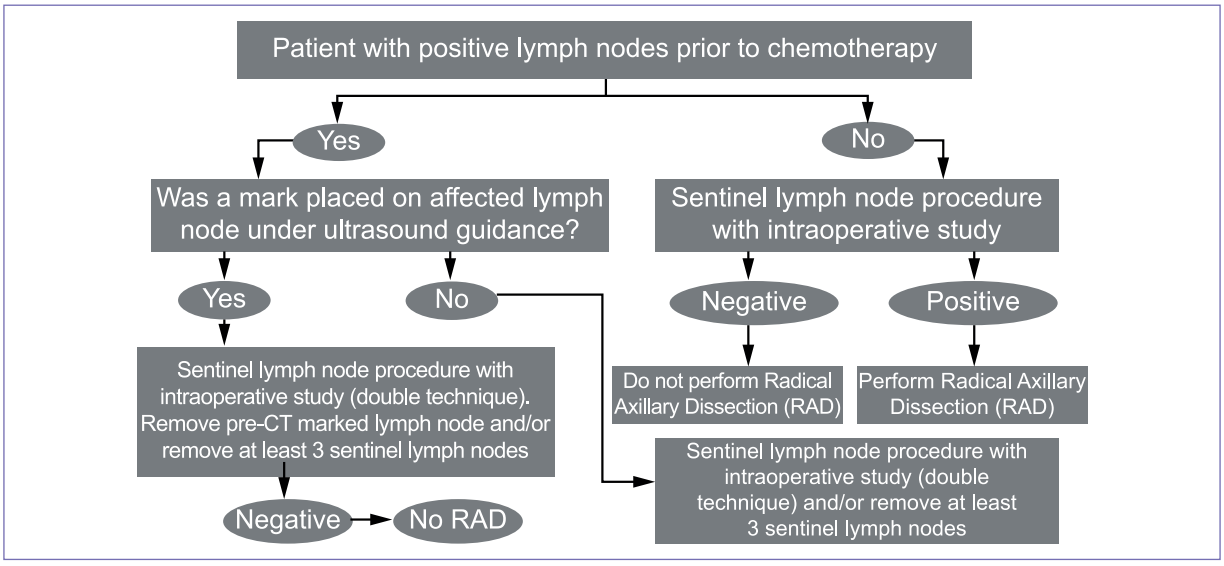


Figure 13. Axillary surgical treatment.
Post-neoadjuvant treatment (cN1)

as optimal (risk of recurrence with < 10 lymph nodes from 5 to 21 % vs. 3 % to 5 % with > 10 lymph nodes).

Completing with RAD is recommended for patients undergoing total mastectomy with SLN procedure in whom the pathological study (intraoperative and/or definitive), reports macrometastatic disease, in addition to those patients in primary surgery with 3 or more positive sentinel lymph nodes, and those in which the disease persists in the post-neoadjuvant treatment pathology evaluation.

1.5 Breast reconstruction

The decision to perform a partial or total mastectomy depends on reconstructive challenges and oncological

considerations. Certainly, the cancer stage and the ability to obtain negative borders at the tumor margins are determining factors, and so are the breast-tumor ratio and tumor location. The decision to perform partial or total mastectomy by the surgical oncologist will mark the start of the reconstructive plan. Joint planning to determine the resection, expectations for subsequent management and reconstructive timing, is a good start for offering the most appropriate personalized treatment for each situation and each patient.

1.5.1 Partial defects reconstructive approach

In general, partial mastectomy defects repair is more adequate for patients with large breasts.[35] Sufficient volume of breast tissue remaining after tumor excision allows breast tissue reorganization in order to shape it.[36] Patients with ptosis are also good candidates for partial mastectomy, given that most techniques employ a mastopexy or breast reduction that repositions the nipple-areola complex higher on the breast mound, thus restoring the youthful appearance of the breast at the time the tumor is removed.[37]

Neoadjuvant chemotherapy can reduce the size of large tumors, and allow patients who respond favorably to be good candidates for breast preservation, and thus perform partial mastectomy, followed by radiotherapy.[38-44]

1.5.2 Reconstruction of partial defects

Tissue remodeling prior to radiotherapy allows the use of techniques with local tissue (oncoplastic), without the need to increase the rates of complications associated with the use of these same techniques in already-irradiated breasts. Immediate reconstruction at the time of partial mastectomy is best used in patients with localized disease when a reliable assessment of intraoperative tumor margin is available.

1.5.3 Reconstructive techniques for partial defects

Reconstruction techniques are often influenced by the timing of reconstruction and association with radiotherapy.[44] Delayed reconstruction in a fully radiated breast often requires the transfer of a flap that sometimes includes a portion of skin. Autologous fat grafting, along with needle-assisted percutaneous cicatricial bands release, is a common method for delayed repair; however, multiple surgical events are generally required. Reconstruction options after partial breast radiotherapy are different; with partial radiotherapy, the remaining breast tissue has not been irradiated and can be used to repair the defect with a lower rate of complications.

Lower and external quadrant defects often require repair with transposition of flaps, such as thoracodorsal artery or latissimus dorsi musculocutaneous flaps, with an island of skin if necessary. It is important for the symmetry of the contralateral breast to be favored at the same surgical time whenever possible.

1.5.4 Reconstructive approach after total mastectomy

Timing of reconstruction is the most important factor in the decision-making process. If we leave out patient particular characteristics such as age, associated morbidity, body mass index, among others, in case radiotherapy is required or if the patient is at risk of requiring it, delaying definitive reconstruction (implant or autologous tissue) and placing an anatomical tissue expander to preserve the breast skin for late reconstruction (after radiotherapy) is usually the best option. If radiotherapy is not required, immediate reconstruction is appropriate and allows better esthetic results, either with an expander/implant or with autologous tissue (free or pedicled flap).

On the other hand, if breast reconstruction is performed at the time of mastectomy, and the histopathology result shows lymph node involvement, postoperative radiotherapy should be administered. Complication at the level of the surgical wound is the most common, caused by radiotherapy. On the other hand, lymph node chains irradiation in this context can be complex and highly conformed techniques can be used to adequately cover the internal mammary chain and axillary levels in order to reduce the dose to healthy organs such as the lung.[45]

For these situations, there is the option of performing deferred-immediate or “late-immediate” reconstruction, which consists of placing a retromuscular tissue expander in a first surgical stage and reserving a definitive implant for a second surgical stage, or an option of autologous tissue. With delayed-immediate reconstruction, patients who do not require radiotherapy can achieve surgical wound results that are similar to those obtained with immediate reconstruction, and patients who require radiotherapy can avoid the esthetic problems associated with radiation administration after immediate breast reconstruction.

However, recent international evidence (level 3) indicates that, if a patient is candidate for reconstruction with autologous tissue in favorable health conditions, she should undergo immediate reconstruction, even if post-mastectomy radiotherapy is required. This is supported by the fact that there are no differences that impact patient satisfaction in terms of the shape and texture of the flap, as well as no differences in the percentage of fat necrosis. Flap fibrosis was not a relevant factor for breast shape or patient dissatisfaction.

Reconstruction is performed with the best available option; i.e., autologous tissue, implant, or a combination of both. It is important mentioning that expansion must be interrupted prior to radiotherapy planning. If the skin is considered to be in poor condition or has too much hypotrophy, it is advisable to reduce the expander volume prior to radiotherapy. Final reconstruction is carried out 12 months after radiotherapy completion in order to reduce the rate of complications associated with surgical site morbidity.

1.5.5 Breast reconstruction complete process

Regardless of the multiple scenarios that may arise in patients with breast cancer, except for exceptional cases, total reconstruction is achieved in two surgical times, to which a third local procedure can be added for refinements. In this regard, we present the various available options.

1.5.6 Reconstruction with expander/implant

This type of reconstruction involves the placement of a retro-muscular expander in a first surgical time, infiltrations for expansion in the office, and when the desired volume is achieved, eventual placement of a definitive implant. The process can be completed in a period of 10 to 18 weeks.

1.5.7 Reconstruction with expander + dermal matrix/implant or implant + graft or fat injection

An acellular dermal matrix is used to cover the expander lower pole and the pectoralis major muscle will cover the upper pole. A recent trend consists of providing complete coverage of the expander with acellular dermal matrix in order to potentially reduce the occurrence of capsular contracture. Using this technique, the entire expander is covered with a large sheet of acellular dermal matrix and the pectoralis major remains underneath, thus reducing postoperative pain. This method is known as pre-pectoral reconstruction. The second reconstructive time involves the placement of the definitive implant, with or without the use of fat graft for breast contour. The dermal matrix favors skin flaps thickness, in order for them to be a suitable container for the fat graft.[37,42]

1.5.8 Direct reconstruction (single surgical time)

The safety of nipple-sparing mastectomy led to an increased use of this resource. This process is more recommended in risk-reducing mastectomy scenarios, and for women with early stage breast cancer.[37,43]

By preserving the nipple-areola complex, the three-dimensional shape in maintained and it allows a suitable pocket for the insertion of a definitive implant or a free flap.

1.5.9 Reconstruction with flaps

Pedicled flaps

The latissimus dorsi muscle and the thoracodorsal artery perforator flap continue to play important roles in post-mastectomy reconstruction. These flaps are good options for obese patients, in whom reconstruction with implants is not always safe, especially when large volumes are not required. These flaps are also suitable for patients who have undergone radiotherapy and who have partial defects, since the additional blood supply provided to the reconstructed breast can help improve tissue quality by transferring non-irradiated cellular elements to the irradiated site.

Abdominal free flap

In clinical practice, breast reconstruction is performed with a free flap of lower abdominal tissue, better known as deep inferior epigastric perforator (DIEP) flap. For patients who received radiotherapy and in whom the skin was not preserved, this flap is used for delayed reconstruction, adding and replacing the necessary skin. The DIEP flap can also be obtained simultaneously with mastectomy, which allows immediate reconstructions to be carried out, especially in patients in whom using radiotherapy is not expected.

The reconstruction variant with pediculated abdominal tissue, better known as TRAM flap, is considered obsolete and should be avoided due to its morbidity at

the donor site and short-lasting results. This reconstructive option is reserved for centers where no infrastructure and microsurgery-qualified personnel are available.

Non-abdominal free flap

In this regard, options are multiple. The decision about the tissue donor site will depend on each patient's physical characteristics, as well as recipient vessels availability. Some options for this alternative include transverse upper gracilis (TUG) free flap (oblique, transverse, vertical), superior or inferior gluteal artery perforator (SGAP, IGAP) flap, profunda femoris artery perforator (PAP) free flap, lumbar artery perforator (LAP) flap, among others. The technique and success of these options is also linked to proper selection and planning.[44,45]

Fat transfer or graft

Fat transfer is an increasingly popular method for perfecting breast reconstructions. Currently, available evidence does not suggest an increased risk of breast cancer recurrence on fatty graft; it is a useful and safe complement for breast reconstruction.[46]

Reconstruction and radiotherapy considerations

The most recommended method when postoperative radiotherapy will be required is with autologous tissue. Late reconstruction is recommended at least 12 months after RT conclusion.

With a tissue expander, the same expansion volume must be maintained during planning and all radiotherapy, and making the change for the definitive prosthesis is recommended 6-12 months after having completed RT.

With definitive implants, there is 21 % of associated capsular contracture, which might cause pain or asymmetry.[47-49]

1.6 Risk-Reducing Mastectomy (RRM)

RRM is an intervention option in women at high risk for developing breast cancer.[50] Its practice has increased in recent years, due to general availability of genetic testing for women seeking information on their risk for developing said neoplasm.[51-52] The decision to perform RRM is influenced by a variety of factors, including self-perceived risk of breast cancer, anxiety generated by screening, diagnostic procedures, and expectations the patient has about surgical cosmetic results.[53]

The surgical oncologist can help in the decision-making process, providing an accurate estimate of individual risk for breast cancer, taking genetic and non-genetic factors into account (Table 12).

There are tools to calculate five-year and lifetime risk. Various mathematical models to calculate risk are available. The most widely used are the Claus model, Gail model, Tyrer-Cuzik model, etc.; however, currently there is no one that includes all risk factors.[54]

Genetic testing for people who are carriers of mutations in the BRCA 1 and 2 genes provides information on the type of mutation and lifetime risk for developing breast cancer.

There is no single risk value above which RRM is clearly indicated, and it is important that the surgeon and the multidisciplinary team explain to the patient not only the risk assessment, but also all available intervention strategies in order to facilitate a shared process in decision-making (see Chapter IV. Primary prevention). Counseling should include a discussion about the degree of protection, reconstruction options and risks. In addition, family history and breast cancer residual risk with age and life expectancy should be considered during counseling.[50]

RRM is the most effective way to decrease the incidence of breast cancer. It has been shown to reduce risk by up to 90 % in women who are carriers of mutations in the BRCA 1 and 2 genes, and by 95 % when accompanied by risk-reducing bilateral salpingo-oophorectomy (RRSO).[50]

Studies have shown that this protection is close to 95 % when a meticulous surgical technique is used to remove as much of breast tissue as possible. Cancer incidence after RRM is attributed to residual breast tissue.[55]

Available data also confer a survival advantage to higher-risk women who undergo the procedure at a relatively early age. Large studies with long-term follow-up are necessary to demonstrate the real benefit in overall survival, but patients should know that the evidence confers the greatest benefit of RRM to BRCA 1 and 2 genes mutation carriers, at an early age (under 40 years), and especially when accompanied by RRSO (from 35 years of age on).

Some considerations for selecting patients for RRM are:

- Women with a high-risk genetic mutation.
- History of familial breast cancer.

Table 12. Risk factors and their relative risk[54]

Risk factor	Relative risk
Genetic risk factors	
Female gender	114
Age	4-158
Mutation in high penetrance gene (BRCA1, BRCA2, p53, STK11)	26-36
Mutation in moderate penetrance gene (PTEN, p16, PALB2, CDHI, NFI, CHEK2, ATM, BRIP1)	2.0-2.7
History of breast cancer in mother, daughter or sister	1.55-1.8
Non-genetic factors	
Mantle field radiation (treatment of lymphoma)	5.6
Genetic risk factors	
Number of alveoli per lobe in benign breast tissue 11 to 20 (mammary involution)	2.8
21-40	3.23
C 41	1.85
Mammographic density	
25 % to 50 % (disperse densities)	2.4
20 % to 75 % (heterogeneously dense)	3.4
75 % (dense)	5.3
Lobular carcinoma in situ on breast biopsy	5.4
Atypical hyperplasia on breast biopsy	5
Increased bone mineral density	2.0-2.5
Age at first delivery (35 years)	1.31-1.93
Obesity (body mass index 30 kg/m^2)	1.2-1.8
Any breast benign disease	1.47
High level of circulating insulin	1.46
Five years on combined hormone replacement therapy (e.g., estrogen and progestin)	1.26-1.76
Nulliparity (no live births)	1.26-1.55
Consumption of more than one alcoholic beverage per day	1.31
Menarche before 12 years of age	1.21

- History of chest radiotherapy at young age (< 30 years of age).
- Lobular carcinoma in situ (lobular neoplasm in situ).

Surgical options include:

- Total mastectomy (simple).
- Skin-sparing mastectomy.
- Nipple-sparing mastectomy (NSM).

All should include axillary prolongation (tail of the breast), and pectoral fascia.

According to current evidence, the gold standard appears to be represented by nipple-sparing mastectomy, which, thanks to the preservation of the skin envelope and the areola-nipple complex (ANC), can optimize oncologic surgery and esthetic results. This technique does not appear to compromise oncological/preventive efficacy in comparison with other types of mastectomy; however, NSM must be carried out with technical skill in order for not to leave macroscopic residues of the mammary gland, particularly in the axillary prolongation, lateral and medial regions of the gland and the ANC; careful dissection and meticulous preparation of the skin flaps and ANC, which must be reasonably thin, without compromising its vitality, are necessary.[56]

Sentinel lymph node biopsy is not indicated in any procedure.[57,58]

An accurate preoperative radiographic study with mammography, ultrasound, and sometimes MRI, should always be carried out in order to rule out the presence of suspicious breast lesions and minimize the risk of occult carcinomas by definitive histological examination.

In the absence of contraindications, all patients should be candidates for immediate breast reconstruction in order to minimize the negative physical and psychological impact of mastectomy.

Breast reconstruction should be carried out by plastic surgeons, with permanent prostheses or autologous tissues; the choice of the most appropriate reconstructive technique depends on several factors, such as patient physical/anatomical structure, breast morphology/ptosis degree, comorbidities and also patient wishes and preferences.[59,60]

In NSM, complications such as partial or total necrosis of the skin flaps and the nipple can occur, as well as loss of sensitivity of the latter, which is why the patient must be informed about this before the surgical procedure. The complication rate is higher in patients with large breast volume, breast ptosis, senile patients, and smokers.

1.7 Contralateral Risk-Reducing Mastectomy (CRRM)

It is defined as a healthy-side mastectomy in a woman with unilateral breast cancer. CRRM prognostic impact is difficult to assess, since available data are largely from retrospective studies. A Cochrane review on the efficacy of this procedure concludes that CRRM

reduces the risk of contralateral breast cancer by 90 % to 100 %; however, it does not appear to have an impact on overall survival.[61] Clearly, the use of endocrine therapy and systemic chemotherapy has an impact on contralateral breast cancer development incidence decrease, and these factors should be fully considered in the decision-making process around CRRM and its actual usefulness.[52]

The practice of this procedure is increasing, many times at the request of patients themselves, given that they tend to perceive that the risk for developing contralateral cancer is higher than real risk, and that CRRM is associated with longer survival.

In patients who are not at high risk of contralateral breast cancer, a discussion about the risk associated with the procedure and the lack of a survival benefit with CRRM and a recommendation against the procedure (when it does not offer benefit) by the surgeon is effective for reducing unnecessary use.[54]

CRRM is an option for women who are carriers of BRCA 1 and 2 mutations, with early-stage breast cancer who will undergo total mastectomy.[62]

The anxiety associated with breast cancer phobia can lead to the performance of procedures without clinical benefit, and efforts in education and proper advice should therefore be broad.[63]

As we move towards an increasingly personalized and patient-centered approach to care, we must carefully consider respecting patients' preferences and autonomy.[64]

2. Adjuvant systemic treatment

In order to determine optimal adjuvant therapy, the clinical oncologist must have complete information about the tumor biological characteristics. In particular, expression or not of hormone receptors and HER-2 neu (potential therapeutic targets), since they are of significant importance for offering the best individualized treatment.

2.1 Definition, objectives and indications

Any antineoplastic treatment administered after surgical management is referred to as adjuvant; its purposes are to prolong the disease-free period, reduce local and systemic recurrences, and increase overall survival.[1-3] Adjuvant systemic treatment (hormonal therapy ± chemotherapy ± trastuzumab) should be evaluated and administered by a medical oncologist, given the degree of updating that is necessary, as well as the complications and toxicities that may be related to it.

Among patients with positive lymph nodes, given the high risk of relapse in this group, all should receive some form of adjuvant systemic treatment (chemotherapy ± hormonal therapy ± trastuzumab), regardless of the number of compromised lymph nodes (see 2.3 Genomic profiles).

In patients with negative lymph nodes, systemic adjuvant treatment (chemotherapy ± hormonal therapy ± trastuzumab) administration is recommended, when any of the following conditions exists:[4,5]

- > 1 cm tumor (more than 3 cm for favorable histologies such as tubular and mucinous cancer), with positive hormone receptors and HER-2-negative (hormonal therapy ± chemotherapy).
- > 5 mm triple-negative tumor (chemotherapy).
- > 5 mm tumor with HER-2 neu oncogene overexpression (chemotherapy + trastuzumab ± hormonal therapy).
- Genomic signature of high risk of recurrence, when available (chemotherapy + hormonal therapy).

Systemic treatment (chemotherapy ± hormonal therapy ± trastuzumab) should also be considered if any of the following characteristics is present:

- High-grade tumor.
- Presence of lymphovascular invasion.
- Oncotype DX with a score > 25 or > 50 years of age with a score of 16 to 25.[6]
- Age < 35 years.

2.2 Choice of adjuvant systemic treatment

Systemic therapy should be started as soon as possible, preferably before 6 weeks after surgical treatment. Radiotherapy and chemotherapy simultaneous use is not recommended, due to toxicity increase. When both are indicated, chemotherapy will be administered first, and, at its completion, radiotherapy will be applied. Chemotherapy and hormonal therapy are not suggested together either; the latter should be started until the conclusion of the former.

2.3 Optimal timing for starting adjuvant chemotherapy

In recent years, the impact of treatment early initiation has been described, in terms of time to recurrence reduction. Different studies have shown that the time to start adjuvant chemotherapy after definitive surgery should be less than 60 days; the longer the treatment initiation time, the higher the probability of recurrence

and death (HR, 1.20 and 1.36, respectively).[7] It should be noted that, in various studies, delays in adjuvant chemotherapy administration are more common in older patients, with more comorbidities and with sociodemographic disadvantages.[7]

On the other hand, triple-negative and HER-2-positive tumors have been shown to be the subtypes in which the delay in the start of adjuvant treatment acquires more importance (HR, 1.54 and 3.09, respectively).[7]

Recently, the results of a cohort analysis of patients with triple-negative tumors were published. This analysis describes that the start of adjuvant chemotherapy should be at less than 30 days, since it is associated with better DFS and OS and that, conversely, starting chemotherapy after this time has elapsed is associated with a 10 % lower 10-year OS.[8]

2.4 Adjuvant treatment with chemotherapy

2.4.1 General guidelines

Chemotherapy should be indicated and duly supervised by a medical oncologist, in a suitable area and with the help of nursing personnel specialized in oncology and antineoplastic drugs administration. It is necessary to have the required antiemetic drugs in order to reduce digestive toxicity, as well as colony-stimulating factors to prevent or treat neutropenia.

Use of anthracycline-based regimens is recommended, due to the modest benefit in disease-free and overall survival, when compared with first-generation regimens such as CMF.[1-3] In addition, administration of taxanes has shown moderate clinical benefit, regardless of hormone receptor expression, number of compromised axillary lymph nodes or ovarian function.[3,9,10]

In patients with triple-negative tumors, using the same already-mentioned regimens is recommended, given that so far there is not enough evidence to indicate other regimens or medications.

The greatest evidence of benefit with adjuvant chemotherapy in HER-2-negative patients is obtained with third-generation regimens:

- EC/AC followed by weekly paclitaxel.[11,12]
- AC followed by triweekly docetaxel.[13]
- TAC.[14]
- TC.[15]
- Dose-dense AC, followed by dose-dense paclitaxel.[16]
- Dose-dense AC, followed by weekly paclitaxel.[16]
- FAC or FEC followed by weekly paclitaxel.[17,18]
- FEC-100 followed by triweekly docetaxel.[19]

Dose-dense chemotherapy regimens with biweekly AC, followed by weekly paclitaxel plus filgrastim, achieve a 26 % reduction in the risk of recurrence and a 31 % reduction in the likelihood of death.[16]

Regarding the application sequence between anthracyclines and taxanes, a meta-analysis supports the use of taxanes, followed by anthracyclines, as a reasonable option in daily clinical practice. The results obtained in pathological responses, in some phase III clinical trials, also support this suggestion.

Adjuvant capecitabine should be considered in patients with triple-negative disease who do not achieve a pathological complete response to neoadjuvant treatment.[20] Adjuvant inclusion of other drugs such as gemcitabine, or platinum salts added to anthracycline and taxane regimens, is not routinely recommended, since studies so far have not shown clinical benefit.

2.5 Adjuvant treatment with hormonal therapy

Adjuvant hormonal therapy should be indicated for at least 5 years to all patients with positive hormone receptors in order to prevent metastatic disease, locoregional recurrence, and contralateral tumors. This reduces recurrence rates by 10 % to 30 % in tumors with moderate expression and 40 % to 50 % in tumors with elevated expression.[21]

The superiority of aromatase inhibitors (AIs) in the adjuvant setting over tamoxifen alone is modest: 3 % reduction in recurrence and 2 % reduction in 10-year mortality. The benefit of AIs is most valuable in the treatment of high-risk cancer (according to clinical stage or biological characteristics), and in the treatment of lobular tumors.[22]

2.5.1 Carcinoma *in situ*

For ductal carcinoma in situ (DCIS), tamoxifen (20 mg/day) for five years is recommended as relapse risk-reduction therapy in patients with breast-conserving surgery and positive hormone receptors.[23-25]

For postmenopausal women, aromatase inhibitor treatment for 5 years may be considered.[26,27]

In case of mastectomy, see Chapter XXI. Chemoprevention.

2.5.2 Invasive carcinoma

Premenopausal status at diagnosis

Tamoxifen (20 mg/day) is recommended for a duration of five years in premenopausal or perimenopausal

women with positive or unknown hormone receptor status.[25]

In women who remain premenopausal after having received chemotherapy (or who have recovered ovarian function within the first eight months after chemotherapy conclusion), and who have any high risk factor, such as being younger than 40 years, having tumors at advanced stage and/or positive lymph nodes, or tumors with adverse biological characteristics (luminal B, low ER expression, high grade and high Ki-67 proliferation index), exemestane or other AI plus ovarian ablation is recommended (SOFT and TEXT trials); tamoxifen plus ovarian ablation it is not recommended.[28,29]

The frequency of adverse events was higher in the two groups that received ovarian suppression than in the tamoxifen-alone group.

Starting with medical ablation is recommended in order to assess tolerance and adverse effects before recommending a permanent ablative method with surgery and radiotherapy.[30]

Postmenopausal status at diagnosis

Aromatase inhibitors for 5 years or sequential therapy are recommended: tamoxifen for 2 to 3 years and then continuing with an aromatase inhibitor for 7 to 8 years or tamoxifen for 5 or 10 years, according to risk factors (tumor size, positive lymph nodes, grade), intolerance, contraindication or lack of access to aromatase inhibitors.[31]

2.5.3 Extended adjuvant hormonal therapy

Extended hormonal therapy is aimed at patients at high risk for late recurrence: > 2 cm tumors plus associated risk factors such as positive lymph nodes, high-grade tumors, premenopausal status, high risk for second primary cancer. Prior to considering the prescription of extended therapy, it is important for life expectancy, presence of high-risk clinicopathological factors, previous treatment tolerance, each patient's comorbidities and side effects to be evaluated.[30,31]

The results of the tamoxifen studies ATLAS,[32] aTTom,[33] five of AIs,[33-39] and ASCO 2018 guidelines[31] justify extended adjuvant hormonal therapy (HT) for up to 10 years in patients with positive lymph nodes. In the case of premenopausal women, tamoxifen has increased overall survival rate, and in postmenopausal patients, an AI is associated with a lower risk of breast cancer and contralateral breast cancer recurrence in comparison with placebo.[34-39]

According to the results of the MA-17 trial, in premenopausal women who at the end of 5 years of adjuvant treatment have become postmenopausal, continuing with AIs for 5 more years can be considered.[30,38-39]

Menopausal women are defined as patients with bilateral oophorectomy, age ≥ 60 years, age ≤ 60 years and amenorrhea for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol levels at postmenopausal ranges. In case of being on treatment with tamoxifen and being ≤ 60 years of age, FSH and serum estradiol levels at postmenopausal values are necessary. In women who at the beginning of chemotherapy are premenopausal, amenorrhea is not a menopausal status indicator, and carrying out serial measurements of these hormonal levels is therefore recommended prior to the aromatase inhibitors indication.[39,40]

2.6 Adjuvant treatment with targeted therapies (trastuzumab/pertuzumab)

In patients with tumors with HER-2 neu +++ overexpression by IHC or FISH +, the use of the monoclonal antibody trastuzumab in combination with adjuvant chemotherapy has allowed obtaining benefits both in relapse-free survival (HR, 0.62) and overall survival (HR, 0.66).[41-43]

Starting adjuvant treatment with trastuzumab together with taxane-based chemotherapy after the use of anthracyclines is recommended, given that this sequence has been shown to be useful and safe.[44]

Trastuzumab and anthracyclines simultaneous administration is not recommended, given that it increases cardiotoxicity.

The TCH regimen (docetaxel, carboplatin and trastuzumab) for six cycles, without the use of anthracyclines, should be considered in patients at high risk of cardiovascular disease (history of heart failure, older age, hypertension, obesity or previous use of anthracyclines).[45,46]

Currently, the duration of adjuvant treatment with trastuzumab is recommended to be one year, since administration for less or more time have so far not demonstrated better results.[46-49]

In selected cases with negative lymph nodes and small tumors (< 3 cm), the weekly paclitaxel + trastuzumab regimen for 12 weeks, followed by trastuzumab every 3 weeks until completing one year, may be an option.[50]

Patients receiving trastuzumab should be carefully evaluated due to the risk of cardiotoxicity, especially those with a personal history of heart disease or high risk. Left ventricular ejection fraction (EF) should be assessed prior to starting this agent, every 12 weeks and at treatment completion. All patients receiving this drug should be monitored with echocardiography or nuclear scintigraphy in order to early detect ventricular function decrease (Table 13).

Currently, the use of adjuvant anti-HER-2 double blockade (trastuzumab + pertuzumab) can also be considered, but only in patients with positive lymph nodes.[51,52]

Table 13. Behavior to be followed for cardiologic surveillance and drug dose adjustment

	LVEF absolute decrease		
	< 10 %	10-15 %	>15 %
Normal LVEF	Continue	Continue	Discontinue
1 % to 5 % below LVEF NL	Continue	Discontinue*	Discontinue*
> 5 % below LVEF NL	Discontinue*	Discontinue*	Discontinue*

2.7 Bisphosphonates and receptor activator of NF-KB ligand (RANKL) inhibitors in the adjuvant setting and with aromatase inhibitors

Both bisphosphonates and receptor activator of NF-KB ligand (RANKL) inhibitors allow improving bone health outcomes by reducing osteopenia or osteoporosis secondary to systemic treatment.[53-55]

– Adjuvant therapy
  - Bisphosphonates as adjuvant therapy are recommended for postmenopausal women or premenopausal women treated with gonadotropin-releasing hormone (GnRH) analogues, with early breast cancer and high risk of recurrence.
  - Treatment should be started together with (neo) adjuvant CT and continued for 2 to 5 years.
  - Zoledronic acid recommended dose is 4 mg IV every 6 months.
  - Bisphosphonates, as disease-modifying agents, are not recommended in premenopausal women, and in men or women with other solid tumors either.
  - Denosumab is not recommended for the prevention of metastasis.[56,57] (Figure 14)

Aromatase inhibitors (AIs)-related bone loss

– Patients starting with an AI should undergo hip and spine bone mineral density (BMD) measurement, as well as an assessment of risk factors for fracture following the behaviors indicated in Figure 15.

Zoledronic acid 4 mg IV is recommended every 6 months for the 5 years of AI therapy or denosumab 60 mg SC every 6 months for 2 years.

Bone turnover biomarkers determination is not routinely used in patients receiving AI.[59,60]

Recommendations with the use of bisphosphonates and RANKL inhibitors[59-62]

– Oral evaluation prior to their administration.
– Oral cavity examination every 6 to 12 months.
– Avoid dental surgeries during treatment.
– Not recommended in patients with preexisting oral infections or poor oral hygiene.
– Zoledronic acid is contraindicated in patients with creatinine clearance < 30 mL/min.
– Denosumab should be used with caution in patients with creatinine clearance < 40 mL/min.
– The patient should receive calcium (1,200 mg) and vitamin D (1,000 mg) daily supplements.
– Control bone mineral density every 1 to 2 years.

2.8 Genomic profiles and systemic adjuvant therapy

Genomic profiling tests can be used to support prognosis and/or decision making for administering systemic adjuvant therapy in patients with ER/PR-positive, HER-2-negative tumors. They should not be used in patients with triple-negative or HER-2-positive tumors. The recommendations for the use of the four molecular signatures available in Mexico (Oncotype DX, MammaPrint, Endopredict and PAM50) are the following.

2.8.1 Oncotype DX

Test involving 21 genes with prognostic and predictive value, with a wide validation in which a recurrence score is generated according to the expression of each one of the genes. It is recommended in HR-positive, HER-2-negative, 1.1 to 5 cm tumors (or 0.5 to 1 cm and any unfavorable characteristic: moderately or poorly differentiated or lymphovascular invasion) and negative axillary lymph nodes.

In case of recurrence score < 26, only endocrine therapy is recommended; 26 to 30, endocrine therapy + adjuvant chemotherapy; and > 31, endocrine therapy + adjuvant chemotherapy.

In women aged < 50 years with a score of 16 to 25, consider adding adjuvant chemotherapy for benefit in

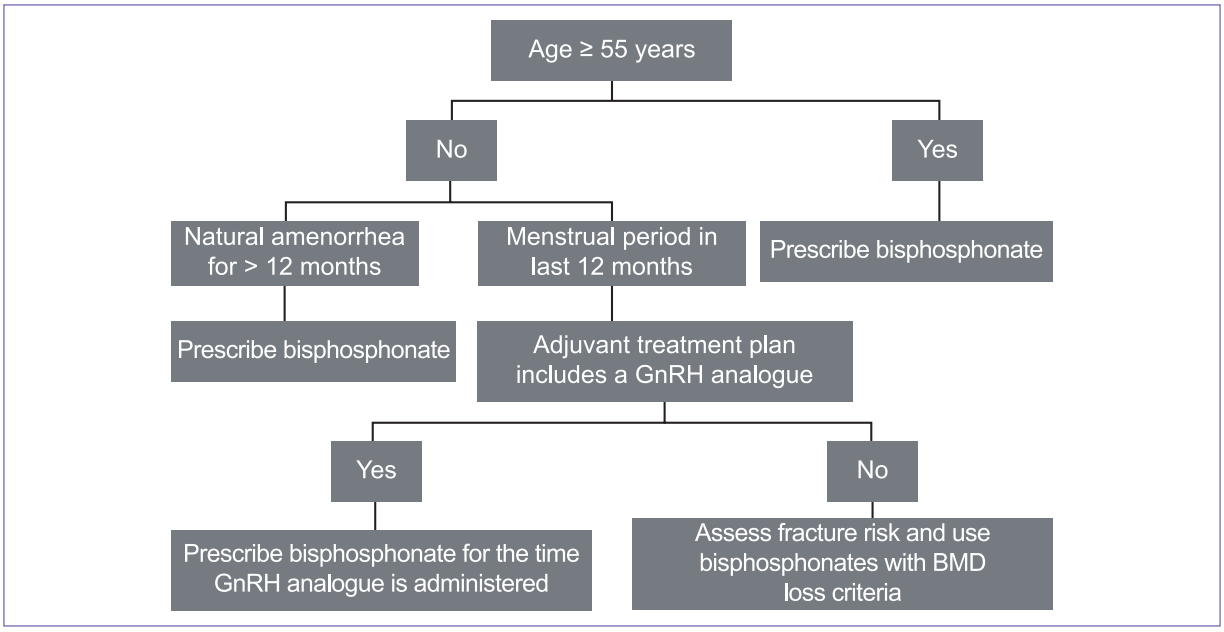


Figure 14. Decision flow chart for treatment with bisphosphonates as adjuvant therapy[58].

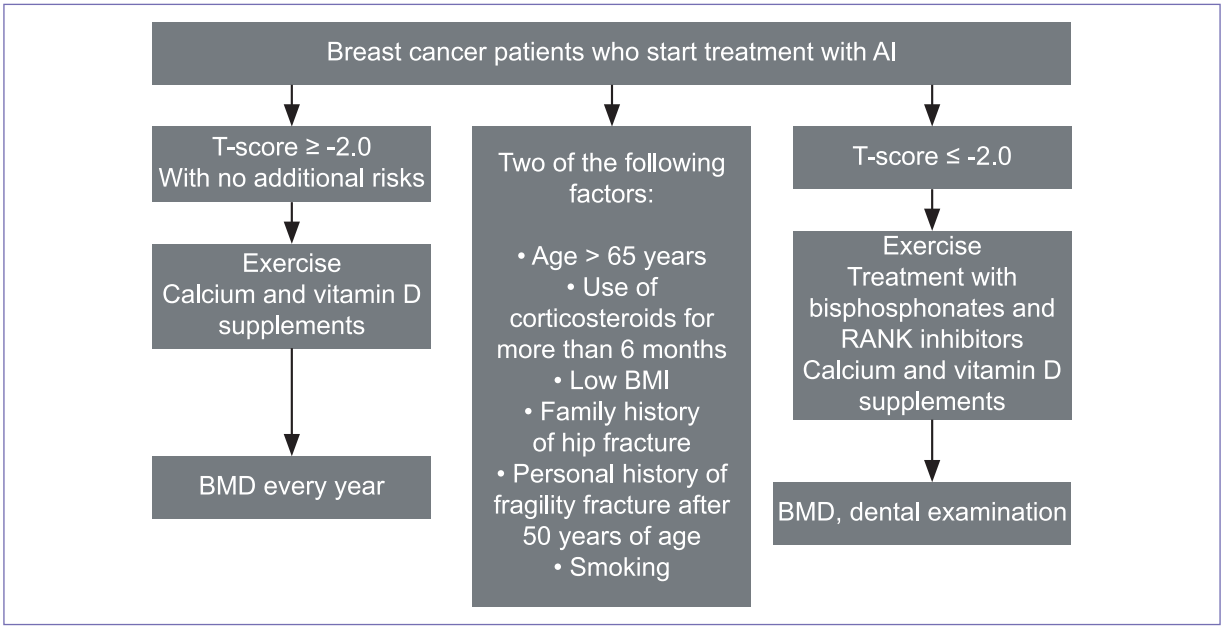


Figure 15. Flow chart for assessing fracture risks.

distant recurrence.[63,64] It can also be used in postmenopausal patients with hormone receptor-positive tumors, 1 to 3 positive lymph nodes. In postmenopausal women with a recurrence score < 25, adjuvant chemotherapy administration may be omitted due to lack of benefit in invasive disease-free survival. In the group of premenopausal women with 1 to 3 positive lymph nodes, the use of Oncotype is not recommended for decision-making regarding systemic adjuvant therapy.[65]

2.8.2 MammaPrint

Test involving 70 genes that has prognostic utility whereby a result regarded as low or high genomic risk is generated. It is recommended in patients with hormone receptor (HR)-positive, HER-2-negative, smaller-than-5 cm tumors, negative axillary lymph nodes and high clinical risk (> 3 cm; > 2 cm if moderately or poorly differentiated; > 1 cm if poorly differentiated). Endocrine therapy without chemotherapy is recommended in patients with a low genomic risk outcome. It can be used in patients with positive hormone receptors, 1 to 3 positive lymph nodes and high clinical risk (> 2 cm; or moderately/poorly differentiated). In patients with positive lymph nodes and low genomic risk, the benefit of adjuvant chemotherapy in metastasis-free survival is limited.[66]

2.8.3 EndoPredict

Twelve-gene test that can be used in patients with HR-positive, T1 or T2 HER-2-negative tumors and negative lymph nodes. Patients with a low risk score (< 3.3287) have a prognosis similar to T1a-T1b N0 M0, with a 10-year distant recurrence rate of 4 %. Patients with 1-2 positive lymph nodes and a low risk score have a 10-year likelihood of distant recurrence of 5.6 %.[67]

2.8.4 PAM50 (Prosigna)

It can be used in patients with HR-positive, HER-2-negative, T1 or T2 tumors, and negative lymph node status. Patients with a low recurrence score (0-40) have a prognosis similar to that of T1a-T1b N0 M0. In patients with 1-3 positive lymph nodes and a low recurrence score, the risk of 10-year distant recurrence is lower than 3.5 % if they are treated only with endocrine therapy.[66]

2.9 Breast cancer medical treatment-derived mid- and long-term toxicity

Early diagnosis and new therapeutic advances implementation have improved the prognosis of patients with early breast cancer and significantly increased the number of survivors. Hence, knowing medical treatment-derived toxicities and being familiar with their recommended management is essential given the huge impact they produce on patients' quality of life.[68]

2.9.1 Cardiotoxicity

Anthracyclines

Cardiotoxicity related to the use of adriamycin or epirubicin occurs as an asymptomatic systolic dysfunction, with a decrease in ejection fraction (EF) of up to more than 15 % when doxorubicin cumulative doses higher than 240 mg/m^2 are used. The risk for the development of cardiotoxicity with epirubicin is 1 % with cumulative doses of 550 mg/m^2 and 1.5 % with cumulative doses of 700 mg/m^2; the risk increases significantly with higher doses, which is why doses higher than 900 mg/m^2 are not recommended. A small percentage of patients can experience heart failure, which increases with cumulative dose and generally is not reversible.[69]

Associated risk factors

- Age older than 65 years.
- History of hypertension or cardiac comorbidities.
- High cumulative doses (1 % risk with doses of 240 mg/m^2, 5 % with 400 mg/m^2, and a dramatic risk increase from 550 mg/m^2 on with adriamycin).
- History of radiation to the mediastinum.
- Combination with trastuzumab.

Recommendations:

- Perform baseline echocardiogram or multigated acquisition scan (MUGA) in patients older than 50 years or in young women with cardiac comorbidities.
- Do not exceed the dose (risk is low with AC x 4, FAC x 4, EC x 4 or FEC x 4).
- Clinical monitoring of symptoms and, where appropriate, timely referral to the cardiology department.

Trastuzumab

Trastuzumab-related cardiotoxicity is generally reversible and is associated with damage caused by anti-HER-2 blockade at the level of cardiac myocytes. The incidence of heart failure ranges from 1.5 % to 5 %, but that of EF asymptomatic decrease is 4 % to 20 %. Risk factors are unclear; however, older patients, with baseline EF of 50 % to 54 %, cardiac comorbidities and who use antihypertensive drugs are known to be at higher risk.[70,71] The risk of cardiotoxicity may be higher in those who are treated with sequential anthracyclines.

Management with beta-blockers and angiotensin-converting enzyme inhibitors improves ejection fraction and, in many cases, cardiac function can be normalized. In selected patients, reinitiating treatment with

trastuzumab is possible, but this should only be done in those who are managed jointly with a cardiologist.

Recommendations

- Echocardiogram or MUGA scan prior to starting treatment and every 3 months until its completion (months 0, 3, 6, 9 and 12).
- If there is EF decrease, discontinue trastuzumab and treat heart failure.
- If EF improves, resuming the treatment is possible under close supervision by the cardiology department.

2.9.2 Leukemia and myelodysplastic syndrome

Acute myeloid leukemia and myelodysplastic syndrome have been associated with the use of alkylating agents and occur between 5 and 7 years after treatment.[72] An increased risk for secondary hematological neoplasms has also been reported with topoisomerase II inhibitors administration, including anthracyclines, and they usually occur 3 to 5 years after their use. The risk associated with the use of taxanes is not well characterized, given the relatively recent introduction of this type of drugs. After antineoplastic therapy, 5-year cumulative rate is 0.24 %, but it rises to 0.48 % 10 years after treatment conclusion. In comparison with patients treated only with surgery, those who receive chemotherapy have a 6.8-fold higher risk, and the risk increases 7.6 times if they are treated with chemotherapy and radiotherapy; however, it is important to remember that the absolute number of patients who develop a secondary hematologic malignancy is small, with a rate of 0.46/100 person-years in patients treated with chemotherapy.[73]

2.9.3 Neuropathy

Neuropathy is a highly common complication in patients receiving treatment with taxanes. The incidence ranges from 13 % to 27 % and varies according to the type and frequency of the taxane used.[74] In severe cases, this complication can become disabling and permanent. Factors associated with this toxicity include: advanced age, ethnicity, obesity, diabetes mellitus, and history of alcohol abuse. To date, there is no efficacious preventive method and therapeutic options have limited benefit.[75,76]

Treatment

- Duloxetine.
- Gabapentin, pregabalin. Limited benefit in clinical trials; their effect appears at high doses and after weeks to months of treatment. Their administration is limited by the somnolence and tiredness that they cause.
- Opioids in severe cases.
- Antidepressants. Nortriptyline, venlafaxine and fluoxetine have shown effects in the management of diabetic neuropathy and postherpetic neuralgia. There are no data in patients with neuropathy associated with the use of taxanes.
- Acupuncture.
- Relaxation therapy.
- Occupational therapy.
- Electrical neurostimulation.
- Massage.

2.9.4 Fatigue

This is the name given to a persistent sensation of tiredness that is disproportionately associated with physical activities. It occurs in up to 80 % of chemotherapy-treated patients and persists for 6 to 12 months after treatment completion in 30 % of cases. Unfortunately, therapeutic strategies are limited, with symptom improvements occurring slowly. On the other hand, evidence has demonstrated that increasing physical activity is the most efficacious strategy for improving fatigue.[77]

Recommendations

- Assess for the presence of fatigue at regular intervals.
- If fatigue is moderate-severe, rule out other causes (disease recurrence, wakefulness-sleep disturbances, depression, anxiety, pain, nutritional abnormalities, hypothyroidism, vitamin D deficiency, etc.) and treat accordingly.

Interventions

- Physical activity increase (150 min of moderate aerobic exercise per week and two to three strength training sessions).
- For patients who are not in conditions to exercise, walking is recommended or, at least, physical therapy.
- Cognitive and psychosocial interventions. Relaxation techniques, support groups, etc.
- Mind-body interventions. Yoga, acupuncture, massage.
- Pharmacological interventions. This type of strategies should be considered only when all previously-mentioned alternatives have been evaluated.

Modafanil or methylphenidate can be used; randomized trials have demonstrated little efficacy in patients with breast cancer, but there can be improvement in severe fatigue cases. Evidence suggests that symptom improvement is common when modafanil is used during

treatment, with limited efficacy in patients who have completed therapy.[78,79]

2.9.5 Cognitive dysfunction

The causes of this complex toxicity that occurs in the medium and long term are so far unclear. The incidence of cognitive damage secondary to chemotherapy is 20 % to 30 %. There are reports indicating that 17 % to 75 % of women suffer cognitive changes owing to the implemented treatment and probably also due to the impact caused by diagnosis. Currently, there are no proven interventions for the prevention or management of breast cancer diagnosis- and treatment-related cognitive alterations; international guidelines do not propose specific directions either.[80] In patients with persistent cognitive impairment, neurocognitive evaluation is essential.

2.9.6 Medical treatment-induced menopausal symptoms

The prevalence of chemotherapy- and hormonal therapy-induced climacteric symptoms (hot flashes and night sweats, vaginal dryness and atrophy, incontinence, dyspareunia, insomnia, irritability, arthralgia, fatigue) varies according to age, type of treatment and number of administered chemotherapy cycles. These symptoms get to occur in more than 40 % of patients.

Since hormone replacement therapy is contraindicated (see Chapter XX. Hormone Replacement Therapy, HRT), multiple medications have been used as pharmacological management with generally unsatisfactory results.

Recommendations

- Physical exercise.
- Paused breathing.
- Muscle relaxation, meditation, yoga.
- Cognitive-behavioral therapy.
- Combination of behavioral interventions.
- Hypnosis.
- Acupuncture.
- Venlafaxine.[81]

2.9.7 Chemotherapy-induced ovarian failure

All patients of childbearing age should receive counseling on the probable loss of ovarian function and be referred to an oncofertility specialist if possible. There are important advances in this field: there are clinics in this area that propose cryopreservation or ovarian stimulation or ovarian protection protocols, with a good safety margin. There is evidence that goserelin simultaneously administered with chemotherapy in patients with hormone receptor-negative tumors helps to preserve ovarian function. A more detailed review of this subject can be found in the section on breast cancer in younger women.

In breast cancer survivors, limited evidence suggests that post-treatment pregnancy does not increase recurrence rates and neither compromises the baby's health. Patients who wish to become pregnant are advised to do it 2 to 3 years after chemotherapy conclusion. All should receive close counseling from their oncologist and their gynecologist.[82]

3. Postoperative radiotherapy in early breast cancer

Radiotherapy initiation timing should be a priority factor for doctors and authorities. Radiotherapy initiation after breast-conserving surgery without adjuvant chemotherapy should occur within the first 8 weeks, after neoadjuvant chemotherapy and surgery, within 30 days and after surgery and adjuvant chemotherapy within the first month (do not delay more than 7 months after surgery).

3.1 Postoperative radiotherapy in women treated with breast-conserving surgery (stages T1-T2, N0)

Patients treated with breast-conserving surgery should receive external-beam radiotherapy to the breast. The dose shall be 40 to 42.5 Gy in hypofractionation, or 50 Gy in standard fractionation.[1] Additional dose to the surgical bed (boost) shall be 10-16 Gy, depending on the clinical context. It is recommended that the surgeon should place radiopaque references at the surgical bed in order to facilitate higher precision in the boost administration.[2]

3.1.1 Hypofractionation

Hypofractionation (higher dose per fraction, lower number of fractions and less treatment total time) is carried out with 3D planning. It is recommended for the PTV 95 % volume coverage to receive 95 % of the dose and not more than 105 % with regard to the prescribed dose.[1] Hypofractionation offers the same local control as standard fractionation without negatively impacting on the cosmetic result.[1]

3.1.2 Hypofractionation at early stages

Hypofractionated radiotherapy is indicated after breast-conserving surgery for invasive carcinoma. Moderate hypofractionation schemes administer doses of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions. Five-year results of extreme hypofractionation with 26 Gy in 5 fractions are not inferior to moderate hypofractionation schemes in local control and cosmesis.[3] The decision to prescribe these schemes should be at radiation oncologist's judgement, provided the restriction doses to healthy organs specified for each scheme are complied with (Table 14).[4]

Table 14. Restriction dose to healthy organs

Scheme	Total dose/fr.#	Ipsilateral lung/ heart DVH
Breast cycle moderate hypofractioning	42.6 Gy/16fr. 40 Gy/15fr.	V16 %<16 %
Extreme hypofractioning	26 Gy/5fr.	Ipsilat lung V8 <15 % Heart V7 <5 %, V1.5 %<30 %
Breast partial irradiation Intraoperative IMRT /3D	20 Gy/1fr. 40 Gy/10fr. 30 Gy/5fr.	Skin >5 mm. Contralat lung V5 <10 % Ipsilat lung V10 <20 % Heart V3 <10 % Ipsilat healthy breast V15 <50 % Contralat breast Dmx 1 Gy

3.1.3 Accelerated partial breast radiotherapy

It is an alternative treatment that only includes the radiation target to the area surrounding the lumpectomy cavity after breast-conserving surgery. The criteria for treating patients with this modality are: age > 50 years, < 2 cm tumors, negative lymph nodes, surgical margin > 2 mm, positive estrogen receptors.[5-11]

Modalities for this approach include interstitial brachytherapy, intraoperative radiotherapy and intensity-modulated radiotherapy (IMRT).[12-15] Brachytherapy is the technique with the most information and follow-up with a 10-year local control comparable to 3D external-beam radiotherapy, with standard fractionation, but with less skin toxicity and better cosmetic results.[16]

The IMRT technique has favorable and comparable results to those with 3D external-beam radiotherapy with standard fractionation.[17] Heart disease patients with left breast cancer who meet the aforementioned criteria obtain greater benefit because the dose to the heart is lower.[18]

3.1.4 Surgical bed boost

In selected patients, after breast-conserving surgery, an additional radiotherapy dose to the surgical bed should be offered due to the risk of local recurrence.[19]

Based on international guidelines, this treatment is offered with doses of 10-16 Gy: Women aged < 50 years, 51-70 years with high-grade tumors, positive unresectable margins, > 3 cm tumors, extensive intraductal component, lymphovascular invasion, lymph node involvement, multicentric or multifocal disease or residual disease after neoadjuvant chemotherapy.[20,21] Dose escalation to > 16 Gy can be considered in patients aged < 40 years with close or positive margins with triple-negative disease.[19] The boost can be omitted in patients who meet the following characteristics: Women aged > 70 years with low- or intermediate-grade tumors, positive hormone receptors with resection margins > 2 mm.[20-22] Women aged > 50 years with < 3 cm unicentric, unifocal tumors, without lymph node involvement, with resection margin > 2 mm, with no lymphovascular invasion, or extensive intraductal component, or triple-negative disease who are to receive endocrine therapy.[20-22]

3.2 Indications for postoperative radiotherapy to lymph node chains

In patients with pT1-2 and pN1-3 disease, the need for radiotherapy should be determined based on the following clinical and histopathological factors: Age <4 0 years, capsular rupture or more than two of the following factors: Premenopausal status, negative hormone receptors, lymphovascular invasion, high-grade tumors, initial tumor ≥ 2 cm and extensive intraductal component.[23]

3.3 Radiotherapy associated with chemotherapy, targeted therapies and hormonal therapy

The use of radiotherapy concomitant with chemotherapy is not recommended. There is no information to contraindicate radiotherapy concomitant administration with targeted therapies. Concomitant use of hormonal therapy with radiotherapy has not shown a statistically significant increase in pulmonary, cardiac or skin toxicity;

however, hormonal therapy initiation after radiotherapy allows treating physicians to know to which of the two treatments to attribute certain adverse effects.[24]

XI. Neoadjuvant management

1. Introduction

Although neoadjuvant therapy was initially used at locally advanced stages, this treatment modality is currently also used in patients with tumors initially considered operable, larger than 2 cm and/or with positive lymph nodes, which is why this chapter comprises the treatment of stage III breast carcinomas and certain cases of stage IIA/IIB tumors or T2-3 N0 M0, and T1-2, N1 M0, stages,[1] especially the HER-2-positive or triple-negative subtypes.

Initial approach to these patients should include:

- Clinical evaluation.
  - Bilateral mammography and breast and axillary ultrasound and/or MRI in indicated cases.
  - Primary tumor core needle biopsy and axillary lymph nodes fine needle aspiration biopsy (FNAB).
  - Complete histological evaluation that includes hormone receptors and HER-2 neu determination.
  - Imaging studies of the primary tumor and potentially metastatic sites by chest X-ray or CT, abdominal ultrasound or CT, bone scan (the latter for patients with stage III tumors). 18-FDG PET-CT is an alternative for staging.
- The following is also suggested:
  - Placement of a radiopaque clip on the tumor bed and/or axillary lymph nodes in patients who are candidates for breast-conserving surgery and/or sentinel lymph node procedures.
  - Determination of a monogenic (BRCA) or mutigenic panel in patients with triple-negative tumors or hereditary cancer suspicion.
  - In premenopausal women, consider the possibility of using LHRH analogues to preserve fertility and/or ovarian function and timely reference to the reproductive biology department.

The therapeutic proposal should be defined by the multidisciplinary medical group and must be based on each patient's characteristics (age, menstrual status, concomitant diseases, preferences, etc.), clinical status of the disease and primary tumor histological and immunohistochemical variables.

Even if the patient has a tumor at locally advanced clinical stage, initial surgery is recommended when the disease is technically resectable, the breast-conserving surgery option is not desired by the patient, in tumors with favorable histologies (e.g., well-differentiated tumors, mucinous or tubular histology, positive hormone receptors with high titers, HER-2-negative) or low probability of response to chemotherapy with a high risk of toxicity.[1]

1.1 Advantages of neoadjuvant chemotherapy

- Allows locoregional breast and axillary surgical management de-escalation.
- Pathological response evaluation.
  - Pathological complete response (pCR) defined as ypT0/is, ypN0
  - This outcome is associated with better prognosis (HR for OS: 0.36; 95 % CI 0.30-0.44).[2]
- Allows adjuvant treatment individualization based on initial response to chemotherapy.

1.2 Disadvantages of neoadjuvant chemotherapy

- Loss of initial staging information.
- Possibility of over-treatment if the information is based on incomplete data (for example, the lesion size may be overestimated due to the association of carcinoma in situ observed by imaging).
- Disease progression, which can occur in 2 % of cases.
- Increased probability of recurrence (15.7 % vs. 5.6 %) in patients treated with breast-conserving surgery in comparison with those treated with mastectomy.[3]

If the patient starts with neoadjuvant chemotherapy, primary tumor site marking with radiopaque clip is recommended for adequate surgical evaluation.[4] It is important to highlight that, prior to neoadjuvant treatment, the number of lesions, their location, distance to the skin and chest wall, as well as extension towards the nipple should be documented and recorded.

The possibility of obtaining a pCR after neoadjuvant therapy is known to be related to the cancer subtype: hormone-sensitive/HER-2-negative, 7 %; triple-negative, 30 %; and HER-2 positive, 32 % to 67 %.[5] In HER-2-negative hormone-sensitive tumors, the use of genetic signatures (Oncotype DX) can predict the response to neoadjuvant chemotherapy (higher in RS > 30); thus, if this resource is available, its use can be considered.[6]

2. Neoadjuvant chemotherapy and targeted therapies

The recommended neoadjuvant treatment is based on 6–8 chemotherapy cycles since they are associated

Table 15. Recommended neoadjuvant chemotherapy regimens according to tumor subtype

	Hormone-sensitive tumors	HER2-positive tumors	Triple-negative tumors
Recommended regimens	ddACx3-4 cycles followed by taxanes* Acx3-4 cycles followed by taxanes	ACx 4- Taxane + trastuzumab + Pertuzumab x 4 or TCHP x 6 or ACx4-Paclitaxel/trastuzumab x12	ddACx4-ddPaclitaxelx4 ddACx4- weekly paclitaxel x 12+Carboplatin ACx3-4-Docetaxelx3-4 +Carboplatin

with a higher likelihood of pCR.[5,7] The main recommended regimens are specified in Table 15.

Addition of other drugs to the neoadjuvant regimen such as gemcitabine, capecitabine and nab-paclitaxel is not indicated. Although concomitantly-administered immunotherapy (check-point inhibitors, i.e., pembrolizumab/atezolizumab) for triple-negative tumors has been shown to increase the rate of pathological complete response, it is not yet approved in our country and, therefore, it is not recommended.[8,9]

As for HER2-positive tumors, HER-2 double-block therapy with lapatinib, neratinib, or TDM-1 is not recommended.

2.1 Inflammatory breast cancer

Inflammatory breast cancer should be treated with neoadjuvant chemotherapy (plus trastuzumab/pertuzumab in tumors with HER-2 neu overexpression). Based on the response to systemic treatment, locoregional management with modified radical mastectomy and postoperative radiotherapy should be evaluated. If the response to neoadjuvant chemotherapy is poor and the tumor is not resectable, radiotherapy and then radical surgery may be considered.

3. Neoadjuvant hormonal therapy

Neoadjuvant hormonal therapy is recommended in postmenopausal women with positive hormone receptors and stages II-III or in patients in whom chemotherapy toxicity is not acceptable or who have multiple comorbidities. The aim is to increase the possibility of tumor resection and/or breast-conserving surgery. The use of neoadjuvant endocrine therapy has been associated with pathological complete response rates of 14 %, with a high likelihood rate for breast-conserving surgery to be performed.[10]

The use of an AI is recommended. After starting hormonal therapy, if an objective response is obtained, continuing it for at least 4-6 months is recommended, followed by local surgical treatment. Continuing hormonal therapy or adjuvant chemotherapy will be considered according to the pathological response and patient conditions.[11]

The use of CDK 4/6 inhibitors in combination with neoadjuvant aromatase inhibitors is not indicated.[12]

4. Response evaluation during neoadjuvant treatment

Response should be evaluated after each chemotherapy cycle and, after three to four cycles, clinically assessing the response is recommended. In cases with stable disease and/or progression, radiological correlation is suggested; mammography, tomosynthesis and ultrasound are adequate to evaluate the response to neoadjuvant treatment.[13] If there is objective response, neoadjuvant treatment should be continued until its completion. Otherwise, if there is no response or signs of progression are observed, a change in the chemotherapy regimen (taxanes or anthracyclines) for two to four additional cycles may be considered and, subsequently, according to the response, evaluate surgery and/or radiotherapy.

Although the best imaging method to evaluate the response is magnetic resonance imaging of the breast, given that it has the highest correlation with pathological response, it is not indispensable or is not available in all centers. In case of having access to this method, also performing it before starting systemic treatment is recommended in order to have a baseline comparison. On the other hand, it is important to note that MRI tends to overestimate or underestimate residual lesion size according to the type of response (concentric or fragmented).[14]

Fragmented response is particularly difficult, since only in 65 % of cases a reduction of more than 50 % in the lesion size is observed; this should be

individually evaluated and probably consider the use of oncoplastic surgery to ensure a negative margin.[15]

5. Treatment after neoadjuvant therapy

5.1 Surgical treatment

Current trend in surgery is to achieve a good oncological result, reducing its extent and morbidity; the performance of breast-conserving and sentinel lymph node surgery, instead of elective axillary dissections and mastectomy, is an example of this trend.

In theory, surgery after neoadjuvant treatment allows the possibility of breast-conserving surgery to be increased; however, this only happens with proper planning of the procedure to be performed. Patients considered for neoadjuvant treatment should be evaluated by the surgeon prior to the start of treatment. Important strategies in surgery planning include preoperative marking of both the primary lesion and suspicious lymph nodes, and the decision of the type of study to be performed to assess the response to systemic treatment. Currently, breast-conserving surgery after neoadjuvant treatment has shown the same result in terms of overall survival and disease-free period in comparison with mastectomy.[2]

The process to be followed in surgery planning is similar to the case of primary surgical treatment. Non-palpable lesions should be preoperatively localized; this can be done with harpoon-shaped guided wires or radioactive seeds if this resource is available; both strategies are adequate and equivalent in effectiveness for marking the lesion. After a complete clinical or radiological response, the area with the clip should be resected with a portion of surrounding tissue, without the need to enlarge the area where the lesion was initially located. An imaging study of the resected tissue should be performed to confirm the presence of residual lesion and/or pre-treatment marking.[16] Considering all subtypes, the possibility of being eligible for breast-conserving surgery after neoadjuvant CT is 69-87 %, and with neoadjuvant endocrine therapy, it is around 77 %.[17-18]

Currently, the use of core needle biopsy after neoadjuvant CT in patients with complete or partial radiological response (and an area of enhancement of less than 2 cm on MRI) is not adequate for determining pathological complete response (false negatives of 37 % - 71 %), which is why surgery should continue to be considered the standard.[19]

In case the requirements for breast-conserving surgery are not met, total mastectomy should be performed. Axillary management is independent of breast management.

5.2 Adjuvant systemic treatment

In patients with positive hormone receptors, hormonal therapy will be indicated.

(see Chapter X).

In HER-2 neu-positive tumors that show pathological complete response, trastuzumab/pertuzumab or trastuzumab will be continued until completing 1 year of treatment.

In triple-negative tumors that do not achieve pathological complete response, i.e., that have had residual disease in the breast and/or axilla, capecitabine administration for 6 months (8 cycles) is recommended.[20]

In HER-2 neu-positive tumors that do not achieve pathological complete response, the use of triweekly TDM-1 for 14 doses is recommended.[21] If the drug is not available, continuing with trastuzumab is suggested.

5.3 Radiotherapy

5.3.1 Indications

Radiotherapy to the breast or chest wall and axillary-supraclavicular lymph node regions and internal mammary chain is a standard in patients with locally-advanced breast cancer. Its indication is independent of the response to neoadjuvant chemotherapy and should be offered based on clinical stage at diagnosis.[22,23]

Patients who obtain the highest benefit in local control and disease-free survival are those with ypN2-3 disease and patients with triple-negative and pure HER-2 neu molecular subtypes.[24,25]

Indications include:

- T3 or T4 initial tumors.
- Positive surgical margins.
- More than 3 positive axillary lymph nodes (N2).
- Breast-conserving surgery after neoadjuvant chemotherapy.

The recommended radiotherapy dose to the chest wall and lymph node-bearing areas is 50 Gy. In case of positive margin, administering an additional dose to the chest wall is recommended.[22-27]

Hypofractionation at advanced stages

Although there are studies with favorable results, the use of hypofractionated radiotherapy is not a standard in mastectomized patients with locally-advanced breast

cancer.[28,29] Hypofractionation is not used in any case in mastectomized patients with breast reconstruction.[30]

5.3.1.2 Indications for the use of modern techniques

Currently-available various techniques allow to improve the distribution of the dose in the volume to be irradiated and to reduce the radiation dose to healthy tissues. Table 16 summarizes the precise indications for their use:[31-33]

Table 16. Indications for the use of modern radiotherapy techniques

Deep inspiration breath-hold technique
It decreases doses to coronary arteries in left breast cancer[34]
Intensity-Modulated Radiation Therapy or Volumetric Modulated Arc Therapy
These techniques reduce the incidence of radiodermitis[35] They improve the coverage of lymph node areas when this is not possible with conformal RT [36] Unfavorable anatomy (Pectus excavatum, pectus carinatum, barrel chest o kyphoscoliosis)
Bolus in mastectomized patients
It is used to achieve adequate irradiation of the skin. The use of wet gauze is strongly discouraged. Its efficacy to prevent recurrences in the chest wall has not been proven.[37] It is used at the discretion of the treating radiation oncologist

5.3.2 Inflammatory disease

Patients with T4d disease require postoperative radiotherapy to decrease the potential for progression. Total dose with conventional fractionation is 60 Gy.[38,39] This dose can be scaled to 66 Gy in case of residual disease after neoadjuvant chemotherapy, close or positive margins, or in patients younger than 45 years.[39] Radiotherapy should be directed in the first phase to the thoracic wall and all lymph node regions, including the internal mammary area, and in the second phase, to the chest wall; photon, electron or both fields can be used, making sure to obtain an adequate coverage of the dose on the skin.[40]

5.3.3 Radiotherapy-related toxicity

The tolerance doses of at-risk organs close to the irradiation zone should be respected. These dose restrictions have been established for each organ and treatment volume in particular by the group for Quantitative Analysis of Normal Tissues Effect in the Clinic (QUANTEC) and by protocols of the Radiotherapy Oncology Group (RTOG), among others.[33]

Acute and chronic toxicity

Radiation-induced dermatitis

Up to 95 % of patients who receive radiotherapy will develop dermatitis. The degree of skin involvement depends on factors such as: irradiation in areas with folds or where skin integrity is altered, elevated body mass index, concomitant use of chemotherapy or immunotherapy, comorbidities, smoking, chronic sun exposure, skin type, weight and radiotherapy technique used. This effect is expected and is bound to occur.[34] 10 % of patients will develop moist dermatitis, predominantly on skin folds. This complication is reversible and does not require treatment discontinuation, but it does require adequate management and close monitoring.[35]

Table 17. Dosimetric factors that favor the development of radiation pneumonitis

% of total lung volume that receives >20 Gy (V20), >30 %
% of total lung volume that receives >5 Gy (V5), >65 %
Mean lung dose, >20 Gy
Absolute lung volume that receives >5 Gy, <500cc

5.3.3.2 Subacute and chronic toxicity

Lung toxicity

Lung toxicity occurs in 1 % to 5 % of breast cancer patients who are treated with radiotherapy. Factors that increase the risk of radiation pneumonitis include concomitant use of chemotherapy or hormonal therapy, radiation to the chest wall with electrons, supraclavicular field, history of smoking, chronic obstructive pulmonary disease, or interstitial lung disease.[36] The incidence of grade > 2 pneumonitis is 1.8 % in modern series of patients treated with hypofractionated schemes or with normal fractionation, and it is often diagnosed 7.5 weeks after having started radiotherapy.[37,42]

Irradiated lung volume is a predictive factor for the development of pneumonitis (Table 17).

Table 18. Dose restrictions for ipsilateral lung according to fractioning

Conventional with tangential fields	Conventional with tangential fields and lymph nodes	Hypofractionated with tangential fields	Hypofractionated with tangential fields and lymph nodes
V20 Gy <20 %	V20 Gy <30 %	V16 Gy <15 %	V18 Gy <35 %
V10 Gy >35 %	V10 Gy <50 %	V8 Gy <35 %	
V5 Gy <50 %	V5 Gy <65 %	V4 Gy <50 %	

Table 19. Dose restrictions for the heart according to fractionation

Conventional with tangential fields	Conventional with tangential fields and lymph nodes	Hypofractionated with tangential fields	Hypofractionated with tangential fields and lymph nodes
Mean dose <4 Gy	Mean dose <4 Gy	Mean dose <3.2 Gy	Mean dose <3 Gy
V20 Gy <5 %	Left Breast V15 Gy <30 % V25 Gy <5 %	Left Breast V16 Gy <5 %	Left Breast V22.5 Gy <10 %
	Right Breast V25 Gy <0 % V15 Gy <10 %	Right Breast V16 Gy <0 %	Right Breast V22.5 Gy <2 %

Complying with the lung dose restrictions according to the radiotherapy scheme and fractionation that is chosen is strongly recommended (Table 18).

Cardiac toxicity and cardioprotection

Early toxicity is subclinical with identifiable changes 6 months after radiotherapy completion in patients with left breast cancer. They are characterized by alterations in Doppler echocardiography and myocardial perfusion as well as type b natriuretic peptide and troponin I elevation. Late toxicity is characterized by coronary stenosis and ischemic heart disease with a latency period of 10 years. The use of modern radiotherapy techniques helps to reduce cardiac radiation dose. It is necessary to use the best available technique to achieve this purpose.[24] Dose restrictions depend on the used fractionation (Table 19).

5.4 Second primary tumors

There is an increased risk of non-mammary second tumors associated with radiotherapy to the chest wall for breast cancer (1.12 RR). The risk for developing radiation-induced lung or esophageal cancer or sarcoma should be taken into account when planning radiotherapy (1.39 RR, 1.53 RR and 2.53 RR, respectively).[25]

XII. Treatment of metastatic/recurrent breast cancer

1. Introduction

Metastatic breast cancer is a heterogeneous, so far incurable disease with variable clinical manifestations, and the treatment of which depends on the site and number of metastases, patient characteristics, tumor immunophenotype, and sensitivity or resistance to previous cancer medical treatments.[1]

This stage of the disease is not curable; however, in coincidence with the introduction of novel and more effective systemic treatments, including early supportive therapies, an improvement in median survival has been observed in the past two decades, with highly variable ranges, from months to many years, depending on the immunophenotype.[2-4]

The goals of treatment in metastatic breast cancer are:

– To prolong progression-free interval and overall survival.

– To palliate disease-related symptoms.
– To maintain an adequate quality of life with good performance status.

The most important clinicopathological factors to decide the best therapeutic strategy are:

– Age.
– Disease-related symptoms and performance status.
– Concomitant diseases.
– Disease-free interval.
– Number and location of metastases.
– Previous treatment and response to it.
– Hormone receptors, HER-2 neu and BRCA 1 and 2 mutations.
– Patient preferences.[1,3]

In patients with stages I to III and who subsequently exhibit tumor recurrence, evaluation of the extent of disease is recommended, including performing a biopsy on a metastatic site to confirm the diagnosis and determine hormone receptors and HER-2 status, since up to 30 % of cases have been shown to change their immunophenotype. This means that a significant proportion of patients will have to have their treatment changed in order to avoid insufficient or excessive therapies and this can dramatically modify survival. Assessing for the presence of BRCA 1 and 2 germline mutations is also recommended in view of the availability of approved therapeutic options. Evaluation of other biomarkers is not recommended.[1,5-8]

2. Treatment according to breast cancer subtype

2.1 Metastatic breast cancer with positive hormone receptors and negative HER-2 neu

Endocrine therapy plus a cyclin inhibitor is the treatment of choice because it has been shown to increase overall survival in both first and second lines of treatment,[1] as well as improvements in other efficacy parameters such as progression-free survival and response rates, including patients with visceral disease. However, in patients with significant symptoms and/or rapidly-progressing visceral metastases (visceral crisis),[2] chemotherapy should be the first option, since it produces higher response and palliation percentages.

2.1.1 Hormonal treatment in premenopausal patients

Owing to the benefits of endocrine therapy + other targeted therapies in postmenopausal patients, medical or surgical ovarian ablation is recommended in premenopausal patients, and treat them as postmenopausal.[2]

An aromatase inhibitor (preferably) or tamoxifen + ribociclib is indicated as first-line treatment in premenopausal patients.[3]

Tamoxifen as monotherapy is an option in patients who do not accept ovarian suppression or ablation.

2.1.2 Hormonal treatment in postmenopausal patients

First line

In case of de novo metastatic disease or recurrent disease, with a period longer than one year after having concluded adjuvant hormonal therapy, the recommendation is an aromatase inhibitor + a CDK 4/6 inhibitor.[4-7]

The efficacy of CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) is similar, with the difference lying in the toxicity profile; the choice will be made by the treating physician according to the patients' comorbidities and characteristics.

An aromatase inhibitor is also an option in patients for whom CDK 4/6 inhibitors are not available.[8]

Another additional first-line possibility is fulvestrant, mainly in patients with no visceral metastases.[9]

Second line

If patients have already received a non-steroidal AI (anastrozole/letrozole) or show progression during adjuvant treatment with non-steroidal AI, treatment options can be:

– Fulvestrant + CDK 4/6 inhibitor (palbociclib, ribociclib or abemaciclib) as long as the latter has not been used on first line.[10-13]
– Exemestane plus everolimus.[14-15]
– Steroidal AI (exemestane).[16-17]
– Fulvestrant.[17]
– Fulvestrant + everolimus.[18]

Third line

The third line will depend on the received first and second lines. So far there is no standard sequence.

Abemaciclib monotherapy is a third-line treatment option in patients who have not received a CDK 4/6 inhibitor in previous lines, either as endocrine treatment or with chemotherapy.[19]

In patients with a response or clear initial clinical benefit with hormonal therapy and who progress with a first line, a second, third and even fourth hormonal lines should be tried, depending on the previously-used drug, since a new tumor response is often obtained, which means the possibility of chemotherapy-free survival with better quality of life. In case of proven resistance to hormonal management, switching to chemotherapy should be carried out.

For patients with positive receptors who have received chemotherapy to maximum benefit, continuing with maintenance hormonal therapy is suggested, and the selected drug should be administered until progression.[2]

2.2 Metastatic/recurrent breast cancer with positive hormone receptors and positive HER-2 neu (triple-positive)

The recommended treatment is chemotherapy associated with anti-HER-2 therapy, due to the demonstrated increase in overall survival (see Section 2.3).[20,21]

In patients with a complete response and/or who exhibit dose-limiting toxicity, chemotherapy can be discontinued and anti-HER-2 blockade in combination with endocrine therapy (monotherapy) be continued.[22,23]

In postmenopausal patients who are not candidates for chemotherapy, with high HR expression, de novo or with a long disease-free period and absence of visceral disease, double anti-HER-2 blockade (trastuzumab/lapatinib or pertuzumab/trastuzumab) could be used, in combination with a non-steroidal aromatase inhibitor. This strategy demonstrated a benefit in progression-free survival (PFS), but not in overall survival. Anti-HER-2 therapy (trastuzumab or lapatinib) with endocrine therapy is another alternative, but the fact that it has an inferior median PFS should be taken into account.[20-26]

2.3 Metastatic/recurrent breast cancer with negative hormone receptors and positive HER-2 neu

To decide the type of palliative management, it is important for patients to be stratified based upon previous exposure to anti-HER-2 therapies and the time elapsed between the last dose of anti-HER-2 therapy and disease recurrence or progression.[27]

2.3.1 First line

Standard treatment for patients at stage IV de novo or exposed to anti-HER-2 therapy in the neo/adjuvant setting and with more than 12 months of DFS is docetaxel or paclitaxel in combination with double anti-HER-2 blockade based on trastuzumab and pertuzumab, since it has clearly shown benefit in overall survival, progression-free survival, and response rate.[28,29]

In patients who cannot receive pertuzumab, the combination of trastuzumab plus taxane or vinorelbine should be considered as an alternative.[30,31]

If a patient exposed to anti-HER-2 therapy in the neo/adjuvant setting experiences disease progression during treatment or within a period of less than 6 months after administration of the last dose, it is advisable to use TDM1.[32]

2.3.2 Second and subsequent lines

Based on the results of the PHEREXA trial, the use of pertuzumab is not recommended beyond progression to the first line of treatment.[33]

In patients previously treated with a trastuzumab-based regimen and with disease progression, the indicated treatment is TDM-1.[32]

In patients who cannot receive TDM-1, the option of continuing with trastuzumab in combination with a chemotherapy agent or lapatinib/capecitabine should be considered. The previously-mentioned regimens and double blockade with trastuzumab/lapatinib can be used on third and subsequent lines.[34]

In all patients, it is recommended to maintain the blockade with anti-HER-2 therapy during all phases of antineoplastic treatment, except in cases where it is contraindicated, since its impact on disease control has been demonstrated.[35-38]

2.4 Metastatic/recurrent triple-negative or hormone receptor-positive, HER-2-negative breast cancer not candidate for hormonal therapy (BRCA-positive/negative)

The choice of treatment must take adjuvant treatment (Table 1) and recurrence-free interval into account. In patients with an interval longer than 1 year, it is possible for drug re-induction to be evaluated. For patients with triple-negative tumors, standard treatment is chemotherapy, and currently it is not possible for a specific regimen or sequence to be recommended.[39-31]

In previously-treated patients with a BRCA germline mutation, the use olaparib may be considered.[42]

Table 20. Triple-negative or hormone receptor-positive, HER-2 neu-negative metastatic breast cancer not candidate for hormonal therapy

ADYUVANT SETTING				
	Did not receive	**With taxane + anthracycline**	**With taxane**	**With anthracycline**
1st line	Regimen based on: – Anthracycline – Taxane	– Capecitabine – Eribulin – Gemcitabine – Vinorelbine – Platinum salts	Regimen based on: – Anthracycline	Taxane ± – Capecitabine – Gemcitabine
2nd line	According to previously-used treatment			
3rd line	According to previously-used treatment			

2.4.1 First-line chemotherapy: in combination or sequential?

Combination chemotherapy is usually not recommended. Treatment with drugs as monotherapy and sequentially is preferred due to better tolerance and less quality of life deterioration. The use of polychemotherapy can be considered in patients with good performance status, in whom a rapid response or symptom palliation is sought, and/or in case of visceral crisis and/or in cases in which life expectancy is considered to allow only one chance for treatment.[39,40,43,44]

Regarding the above, visceral crisis is a serious organ dysfunction represented by signs and symptoms, laboratory tests and rapidly progressive disease. Visceral crisis does not exclusively refer to the presence of visceral metastases, but rather implies significant visceral compromise that mandates an efficacious, rapid-acting therapy, particularly if another treatment option, after further progression, is potentially not possible.

The cornerstone of first-line chemotherapy is based on anthracyclines and taxanes. In previously-exposed patients, treatment options include capecitabine, gemcitabine, vinorelbine, or eribulin (Table 20).

In case a combination is chosen, a taxane (paclitaxel or docetaxel) plus capecitabine or gemcitabine is recommended. Both regimens have been associated with higher response rates and progression-free interval vs. taxane monotherapy.[45-50] The efficacy of both regimens is similar and the choice will depend on each patient's characteristics and available resources.

The choice of treatment depends on patients' characteristics, tolerance and response to previous treatments, as well as on availability.[39,40]

Eribulin is the only drug that has shown an impact on overall survival in patients previously treated with taxanes/anthracyclines in the population with triple-negative tumors.[54-56]

2.4.2 Platinum salts

There are studies that show the effectiveness of platinum and its derivatives in triple-negative tumors.[57-59] The TNT study, a phase III trial, evaluated the use of docetaxel vs. carboplatin and failed to show superiority of the platinum salt in a triple-negative unselected population (BRCA germline mutation vs. mutated); however, in the population with BRCA germline mutation present, a superiority in progression-free survival was observed in favor of carboplatin.[60] Although platinum salts are not recommended as first-line therapy in unselected population, they may represent an option in the population with BRCA germline mutations.[57-59]

2.4.3 Bevacizumab

The use of bevacizumab plus a chemotherapy agent increases disease control and progression-free survival, but does not impact on overall survival as first-line therapy in metastatic breast cancer.[60-65] Bevacizumab plus taxane is a treatment option in patients with triple-negative tumors or in those with positive hormone receptors who have a clinically aggressive evolution and are considered candidates for first-line chemotherapy.

2.4.4 Immunotherapy

Atezolizumab plus nab-paclitaxel (the use of atezolizumab with paclitaxel is not recommended), as first-line therapy, demonstrated an increase in progression-free survival in a PDL1-positive population (VENTANA/SP142).[66]

In patients with advanced triple-negative breast cancer that expresses PDL1 (CPS > 10 %/IHC 22C3 pharmDx clone), pembrolizumab plus chemotherapy (paclitaxel, nab-paclitaxel or gemcitabine plus carboplatin), as first-line therapy, was shown to be superior vs. chemotherapy in progression-free survival.[67]

2.4.5 Olaparib

In patients with breast cancer and BRCA germline mutation, previously treated with no more than 2 lines of treatment, olaparib demonstrated an impact on progression-free survival, but not on overall survival, which is why it can be regarded as a treatment option.[42.68]

2.4.6 Treatment duration

Treatment duration has not been fully defined. Several studies have shown that continuing chemotherapy can increase progression-free interval, but without prolonging survival.[69,70]

In clinical practice, continuing chemotherapy until progression or toxicity is recommended, depending on the administered drug (intravenous versus oral), maximum cumulative doses and the impact on patients' quality of life.

3. Bisphosphonates and receptor activator of NF-KB ligand (RANKL) inhibitors in bone metastases

Both bisphosphonates and receptor activator of NF-KB ligand (RANKL) inhibitors, improve the results in the management of bone metastases, malignant hypercalcemia and bone health by reducing systemic treatment-secondary osteopenia or osteoporosis.[1-3]

Patients with radiographic evidence of bone metastases should receive treatment, either with denosumab (120 mg subcutaneously every 4 weeks), 4 or with zoledronic acid (4 mg intravenously over 15 minutes) every 3 to 4 weeks.[5-7]

- Total duration of bisphosphonate treatment should be up to 2 years.
- Zoledronic acid can be administered every 3 to 4 weeks or every 3 months, since the beginning.[8]
- After 1 year of treatment, and in case of stable disease, administering zoledronic acid every 12 weeks is recommended during the second year,[9] and then reconsider its use according to bone metastatic activity.
- Denosumab treatment optimal duration is not known. The general recommendations with the use of bisphosphonates and RANKL inhibitors are the same as in adjuvant (see Chapter X, Management of early breast cancer).

4. Role of surgery in metastatic disease

Stage IV breast cancer standard treatment traditionally focuses towards a palliative territory, which includes chemotherapy, radiotherapy, hormonal therapy and targeted therapies, leaving the role of surgery only for prevention or treatment of local symptoms;[1] however, over the past 20 years, centers around the world have published series of patients with metastatic breast cancer who underwent resection in several sites (liver, brain, lung), with favorable results being reported,[2] mainly in those with metastases at diagnosis. In fact, median overall survival for metastatic breast cancer has nearly tripled, from 13 months in 1985 to 33 months in 2016, thanks to multimodal treatment.[3,4]

4.1 Metastatic disease resection

4.1.1 Liver metastases

The liver, as only distant metastasis site, accounts for only 10 % of cases, which is why liver resection has had a limited role in treatment, since breast cancer is most often accompanied by metastasis at another level.[5] The 5-year survival rate after surgical resection of liver metastases, combined with systemic therapy, has been reported to range from 40 % to 61 %. Current surgical techniques allow resection to have a postoperative mortality of less than 6 % and a morbidity of between 0.8 % and 5.4 % in referral centers.[6] Another valid option is to use ablation of metastases with radiofrequency or with laser-induced interstitial thermotherapy, by means of which a mean survival of 30 to 60 months and 5-year survival of 27 % to 41 % are reported.[7]

Regarding prognostic factors, most studies emphasize the importance of R0 resection, since positive margin is an adverse factor for survival.[6,7] Other adverse predictive factors for survival have been the lesion size (> 5 cm), negative hormone receptor status, poor chemotherapy response, vascular invasion, number of metastases, and disease-free interval < 1 year after primary breast cancer resection.[8]

4.1.2 Lung metastases

Metastatic disease is usually generalized and rarely is it only localized at the pulmonary level. In a series of 13,502 breast cancer patients at the Mayo Clinic, only 60 (0.4 %) were found with isolated lung metastases, out of whom 40 underwent resection.[9]

Lung metastases complete surgical resection can be performed with low morbidity and mortality, either by thoracotomy or video-assisted thoracoscopic surgery (VATS). Case series analysis has established the following well-accepted surgical selection criteria:

- Primary disease is under control.
- Metastases limited to the lung and pleura.
- Ability to completely remove metastatic disease.
- Lung physiological reserve to tolerate the planned procedure.[10]

A common finding in most studies assessing the role of lung metastases resection is that the disease-free interval between initial management of the primary tumor and the appearance of lung metastases has a highly significant impact on survival. A disease-free interval of more than 36 months to recurrence has achieved 5-year survivals of up to 75 % in single lesions undergoing resection and systemic treatment.[11]

Other factors that have been associated with survival improvement are positive hormone receptors, positivity for HER-2 neu, and solitary metastases. As in the case of liver metastases, patients with single lesions and prolonged disease-free interval should be considered candidates for pulmonary metastasectomy.

4.1.3 Brain metastases

Breast cancer represents the second cause of metastatic lesions in the brain and they are generally associated with tumors with negative hormone receptors, HER-2-positive, premenopausal patients and with metastatic disease in lung and/or liver.[12] Patients who do not receive any type of treatment, have a survival prognosis of 1 to 2 months, which increases to up to 6 months in those who receive radiotherapy, and when surgery is indicated, it can even reach up to 16 months.[13]

Indications for surgery are limited, with surgical approach being a reasonable option in single lesions of < 5 cm in size, absence of extracranial metastases and especially in patients with adequate performance status.

4.1.4 Other metastatic sites

This group is less studied and, in general, it has not shown survival benefit. An example is that of bone metastases; according to several reports, surgical resection has not shown prognostic improvement in these patients,[14] with radiotherapy being the palliative modality of choice. On the other hand, some studies have reported that resection of metastases in the sternum or rib cage is associated with a survival increase.[15] Even less studied due to their low frequency are adrenal, ovarian and gastrointestinal metastases; in these cases, resection is not recommended, except in situations of symptom palliation.

4.2 Primary tumor resection in metastatic disease

This is a clinical scenario where controversies are even bigger, since recommendations are based on retrospective studies, where some of them show overall survival benefit; however, they should be taken with caution given their selection bias, mainly based on low tumor burden, absence of visceral metastases and younger age, among other factors.[16-21] Other studies, however, also retrospective, have not shown benefit derived from primary tumor resection in this context.[22-24]

Prospective studies in this scenario are few, and the results are also controversial. Among them, a Turkish study (Protocol MF0701), at 40 months of follow-up, is the only one that has shown a survival benefit by reducing the risk of death by 34 %, especially in patients younger than 55 years of age with positive estrogen and progesterone receptors, negative HER2 neu and solitary bone metastases.[25] Notwithstanding, other studies, such as one carried out in India, failed show any overall survival benefit in neither subgroup of clinical stage IV patients, with primary tumor resection, after receiving systemic treatment.[26] Similarly, a prospective phase III study (ABCSG20 POSYTIVE) carried out in Australia[27] and the TBCRC 013 trial conducted in the United States,[28] also failed to show benefits in overall survival at 37.5 and 54 months of follow-up, respectively.

Available data are not conclusive, which is why primary tumor resection in patients with clinical stage IV disease at diagnosis should not be considered as a treatment option in any of them. However, it seems to be a reasonable alternative that can be discussed with selected patients with favorable clinical characteristics, good general condition, younger than 55 years of age, disease with positive hormone receptors, HER2 neu-negative, limited tumor volume and solitary bone metastases.

4.3 Primary tumor palliative resection in metastatic disease

In this clinical scenario there is no controversy: surgery is indicated in patients with a fungating, ulcerated or hemorrhagic tumor, and is intended to improve quality of life, without expecting an impact on survival. In the case of unresectable primary tumors, palliative radiotherapy may be considered.[29]

5. Role of radiotherapy in metastatic disease

The treatment of metastatic disease distinguishes three groups, according to different characteristics: the first includes patients with good general conditions, controlled primary tumor and disease confined to three or fewer sites; there is another group with poor performance status or extensive metastatic spread; and there is a third group that requires local control for bleeding, infection or pain. Treatment decision for these patients should be made by a multidisciplinary team.

5.1 Radiotherapy to the primary lesion

Local management of this group of patients is controversial and must be individualized. The phase III ECOG-ACRIN 2108 trial on local treatment efficacy after chemotherapy in patients with de novo metastatic cancer, reported that local control was higher in patients treated with surgery and radiotherapy, with a risk of local progression or recurrence 2.5 times higher in patients receiving only chemotherapy. These findings emphasize the need for multidisciplinary treatment.[1,2]

5.2 Bone metastases

The dose and volume to be irradiated are selected according to the treatment intention. The aim is to control symptoms and disease evolution. Radiotherapy schemes include 37.5 Gy in 15 sessions, 30 Gy in 10 sessions, 20 Gy in 5 sessions, or a single 8 Gy dose.[3]

5.3 Brain metastases

Radiotherapy modalities include: whole-brain radiation, stereotactic radiosurgery (SRS), and hippocampal-sparing whole brain radiation. Whole-brain radiotherapy is used in multiple metastatic brain lesions, patients with leptomeningeal disease, uncontrolled primary tumor or poor performance status.[4] The 2018 Cochrane updated revision favors the use of the 30 Gy scheme in 10 fractions.[5] Provided hippocampal protection technique is available, its use is recommended with the purpose to reduce cognitive impairment caused by whole-brain radiotherapy.[6] Single-dose SRS is the standard for patients with 1-10 < 3 cm metastatic lesions and good performance status.[7,8] In patients with > 3.1 cm lesions, SRS in 2-5 fractions is preferred.[8]

5.4 SBRT in Oligometastatic disease

The ESTRO-ASTRO guidelines define oligometastatic disease as the presence of 1-5 lesions, detectable by imaging.[9] In breast cancer, bone, lung and liver metastases are the most common.

5.4.1 Stereotaxic body radiation therapy (SBRT) in bone and vertebral metastases

It is used as a high-precision technique that administers 1-8 fractions with ablative purposes and sub-millimetric precision. It improves overall survival in addition to disease-free survival, and due to a high local control, it allows the start of systemic therapy or transition to the next line of treatment to be delayed.[10] For spinal bone metastases, indications for this treatment are: KPS > 60, confirmed metastatic disease, single or multiple lesions (≤ 2 consecutive vertebrae or up to three non-contiguous sites), no data consistent with spinal cord compression or pathological fracture, residual or recurrent tumor after surgery and with an interval longer than 6 months in cases of re-irradiation.[10]

5.4.2 SBRT in liver metastases

Indicated in patients who are not candidates for surgical management or who reject surgery. The criteria for offering this technique include: women with adequate liver function, 0-2 ECOG performance status, absent or stable extrahepatic disease, 1-5 lesions with a maximum diameter of 10 cm and healthy liver volume> 1000 cm3. Chemotherapy should be discontinued at least 3 weeks before the procedure and should be restarted 2 weeks after it.11

5.4.3 SBRT in lung metastases

SBRT in lung metastases provides local control of 80 %, 58 %, and 46 % at 1, 3, and 5 years, respectively. It is associated with longer survival in small lesions with a volume <11 cc and a biological equivalent dose (BED) ≥ 100 Gy.[12] Complications are low.[13]

5.5 Radiotherapy for symptom control

It is offered with hypofractionated schemes in cases of pain, foul-smelling discharge and bulky disease, tumor bleeding, oncological emergencies and meningeal carcinomatosis.[14-15]

6. Evaluation and management of locoregional recurrence

Recurrent disease, exclusively in the breast or axilla, is an event with a frequency of less than 10 %.[1] Initially, the extent of recurrence should be established, i.e., whether there is distant disease or not. The distinction of purely recurrent disease or second primary lesions takes into account classic factors such as those indicated by Warren, in addition to considering the quadrant of the lesion, hormone expression, even genetic, profile, which can be modified by previous treatment.[2]

MMG/US, extension of disease (only local, regional and/or remote) assessment should be carried out. In case of distant disease, the recommendations for metastatic disease should be followed. Studies to rule out distant disease are PET, bone scan, or CT scan.

The management of recurrent disease should consider that this event is itself a predictor of distant disease and an adverse prognostic factor, and systemic treatment should therefore be considered in any of its forms.

6.1 Surgical management

Multidisciplinary decision on the management of locoregional recurrence is recommended, according to initial treatment of the primary lesion. Patients with prior mastectomy and chest wall recurrences can undergo local resection. Most occur on the skin and subcutaneous tissue, although recurrence to the chest wall can occur in about 59 % of cases.[3] Resectability will depend on extension to the skin, the possibility of soft tissue coverage and bone structures involvement.

On the other hand, in patients previously treated with breast-conserving surgery who develop local recurrence, mastectomy is accepted as standard management in ipsilateral breast cancer recurrence.

Axillary re-staging with levels I and II dissection is the standard management. Sentinel lymph node procedures after previous axillary surgery are possible; identification rate varies from 66 % to 71 %,[4] and localization of non-axillary SLN increases to up to 43 %,[5] although the rate of positive SLN appears to be low (8 %). The false-negative rate is 9.4 % and accuracy of the procedure is 97.1 %. Using more than one identification technique (dye, radiotracer, magnetic) and considering possible extra-axillary drainage is suggested.

6.2 Management with radiotherapy

It could be considered in 3 scenarios:

- As local control after recurrence resection in patients without a history of radiotherapy, in which case the already known irradiation techniques are applied depending on whether the procedure corresponds to mastectomy or breast-conserving surgery.
- A second course of radiotherapy can be applied to the previously treated breast, chest wall, or lymph node areas for a recurrent or second primary tumor, taking into account previous radiation dose, the site to be irradiated, and the radiation dose the surrounding organs received.
- As re-irradiation of unresectable disease for local control and palliation of symptoms such as bleeding or pain.[6]

Patient selection is complex and should be carried out by a multidisciplinary team, since the risk of local toxicity tends to increase with re-irradiation. The fact that a tumor that recurs at an irradiated site may be more resistant to a new treatment regimen should also be considered. The techniques that are used are varied and include limited fields, electrons, bifractionation, superficial brachytherapy, intraoperative radiotherapy, partial breast irradiation, concomitant systemic treatment, and hyperthermia. Although these are interesting alternatives, they have only been tested in small samples and their use should be limited only to the context of clinical trials.[7,8]

6.3 Systemic management

In women with local recurrence and once complete resection of the disease has been carried out, adjuvant treatment administration has shown an improvement in disease-free and overall survival in all patients, with higher benefit in the group of women with negative hormone receptors.[9] As with distant recurrence, if possible, having a reevaluation of the tumor subtype is recommended in order to determine the best recommended systemic treatment, according to previous management, time to recurrence and patient characteristics.

XIII. Supportive and palliative care integration in the management of patients with advanced breast cancer

1. Introduction

Disease-modifying treatment options in patients with breast cancer are increasingly varied, which has impacted on improvement of their survival; however, as the

disease progresses, the possibilities of response decrease, and centrality in patient management consists of providing comfort, through supportive and palliative care.[1]

Palliative care is defined by the International Association of Hospice and Palliative Care[2] as active, holistic care of people of all ages with severe, health-related suffering due to a serious illness, and especially of those who are close to the end of life. Its purpose is to improve the quality of life of patients, their families and caregivers. It includes prevention, early identification, comprehensive evaluation and control of physical problems, including pain and other distressing symptoms, psychological suffering, spiritual suffering, and social needs.[2]

Early integration of supportive and palliative care into the management of cancer patients can improve quality of life, symptom control, patient and family satisfaction, end-of-life care, survival, and costs of care.[3]

The American Society of Clinical Oncology (ASCO), on its management guidelines establishes that patients with advanced cancer should receive early supportive and palliative care, simultaneously with antineoplastic treatments (Table 21).[4] Strategies for integration are currently under study; however, it is important for the oncologist to acquire the necessary knowledge for providing basic supportive and palliative care as part of his clinical practice, by referring cases that require more specialized management for symptom relief to palliative care specialists.[5]

2. Evaluation of palliative care needs

Systematic and structured evaluation of physical, psychological, psychiatric symptoms, cognitive alterations, the concept of disease and prognosis, care needs, existential concerns, as well as emotional and economic distress, is essential. A good systematic control improves the confidence of patients and their families.

The use of validated symptom assessment instruments helps to identify, treat, and monitor symptoms. Self-assessment of symptoms through different available scales is important, since doctors tend to underestimate their severity, which impacts the opportunity to establish a treatment that can contribute to improve both the symptom and the quality of life.

In this model, it is essential for the symptomatic complexity of the patient to be evaluated on seven basic aspects.

- Physical aspects of care (symptoms).
- Psychological and psychiatric aspects.
- Social aspects.
- Spiritual, religious and existential aspects.
- Cultural aspects of care.
- Care of the patient approaching the end of life.
- Ethical and legal aspects of care.

A strategy that is frequently used in supportive and palliative care services is family meetings, in which medical aspects, treatment goals, identification of support networks and recommendations for the primary caregiver are covered.

This multiple-domain assessment is not common in cancer consultations, since evidence shows that they are mainly focused on cancer treatment, the response to it and medical complications, while symptoms and coping skills, which routinely are addressed by supportive and palliative care services, are undervalued.[5,6]

The discussion about comprehensive oncological-palliative evaluation should include a review, both of risks and benefits, of anti-cancer therapy and prognosis, in addition to ensuring that the patient and her family understand the incurable nature of the disease. In this context, the oncologist's opinion on the benefit of referral to supportive and palliative care services must be considered (Figure 16).[6]

3. Symptom management by the oncologist

The symptoms experienced by the patient with breast cancer are varied and changeable during the disease process, but they are accentuated at advanced stages and at terminal phase. Pain, depression, anxiety, fatigue, dyspnea, insomnia, nausea, and weight loss are common symptoms that increasingly cause dependence in patients, and significantly contribute to increase their suffering. Other symptoms associated with spinal cord compression, brain metastases, lymphedema and anemia also negatively impact quality of life.[6-8]

3.1 Pain

Cancer pain is a syndrome characterized by a constellation of symptoms and signs; it is present in up to 70 % of patients with advanced breast cancer due to disease progression.[6-8] Its management requires an approach that includes antitumor therapies, analgesic therapy, and psychological care.

The most common cause of cancer pain in this group of patients is related to the presence of bone metastases and their complications. Other causes include

Table 21. Integration of supportive and palliative care in standard cancer care: Clinical Practice Guidelines update, (ASCO). Main recommendation

Supportive and palliative care should be started simultaneously with antineoplastic treatment. Referral to a palliative support care service can be complemented with the oncologist's usual approach. This referral should include patient relatives (evidence based on: benefits outweigh risks; quality of evidence, intermediate; strength of recommendation, strong).
Essential components of supportive and palliative care services should include: – Ability to establish empathic and committed relationships with patients and their family members – Management of symptoms, distress, and functional impairment (e.g., pain, dyspnea, fatigue, insomnia, anxiety, depression, etc.) – Strategies to evaluate and educate on the concept of disease and prognosis – Guidance for establishing treatment goals – Assessment of and support on coping mechanisms and needs – Assistance with medical decision making – Coordination with other specialists – Reference and counter-reference criteria
In patients newly diagnosed with advanced cancer, the expert panel suggests incorporating supportive and palliative care within the first 8 weeks after diagnosis. Evidence based on: informal consensus; quality of evidence, intermediate; strength of recommendation, moderate
In outpatient oncology models, there should be programs and resources for providing supportive and palliative care on an outpatient basis to highly symptomatic patients or with unmet physical or psychosocial needs. Evidence based on: the benefits outweigh the risks; quality of evidence, intermediate; strength of recommendation, moderate

chest wall infiltration pain, brachial plexopathy, and abdominal distension pain, among others.

Neuropathic pain secondary to the use of taxanes impacts the quality of life of patients, and presents important challenges in its management. Identification of biomarkers is an active field of research. Antidepressants such as duloxetine have shown promising results.

It is important for the oncologist to become familiar with the pharmacological options for pain management, particularly with the use of strong opioids for the treatment of severe pain.

Figure 17 shows some recommendations for pain management. We emphasize the possibility of consulting pain and palliative care specialists in complex cases.[7]

3.2 Dyspnea

Dyspnea is a common symptom in patients with breast cancer with lung metastases. The American Thoracic Society defines it as a subjective experience of respiratory discomfort, which consists of qualitatively different sensations that vary in intensity. Treatment of underlying causes should always be considered (anemia, heart failure, asthma, lung infection, etc.). Opioids (low-dose oral morphine) are the drug of choice for symptom palliation. Figure 18 describes the flowchart for their handling.[6-8]

3.3 Fatigue

The sensation of fatigue is common in patients during disease-modifying therapy, and it can persist even in survivor patients. Evaluation of this symptom should rule out potentially treatable factors such as anemia, thyroid dysfunction, pain, depression, and insomnia.

3.4 Anorexia

Anorexia and weight loss are common in patients with advanced cancer and contribute to the sensation of fatigue, which is an important part of familiar concerns. Megestrol acetate stimulates appetite and weight gain, but does not improve quality of life, and neither does it increase muscle mass; however, it increases the risk of edema and thromboembolic phenomena. Corticosteroids improve appetite; however, prolonged use causes multiple side effects.

3.5 Delirium

Delirium is the most common neuropsychiatric complication in patients with advanced metastatic breast cancer. It is characterized by global brain dysfunction of undetermined etiology, characterized by fluctuations in alertness, attention, thinking, perception, memory, psychomotor behavior, emotions, and in the sleep-wake cycle. Most times, its etiology is multifactorial; it can be caused by alterations directly in the CNS (metastasis) or by indirect effect of the disease or treatment. Delirium

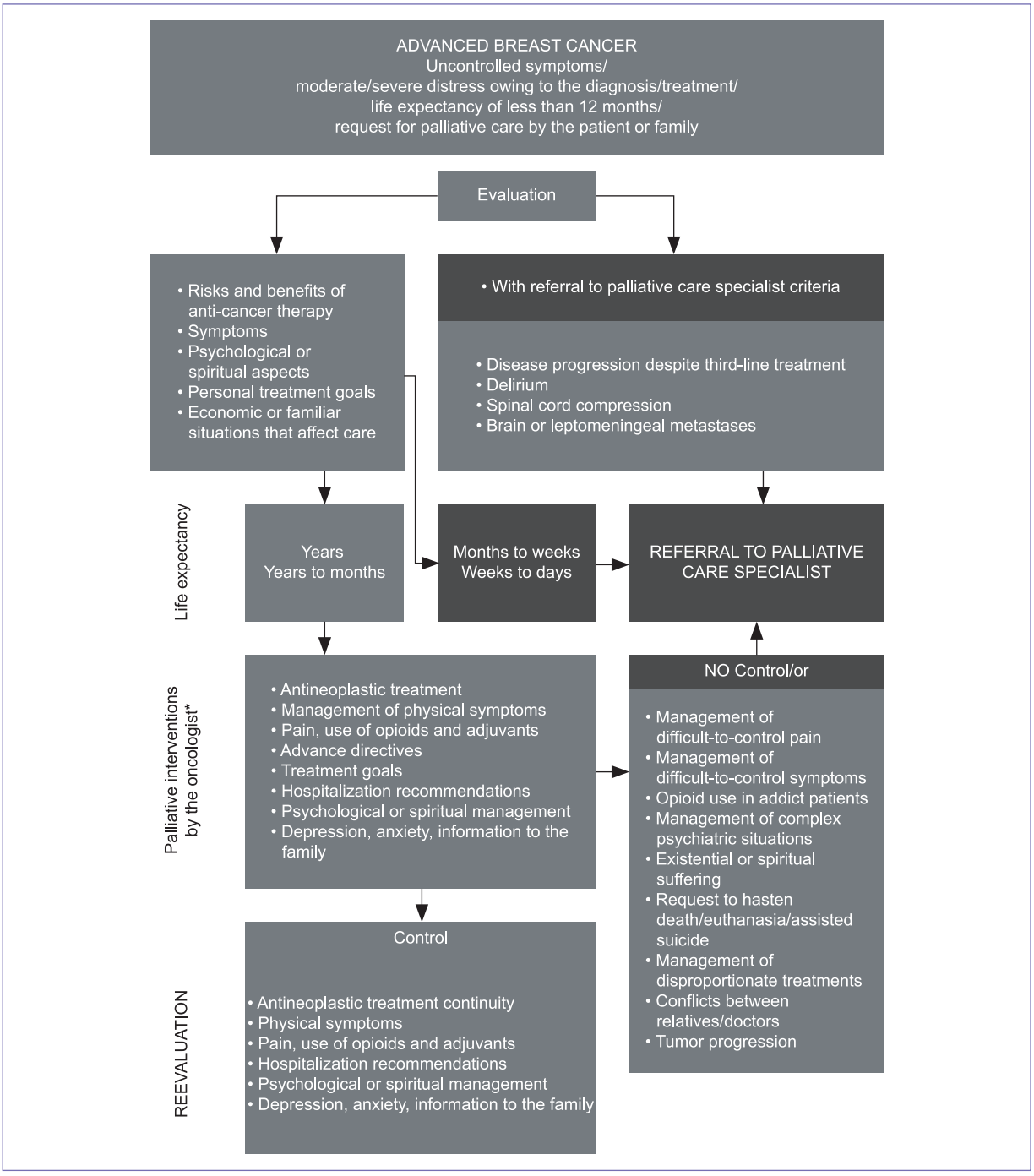


Figure 16. Role of the oncologist in palliative care.

can be hyperactive or hypoactive, with the latter being the most common, and is underdiagnosed in patients with advanced cancer on palliative care. There are different screening instruments for delirium evaluation, with the simplest being the Confusion Assessment Method (CAM).

4. Criteria for referral of outpatients to supportive and palliative care

Interaction with supportive and palliative care specialists will enrich the practice of oncology in difficult-to-control symptoms, in some situations at the end of life and during grief.[9]

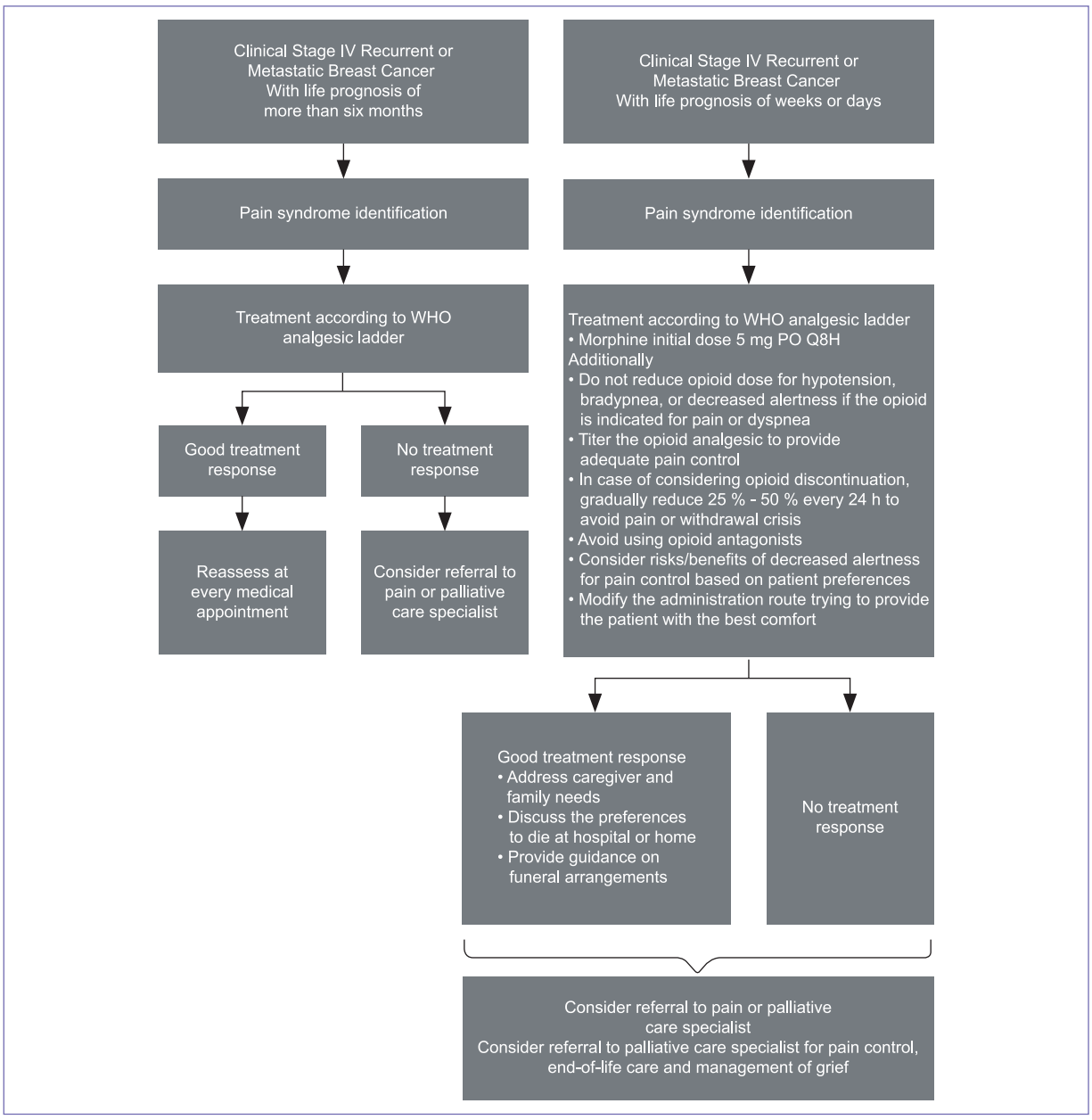


Figure 17. Pain management.[8] WHO: world health organization.
Modified from Clinical Practice Guidelines in Oncology. Version 1.2016.

In patient follow-up, incorporation of telemedicine is a field that should be considered.

5. Conclusion

The symptomatic supportive and palliative approach, in addition to improving the quality of life of patients with breast cancer, can help them and their families to have a realistic vision of the treatment goals in the short and long term. In addition, it can help the oncologist to incorporate essential aspects in the care of his patients and accompany them throughout the stages of the disease. The symptoms addressed in this section do not cover all the problems occurring in women with advanced breast cancer; however, they provide an overview of the supportive and palliative symptomatic approach for oncologists. The vision shall be, at all times, centered on the patient and her needs.

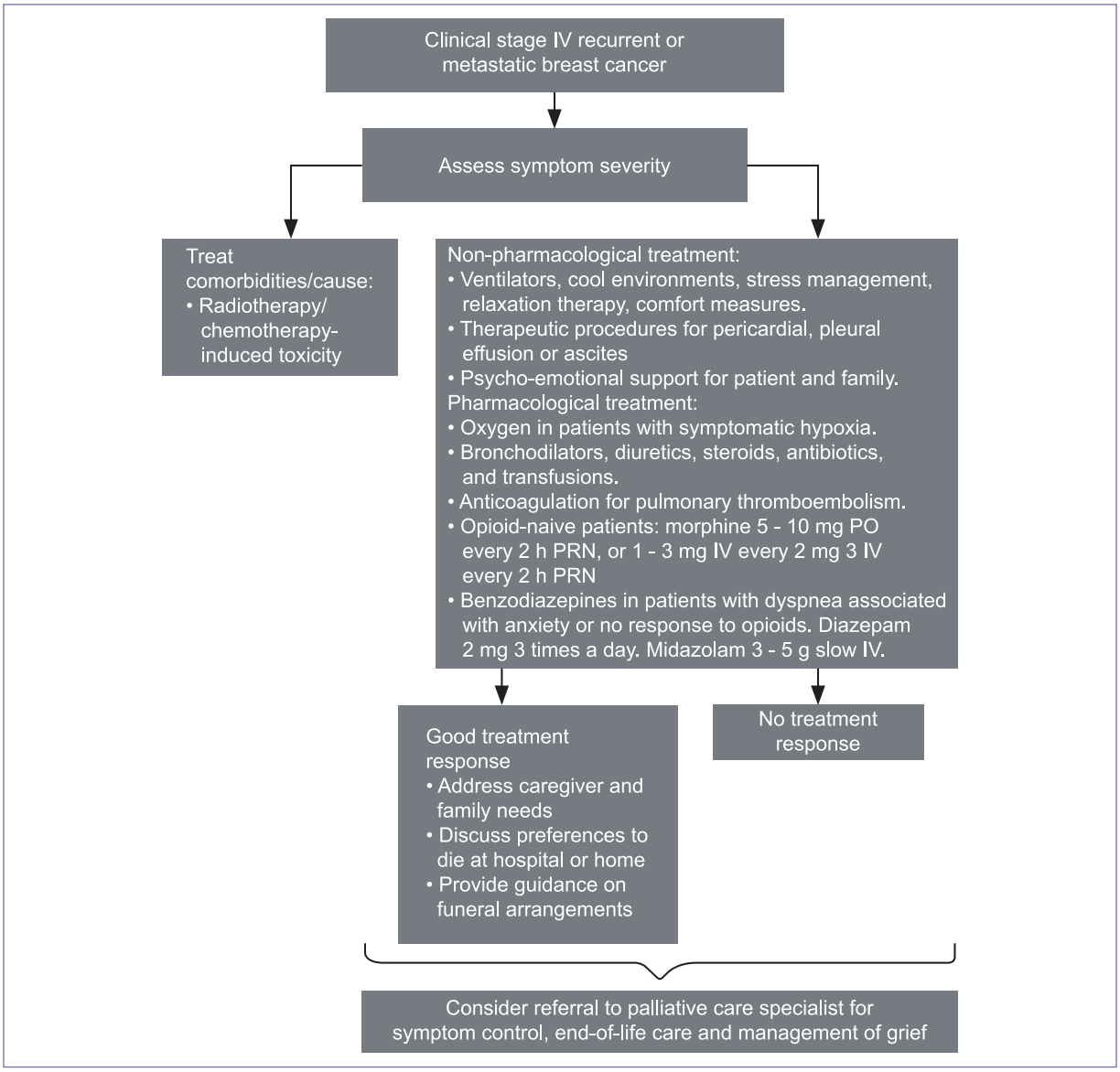


Figure 18. Dyspnea.[8] PRN: for necessary reasons.
Modified from Clinical Practice Guidelines in Oncology. Version 1.2016.

XIV. Breast cancer in young women

1. Introduction

The definition of a young patient with breast cancer for this Consensus is considered to be that with an age equal to or less than 40 years of age. This delimitation is based on the differences observed with regard to risk factors, tumor characteristics and clinical outcomes, as well as the particular interests for this age group: fertility, self-image, quality of life perception, and personal goals. Treatment long-term side effects are particularly important in young patients due to their potential for having a long survival.

In Mexico, this group of young patients with breast cancer has been reported to face unmet needs in terms of psychological support, information on fertility preservation, guidance on the use of effective contraceptives, and counseling on aspects of sexuality.[1-6] In addition, young Mexican women require more medical information, both in writing and electronically, and request a more effective form of communication from their health providers.[4]

2. Multidisciplinary approach

The following are concepts related to the diagnosis and recommended treatment for this group of patients:

Young age should not by itself be a reason to prescribe more aggressive therapy than that in general recommendations.[7,8]

Multidisciplinary treatment is highly recommendable, as well as individual treatment planning in the following aspects:

- Personalized psychosocial support.
- Genetic counseling.
- Reference for ovarian reserve and fertility preservation.
- Approach to sexual and body image alterations. Symptoms of premature menopause.
- Overweight or obesity.
- Bone health.
- Promotion for joining support groups.
- Provision of educational material (suggested support material: www.jovenyfuerte.com.mx).

2.1 Specific recommendations for diagnosis and treatment

2.1.1 Diagnosis

Diagnosis, imaging studies and staging in young women should follow standard algorithms, consistent with those for older women (see Chapter V). Further consideration may be given to breast tomosynthesis, US and MRI in young women, particularly in patients with extremely dense breast tissue or genetic predisposition.

2.1.2 Surgical and radiotherapy management

The recommendations for surgical treatment in young women with early breast cancer should not differ from those indicated for older patients. Although young age is an independent risk factor for local recurrence,[9] treatment with breast-conserving surgery and radiotherapy does not affect overall survival when compared with surgical treatment with mastectomy and may be considered an option for this group of patients.[10-12]

Specific recommendations for adjuvant radiotherapy for the group of young patients with breast cancer are reviewed in the corresponding radiotherapy section.

2.1.3 Adjuvant systemic treatment

Indications for chemotherapy are the same as in other patients. Although the use of genomic signatures in young patients has not been studied in a targeted manner, there is growing evidence about their use in premenopausal women, which supports their use to predict adjuvant chemotherapy additional benefit in patients with hormone-sensitive breast cancer aged 40 years or younger.[13]

Patients with hormone-sensitive breast cancer should receive adjuvant endocrine therapy for at least 5 years (see Chapter XII). If a GnRH analogue is used in this age group, it should be monthly administered (rather than every 3 months) in order to optimize ovarian suppression and efficacy.[14] In patients receiving aromatase inhibitors, adequate ovarian suppression should be verified by periodically measuring estradiol levels.[15] In case of inadequate suppression, alternative strategies (oophorectomy or continuing with tamoxifen alone) should be discussed.

In premenopausal patients who are under ovarian suppression with double hormonal blockade, addition of zoledronic acid every six months should be considered.

2.1.4 Systemic treatment for metastatic disease

Recommendations for the management of advanced breast cancer do not differ from those for other age groups (see Chapter XII).[16]

In the case of young patients with HER2-negative hormone-sensitive metastatic breast cancer, using adequate ovarian suppression or ablation and using the same lines of treatment with endocrine agents or targeted therapies as in postmenopausal women (aromatase inhibitors, fulvestrant, cyclin inhibitors, everolimus) is recommended (see Chapter XII).[7,8]

2.2 Relevant aspects to be considered in young patients with breast cancer

2.2.1 Genetics

Every young women aged 40 years or younger with breast cancer should be offered genetic counseling, regardless of breast cancer subtype (see Chapter XXI).[7,8] Mutation status should be part of the algorithm for individualized screening in patient decision-making. All different treatment options should be discussed with a sufficient amount of time and with psychological support, given the long-term implications and consequences they can produce. Women who did not receive counseling at the time of breast cancer diagnosis should be offered it during follow-up in order to address

monitoring issues and strategies for reducing the risk of additional primary tumors in the patient and her family.

2.2.2 Fertility and ovarian preservation aspects

Patient's interest in having children in the future should be systematically asked. Those who are interested should be informed about the approved strategies for fertility preservation and should be referred for consultation by specialists in reproductive biology prior to starting systemic treatment.[17,18]

Monthly administration of GnRH analogues concomitantly with chemotherapy may be considered in premenopausal breast cancer patients interested in preserving ovarian function and/or fertility.[18,19] Their use in patients with positive and negative hormone receptors does not confer risk of recurrence.[20] The use of GnRH analogues does not replace the use of preservation methods, and thus they should continue to be offered if the patient seeks to preserve fertility, and reference to the specialist in reproductive biology for evaluation and management should be made. GnRH analogues indication should not delay chemotherapy treatment initiation.

Patients should be informed on the possibility of pregnancy even during endocrine therapy despite the presence of amenorrhea and should be informed about the need for an adequate non-hormonal contraceptive.

The use of exogenous hormonal contraceptives is contraindicated in young survivor women, and alternative strategies should be considered:

- If the patient has completed her childbearing plans, seek definitive options (bilateral tubal occlusion or vasectomy).
- If the patient has not yet completed her childbearing plans, IUD (copper T).

The use of levonorgestrel-releasing IUD is controversial.

- Another option for patients with non-completed childbearing plans is condom (consider failures associated with incorrect use).
- Inquire on hormonal contraceptives use and indicate discontinuation.
- Performing a pregnancy test is recommended before starting systemic treatment with chemotherapy and/or hormonal therapy.

No detriment in the prognosis of patients with subsequent pregnancies after breast cancer diagnosis has been demonstrated.[21,22] Physicians should discuss this possibility on a case-by-case basis with those interested in seeking pregnancy and not discourage their maternity desire, including those with positive hormone receptors or with the presence of a BRCA germline mutation.[7,17,18,23,24]

The time to seek pregnancy should be personalized, taking into account patient age and ovarian reserve, previous antineoplastic treatments and time of their completion, as well as individual relapse risk.[23] In general, seeking pregnancy 2 to 3 years after chemotherapy conclusion is recommended in patients with hormone-negative tumors.[25] For patients with hormone-sensitive breast cancer, the POSITIVE trial is active, which allows anti-hormonal treatment temporary discontinuation for 2 years, and the results are expected shortly.[27]

All young women should be informed and advised about the risks and related symptoms of amenorrhea and premature menopause resulting from systemic treatment prior to its initiation (chemotherapy or endocrine therapy). During treatment and surveillance, the physician should routinely inquire about symptoms related to menopause and their impact on quality of life in order to offer management alternatives and, if necessary, modify endocrine therapy.

Treatment-related premature menopause and/or amenorrhea increase the risk of bone density decrease in premenopausal patients; therefore, monitoring and treating it accordingly is recommended (see Chapter X, Section 2.7).

2.2.3 Psychological aspects

Young women with breast cancer are at higher risk for psychological stress. All patients with psychological discomfort or needs should be regularly evaluated. Psychological care should be available and integrated in routine cancer treatments and follow-up. Care for patient spouses and families should be early integrated and psychosocial couple interventions should be timely proposed, if required.

The practice of mindfulness meditation through a short intervention program (6-8 weeks) is recommended in young patients with depressive symptoms, since it decreases said discomfort in a sustained way for 6 months. In addition, this practice improves symptoms of anxiety, hot flashes, fatigue and insomnia. Currently, there are virtual trainings for these practices. Providing educational sessions is associated with improving depressive symptoms.[27]

XV. Treatment in older adult female patients

This consensus considers an age ≥ 65 years to define an older adult.[1] In these patients, chronological age does not necessarily reflect physiological age, and should therefore not dictate treatment.[2] Geriatric assessment allows recognizing not usually found problems, identifies vulnerable/frail patients, and leads to changes in planned management in up to 50 % of cases. In addition, it allows calculating life expectancy and predicting toxicities and hospitalization risk, which can improve therapeutic decision-making and generate interventions aimed at preventing complications and reducing the negative impact of treatment on quality of life.[2,3]

1. Recommendations for geriatric assessment

Use the G8 geriatric screening tool (Table 22) in all women aged ≥ 65 years at the beginning of treatment. Patients with a G8 score > 14 points do not require additional evaluations.[3-5]

In patients with a G8 score ≤14 points, referral to a physician with experience in geriatrics is recommended for geriatric assessment, which shall include the domains in Table 23.[3,5]

According to geriatric assessment, patients can be classified into three groups (Fit, Frail or Vulnerable), which can be used for therapeutic decisions[6] (Figure 19).[6]

Consultation with the geriatrics department is recommended in order to implement multidisciplinary interventions aimed at treating the deficits found in the geriatric assessment concurrently with treatment.[3,7]

2. Life expectancy calculation

We recommend using the Suemoto index (validated in Mexico and available at https://eprognosis.ucsf.edu/suemoto.php) to calculate 10-year life expectancy. In option “Does your patient have cancer?” NO should be selected to obtain mortality from competitive risks. This will help to weigh the risk-benefit ratio of therapeutic interventions and to individualize treatment.[3,8]

3. Chemotherapy-related toxicity

We recommend using the Cancer and Aging Research Group (CARG) toxicity calculator specific for breast cancer.[9] This calculator should not be used to determine which patients may or may not receive treatment, but rather to identify patients with higher risk of serious toxicities with the purpose to implement preventive measures and close follow-up. Another alternative is the CRASH calculator, available at www.moffitt.org/eforms/crash*score*form.[10]

4. Specific treatment recommendations

4.1 Surgery

In older adults, age is not a factor that determines the type of surgical treatment. However, it is important to evaluate surgical risk based on associated comorbidity, since it has been observed to limit the opportunity for said treatment and can lead to functional deterioration.[11]

4.2 Radiotherapy

In older adult female patients eligible for radiotherapy, deciding on treatment based on geriatric assessment and discussing its risk-benefit ratio is recommended.

In patients with stage 0/I with good prognosis (Grade 1, negative lymph nodes, HR+) treated with hormonal therapy, adjuvant RT after conservative surgery impacts on locoregional control, although there does not appear to be a benefit in overall survival or distant recurrence-free survival.[12,13] Therefore, not administering RT may be an acceptable option in these patients, considering a 10-year local recurrence rate of 10 %.

4.3 Systemic treatment

The benefit of adjuvant CT and/or HT should be determined using standard genomic and clinical tools, and be weighed against life expectancy and toxicity risk. There are no specific adjuvant regimens for older adults, but modified regimens (such as capecitabine monotherapy) are less effective, and thus we recommend standard regimens.[14] In older women who are candidates for CT, regimens without anthracyclines (such as TC) entail less hospitalization risk and may be preferred, especially in HR+ disease.[15] Primary endocrine treatment can be used in frail patients with HR+ tumors who are not candidates for surgery.[16]

In metastatic disease, the same treatments are recommended as in younger patients. We recommend

Table 22. G8 Geriatric screening questionnaire

	Items	Possible answers (points)
F	Does the patient take more than 3 medications per day?	0 = yes 1 = no
G	In comparison with other people of the same age, How does the patient consider her health status?	0 = not as good 0.5 = does not know
H	Age	0 = >85 years 1 = 80-85 years 2 = <80 years
	Total Score (0-17)	

Table 23. Geriatric assessment in breast cancer[3]

Domain	Suggested tool*
Functionality	Katz's basic activities (bathing, dressing, going to the bathroom, transfers, eating, continence) Lawton's instrumental activities (telephone, public transportation, finances, shopping, preparing meals, housekeeping, laundry, take her own medications)
Comorbidity	Charlson Index
Depression	PHQ-2
Cognition	Mini-Cog
Nutrition	Unintended weight loss >10 %
Falls	≥ 1 fall within last six months

PHQ-2: Patient Health Questionnaire 2. The tools can be obtained at http://consensocancermamario.com/

using geriatric assessment to determine if patients are candidates for CT.[3,5]

XVI. Male breast cancer

1. Introduction

Male breast cancer accounts for less than 1 % of all breast cancer cases.[1] In 2020, 2,620 new cases were estimated in the USA.[2] Main risk factors are BRCA 2 gene mutation, Klinefelter syndrome, cryptorchidism, previous radiotherapy to the chest and use of exogenous estrogens.[3,4] Average age at diagnosis is 68.4 years,[5,6] in comparison with 58.2 years reported in the female counterpart.[7] The predominant histological type is ductal invasive, present in around 90 % of cases. More than 90 % are luminal, while HER-2 is positive in only 11 % of tumors, and less than 3 % are reported as triple-negative.[8-10] In males, the diagnosis is made at more advanced stages, due to a low diagnostic suspicion,[11] with a 5-year overall survival of 85.0 % being achieved, compared with 90.2 % achieved in the female gender.[12]

2. Treatment

Breast cancer treatment in men has been practically extrapolated from available data on breast cancer in women, and it is treated similarly by stages, taking patient age and general health condition into account, as well as tumor pathological characteristics, including hormone receptors and HER-2 neu expression.

Recommended local treatment is radical modified mastectomy, with sentinel lymph node or axillary dissection, according to clinical stage.

Breast-conserving surgery is not indicated. Chemotherapy and radiotherapy recommendations follow the same guidelines as for women.[13]

Tamoxifen for 5 years is recommended as standard treatment in patients with hormone receptor-positive tumors. Tamoxifen use for 10 years also follows the same guidelines as for women. Aromatase inhibitors are not indicated.

The use of genomic platforms such as OncoType, Mammaprint or Endopredict is not recommended for adjuvant treatment decisions, since there is insufficient information for evaluating their usefulness. On the other hand, although there is no evidence on the benefit of adjuvant trastuzumab in men with HER-2 neu-positive breast cancer, its use should be considered according to established indications.[13]

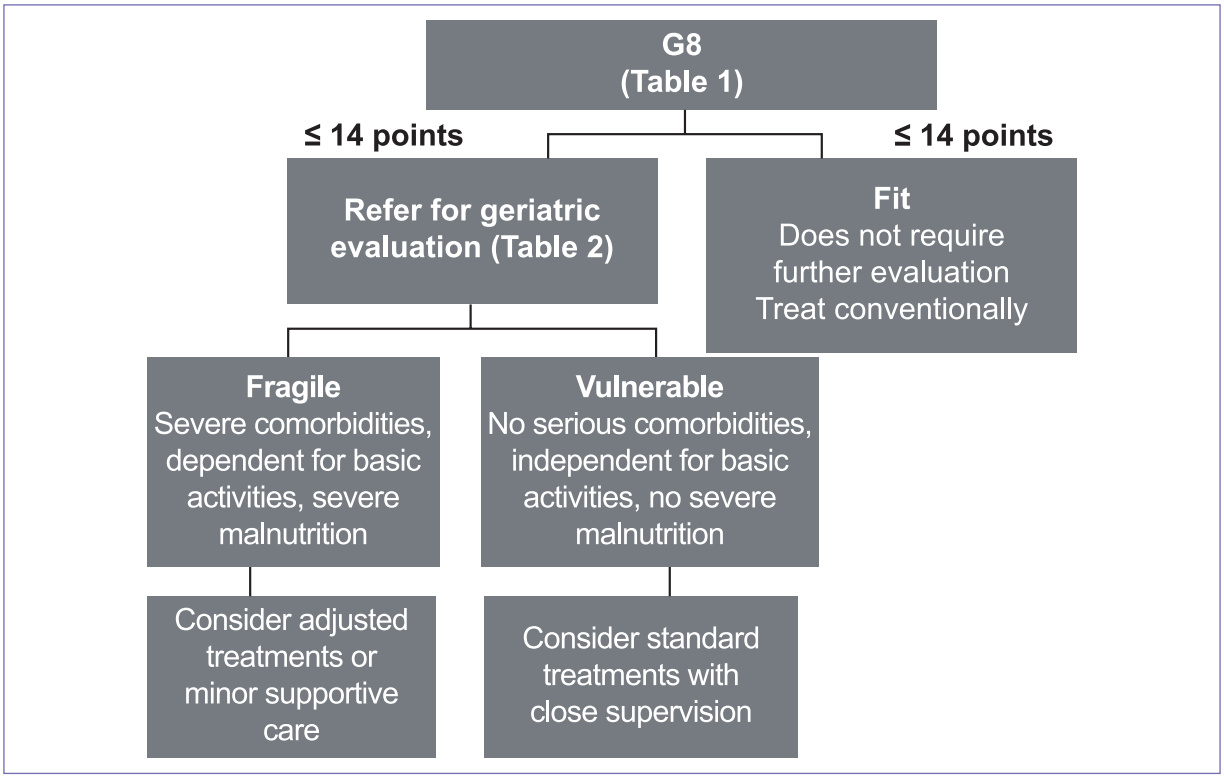


Figure 19. Geriatric assesment classification.

As for locally advanced breast cancer, up to 40 % are diagnosed at this stage. They must be treated following the guidelines proposed for women.

In hormone receptor-positive metastatic disease, tamoxifen is the treatment of choice, except in cases of rapidly growing tumors or with visceral metastases, where seeking a prompt objective response with cytotoxic therapy is necessary. Management with aromatase inhibitors + LHRH agonist should be considered, as well as the use of CDK4/6 inhibitors or everolimus + double hormonal blockade with the same indications as in women.[14]

Finally, in patients with negative receptors or who are hormone-refractory, chemotherapy with regimens and doses equal to those used in women is the treatment of choice.

Patients with HER-2 neu-positive tumors should be assessed for the addition of trastuzumab and pertuzumab to their systemic management, based on the same guidelines as for women.[15] In patients with BRCA1/2 germline mutation, consider the use of PARP inhibitors;[16-18] and in triple-negative cases with PD-L1 expression > 1 %, the use of atezolizumab + nab-paclitaxel should be evaluated.[19]

XVII. Breast cancer associated with pregnancy and breastfeeding

1. General guidelines

Cancer associated with pregnancy is defined as that which is diagnosed during the gestation period, and up to the first year after pregnancy termination.[1]

Physiological changes in the mammary gland during pregnancy and breastfeeding hinder and delay diagnosis.[2]

Treatment of pregnant women with breast cancer must be multidisciplinary and include the oncological group, specialists in obstetrics-gynecology, in maternal-fetal medicine, pediatrics and psychology.[1,3]

Referring these patients to specialized centers in the area is recommended, and including them in multicenter working groups should be considered.

Fetal surveillance should be carried out every 3-4 weeks or, where appropriate, prior to each chemotherapy cycle.

2. Diagnosis

The recommended initial imaging study is breast ultrasound.[4]

Mammography should be requested in order to assess the extent of disease, the presence of microcalcifications, rule out multicentricity, and to assess the contralateral breast. It should be carried out with abdominal protection. The dose received by the uterus is lower than 0.03 Gy.[2,5]

To corroborate the diagnosis, a core needle biopsy should be carried out under local anesthesia; it is important for the pregnant state of the patient to be informed to the pathology department that will handle the specimens.

Suggested extent of disease evaluation workup includes:[5,6]

- Chest X-ray with abdominal protection.
- Liver ultrasound.
- Magnetic resonance imaging of the thoracolumbar spine, without contrast medium, in case of suspected bone disease.
- With limited information, whole-body MRI has been proposed during the second and third trimesters, as an option to other extent of disease evaluation methods.[7]

The following should be avoided:

- Procedures that expose the fetus to high radiation such as computed tomography, nuclear medicine studies and PET/CT.
- Contrast media such as Gadolinium.[5,8]

3. Surgery

Surgery is a safe procedure during any trimester of pregnancy.

The decision about the type of surgery should be made according to tumor characteristics, clinical stage and pregnancy trimester.

In stages I and II, mastectomy has not been shown to offer greater survival in comparison with breast-conserving surgery.[9]

- Breast-conserving surgery is indicated in the second and third trimesters of pregnancy, followed by radiotherapy at the end of pregnancy.
- Standard axillary treatment is level I and II dissection. Regarding sentinel lymph node procedure, technetium 99 (99mTc) radiocolloid appears to be safe at any pregnancy trimester; however, due to the little scientific information so far, using it at third trimester of gestation is recommended. The recommended dose is 18.537 MBq (0.5 1.0 mCi) with a half-life of 6 hours; at this dose, uterus exposure to radiation is lower than 5 mGy.[5,10]
- The use of colorants such as patent blue or methylene blue should be avoided.
- Owing to pregnancy-inherent physiological changes that generate greater breast congestion and volume and limited published experience,[11] the members of this consensus do not recommend immediate breast reconstruction during pregnancy.

4. Radiotherapy

Treatment with radiotherapy is contraindicated throughout pregnancy due to its teratogenicity and malignancy induction, as well as hematological alterations.[12]

5. Systemic treatment

5.1 Chemotherapy

Chemotherapy is recommended from the second trimester of gestation on.[13]

Performing a fetal examination with ultrasound prior to the start of chemotherapy is recommended in order to rule out preexisting abnormalities, as well as blood pressure measurement and proteinuria determination prior to each cycle.[14,15]

Regimens based on anthracyclines and taxanes are recommended. Doses should be calculated according to real body surface area.[16] Experience in retrospective cohorts has not shown fetuss damage increase.[17,18] Weekly paclitaxel is preferred over docetaxel. Dense doses and platinum salts efficacy and safety are still not entirely clear.[19]

Exposure to chemotherapy in utero after the second trimester does not affect children cognitive, cardiac, and physical development.[20] Exposure to anthracyclines and their long-term effect do not appear to cause developmental effects. Regarding taxanes, there is not enough information.[21,22]

Chemotherapy administration after the 35th week of gestation should be avoided in order to prevent obstetric complications.[23,24]

Starting chemotherapy at standard doses is recommended, and after the first cycle, making the pertinent modifications.

5.2 Biologic therapies

Currently, the use of anti-HER-2 therapies during pregnancy is contraindicated, since they have been associated with oligo/anhydramnios and pulmonary hypoplasia.[25-27]

On the other hand, the MotHer trial, which is an observational study of two prospective cohorts of women

who received Trastuzumab, Pertuzumab and T-DM1 during pregnancy or at six months prior to pregnancy (Clinical Trials: NCT00833963),[28] will provide us with further information on the subject.

5.3 Endocrine therapy

The use of tamoxifen or other endocrine therapy during pregnancy is contraindicated.[1]

5.4 Antiemetic drugs and supportive therapies

Antiemetic drugs and colony-stimulating factors should be used according to usual management recommendations.

The use of bisphosphonates is not recommended.

5.5 Pregnancy termination

The time at which the pregnancy should be interrupted and the route of gestation termination should be dictated by obstetric indications.

In case of receiving chemotherapy, it should not be administered for 3 weeks prior to the probable date of delivery or after week 35 in order to avoid NADIR.

Pregnancy interruption during the first trimester should only be considered at advanced stages that require systemic treatment due to a high teratogenic risk. This decision should be made by the patient in conjunction with the multidisciplinary group.[29]

5.6 Breastfeeding

Breastfeeding should be avoided if the patient is receiving systemic therapy, biological therapies or radiotherapy.[13]

6. Prognosis

Early termination of pregnancy does not improve survival.

There is contradictory information to consider the presence of pregnancy, by itself, as an independent factor of poor prognosis.[30,31]

7. Other aspects

BRCA1 and BRCA2 mutation carriers are not protected by early pregnancies,[24] and neither has it been identified that they are at higher risk of breast cancer during pregnancy.[32]

Regarding immunotherapy and CDK4/6 inhibitors, there is not enough information for issuing any recommendation.

The use of dexamethasone and colony-stimulating factors is not contraindicated according to retrospective evidence.[33,34]

XVIII. Management of rare histologies

1. Phyllodes tumor

Phyllodes tumor (PT) is a fibroepithelial neoplasm that accounts for 1 % of breast tumors.[1] Patients with Li-Fraumeni syndrome with a TP53 mutation are at higher risk for developing PT.[2,3]

Age of presentation is highly variable, with an average of 40 years.[4-6] PTs are generally large and rapidly growing tumors; occasionally they can ulcerate the skin or invade the chest wall. Asymptomatic patients, PT smaller than 3 cm, multifocality and/or bilaterality, are infrequent.[7,8]

1.1 Diagnosis

On imaging studies, PTs resemble fibroadenomas. On ultrasound, well-defined and circumscribed rounded oval or lobulated lesions with heterogeneous content and non-enhanced internal septa are identified. The presence of poorly-defined margins, with a high resistance index, posterior acoustic shadowing and marked hypoechogenicity, suggest borderline or malignant PT.[9,10] On mammography, the tumor may have darkened margins or thick calcifications.[11] On magnetic resonance imaging, the nodule corresponds to a T1-weigted hypointense signal and a T2-weighted hyper/isointense signal.

Core needle biopsy is the recommended diagnostic method; however, thorough examination of the surgical specimen is necessary for classifying it, since the tumor is often heterogeneous. Fine needle aspiration biopsy (FNAB) is not recommended due to a low diagnostic efficacy.[12-14] Unlike fibroadenomas, PTs have higher stromal cellularity and mitotic activity.

In the presence of clinical suspicion of PT in a patient with a tumor reported as fibroadenoma on biopsy, excision should be carried out in order to rule it out.

Table 24. WHO classification for phyllodes tumor (2012)

Characteristic	Benign	Borderline	Malignant
HISTOLÓGICA			
Stromal cellularity	Mild	Moderate	Marked
Stromal cellular atypia	Mild	Moderate	Marked
Mitosis (per 10 high-power fields)	<5	5-9	≥10
Overgrowth	Absent	Absent or focal	Present
STROMAL			
Tumor margins	Well defined (pushing)	Well defined (pushing)	Infiltrating
		focally infiltrating	

Intraoperative examination is recommended to evaluate margins, not to rule out PT.

1.2 Classification

The classification accepted by the World Health Organization (WHO) divides PTs into benign, borderline or malignant, taking into account stromal hypercellularity, cell pleomorphism, mitosis, margins, stromal pattern and heterologous elements (T1) (Table 24).[15-17]

A single tumor can contain several features at the same time. The frequency of benign PTs is 41 % to 67 %; borderline, 11.8 % to 45 %; and malignant, from 12 to 33 %.[5,18,19] In the largest Mexican PT series, the frequency was 72.3 %, 16.2 % and 11.4 %, respectively.[4]

Differential diagnoses include fibroadenoma, hamartoma, adenoma, lipoma, juvenile papillomatosis, sarcoma, carcinoma and metastatic tumors.[1]

1.3 Surgical treatment

Surgical treatment is the therapeutic cornerstone, either by wide excision or mastectomy, with the premise of obtaining tumor-free margins. In the case of benign PTs, negative three-dimensional margins > 1 mm are recommended, while in borderline and malignant PT the ideal is > 1 cm, since it is the main prognostic factor of local recurrence.[20-22]

Borderline and malignant PTs have a high risk of recurrence, which is why mastectomy is the most recommended treatment. Surgical re-interventions to widen tumor-free margins occur in 12.7 % to 34 %.[4,23] Oncoplastic procedures can be used to improve the esthetic result, with breast-conserving surgeries being reported in up to 23 %.[4] Immediate breast reconstruction can be performed; however, it is not recommended when there is the possibility of adjuvant radiotherapy.

Table 25. Recommendations for radiotherapy in phyllodes tumor

Characteristic	Recommendations
Benign	None
Malignant PT characteristics: – Stromal overgrowth – Cellular atypia – High mitotic count	Radiotherapy to the chest wall in any of the following conditions: – After mastectomy and if margins are positive or close (< 1 cm) – Muscular fascia or chest wall involvement – Tumor larger than 5 cm – After breast-conserving surgery with <1 cm margins – Positive Lymph nodes
Recurrence	After recurrence surgical resection (borderline or malignant) or in case it is unresectable

Axillary dissection is not indicated, since lymph node metastases occur in < 5 %.[11] Lymphadenectomy shall only be performed in patients in whom there is clinically-determined lymph node involvement.

1.4 Adjuvant therapy

1.4.1 Postoperative radiotherapy

So far, there are no prospective randomized trials to support its routine use as adjuvant treatment. The decision to use it is based on histopathological criteria, margin status and tumor size, regardless of the type of

surgery.[24] In case local recurrence, radiotherapy can be used.

According to the sparse published literature[5,25,26] and recommendations of other treatment guidelines,[22,27] Table 25 summarizes the indications for radiotherapy in PT.

1.4.2 Adjuvant systemic therapy

Although PTs epithelial component contains alpha estrogen receptors in 28 % to 48 %, beta estrogen receptors in 34.7 % to 58 %, progesterone receptors in 75 % to 95 %, and androgen receptors in 4.5 % to 14 %, hormonal therapy has shown no benefit.[28] The use of cytotoxic chemotherapy with anthracyclines, ifosfamide, cisplatin, and etoposide has not shown disease-free or overall survival benefit either.

1.5 Prognostic factors

The more aggressive the PT, the higher the risk of local recurrence. Poor prognostic factors of local recurrence include: higher mitotic count, stromal cellularity (moderate/severe), infiltrating margins, severe stromal atypia, severe stromal overgrowth, and tumor necrosis. Furthermore, in high-risk subtypes (borderline and malignant PT), breast-conserving surgery and positive margins have been identified as adverse factors.[5,30]

1.6 Follow-up

Breast self-examination is recommended, in addition to biannual clinical follow-up the first 2 years and then annually, with complementary studies such as annual ultrasound, mammography and/or magnetic resonance.[11]

Local recurrences are reported to be from 3.6 % to 18 % for benign, 13 % to 29 % for borderline and from 18 % to 42 % for malignant PT, whereas distant recurrence occurs in 0 %, 2 % and 14 %, respectively, with the lung being the most common site.[5,6,30,31]

In the presence of recurrence, performing chest X-ray with/without contrasted chest tomography is recommended. Treatment of local recurrences consists of wide resection of the lesion, ensuring tumor-free margins, and radiotherapy to the chest wall after resection. In patients with distant recurrence, especially at the lung level, treatment will be based on sarcoma management recommendations.[22]

2. Uncommon histologies in breast cancer

These types of histology are documented in less than 5 % of cases, some of them with a frequency as low as 0.1 %.[1,2] Due to the rarity of these tumors, information obtained from the literature is not conclusive for some treatments, which is why tumor biology should be taken more into account.[3,4]

In most these entities, surgical treatment is the therapeutic cornerstone, following the guidelines already known for mastectomy or breast-conserving surgery, according to clinical characteristics and stage. The recommendations for axillary staging are the same as for invasive ductal carcinoma. The use of chemotherapy is controversial in most good prognosis strains, while in those of poor prognosis, it is widely recommended. In some cases, the recommendation is to use different cytotoxic agents than the usual ones, such as platinum salts.

Hormonal therapy is indicated according to the status of estrogen and/or progesterone hormone receptors; given that experience with androgen receptors is limited in these type of histology, they will not be considered in this section. The indications for adjuvant radiotherapy are the same as those recommended for infiltrating ductal carcinoma. The use of targeted therapies has been suggested in these rare neoplasms according to immunohistochemical characteristics; however, the rarity and lack of homogeneity in oncological management make for this recommendation to continue being limited. Prognosis in these histologies is also highly heterogeneous.[5]

In the classification of tumors of the breast update by the World Health Organization,[1,6] medullary carcinoma is no longer regarded as a histological variant, but is integrated into the different morphological patterns of invasive carcinoma. Two variants were added (mucinous cystadenocarcinoma and tall cell carcinoma with reverse polarity) and the terminology in neuroendocrine tumors was modified.

Tables 26 to 29 describe the main characteristics of these rare histologies, according to prognosis (good, intermediate and poor).

XIX. Follow-up after treatment with curative intent and in metastatic disease

1. Introduction

At the conclusion of breast cancer primary treatment, usually with surgery, chemotherapy and

Table 26. Lineages of good prognosis. Usually positive hormone receptors

	Mucinous carcinoma, pure and mixed[7-9]	Tubular carcinoma[1,2]	Cribriform carcinoma[1,2]	Neuroendocrine tumors[1,10,11]	Papillary carcinoma (intracystic and solid)[12-14]
Frequency	1-4 % (pure)	<2 %. >90 % must have tubular architecture	0.1 – 0.6 %	<1 %	0.7 %
Age of presentation	71	60 (27-92)	54–63	60-70	60-70
Grade	Usually grade I	Usually grade I	Usually grade I	Grade I-II	Grade I, 40-47 %; grade II, 40-50 %
Proliferative activity	Low	Low	Low	Low	Low
Hormone receptors	Usually positive	Usually positive	Usually positive	ER-positive 95 %. PR-positive 80 %	Positive >80 %
HER2	Usually negative	Usually negative	Negative	Usually negative	Negative
Lymph node involvement	Rare, <12 %	4-17 %	10 %	Variable, usually high	3-12 %
Prognosis	5-year DFI 85- 95 % 5-year OS 94- 98 %. 10-year OS 89- 94 % 15-year OS 85 % 20-year OS 81 %	5-year DFI 94 % 5-year OS 88 %	5-year OS 100 % (in pure variant)	Similar to invasive ductal carcinoma stage by stage	5-year OS >80 %. Depends On grade and stage.
Surgical treatment	Recommended	Recommended	Recommended	Recommended	Recommended
Chemotherapy	Poor benefit	Poor benefit	Controversial in mixed variants	Recommended	Limited role
Hormonal therapy	Recommended	Recommended	Controversial in mixed variants	Recommended	Recommended
Radiotherapy	Recommended	Recommended	Controversial in mixed variants	Recommended	Recommended

ER: estrogen receptors; RP: progesterone receptors; HR: hormone receptors (estrogen and/or progesterone); DFI: disease-free interval; OS: overall survival.

radiotherapy, the surveillance and control stage known as "follow-up" begins. The goals of follow-up are: to detect recurrences and contralateral breast cancer, to evaluate and treat treatment-related complications (e.g., osteoporosis, second primary tumors), to motivate the patient to continue endocrine therapy and to treat its side effects.

Table 30 describes internationally-accepted recommendations for the follow-up of these patients. It is important to highlight that the appearance of metastasis after adequate primary treatment is unconnected with medical action; furthermore, anticipating the diagnosis of relapse does not increase survival or quality of life.

1.1 Follow-up in patients with metastatic disease

The purpose is to detect disease progression, avoid toxicity or use of an inefficacious treatment, as well as resources optimization. Patient reassessment is also indicated if there is deterioration, increased

Table 27. Lineages of good prognosis. Usually negative hormone receptors

	Adenoid cystic carcinoma[15]	Secretory carcinoma[16]	Tall cell carcinoma with reverse polarity[1,17,18]	Mucinous cystadenocarcinoma[1]
Frequency	< 1 %. Histology similar to that of salivary glands	0.2 %	< 0.1 %	< 0.1 %
Frequency	58-66	25-40	39-89 (mean 64 years)	41-96 (median 61 years)
Grade	Low	Usually grade I and II	Usually grade I	Usually grade I
Proliferative activity	Low	Low. Absence of nuclear atypia, absence of high mitotic index.	Low. Ki67 expression ~20 %	Low
Hormone receptors	ER-positive, 0-46 %; PR-positive 0-36 %	Usually negative	Usually negative	Usually negative
HER2	Usually negative	Negative	Negative	Usually negative
Lymph node involvement	0-8 %	20-30 %	< 10 %	Very rare
Prognosis	Good. 5-year OS ~90 %	Recurrence reported at 12-20 years	Good. DFI 3-132 months	Good
Surgical treatment	Recommended. Mastectomy is preferred. High percentage of positive margins in breast-conserving surgeries (33-86 %). Axillary staging questionable due to high potential for generation of metastasis without prior lymph node involvement	Recommended	Recommended	Recommended
Chemotherapy	Uncertain benefit	Uncertain benefit	Uncertain benefit	Uncertain benefit
Hormonal therapy	Uncertain benefit	Recommended*	Recommended*	Recommended*
Radiotherapy	If it increases OS	Uncertain benefit. Recommended In breast conserving surgery	Uncertain benefit	Uncertain benefit

ER: estrogen receptors; PR: progesterone receptors; OS: overall survival.
* Recommended in positive hormone receptors (estrogen and/or progesterone).

symptoms or appearance of new signs, regardless of the interval that has elapsed since previous control (Table 31).

XX. Hormone replacement therapy (hrt)

1. Introduction

Mexican women experience climacteric syndrome at around 49 + 5 years of age, and up to 80 % of them will have vasomotor symptoms and insomnia, and 40 % will experience depression, genital atrophy, cardiovascular diseases and bone density decrease.[1]

In women without breast cancer, using hormone replacement therapy (HRT) is often recommended to control and reduce moderate to severe symptoms, but, on the other hand, its administration has been shown to increase the risk of developing breast cancer (1.66) and is directly related to the dose and the time of use.[2]

Table 28. Lineages of intermediate prognosis

	Apocrine carcinoma[19]
Frequency	0.3 - 4 %
Age of presentation	52-61
Grade	Grade II: 50-56 %
Proliferative activity	p53, 29 %; bcl-2, 25 %; MIB-1 index 29 %
Hormone receptors	Usually HR-negative. Usually positive androgen receptors
HER2	Positive in 33-54 %
Lymph node involvement	21-26 %
Prognosis	Better than ductal invasive carcinoma
Surgical treatment	Recommended
Chemotherapy	Recommended
Hormonal therapy	Recommended* (aromatase inhibitor)
Targeted therapies	Few evidence with anti-HER-2. Susceptible to targeted therapies
Radiotherapy	Recommended

HR: hormone receptors (estrogen and/or progesterone).
* Recommended for positive hormone receptors (estrogen and/or progesterone).

2. HRT in women with breast cancer

Current literature regarding HRT in women with breast cancer is mainly based on observational studies, with HRT variables being impossible to control in terms of route of administration, whether it is topical, transvaginal, or oral, estrogens or estrogens with progestogens and, on the other hand, they do not include data such as clinical stage, hormone receptor status and lymph node status.[3]

The HABITS study, a controlled, double-blind trial, was stopped in 2003 due to an increased risk of recurrence and death from breast cancer in patients exposed to HRT; however, the randomized Stockholm trial of patients with breast cancer at early clinical stages, 50 % of them with tamoxifen use and only 16 % of them with positive lymph nodes, showed that there is no significant difference in the disease-free interval or in the risk of breast cancer-related death. This study also found that the use of estrogen-based HRT was shown to have lower risk than combination therapy (estrogen with progesterone).[4]

Although tibolone has been used as an alternative for the management of menopausal symptoms, its administration is not recommended due to an increase in the risk of both loco-regional and systemic recurrence (HR, 1.4) in women with a history of breast cancer, according to the results of the LIBERATE trial.[5]

Recent studies have shown that topical vaginal HRT with estrogens in patients with moderate to severe vulvovaginal atrophy does not increase the risk of recurrence in breast cancer survivors, especially in women using tamoxifen, or that it is used for less than 18 months and in women who do not respond to the use of vaginal lubricants. However, regarding the use of oral or topical non-transvaginal hormonal agents, no recommendation has yet been made due to lack of evidence.[6]

Based on the above, this consensus considers that the use of HRT is contraindicated in women who are breast cancer survivors.

XXI. Genetics and breast cancer

1. Introduction

Approximately 20 % of patients with breast cancer have first or second degree relatives with a history of the same disease, which is considered a familial presentation. Five to 10 % of cases are associated with a hereditary syndrome and 25 to 40 % of these patients are younger than 35 years of age.[1,2]

The genes related to hereditary breast cancer can be divided into those that confer high susceptibility for the development of cancer (higher than 50 %) (BRCA1, BRCA2, CDH1, NF1, PTEN, TP53 and STK11) and moderate susceptibility (20 to 50 %) (ATM, BRIP1, CHEK2, PALB2, RAD51C, RAD51D and NBS1).[2-4] The prevalence of BRCA1 and BRCA2 genes germline mutation in the general population ranges from 1 in 50 to 1 in 800, depending on the ethnic group, and is responsible for 3 % to 8 % of all cases of breast cancer. These mutations explain up to 60 % of breast cancer hereditary presentations and cause hereditary breast and ovarian cancer (HBOC) syndrome.[3-6]

Women who are carriers of pathogenic variants (PV) in BRCA1 have a cumulative risk at 80 years of up to 72 % for developing breast cancer, and in the case of BRCA2 PV, of up to 69 %, with a cumulative risk for developing contralateral breast cancer of 40 % in BRCA1 PV carriers and of 26 % in association with BRCA2. Cumulative risk at

Table 29. Lineages of poor prognosis

	Metaplastic carcinoma[20-22]	Metaplastic carcinoma, squamous cell subtype[20-22]	Neuroendocrine carcinoma[1,9,10,23]	Micropapillary invasive carcinoma[24]
Frequency	0.2-0.6 % Divided into pure epithelial and mixed.	<0.1 %, Tumors with squamous-type carcinoma in >90 %	Small cells: 0.1 % Large cells: <0.1 %	Pure: 0.9 – 2 %
Age of presentation	46-61	54-64	43-70	52.5
Grade	Usually grade III	Usually grade III	Grade III	Grade II-III in 75 %
Proliferative activity	High. Ki67 and p53 elevated	High. Ki67 elevated and Cytokeratins 5 and 6 positive, EGFR positive in 85 %, and p63 positive in 70 %	High	High
Hormone receptors	Negative HR 70-100 %	Negative HR >85 %	Positive ER 30-50 % Positive PR <30 %	Positive ER 61-100 % Positive PR 46-86 %
HER2	Usually negative	Usually negative	Negative	Positive in 50 %
Lymph node involvement	<30 %. High capacity for generating metastasis	~30 %	~40 %	66-100 %
Prognosis	5-year OS 63 %. OS of 8 months after recurrence.	5-year OS 50-67 %	Worse than invasive ductal carcinoma, stage by stage	Local recurrence 22-71 % at 30 months
Surgical treatment	Recommended. Generally mastectomy, as these are very large sized tumors	Recommended. Generally mastectomy, as these are very large sized tumors	Recommended according to stage	Recommended
Chemotherapy	Poor benefit. Doxorubicin, ifosfamide	Standard agents for breast cancer have not demonstrated any difference in OS or DFI. Tendency to use platinum salts and taxanes.	Recommended, with regimens used for small-cell lung carcinoma	Recommended
Hormonal therapy	Recommended*	Recommended*	Recommended*	Recommended
Targeted therapies	Potential benefit with tyrosine kinase and PI3K–Akt and MAPK pathways inhibitors.	EGFR inhibitors have been suggested	Anti-angiogenic agents and mTOR inhibitors are under study	
Radiotherapy	Poor evidence in terms of benefit	Initiate as soon as possible due to high risk of local recurrence, although radiosensitivity is questionable.	Recommended, although with questionable survival benefit	Recommended

HR: hormone receptors (estrogen and/or progesterone); RE: estrogen receptors; PR: progesterone receptors; DFI: disease-free interval; OS: overall survival.
* Recommended in case of positive hormone receptors (estrogen and/or progesterone).

80 years for developing ovarian cancer is up to 44 % with BRCA1 mutation and 17 % with BRCA2 mutation.6,7

HBOC has an autosomal dominant inheritance pattern, and first-degree relatives of carrier patients therefore have a 50 % risk of inheriting it.[4] It is essential for medical and paramedical personnel to identify patients at high risk of hereditary cancer, for their referral to the multidisciplinary team, which must include an expert in cancer genetics for comprehensive evaluation. The type of cancer and age at diagnosis in relatives are key to the integration of a

Table 30. Recommendations for follow-up

Procedure	Frequency
Instruction to the patient about the symptoms and signs of recurrence	At the completion of radical treatment
Physical examination	First 2 years every 3 to 4 months. Third to fifth years every 6 months. From fifth year on, annually
Breast self-exploration	Monthly
Mammogram	Annualy
Tumor markers	Not recommended
Chest, abdomen CT, PET, bone scintigraphy and liver enzymes	Only if there are specific symtoms
Screening for other tumors (cervical, colorectal, ovarian, endometrial, etc.)	Follow early detection guidelines
Instructions to the patient on exercise, physical activity and weight control. Evaluate and promote adherence to endocrine therapy and monitor/treat its possible adverse events. Emphasize the use of contraceptive methods (barrier or definitive)	At each appointment

hereditary cancer syndrome. In some cases, there may be no family history of cancer, but this does not exclude the possibility for a hereditary cancer syndrome to exist. Molecular study is indicated in high-risk population (Table 32).[6,7]

Every patient who undergoes a germline molecular study should receive pre- and post-test advice. Incomplete or inadequate assessment is associated with adverse effects, including negative emotional effects, incorrect surgical and follow-up measures, as well as incorrect interpretation of tests, in addition to economic consequences.

Multi-gene panels for hereditary cancer play an important role in the diagnosis of these patients; however, one of the limitations is ignorance about the level of risk for many genes, lack of clinical guidelines and a high percentage of variants of uncertain clinical significance (without direct impact on clinical management), and they should be indicated by healthcare professionals trained in the subject, for a careful interpretation of results and consequent advice. Even in patients who meet clinical criteria for inherited cancer syndrome, the result of a panel can be unexpected.[7-8] This study is not a screening that can be offered to the general population.

The triple-negative tumor phenotype is mainly related to BRCA1 pathogenic variants. Up to 20 % of patients with this tumor phenotype are carriers of germline mutations and, therefore, this characteristic should be included in the diagnostic criteria, regardless of family history.[9,10]

In the Mexican population, between 30-40 % of cases diagnosed with HBOC may have a founding deletion in BRCA1 that consists of the loss of exons 9 to 12, which is why it should be deliberately sought.[11]

2. Follow-up of a patient who is carrier of pathogenic variants of genes that confer high-risk for the development of breast cancer

Starting with monthly breast self-examination from age 18 is recommended; annual or biannual clinical examination, as well as mammography and MRI of the breasts from age 30;[7] however, age of initiation may be according to the earliest age of presentation in the family.

3. Chemoprevention and other procedures in patients who are carriers of pathogenic variants of genes that confer high-risk for developing breast cancer

Chemoprevention with tamoxifen and AI, risk-reducing mastectomy and the combination of mastectomy/oophorectomy-salpingectomy,[1,6] should only be considered in a group of patients carefully selected by a multidisciplinary team, based on the objective risk for developing breast cancer, as well as patient personal wishes after genetic counseling (see Chapter X. Risk-reducing mastectomy [RRM] and Chapter IV. Primary prevention).

XXII. Psycho-oncological aspects in breast cancer

1. Introduction

Psycho-oncology is a specialty that deals with the psychological, social, cultural, anthropological, ethical-spiritual

Table 31. Follow-up of patients with metastatic disease

Evaluation	Baseline	Chemotherapy	Endocrine therapy
Symptom evaluation	Yes	Prior to each cycle	Every 1-3 months
Physical examination	Yes	Prior to each cycle	Every 1-3 months
BC + LFT, BCh	Yes	Every 2-4 cycles	Every 2-6 months
Chest-abdominal CT	Yes	Every 4 cycles	Every 4-6 months
pelvis	Optional	Optional	Optional

Table 32. NCCN criteria, version 2.2021

A. Individuals with a relative who is carrier of a pathogenic or probably pathogenic variant
B. Individual with a previous partial or limited molecular test
Personal history of breast cancer and Diagnosis before age 45 Diagnosis between 45-50 years and Unknown or limited family history Second primary breast tumor A close relative with breast, ovarian, pancreas, or prostate cancer
C. Diagnosis before 60 years age and diagnosis of triple-negative breast cancer
D. Any age and Ashkenazi Jewish ancestry A close relative diagnosed with breast cancer before 50 years age and/or metastatic, ovarian, pancreatic or prostate, intraductual, cribriform or high-grade cancer Three relatives with breast cancer
E. Breast cancer in males
F. Patient with a pathogenic variant identified in somatic panel that could have implication if germinally identified
G. If it can influence on therapeutic decision-making, as in the case of a patient with HER-2 (-) metastatic breast cancer

and sexuality aspects of cancer patients. In this context, breast cancer diagnosis has a threatening meaning for the patient and appears as a premature risk of death. This effect will depend on a variety of factors such as age, socioeconomic situation, coping with the disease, and the social and emotional support the patient has.

2. Psychological problems

One the most prevalent psychological problems in patients with breast cancer is distress, defined by the National Comprehensive Cancer Network (NCCN) as an unpleasant emotional experience of psychological (cognitive, behavioral, emotional), social and/or spiritual nature, which interferes with the ability to cope with cancer, its physical symptoms and/or its treatment.[1]

In this group of patients, distress, depression and anxiety constitute the most prevalent mental health problems, which are closely linked to each other. These problems are associated with sleep disturbances, pain and fatigue, mainly in the subgroup of patients with metastatic cancer, who also experience alterations in body image and psychosocial well-being.[2] Diagnosis and treatment of these pathologies, as well as the type of coping by the patient, are essential, since all this can influence on hospital length of stay, self-care, treatment adherence and quality of life.

In patients, effects on sexuality, depressive symptoms, anxiety, body image alterations, relationship problems, problems in the care of children, stigmatization and a feeling of discrimination can occur. Young women with breast cancer or undergoing preventive intervention are concerned about their future fertility and body image, which constitute extremely important aspects for them, and that require strategies for better coping and enhancing self-esteem by providing information on pregnancy after diagnosis or fertilization techniques, facilitating attendance at support groups or associations for sharing common experiences.[3,4] Survivors may experience anxious symptomatology, decreased executive function, working memory alterations and concentration problems, in comparison with women without a history of cancer.

Primary caregivers of this group of patients have been reported to experience psychosocial disorders such as anxiety, depression and overburden. In addition, cancer has been reported to have a significant impact on couple relationships.[5] The most affected are those who have poor problem-solving skills, marital problems prior to diagnosis and who differ in their perceptions and expectations regarding cancer.[6]

3. Evaluation

There are four brief tools to identify patients and couples with psychosocial intervention needs:

- Distress Thermometer (Holland, 1999). It identifies the level of emotional distress; validated for the Mexican population, by Almanza-Muñoz, Juárez and Pérez (2008).
- Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith, 1983).[7] It identifies anxiety and depressive symptoms; validated for the Mexican population by Galindo et al. (2015).
- Zarit Burden Interview Scale (1980).[8] For the partners of patients who play the role of primary caregivers; validated for the Mexican population by Galindo et al. (2015).[7]
- Dyadic Adjustment Scale (DAS) (1976). It evaluates the quality of the couple's relationship; validated in the Mexican population by Moral de la Rubia (2009).[9]

4. Psychological therapy

Cognitive-behavioral therapies (CBT) are considered as the therapeutic alternative for the oncological population that experiences psychological disturbances. The goal is to modify the cognitions and behaviors that complicate health problems through techniques based on scientific research seeking to correct irrational thinking patterns and beliefs associated with physical appearance, attractiveness and worth, and thus improve coping resources and promote emotional self-regulation.

The goals of CBT in cancer are divided in two groups: 1) Approach to psychological problems associated with the diagnosis, treatment and follow-up period, and 2) management of cancer treatment side effects such as nausea, vomiting, pain, insomnia, incontinence and sexual dysfunction.

These patients can benefit from different forms of professional psychological intervention, which can be classified as follows:

- Educational-informative interventions (counseling).
- Individual psychotherapeutic interventions (behavioral, cognitive, dynamic).
- Group psychological processes-mediated interventions.[9]

CBT modifies the patterns that contribute to problems; it can also use conditioning and learning principles to modify problem behaviors.

There is sufficient evidence that cognitive-behavioral programs are effective for improving the control of some symptoms, affective state related to specific situations, and coping with the disease at its various phases.[10] Further studies are recommended in order to increase the evidence in the Mexican population regarding long-term effects and in underrepresented patient groups.

Finally, in patients with advanced cancer and on palliative care, dignity therapy has shown positive effects on emotional well-being (Table 33).

XXIII. Breast cancer patient physical rehabilitation

1. Introduction

Advances in treatments and increased survival of breast cancer patients demand for rehabilitation methods to be increasingly effective in order to achieve better quality of life, both in survivors of the disease and in end-stage patients. After surgical treatment, complications may occur, some of which are exclusively related to the breast, others with axillary lymph node dissection, lymphatic vessels recanalization,[1] cancer treatment (chemotherapy and radiotherapy) and others with infectious processes.

2. Lymphedema

An estimate of 20 % of patients with axillary dissection will develop lymphedema at six months, 36 % at one year, and 54 %, at 36 months, with the risk increasing according to the number of dissected lymph nodes and radiotherapy. On the other hand, overweight and obesity increase the risk in up to 80 % of cases, which impacts on treatment results.[2-5]

Currently, the indicated rehabilitation is poorly known and, therefore, the incidence of lymphedema is higher than it would be if adequate prevention was carried out.[6]

Lymphedema complications include:[7]

- Recurrent infections (lymphangitis, erysipelas, cellulitis).
- Body-image disorder.
- Low situational and chronic self-esteem.
- Impaired social interaction.
- Personal identity disorder.
- Intolerance to activity.
- Self-care deficit.

2.1 Lymphedema stages

2.1.1 Stage 0: latency

- No clinical data on lymphedema.

2.1.2 Stage I: reversible

- Evident volume increase.
- Generally, limb elevation reduces edema (edema that is not favored with diuretic administration, due to

Table 33. Alternatives for psycho-oncological evaluation and treatment

Objective	Instrument	Treatment period	Therapeutic alternatives
Breast cancer patients			
Assessing the level of emotional discomfort, needs, social support and coping	Distress Thermometer	Diagnosis Treatment initiation	Information Psycho-education Emotional validation Relaxation techniques
Assessing the level of anxiety and depression symptoms	Hospital Anxiety and Depression Scale HADS	Treatment period	Psychiatry and/or neurology Cognitive-behavioral therapy
		Paliative treatment	Treatment
Patients' partners and informal primary caregivers			
Knowing the degree of adjustment (agreement) deemed by the partners within their relationship	Dyadic Adjustment Scale	Diagnosis Treatment initiation Treatment period	Information Psycho-education Cognitive-behavioral therapy
Assessing the level of burden associated with patient care	Zarit Burden Interview Scale	Treatment period Palliative treatment	Cognitive-behavioral therapy

protein concentration in the lymphatic fluid) but does not stop its progression.

2.1.3 Stage II: spontaneously irreversible

- Significantly increased limb volume
- Presence of lymphatic fibrosis (areas of higher stagnation), which reduces lymphatic transport capacity
- Elevation of the limb does not reduce edema

2.1.4 Stage III: lymphostatic elephantiasis

- The limb exaggeratedly increases in volume.
- Presence of lymphatic fibrosis
- Extremities more prone to infection
- Physical disability

3. Management of lymphedema in patients treated with curative intent

The patient should know about the risk of developing lymphedema and its consequences, and that this risk decreases with rehabilitation. Training on scar massage and fascia mobilization once the stitches and drains are removed should be provided. This is effective for reducing adhesions in deep planes, improving flexibility and mobility, decreasing the thickness of the scar and surrounding healthy skin, and for preventing pectoralis major muscle spasm, frozen shoulder, and adhesive capsulitis.

Scapulohumeral joint mobilization should start since the first postoperative day: shoulder flexion and extension with the elbow flexed at 90º. Shoulder abduction movements should not be made for seven days, since it takes that time for axillary lymphatic capillaries to be reestablished.

From the eighth day on, movement of the arm should be initiated with passive exercises (with the help of another person) of shoulder flexion, abduction and rotation. Once the full range of motion is achieved, an active exercise program should be started in order to keep the lymphatic system permeable, as well as a program of shoulder muscle stretching to maintain adequate muscle dynamics. In case of having a catheter port, exercises should be adapted to prevent future injuries.

The measures for reducing the risk of lymphedema in the arm, chest and back on the side of the surgery include:

- Avoiding efforts (lifting a maximum load of 5 kg). Progression can be approached with physical work and with the guidance of a professional.
- Avoidance of wounds, burns, insect bites.
- Not sleeping on the affected arm.
- Ideal weight should be maintained.
- Thermotherapy, cryotherapy, or contrasts should not be applied in the affected quadrant or limb.
- Acupuncture treatments should not be performed on the affected quadrant or limb.
- Using a preventive compression sleeve indicated by a specialized physiotherapist.

– The use of diuretics should be avoided, except for a highly necessary medical indication (e.g., combined lymphedema).

If the patient develops Celsus tetrad (swelling and redness with warmth and pain) in the arm, and it suddenly increases in volume, changes color or its temperature rises, medical help is required; these are signs of alarm to rule out or confirm deep vein thrombosis (DVT) and/or infection.

Specialized preventive compression garment (20-30 mmHg) should be indicated by a specialist in the treatment of lymphedema, who should provide the corresponding indications for traveling, physical activity and for performing stressful activities at home and workplace.

Indicated treatment for lymphedema is complex decongestive therapy (CDT)[8,9] or combined physical therapy for lymphedema (CPTL).[10] Although lymphedema has no cure, this treatment can reduce lymphatic edema and keep it under control.

The four components of CDT are:

– Meticulous care of the nails and the skin of the affected quadrant.
– Manual lymphatic drainage (MLD).
– Compression therapy with short traction or Circaid bandages and medical compression garments.
– Myolymphokinetic exercises.[10]

This therapy is gentle, non-invasive and in most cases restores patient control over her lymphedema and reincorporates her to a functional life. A patient who already has lymphedema should receive treatment before wearing a compression sleeve. The use of the sleeve without treatment causes hand edema and makes the patient and the doctor think that the sleeve does not work.

Neuromuscular bandage with an appropriate technique and respecting the lymphatic anatomy is placed with the purpose to stimulate lymphatic drainage (CDT); thanks to the elasticity and S-shaped adhesive of the bandage, it physiologically stimulates the afferent receptors, exerting a change in interstitial pressure, thus favorably complementing the intervention.[11]

Sequential compression device (SCD) therapy is a complementary part of manual lymphatic drainage (MLD), agreed by consensus under a working pressure of between 20 and 40 mmHg, with an average duration of 20 to 45 minutes.

3.1 Role of exercise in lymphedema control

Physical exercise can also help control lymphedema and musculoskeletal symptoms secondary to pharmacological treatments. Non-pharmacological methods such as physical activity, which include a variety of therapeutic methods, together with the use of analgesics, are intended to help the cancer patient gain or maintain functionality and restore a sense of control over pain.[12]

4. CDT or CPTL and physical therapy as palliative treatment in patients with advanced disease

The purpose of this therapy in patients with advanced or end-stage disease is to maintain self-sufficiency for as long as possible, preserving mobility and muscle strength and significantly reducing pain. Although the lymphedema will not significantly improve, maintaining good control thereof possible.

XXIV. COVID-19 and breast cancer

1. Introduction

The SARS-CoV-2 pandemic, declared as such by the WHO in March 2020, became a global public health emergency that represented a challenge to combining the continuity of care of cancer patients with patients' and workers' safety.[1,2]

SARS-CoV-2 infection clinical spectrum can range from asymptomatic carriers to cases of fulminant pneumonia with acute respiratory distress syndrome.[3] The patients with the highest risk of COVID-19-associated mortality are men, older adults, and those with associated comorbidities such as hypertension, obesity, diabetes, smoking, chronic obstructive pulmonary disease, asthma, kidney failure and cancer.[4-7] Cancer patients have a higher risk of becoming infected and for developing more serious forms of the disease;[6-9] however, breast cancer heterogeneity poses multiple clinical scenarios with different probabilities of COVID-19 complications and different goals in cancer treatment.[4,10] Oncology services should continue to be active, since treatment delay has a negative impact on survival, which is why it will be necessary for prioritization strategies to be established according to the resources of each medical unit for all therapeutic modalities, bearing in mind that multidisciplinary management is vital and non-negotiable; telemedicine can be an additional tool.[11-15]

As long as the pandemic continues, establishing a respiratory triage for outpatient daily care is desirable in order to minimize possible transmission, as well as having control of entrances and exits at the medical unit.[10,13,16]

The use of face masks, hand hygiene and social distancing should be implemented; overcrowding of waiting rooms should be avoided, and patient consultation areas, ambulatory chemotherapy and radiotherapy rooms should have proper ventilation.[10,14] If feasible, assessment of the chest region in radiotherapy simulations and in extension of disease evaluation should be included in order to detect radiological alterations in asymptomatic patients and thus protect health personnel and patients.[4,16]

Patient education is essential in order for them to identify COVID-19-related symptoms and, where appropriate, to seek early medical attention.[3,15]

For patients on follow-up who do not have symptoms, surveillance studies can be postponed;[13] however, if there are symptoms of possible tumor recurrence, the patient shall be instructed to request an oncology appointment as soon as possible in order to rule out or confirm said recurrence.

2. Surgical recommendations

Delays in surgical scheduling should be avoided as far as possible in patients with curative intent, since a reduction in survival begins after 3 months of surgical delay.[11,13] A PCR test should be performed 24 to 48 hours prior to the elective surgical procedure + chest CT.[4,14] If negative, the scheduled surgical treatment program will continue. Surgical procedures for biopsies with atypia, risk-reducing surgery, breast reconstruction and benign disease can be deferred and other diagnoses be prioritized.[12,13]

During the pandemic peak or new wave of infection transmission, the following actions can be implemented in order to optimize surgical shifts:

2.1 Ductal carcinoma in situ (DCIS)

Defer surgical management for 3 to 6 months.

- Prefer neoadjuvant systemic treatments in patients with tumors larger than 2 cm and/or clinically positive axilla, in triple-negative and HER-2-positive phenotypes.
- Patients with cT1a-c, cN0 should undergo surgical procedure.[13,17]
- cT1-3 cN0 patients with hormone receptors expression and low-risk biological characteristics can undergo surgery; even at clinical stages cT1-3 cN1 or cT4 cN0-1 if the circumstances of local health context warrant it.[14]

2.2 After neoadjuvant systemic treatment

- Surgical management could be delayed for 4-8 weeks if necessary.
- Unusual cases/surgical emergencies/special considerations
- Patients with disease progression during systemic management, angiosarcoma and malignant phyllodes tumor should be regarded as a surgical priority and their treatment should not be delayed.[2]

3. Recommendations in medical oncology

Outpatient chemotherapy units should continue with their activities. It is not advisable to discontinue and/or delay systemic treatments with curative and/or palliative intent.[12,13] In patients on palliative treatment with multiple lines of chemotherapy, poor prognosis and compromised performance status, referral to better medical support may be considered.[13]

Until the time of this consensus, there is no evidence that restricts the use of chemotherapy, targeted therapy, anti-HER-2 therapy or immunotherapy in cancer patients during the pandemic; therefore, the prescription of "standard" indications should continue.[9,14,18-20]

If a patient has a SARS-CoV-2-positive PCR test, she must discontinue her treatment until recovery, and if she does not have complications, she can restart her systemic therapy between 14 and 21 days after the onset of symptoms.[13]

In order for the length of stay at the medical unit and patient mobility to be reduced, the following actions can be taken:

Prefer intravenous triweekly regimens, oral and subcutaneous therapies that do not compromise the oncological therapeutic result.[3,12-14,21]

- It is pertinent for patients to attend their outpatient treatments and appointments unaccompanied, except when continuous assistance is required.[22]
- Appointments for follow-up and symptom control should be indicated with the longest time interval and, if feasible, by telemedicine.[3,4,13,14,18,22]
- It is pertinent for the use of colony-stimulating factor to be broadened in regimens with moderate (10-20 %) and high risk (> 20%) of febrile neutropenia, especially in older adults.[4,13]
- Steroids can be used when indicated.
- Response evaluation studies in the metastatic scenario should be deferred as much as possible in the absence of symptoms.[3,13]

- Look for drug supply strategies for longer than usual periods, home delivery, pick-up by a family member, prescription by phone.[2,3,13,22]
- Systemic treatments such as endocrine and anti-HER-2 therapies can be used as "bridge" to avoid gaps in cancer care.[13]
- The use of quarterly zoledronic acid and denosumab is recommended for the management of bone metastases; if feasible, prefer denosumab due to its subcutaneous administration.[3,13]
- Discontinue bone modulators administration (denosumab, bisphosphonates) in the osteoporosis scenario.[3]

3.1 Hormone-sensitive disease (HR+/HER-2-negative)

- Neoadjuvant endocrine therapy can be used in patients with cT1-2 cN0-1 M0, HR+/HER-2-negative and Ki67 lower than 15 %, while waiting for surgical turn.[3,13,14] Aromatase inhibitors in postmenopausal patients, and in premenopausal patients, ovarian suppression with tamoxifen or aromatase inhibitors.[2,3,13,14]
- It is desirable to have genomic signatures available in pT1-2 pN0-1 patients in order to define the real need for chemotherapy in the adjuvant setting.[3]
- In premenopausal patients who are candidates for using LHRH analogues, preference should be given to quarterly dosage.[13]
- Capecitabine is recommended as the first chemotherapy option in patients with endocrine resistance.[3]
- If necessary, the use of cyclin inhibitors as first-line therapy in patients with low tumor burden or bone disease can be deferred, or dose adjustment should be considered in order to reduce the risk of neutropenia.[3]
- The use of mTOR inhibitors should be individualized.

3.2 HER-2-positive disease

- Anti-HER-2 therapy dosage can be extended from three to four weeks in a scenario of pandemic peak or considerable increase of infection transmission.[3]

4. Recommendations for radiotherapy

During this pandemic, actions in radiotherapy treatment are summarized in the acronym RADS (Remote visits, Avoid radiation, Defer radiation, Shorten radiation): remote visits (telemedicine), skip radiation (in safe situations for patients), delay radiotherapy (as long as it is possible delaying it for moments of less SARS-CoV-2 transmission), shorten treatment (use hypofractionation whenever possible).[23]

In case of COVID-19 suspicion in a patient with breast cancer who attends the radiotherapy unit, the following guidelines are recommended:

- Patient who will start radiotherapy and is diagnosed with COVID-19. Do not start treatment until having completed 14 days in home confinement, starting at symptoms onset. Treatment will be restarted according to indications by the department of infectious diseases.
- Patient on radiotherapy treatment + suspicious of COVID-19. Discontinue treatment, perform nasopharyngeal swab and individualize resumption. When restarting radiotherapy, biological equivalent dose (BED) and sessions to be recovered should be calculated.
- Patient on treatment who tests positive for COVID-19. Discontinue treatment and send to home confinement for 14 days. Individualize the return by calculating BED and sessions to be recovered.
- COVID-19-positive patient who requires urgent radiotherapy (spinal cord compression and superior vena cava syndrome). Treatment will be administered as long as the department has the necessary protection material and on the last shift of a single team.[24]

Radiotherapy indications in breast cancer patients are the same, despite the pandemic. Omitting this treatment is not recommended in patients who receive a survival benefit and/or local control. Even in older adults who have an indication for treatment, the appropriate time to receive radiotherapy should be indicated.[3,25]

Cases should be prioritized, depending on the risk of recurrence or life and function compromise as follows:

- Low risk. Patients > 70 years, < 3 cm tumor, negative margins, grade 1-2, luminal A, negative lymph nodes on adjuvant treatment with hormonal therapy. Delaying treatment for up to 16 weeks or to discussing its omission with the patient is considered.
- Intermediate risk. Ductal carcinoma in situ and conditions that do not meet low or high risk criteria. Delaying treatment for up to 16 weeks is considered.
- High risk. Spinal cord compression, bleeding, CNS metastasis, palliative radiotherapy, post-mastectomy

radiotherapy with high-risk factors (inflammatory tumor, positive lymph nodes, high-risk subtypes).[26]

The use of hypofractionation should be favored in most patients during the pandemic. Some exceptions are large volume mammary gland, internal mammary artery inclusion, or some other anatomical situation that causes high radiation doses to healthy organs.[27-29]

5. Vaccination

If the cancer patient has access to an anti-COVID vaccination schedule, it is desirable for her to receive it.[30] If the patient is on active systemic treatment, application of the vaccine should be restricted in case of experiencing severe neutropenia and/or febrile neutropenia.[30] Administering an anti-COVID vaccine within the first 14 days after a surgical procedure is not recommended. Patients under breast cancer surveillance can be vaccinated.[30,31]

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X. EARLY BREAST CANCER MANAGEMENT

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XI. NEOADJUVANT MANAGEMENT

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XII. TREATMENT OF METASTATIC/RECURRENT BREAST CANCER

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1. Introduction

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XIII. SUPPORTIVE AND PALLIATIVE CARE INTEGRATION IN THE MANAGEMENT OF PATIENTS WITH ADVANCED BREAST CANCER

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XVIII. MANAGEMENT OF RARE HISTOLOGIES

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