Breast Diseases

An Evidence-Based Pocket Guide

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This book is dedicated to the thousands of women and their families, who, despite facing breast cancer, decided to fight and overcome the challenges imposed by treatment.

We also dedicate this piece of work to our master, Professor Umberto Veronesi (1925–2016), responsible for training modern mastologists and for various advances in the treatment of breast cancer, avoiding mutilation in thousands of women around the world.

Foreword

It is a great pleasure to represent my friends in the English edition of this work, which today is a national reference for mastologists. In a succinct and objective way, the book addresses the most important and most discussed current themes, placing the pieces of information cited in this book at a high level of evidence.

This new edition discusses issues that are increasingly inserted in our daily life, updating in a clear and objective way everything that has already been written. New views, discussed before the new frontiers of knowledge, provide a new way of looking at reality, making us understand even better that Medicine is the science of transient truths. That is why an updated edition like this is always very important.

Today, we need even more this type of work to guide our understanding and action, giving priority to the neediest of people. Through such people we invest years of our life in order to become specialists with a deep knowledge of the subject: our patients.

For all this, I recommend that my peers read this book entitled "Breast Diseases – An Evidence-Based Pocket Guide", which makes an important contribution to updating and guiding the daily exercise of our wonderful specialty: Mastology.

Congratulations to this important group of friends!

Enjoy it!

Carlos Alberto Ruiz
President of the Brazilian Society
of Mastology (2011–2013)
São Paulo, SP, Brazil

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BI-RADS® Classification

Linei Urban

Definition

The Breast Imaging Reporting and Data System (BI-RADS®) was first published in 1993 by the American College of Radiology (ACR), in collaboration with several American entities, with the aim of standardizing the interpretation and description of reports, systematizing the classification and management of features, and also providing an audit system. Currently, it is in the fifth edition (2013), including mammography (MG), ultrasound (US), and magnetic resonance imaging (MRI). In Brazil, its use is recommended by the Brazilian College of Radiology (*Colégio Brasileiro de Radiologia – CBR*), the Brazilian Society of Mastology (*Sociedade Brasileira de Mastologia – SBM*), and the Brazilian Federation of Gynecology and Obstetrics Associations (*Federação Brasileira das Associações de Ginecologia e Obstetrícia* – FEBRASGO).

Report Organization

The medical report must be written in a clear and concise way, and it must present the following parts:

(a) Indication for examination (screening or diagnosis)
(b) Succinct description of the breast composition
(c) Description of any important findings (according to the lexicon of each exam)
(d) Comparison with previous examinations
(e) Assessment and recommendation

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The final classification should be one for both breasts and always trying to encompass all methods.

Descriptors

The terminology recommended to describe the findings in MG, US, and MRI is summarized in Tables 1, 2, and 3, respectively.

Table 1 Lexicon of mammography according to BI-RADS®

Findings	Terminology	
Breast composition	The breasts are almost entirely fatty There are scattered areas of fibroglandular density The breasts are heterogeneously dense, which may obscure small masses The breasts are extremely dense, which lowers the sensitivity of mammography	
Nodules	Shape	Oval Round Irregular
	Margin	Circumscribed Obscured Microlobulated Indistinct Spiculated
	Density	High density Equal density Low density Fat content
Calcifications	Typically benign	Skin Vascular Coarse or “popcorn-like” Large, rod-like Round Rim Dystrophic Milk of calcium Sutures
	Suspicious	Amorphous Coarse heterogeneous Fine pleomorphic Fine linear or fine-linear branching
	Distribution	Diffuse Regional Grouped Linear Segmental

Table 1 (continued)

Findings	Terminology
Architectural distortion	
Asymmetries	Asymmetry Global asymmetry Focal asymmetry Developing asymmetry
Intramammary lymph node	
Skin lesion	
Solitary dilated duct	
Associated findings	Skin retraction Nipple retraction Skin thickening Trabecular thickening Axillary adenopathy Architectural distortion Calcifications

Note: Table adapted from Atlas BI-RADS® fifth Edition, 2013

Table 2 Lexicon of ultrasound according to BI-RADS®

Findings	Terminology	
Breast composition	Homogeneous background echotexture – fat Homogeneous background echotexture – fibroglandular Heterogeneous background echotexture	
Nodules	Shape	Oval Round Irregular
	Orientation	Parallel Not parallel
	Margin	Circumscribed Not circumscribed (indistinct, angular, microlobulated, spiculated)
	Echo pattern	Anechoic Hyperechoic Complex cystic and solid Hypoechoic Isoechoic Heterogeneous
	Posterior features	No posterior features Enhancement Shadowing Combined pattern
Calcifications	Calcifications in a mass Calcifications outside of a mass Intraductal calcifications	

(continued)

Table 2 (continued)

Findings	Terminology	
Associated features	Architectural distortions	
	Ductal changes	
	Skin changes	Skin thickening Skin retraction
	Edema	
	Vascularity	Absent Internal vascularity Vessels in rim
	Elasticity assessment	Soft Intermediate Hard
Special cases	Simple cyst	
	Clustered microcysts	
	Complicated cyst	
	Mass in or on skin	
	Foreign body including implants	
	Lymph nodes – intramammary	
	Lymph nodes – axillary	
	Vascular abnormalities	
	Postsurgical fluid collection	
	Fat necrosis	

Note: Table adapted from Atlas BI-RADS® fifth Edition, 2013

Table 3 Lexicon of magnetic resonance imaging according to BI-RADS®

Findings	Terminology	
Amount of fibroglandular tissue	Almost entirely fat Scattered fibroglandular tissue Heterogeneous fibroglandular breast Extreme fibroglandular breast	
Background parenchymal enhancement	Level	Minimal Mild Moderate Marked
	Symmetry	Symmetric Asymmetric
Foci		
Masses	Shape	Oval Round Irregular
	Margin	Circumscribed Not circumscribed (irregular, spiculated)
	Internal enhancement characteristics	Homogeneous Heterogeneous Rim enhancement Dark internal septations

Table 3 (continued)

Findings	Terminology	
Non-mass enhancement	Distribution	Focal Linear Segmental Regional Multiple regions Diffuse
	Internal enhancement features	Homogeneous Heterogeneous Clumped Clustered ring
Non-enhancing findings	Ductal preconstrast high signal on T1W Cyst Postoperatory fluid collection (hematoma/seroma) Posttherapy skin thickening and trabecular thickening Non-enhanced mass Architectural distortion Sinal void from foreign bodies, clips, etc.	
Associated findings	Nipple retraction/invasion	
	Skin retraction/thickening/invasion	
	Axillary adenopathy	
	Pectoralis muscle invasion	
	Chest wall invasion	
	Architectural distortion	
Fat containing lesions	Normal/abnormal lymph nodes	
	Fat necrosis	
	Hamartoma	
	Postoperative seroma/hematoma with fat	
Kinetic curve evaluation	Initial phase (slow, medium, fast)	
	Delayed phase (persistent, plateau, washout)	
Implants	Implant material and lumen type (saline, silicone, other material)	
	Implant location (retroglandular, retropectoral)	
	Abnormal implant contour (focal bulge)	
	Intracapsular silicone findings (radial folds, subcapsular line, keyhole signal, linguine sign)	
	Extracapsular silicone (breast, lymph nodes)	
	Water droplets	
	Peri-implant fluid collection	

Note: Table adapted from Atlas BI-RADS® fifth Edition, 2013

Categories and Recommendations

The categories and recommendations are summarized in Table 4. The algorithm for follow-up of the features classified as category 3 is found in Fig. 1. Typical findings for each category are listed in Table 5.

Table 4 Evaluation categories and recommendations under BI-RADS®

Assessment	Management	Likelihood of cancer
Category 0: Incomplete (Additional imaging and/or prior mammograms for comparison are required. They should not be used in MRI)	Recall for additional imaging and/or comparison with previous exams	–
Category 1: Negative	Routine screening	0% likelihood of malignancy
Category 2: Benign	Routine screening	0% likelihood of malignancy
Category 3: Probably benign	Sort-term follow-up (6 months) or specific follow-up according to Fig. 1	>0% but ≤2% likelihood of malignancy
Category 4: Suspicious Category 4A: Low suspicion Category 4B: Moderate suspicion Category 4C: High suspicion	Tissue diagnosis	>2% to ≤10% likelihood of malignancy >10% to ≤50% likelihood of malignancy > 50% to <95% likelihood of malignancy
Category 5: Highly suggestive of malignancy	Tissue diagnosis	≥ 95% likelihood of malignancy
Category 6: Known biopsy-proven malignancy	Surgical excision when clinically appropriate	–

Note: Table adapted from Atlas BI-RADS® fifth Edition, 2013

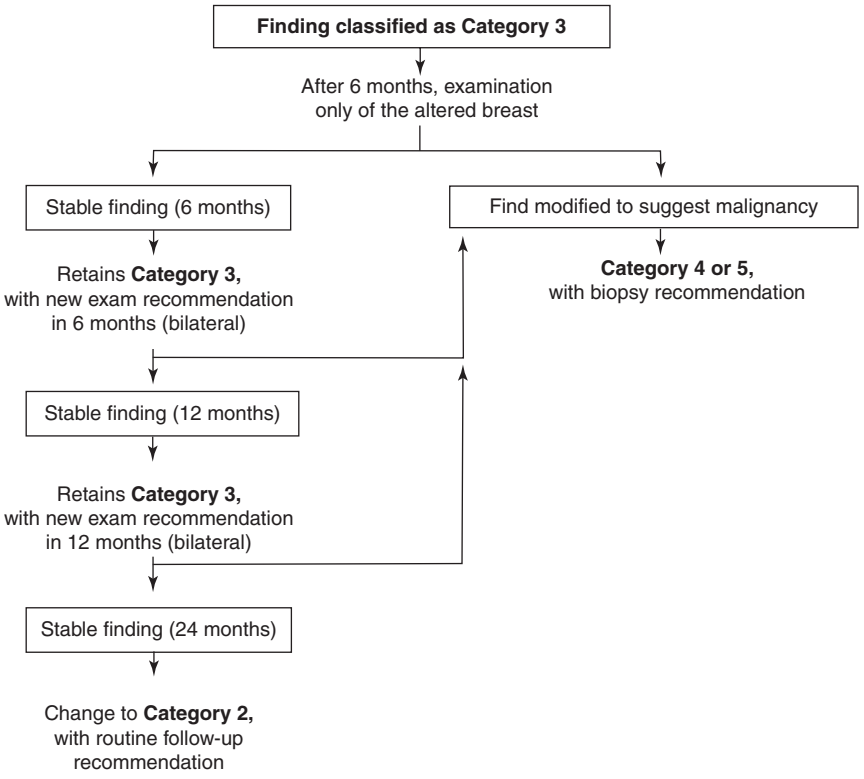

Fig. 1 Management algorithm for lesions in category 3

Table 5 Typical findings in each BI-RADS® category

BI-RADS	Mammography	Ultrasound	Magnetic resonance
Category 1	Normal exam	Normal exam	Normal exam
Category 2	Benign calcifications (skin, vascular, coarse, rod-like, clustered ring, dystrophic, milk of calcium, others) Intramammary lymph node Fat-content mass Postsurgical distortion	Simple cysts Clustered microcysts Multiple complicated cysts Multiple solid masses with criteria of benignity (>2 in one breast and 1 in the other breast) Stable solid mass for >2 years Surgical alterations	Cysts (simple, clustered, enhanced) Fat-containing findings (fat necrosis, hamartoma, oil cyst) Non-enhanced findings (ducts with no contents, architectural distortion, and non-enhanced mass) Multiple solid mass with criteria of benignity (>2 in one breast and 1 in the other) Implants
Category 3	Nonpalpable focal asymmetry Punctiform grouped calcifications	Solitary complicated cyst Solitary clustered microcysts Solid mass with criteria of benignity	Solid mas with criteria of benignity and type I curve Isolated enhanced foci with type I curve Non-nodular enhancement suggestive of hormonal stimulus (TRH)
Category 4	Suspicious calcifications (amorphous; coarse heterogeneous, fine pleomorphic, branched fine linear), developing asymmetry, nonsurgical-related architectural distortion	Solid mass with one or more suspect criteria Solitary dilated duct	Solid mass with one or more suspect morphological or dynamic criteria, non-nodular enhancement with linear or segmental distribution Isolated enhancement foci with type III curve
Category 5	Mass associated with pleomorphic, branched fine linear or segmental calcifications	Solid mass with classic patterns of malignancy	Solid mass with classic dynamic and morphological patterns of malignancy

Recommended Literature

1. American College of Radiology. Breast imaging reporting and data system (BI-RADS). 5th ed. Reston: American College of Radiology; 2013.

Mammography

Radiá Pereira dos Santos and Bruno Hochhegger

Introduction

Mammography is the best method available for early diagnosis of breast cancer, showing a mortality reduction in screening studies.

The detection of breast cancer at a subclinical stage through mammography allows a more appropriate treatment, determining a better quality of life, with less mutilation, and even fewer cases of the disease.

Indications

Diagnostic mammography: performed in symptomatic patients

Screening mammography: recommended for women over 40 years, with annual intervals

Mammography among high-risk women (screening):

- Women with family risk (>20%): start mammography 10 years younger than the age cancer was diagnosed in a first-degree relative (but not before the age of 30).
- Mutation of BRCA 1 and BRCA 2: start screening at 30 years old.
- Women undergoing radiotherapy in the thorax due to Hodgkin's disease at age 10 or before age 30: start mammography 8 years after the end of treatment (but not before the age of 30).

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- Women with borderline histological diagnosis (radial scar, papilloma with atypia, CLIS, HLA, HDA): start immediately after diagnosis.
- The use of magnetic resonance imaging has been advocated in cases of screening in risk groups.

Acquisition of Mammographic Incidences

Mammography is the exam that uses a specific X-ray (low-wavelength) equipment, whose tube (X-ray emitter) is designed to produce high-resolution images, such as those found in breast lesions (0.1 mm lesions).

There are two types of acquisition of the radiological image of the breast: analogic (conventional) and digital. The latter consists of two modalities: CR (computerized radiology) and DR (digital radiology).

Analogic mammography uses the screen film (*écran* film) system for image detection. While the CR mode uses phosphor plate, the DR uses a digital detector installed in the mammograph itself. Recording of the image in the analogic system is the detector itself (film), while in the digital mode, the recording may be not only with film but in any other digital storage media (DVD, HD, CD, among others).

The radiation dose is higher in digital systems (although it does not increase the risk of cancer), but the image quality is justifiable. It should be considered that the radiation dose is related to the optimization of the operators (technicians and technologists) and computer programs (ranging between their modalities, even when considering the same manufacturers).

The image quality produced by digital technology is superior to that of analogic mammography, as there is higher contrast resolution. Thus, images of dense breasts are best viewed in digital systems.

In the digital system, there is the possibility of using high-resolution monitors for reading the images and computer tools of post-processing aid in order to digitally improve the image, thus reducing the rate of new incidents. In addition, there is the possibility of storing the images and eliminating the use of darkroom.

The classic study by Pisano et al. demonstrated that there is no significant difference in diagnosis when comparing the two digital modalities (DR and CR). When comparing the digital and the analogic modality, the first one (digital) showed to be more efficient in dense breasts.

In addition, the CR system and the DR system allow the choice of images to be printed, since they are produced digitally. In this way, there is the possibility of reducing the cost with the use of films.

Mammograms with analogic images are being gradually replaced by digital mammography, especially by those that provide full-field digital images.

Performing the Exam

The mammography exam is one of the most important aspects for detection and diagnosis of breast cancer. When the mammary gland is not positioned correctly, a cancer may not be detected since some segment may be excluded.

Compression is a fundamental element for the acquisition of image that can be interpreted. It reduces the thickness of the breast, allowing less overlapping of structures.

Two conventional incidences are used: craniocaudal (CC) (Fig. 1) and mediolateral oblique (MLO) (Fig. 2). These incidences allow a three-dimensional understanding of glandular structures, facilitating the visualization of structures that can overlap.

Additional incidents may be used to further knowledge of some findings. The most used ones are the following:

- Localized compression (Fig. 3) ("spot"), which allows a better visualization of the margins of a mass, or excludes the presence when it is only about summation of images, since it allows to separate the glandular structures
- Magnification (Fig. 4), used fundamentally for better evaluation of calcifications

In women with breast implants, the Eklund maneuver, which consists of moving the implant posteriorly and compressing the fibroglandular tissue (Fig. 5), is used in addition to the complementary incidences.

In the male breast, mammography is the imaging exam of choice. The major cause is gynecomastia, with the MLO incidence being the chosen one, without the need for CC. Figure 6a shows structure compatible with retropapillary fibroglandu-

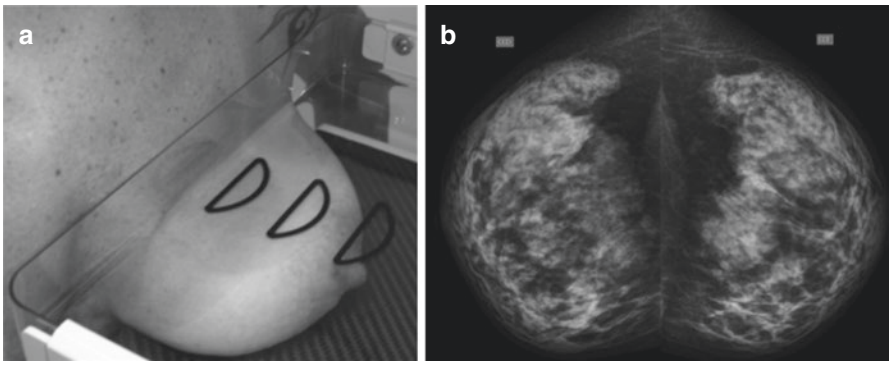

Fig. 1 Craniocaudal incidence. (**a**) Notice the inclusion of the entire gland in the tray. It allows for showing the location of lesions in lateral and medial positions. (**b**) Visualization of all fibrous glandular tissue. Subsequently, the image of the large pectoralis muscle is observed

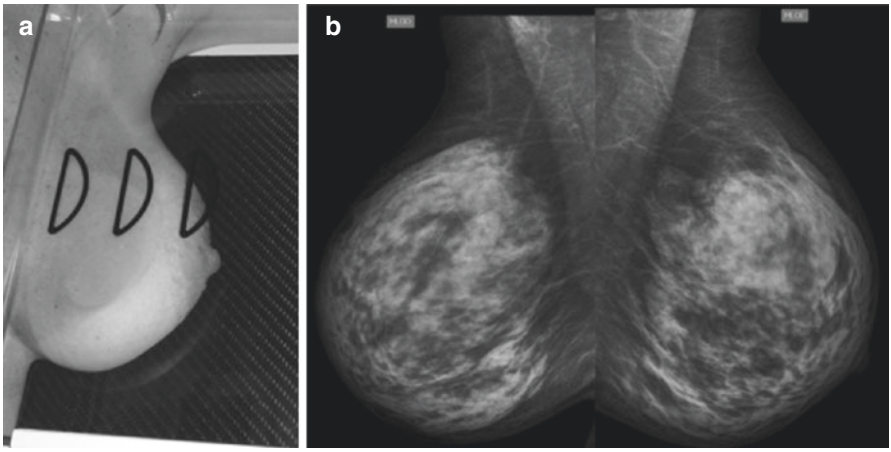

Fig. 2 Mediolateral oblique incidence. (**a**) Notice the inclusion of the entire gland in the tray, including the inframammary sulcus. It allows for showing the upper and lower lesions. (**b**) The image of the major pectoral muscle is observed up to the position of the papilla, which allows an adequate visualization of the whole gland. The papilla should be parallel to the plane of the film

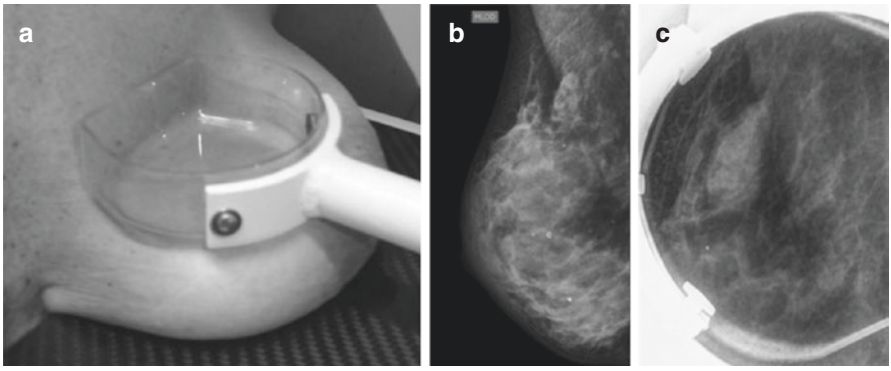

Fig. 3 Localized compression (spot). (**a**) The equipment should be focusing on the area being studied. (**b**) Allows a more adequate visualization of the finding observed in the conventional incidence. (**c**) Local compression of suspicious focus in the breast and more adequate visualization of the lesion

lar tissue, with the characteristics of gynecomastia. In the presence of a suspicious finding, CC incidence is performed (Fig. 6b). Observing nodular lobular retropapillary image and complementation with ultrasound evidenced papillary growth near the wall (PA: papillary carcinoma).

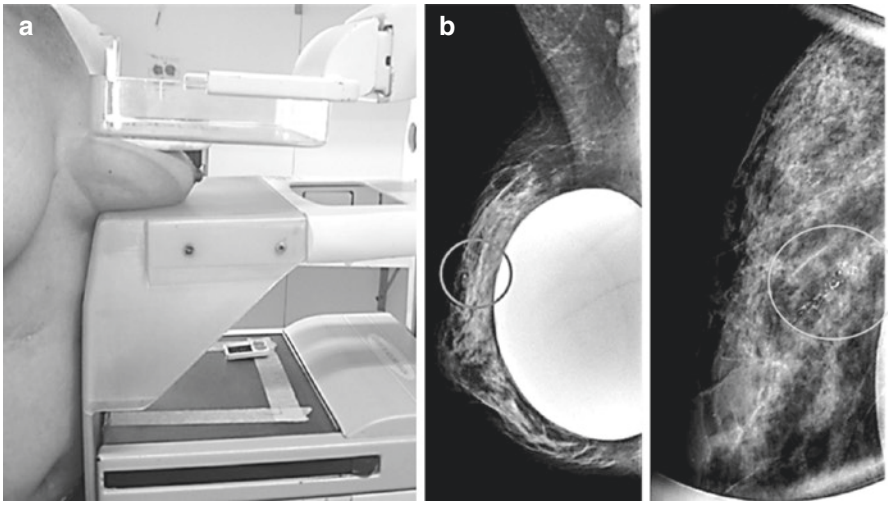

Fig. 4 Magnification. (**a**) Notice the distance of the object (breast), with film. This greater distance allows for more detailed visualization of the mammographic finding. (**b**) The conventional incidence shows the presence of microcalcifications in the projection of the superior quadrants. The amplification shows the morphological characteristics in more detail

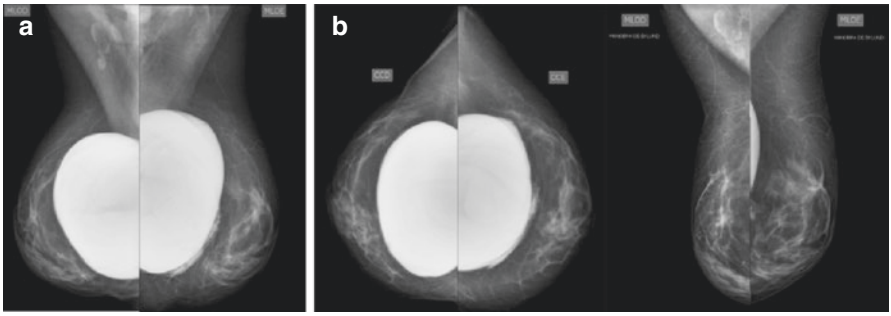

Fig. 5 Eklund maneuver. (**a**) Conventional incidence (MLO), implant whose location is submuscular. (**b**) Eklund maneuver in an implant whose location is submuscular, showing greater definition of the gland due to more adequate compression in the fibroglandular tissue

Tomosynthesis

This is a mode for 3D screening that preserves the high resolution of the 2D image. Several images of the breast are acquired at different angles during a scan of the X-ray tube, allowing the radiologist to detect lesions overlapping the structures of the breast.

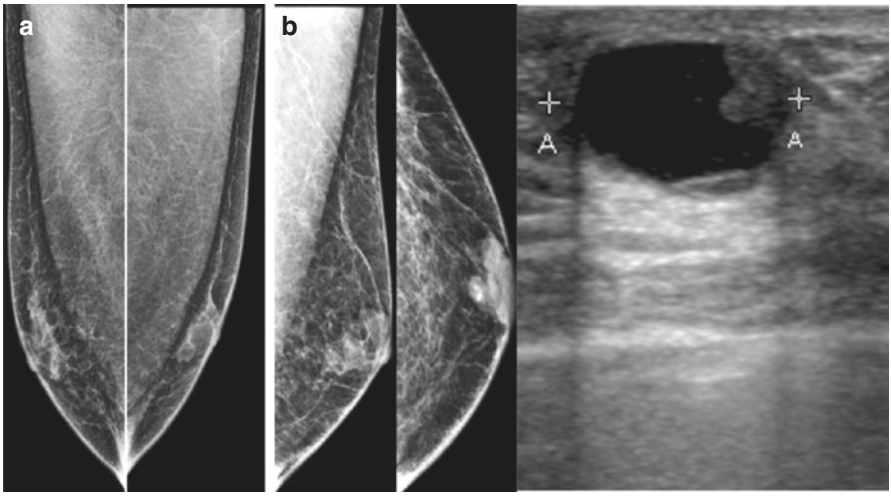

Fig. 6 (**a**) Structure compatible with retropapillary fibroglandular tissue. (**b**) Lobular nodular retropapillary image and complementation with ultrasound, evidencing papillary growth near the wall. (**b**) Notice the nodular lobular retropapillary image and complementation with ultrasound evidencing papillary growth near the wall (*PA* papillary carcinoma)

It is recommended when the mammogram together with the ultrasound cannot establish a diagnostic impression of a finding in the breast. This is particularly used in architectural distortions and asymmetries.

Currently, it is increasingly being used in screening of dense breasts and in high-risk patients, since it allows the visualization of images without overlapping structures.

Characteristics of the Findings

The most important findings are as follows.

1. Mass

Definition: three-dimensional finding, detected in two incidences, with convex margins (Tables 1 and 2; Fig. 7).

Table 1 Masses: shape

Table 2 Masses: margins

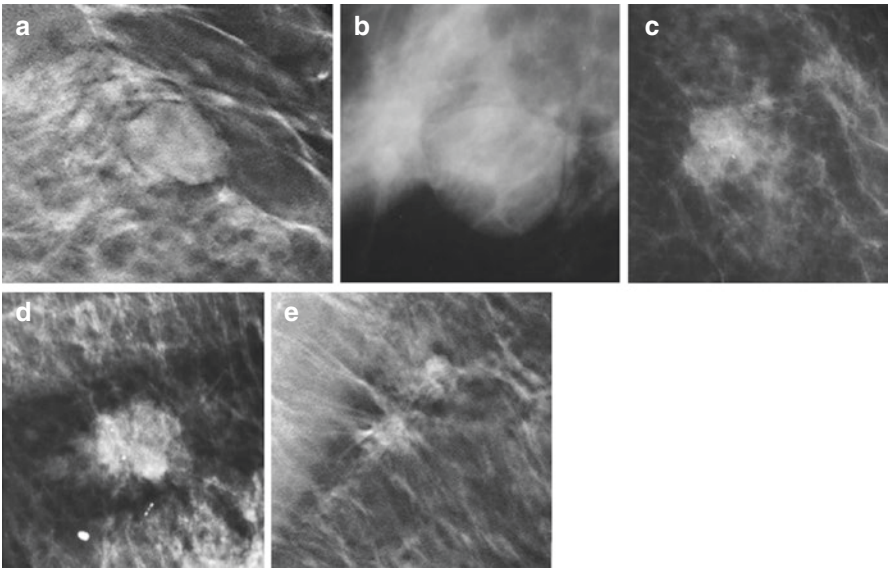

Fig. 7 Masses. (**a**) Circumscribed margin. (**b**) Obscured margin. (**c**) Indistinct margins. (**d**) Microlobulated margin. (**e**) Spiculated margin

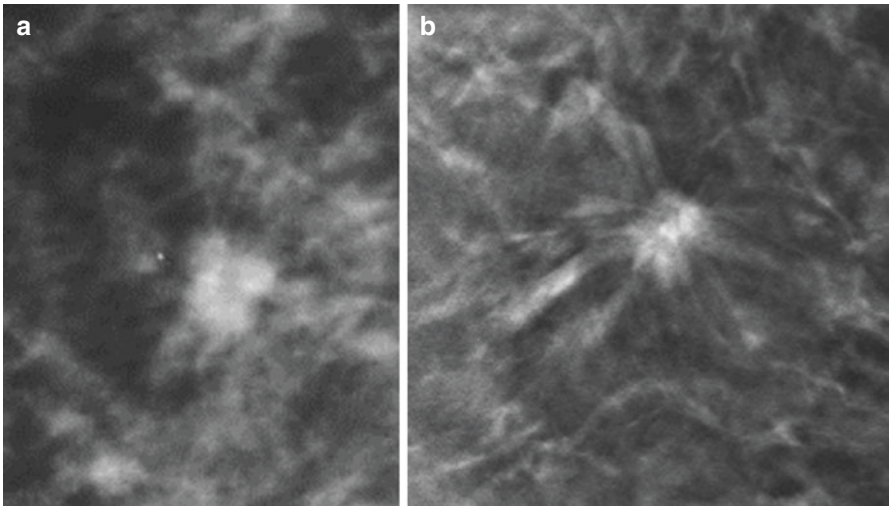

Fig. 8 (**a**) Mass typical of malignity with microlobulated margins. (**b**) Mass with spiculated margins, also typical of malignity

The margin of the mass is the most important feature for radiological diagnosis. Microlobulated and spiculated margins are highly suggestive of malignancy (BI-RADS® category 5) (Fig. 8).

Other features such as density and associated findings (skin, muscle and papilla retraction, trabecular and skin thickening, microcalcifications, and architectural distortion) should also be analyzed. The suspicious masses for malignancy show density equal to or greater than the surrounding tissue; they are not radiolucent, although they may have radiolucent segments, corresponding to the fat trapped inside it (Fig. 8).

2. Calcifications

Calcifications must be differentiated between benign and suspicious. The benign ones (Fig. 9) are usually large, coarse, and round and have regular margins that are more easily visible than malignant ones; and they do not always need to be reported. The following are considered to be benign (BIRADS® 2): calcifications of the skin, vascular, coarse or "popcorn" type, rod-like, round (<1 mm, acini-shaped), punctiform (<0.5 mm), rounded with a radiolucent center, egg shell, "milk of calcium," suture strands, and dystrophic (usually in the irradiated breast, they are coarse and often present radiolucent center).

The distribution of calcifications describes their disposition in the breast and may be diffuse (regional) (occupying space >2 cubic centimeters of breast tissue, not configuring ductal distribution), grouped (occupying space >2 cubic centimeters of breast tissue), linear (arranged in line), and segmental.

In general, calcifications with regional distribution occupy a large volume of breast, and malignancy is less likely, although the evaluation should include mor-

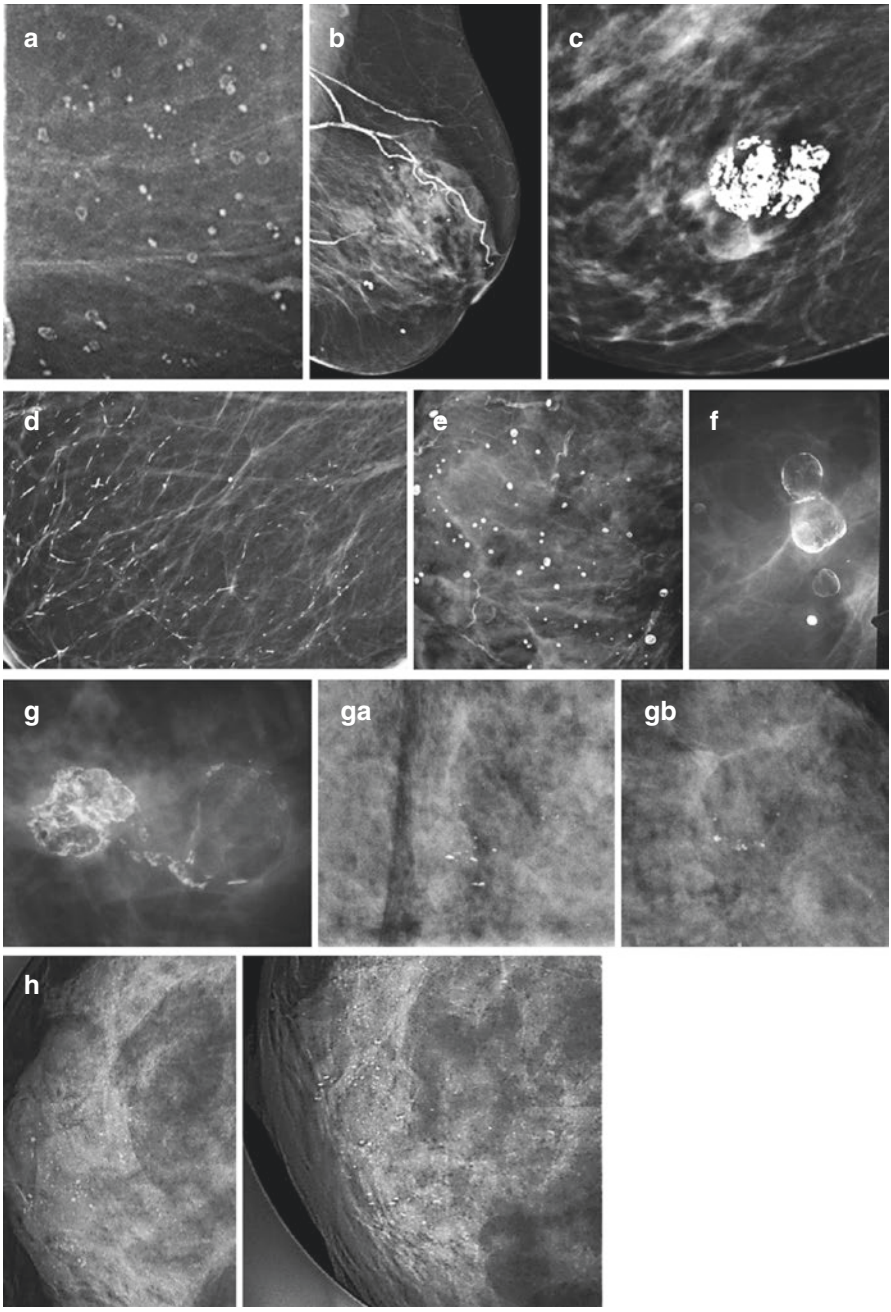

Fig. 9 Typically benign calcifications. (**a**) Skin. (**b**) Vascular. (**c**) "Popcorn" type (fibroadenomas). (**d**) Rod-like (periductal mastitis). (**e**) Scattered round. (**f**) Oil cysts. (**g**) Dystrophic (steatonecrosis). (**Ga**) Milk of calcium (CC incidence). (**Gb**) Milk of calcium (profile incidence). (**h**) Diffuse punctiform

phological characteristics. Linear distribution calcifications may raise the possibility of malignancy, since they suggest duct deposition.

Depending on their characteristics (mainly morphology and distribution), microcalcifications are one of the most important signs of non-palpable breast cancer detected almost exclusively through mammography, thus determining a high probability of cure, mainly in ductal carcinomas in situ (Figs. 10, 11, and 12).

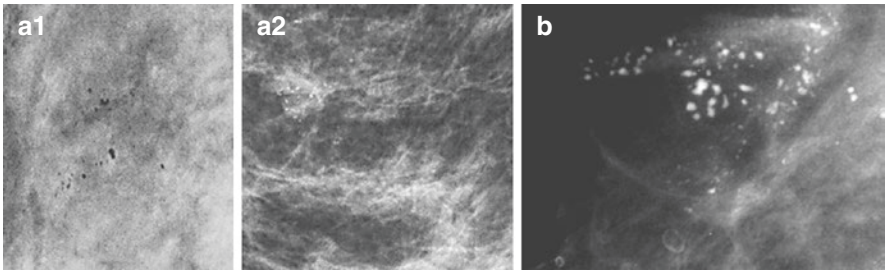

Fig. 10 Suspicious calcifications. (**a1**, **a2**) Amorphous. (**b**) Coarse heterogeneous

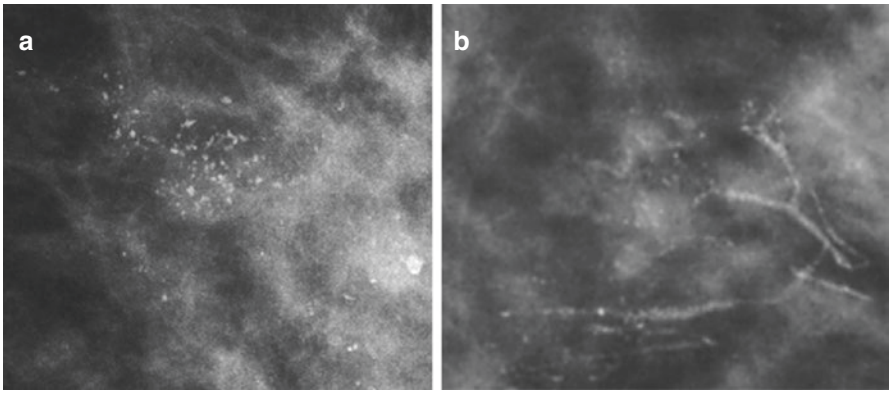

Fig. 11 Suspicious calcifications. (**a**) Fine pleomorphic. (**b**) Fine linear (fine linear branched)

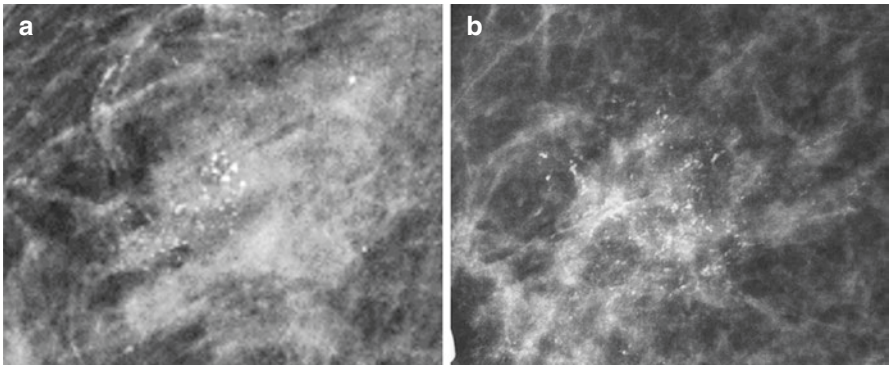

Fig. 12 Clustered, pleomorphic, fine calcifications whose histological result was invasive ductal carcinoma in situ (**a**–**b**)

Suspicious calcifications are small and inaccurate. They may be amorphous and coarse heterogeneous (Fig. 11). Calcifications with high probability of malignancy can be pleomorphic fine (they are more visible than the amorphous ones and do not show characteristics typically malignant or benign), fine, and linear (or fine linear branched).

Architectural Distortion

It is noticed when the architecture of the gland is distorted, without the presence of a definite mass (Fig. 13). It is characterized by fine lines, or spicules, which start from a point. It may be associated with mass, asymmetry, or calcifications. In the absence of trauma, there should be investigation of this finding, because the possibility of cancer cannot be excluded. The differential diagnosis is obtained with radial scar and sclerosing adenosis.

Global Asymmetry

It represents a large volume of breast tissue, not present in the corresponding area of the contralateral breast, without mass, calcifications, or distortions. In general, it corresponds to normal breast tissue, but it should be better evaluated (usually by ultrasound), mainly in cases of palpable abnormality (Fig. 14).

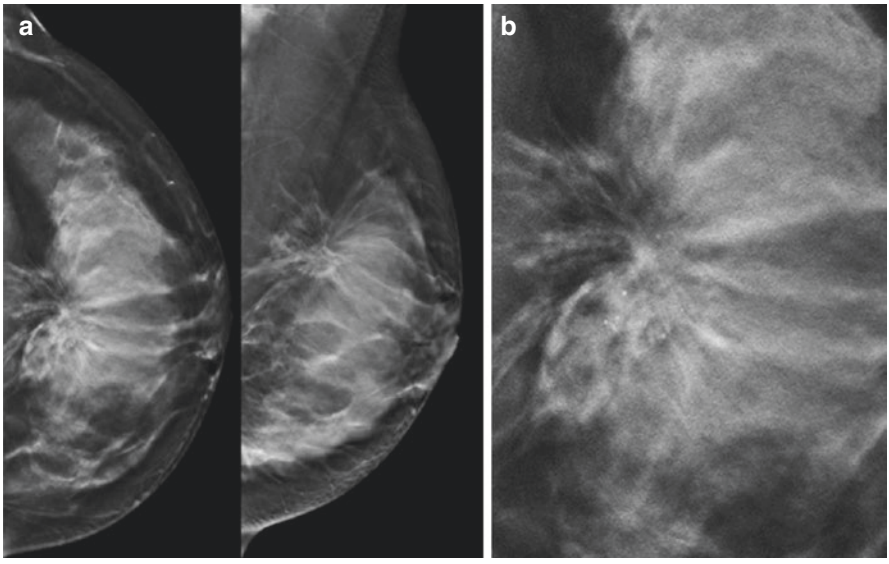

Fig. 13 Architectural distortion. (**a**) CC and MLO incidence showing architectural distortion in the superolateral quadrant of the left breast. (**b**) Magnification for better visualization showing striations that irradiate from a rectified area of the anterior contour of the gland, with no evidence of mass and presence of punctiform monomorphic calcifications. AP: Sclerosis adenosis

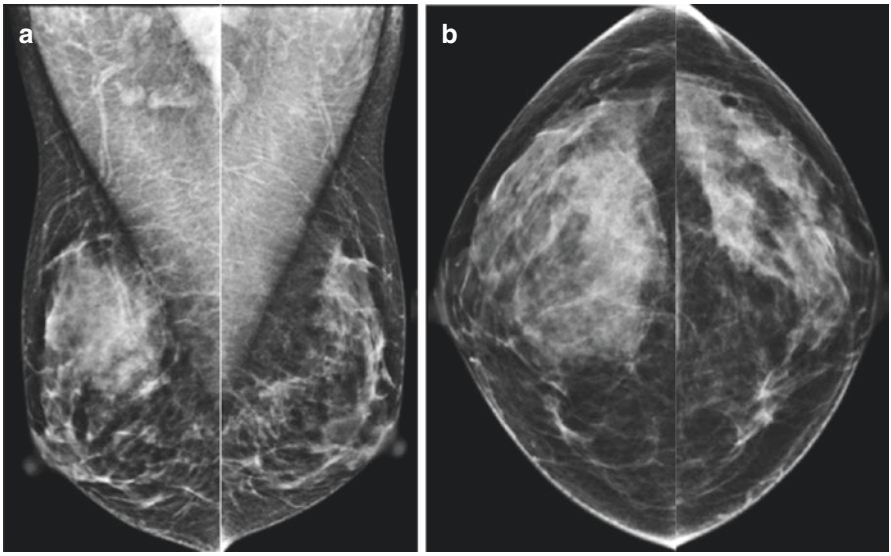

Fig. 14 Any large volume of breast tissue should be better evaluated in the presence of palpable abnormalities. (**a**) MLO incidence. (**b**) CC incidence

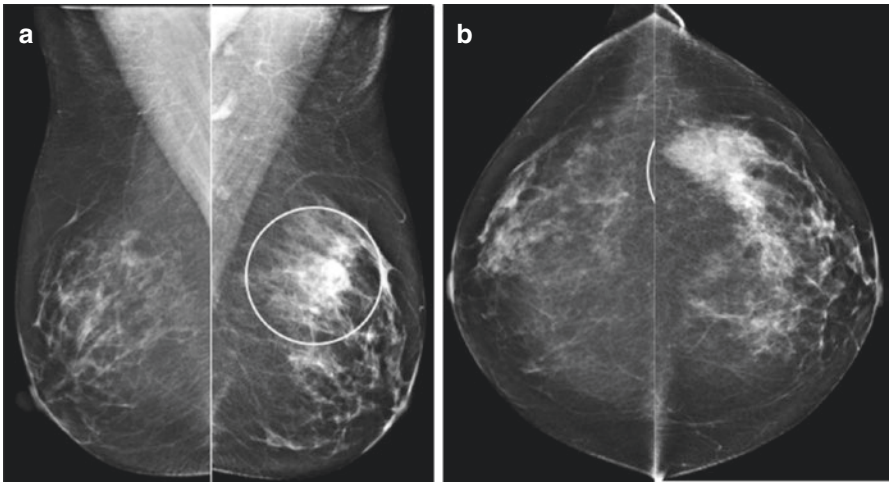

Fig. 15 Focal asymmetry: density increase located in the superolateral quadrant of the left breast (circle), with similar shape in both incidences. (**a**) MLO incidence. (**b**) CC incidence

Focal Asymmetry

Focal asymmetry is considered when the finding does not fit the mass criteria (Fig. 15). It presents similar form in both incidences. It does not show margins and may correspond to normal breast tissue when interspersed with radiolucent areas, corresponding to fat. It may, however, correspond to cancer, in the absence of

signs of benignity, and especially in the presence of palpable alterations. Complementation with ultrasound may be necessary to establish the differential diagnosis.

Associated Findings

Used with masses, asymmetries, or calcifications or described simply as findings, when there is no other abnormality (Fig. 16). Skin and papilla retraction, skin thickening (>2 mm) and trabecular thickening, skin lesion, and axillary adenopathy may be considered as "associated findings."

Correlating Mammographic Findings with BI-RADS®

- BI-RADS® category 0: represents further investigation (e.g., ultrasound, magnification).
- BI-RADS® category 1: no relevant findings. Annual mammography is recommended.
- BI-RADS® category 2: benign findings – masses containing radiolucent area and typically benign calcifications. Annual mammography is recommended.
- BI-RADS® category 3: represents the findings with 2% likelihood of malignancy. The most frequent examples are circumscribed solid mass, asymmetry that attenuates with localized compression, and clustered punctiform calcifications. Mammographic control at 6 months is recommended.
- BI-RADS® category 4: can be subdivided into (optional) categories A, B, and C, depending on the degree of suspicion for malignancy. Histological/cytological evaluation is recommended.
- BI-RADS® category 4A: represents low suspicion. Examples: partially circumscribed solid mass, rounded calcifications, or punctiform calcifications not present in previous exam.
- BI-RADS® category 4B: represents moderate suspicion. Examples: masses with partially indistinct margins, heterogeneous and coarse calcifications, and amorphous calcifications.
- BI-RADS® category 4C: represents suspicion of malignancy, but no definitive signs of malignancy. Examples: pleomorphic fine calcifications, calcifications with linear or segmental distribution, regardless of morphology, architectural distortion, not related to previous surgery.
- BI-RADS® category 5: represents high suspicion of malignancy. Surgery is indicated regardless of the outcome of the percutaneous procedure performed. Examples: irregularly shaped mass and spiculated margins, suspicious calcifications associated with mass with malignant characteristics.
- BI-RADS® category 6: lesions biopsied with malignancy, but not subject to definitive treatment.

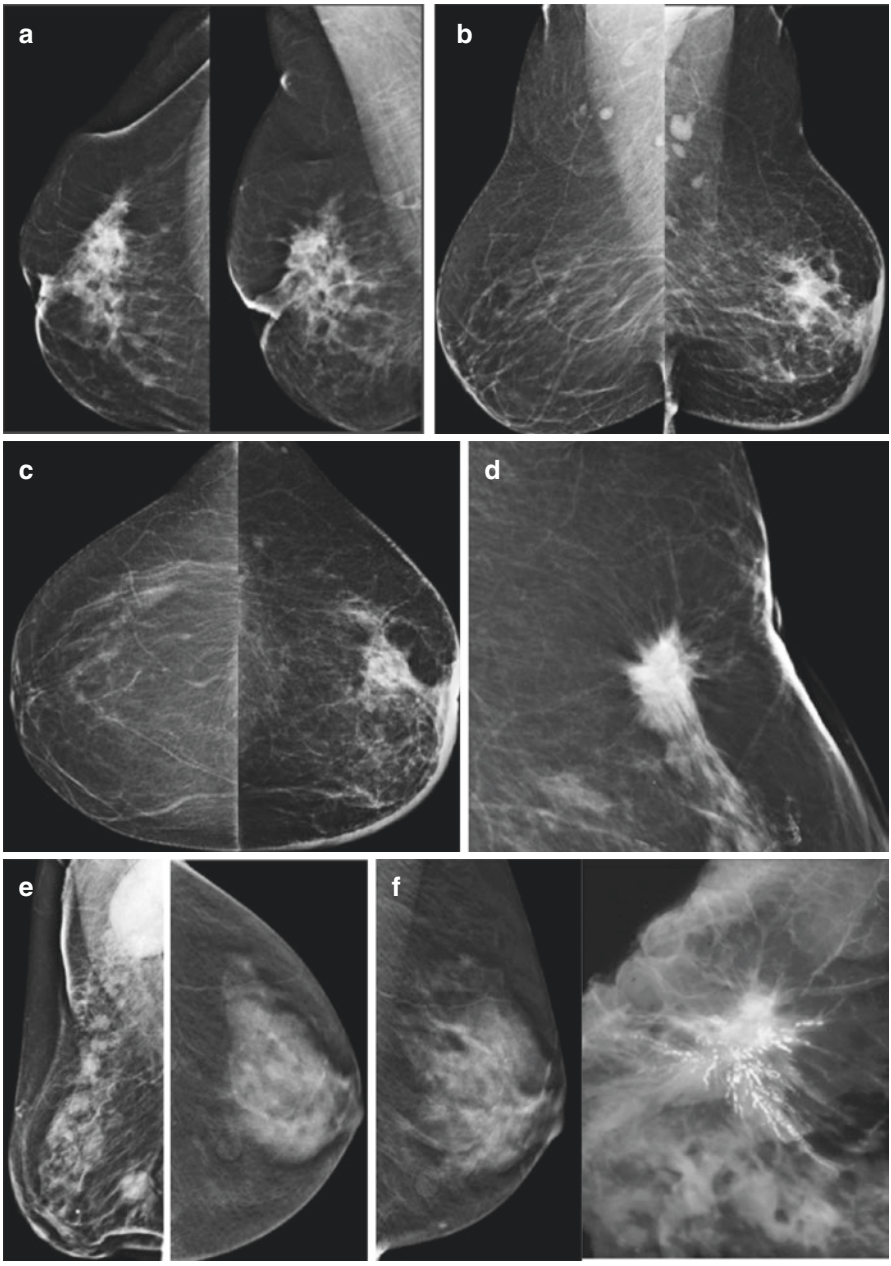

Fig. 16 Associated findings. (**a**) Retraction of papilla secondary to retropapillary cancer. (**b**) and (**c**) Thickening of skin and trabeculae related to breast cancer. Comparison with the contralateral breast makes this finding more evident. (**d**) Retraction of the skin, associated with malignant mass with striations that are directed to the skin, determining retraction. (**e**) Axillary adenopathy, compatible with multifocal cancer metastasis, including skin retraction. (**e**1) and (**f**) Wart-related skin alterations (tomosynthesis). (**f**1) Microcalcifications associated with breast cancer (Raio X of surgical specimen granted by Dr. Raúl Leborgne, 1977).

Recommended Literature

1. Autier P, Héry C, Haukka J, Boniol M, Byrnes G. Advanced breast cancer and breast cancer mortality in randomized controlled trials on mammography screening. J Clin Oncol. 2009;27(35):5919–23. *Meta-analysis of large randomized studies demonstrating that for each unit of reduction in the incidence of advanced breast cancer, there was a reduction in mortality from breast cancer*
2. Giess CS, Frost EP, Birdwell RL. Difficulties and errors in diagnosis of breast neoplasms. Semin Ultrasound CT MR. 2012;33(4):288–99. *Excellent review demonstrating the major limitations and difficulties of radiological diagnosis in mammography*
3. Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database Syst Rev. 2009;4:CD001877. *Meta-analysis of eight studies including 600,000 women included. The final demonstration showed decrease in mortality from breast cancer estimated by 15% relative risk. The reduction in overall mortality was 0.5%*
4. Granader EJ, Dwamena B, Carlos RC. MRI and mammography surveillance of women at increased risk for breast cancer: recommendations using an evidence-based approach. Acad Radiol. 2008;15(12):1590–5. *Meta-analysis that evaluated imaging methods in women with risk factors for breast cancer. In women with an increased risk without the BRCA gene, magnetic resonance (MR) cancer detection rates were 0.011 (95% confidence interval [CI] 0.003–0.019), through mammogram 0.005 (95% CI 0.002–0.008), and by a combination of through, 0.012 (95% CI 0.004–0.020). The data support an essential role of MRI in women with an increased risk for breast cancer.*
5. Pisano ED, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, et al. Diagnostic performance of digital versus mammography film for breast-cancer screening. N Engl J Med. 2005;353(17):1773–83. *A study comparing digital and analog mammography that included 49,528 asymptomatic women at 33 sites in the United States and Canada. The overall diagnostic accuracy of digital mammography was similar, but digital mammography was more accurate in women younger than 50 years, in women with radiologically dense breasts and premenopausal or perimenopausal women*
6. Smith RA, Duffy SW, Tabor L. Breast cancer screening: the evolving evidence. Oncology (Williston Park). 2012;26(5):471–5, 479–81, 485–6. *Excellent review that discusses the latest studies in the area, discussing the orientations of the larger societies*

Ultrasonography

Vera Lucia Nunes Aguillar and Selma di Pace Bauab

Introduction

Ultrasonography (US) is widely used to detect and diagnose breast lesions because it has no radiation, it has no injection of contrast or radioactive material, and it is accessible and inexpensive when compared to other methods. Except for some occasions (pregnancy, lactation, or young women), US is usually performed in combination with mammography. In recent years, breast ultrasound has gained more space due to technologic advances, with better equipments and high contrast and resolution images, and limitation of mammography in women with dense breasts.

Like any imaging method, ultrasonography is operator and machine dependent. The physician performing the examination must know the equipment well and have experience in breast anatomy and pathology, as well as in other breast imaging methods (mammography and magnetic resonance imaging).

Indispensable Items in the Equipment Used for Breast Ultrasonography

1. High-frequency 12–18 MHz linear array transducers – lower-frequency transducer (5 MHz) can be used in women with large breasts or implants for deeper penetration of the sound beam, although with loss of resolution.

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G. Novita et al. (eds.), *Breast Diseases*,
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2. Electronic focal zone (s) adjustment – the focal zone setting determines the spatial resolution, i.e., the ultrasonographic aspect of the lesion. In routine exams, the focal zone should be placed in the middle third of the breast; if there is a mass or other ultrasonography alteration, the transducer focus should be adjusted at the lesion for its better characterization. Structures of the breast outside the focal zone may have their echotexture modified, making it difficult to differentiate between simple cysts and solid masses, for example.
3. Field of view (FOV) – this is the visualized area of the breast ranging from the skin to the pectoral muscle. The pectoralis muscle must be along the posterior margin of FOV. The ideal transducer size is 5 cm, with penetration of 4–5 cm, so that the entire breast is included in the field of view. Extended visual field (panoramic image) may be useful in the study of large masses or implants.
4. Overall gain and gain compensation slope (define the shades of gray) – they are parameters that should be adjusted for each exam, according to the characteristics of the patient's breast. When these variables are not correct, solid masses can be misinterpreted as cysts or vice versa.
5. New parameters – current US machines present new elements, such as harmonic image and spatial compound of real-time images, which reduce artifact echoes. This helps to differentiate hypoechoic lesions – thick-containing cysts versus solid masses – and increases the resolution of the margins of the masses. The sonographer must understand how to use these resources in order to get the best picture, case by case.

Performing the Exam

US is operator dependent and meticulous attention to scanning technique is necessary. The exam should be performed with the patient in the supine position and the arms flexed behind the head: this position allows the chest wall to be used as a support to compress the breast with the transducer during the exam, as well as to reduce breast mobility and minimize thickness of the tissue that the sound beam must cross. To study the lateral regions, where there is usually a greater amount of fibroglandular tissue, the patient should be obliquely rotated to the contralateral side. Medial lesions and upper regions of the breasts should be scanned supine with the arms along the body. This position can also be used in the preoperative locations, since this is the position usually employed during breast surgery.

Scan the entire breast, from the mid-axillary line to the parasternal region, from the infraclavicular region to the inframammary sulcus, and from the posterior chest wall to the nipple, axilla, and retroareolar regions. Remember that the peripheral region of the breast may not be included in the mammographic views, so it is very important to study them by ultrasonography.

Survey scanning should always be performed in, at least, two orthogonal planes: transverse and sagittal. The radial planes – for visualization of ductal

abnormalities – and the antiradial planes (perpendicular to the radial) should be used to study the subareolar region, with lots of gel or displacement of the papilla, to avoid the acoustic shadow behind the nipple, which impairs visualization of this area. The axillary regions should be examined for axillary breast tissue or lymph node enlargement: in general, it is possible to visualize lymph nodes of level 1, between the large and small pectoralis muscles, at the level of the axillary extension. In patients with current or treated breast cancer, one should always examine the subclavicular, supraclavicular (medial to sternocleidomastoid), and parasternal regions (three first intercostal spaces) to exclude lymph node enlargement.

Label the images or lesions: right/left breast, clockface, nipple distance, and transducer orientation, for example, Rt, 3 H/5 cm nipple/sagittal. Lesions, other than simple cysts, require orthogonal views, with and without calipers, for margin analysis. Use split screen, easier for follow-up comparison. Document one image per quadrant, one behind the nipple and one from the axilla, if the examination is negative. Use power Doppler for study of masses.

Normal Anatomy

- Skin: hyperechogenic, up to 2 mm thick.
- Pre-mammary adipose tissue: hypoechogenic. Fat lobules are often oval in one plane and elongated in the orthogonal plane, thus allowing differentiation with true solid masses.
- Fibroglandular tissue: in general, hyperechogenic and heterogeneous (hyper- and hypoechogenic interspersed areas); it may be hypoechogenic in young women and in women at lactation.
- Retromammary adipose tissue: thin hypoechogenic layer, sometimes not visible (in very dense breasts).
- Pectoralis muscle: it should be visualized on the ultrasonography exam because it confirms that the entire thickness of the breast was included in the field of vision. It presents lower hypoechogenicity in relation to the fibroglandular tissue.
- Costal arches: not to be confused with breast lumps. They are located behind the pectoralis muscle; they are oval in one plane and elongated in another, with posterior acoustic shadow.
- Axillary lymph nodes: level 1 lymph nodes, between the large and small pectoralis muscles, at the axillary extension level (Fig. 1).

Indications for Ultrasonography

The indications for breast ultrasound continue to evolve. Although the original applications for breast ultrasound have not changed, new indications have been developed.

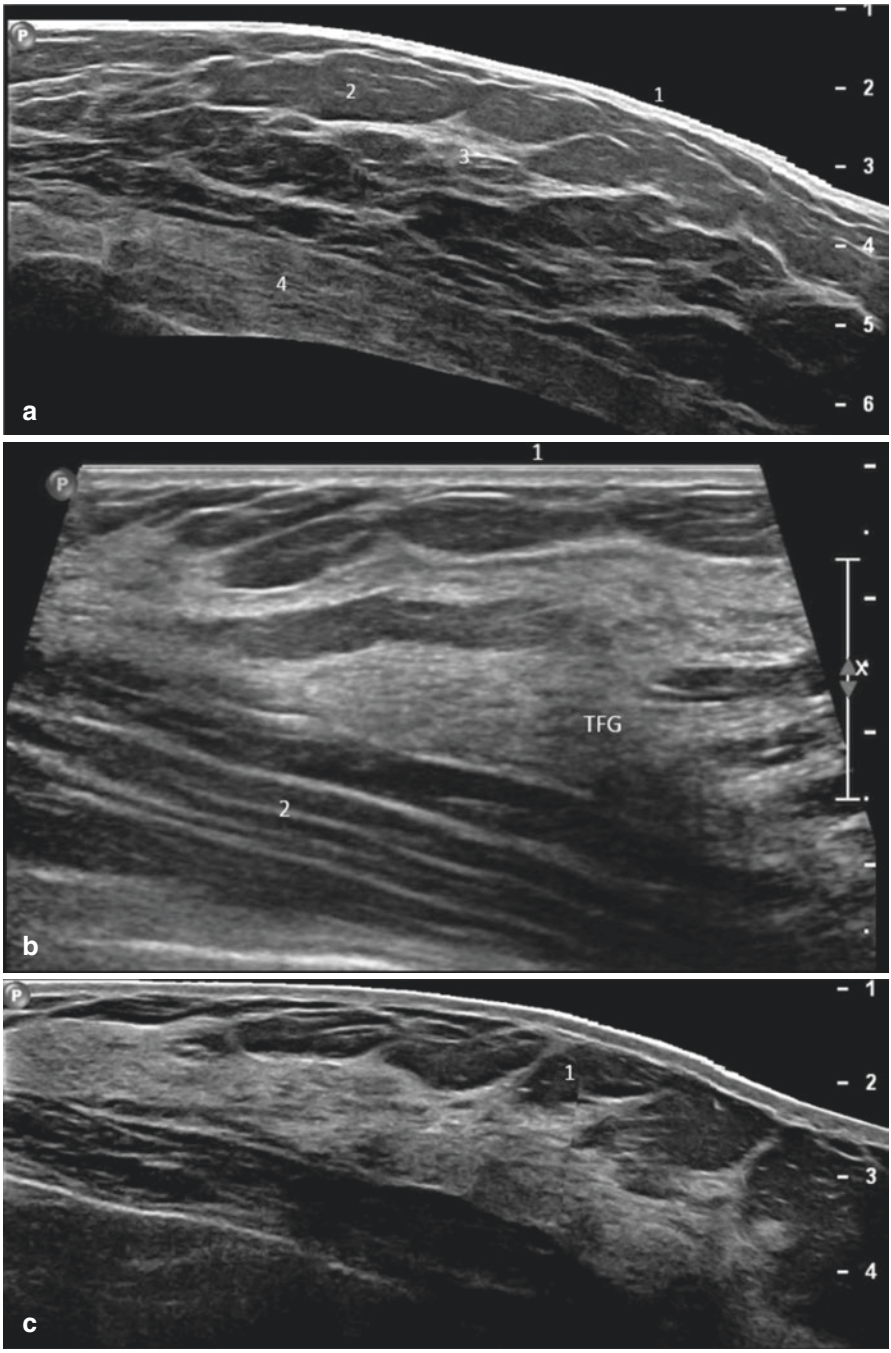

Fig. 1 Ultrasonographic anatomy of the breast. (**a**) 1. Skin. 2. Subcutaneous adipose tissue. 3. Fibroglandular tissue. 4. Pectoral muscle. (**b**) Visual field of the breast should include from the skin (1) to the pectoralis muscle (2). TFG: Fibroglandular tissue. (**c**) Cooper ligaments

1. Evaluation of palpable abnormalities: This is the most common indication for targeted diagnostic breast ultrasound. Every patient with a palpable abnormality should be evaluated sonographically.
2. Evaluation of mammographic abnormalities (palpable or not): Differentiation of collections of normal breast tissue, cysts, or solid masses. It is important to correlate size, shape, and location to ensure the sonographic finding does, in fact, correlates with the mammographic abnormality.
3. Differentiation of solid masses: Probably benign or probably malignant characteristics.
4. First and, usually, the only test to evaluate clinical findings in young, pregnant, or lactating women.
5. Study of breast implants to detect intracapsular ruptures or fluid collections.
6. Evaluation of focal pain. Look for cysts, masses or inflammation (use Power Doppler), or ductal ectasia.
7. Evaluation of nipple discharge. Ultrasound is very useful in patients with nipple discharge, especially in the study of subareolar ducts for presence or exclusion of solid intraductal lesions (papillomas). US has another benefit in these cases which is ultrasound-guided vacuum-assisted biopsy for small subareolar intraductal lesions.
8. Guidance of percutaneous procedures, including fine-needle aspiration, core biopsy, vacuum-assisted biopsy, and preoperative localizations. Interventions guided by ultrasound are faster and more comfortable to the patient (done in the supine position) and should be used whenever the lesion is characterized by this method. Another advantage of the US is that it provides real-time guidance – one can keep the lesion and needle in the visual field at all times.
9. Lymph node evaluation and local staging of breast carcinoma: US is invaluable for assessing regional lymph nodes in patients with known breast cancer. If lymph nodes are morphologically abnormal – the hallmark is eccentric cortical thickening – they can undergo ultrasound-guided biopsy. US can also be performed to search for multifocality, multicentricity, or bilaterality in a patient with known breast cancer, although magnetic resonance imaging has more sensitivity.
10. Follow-up of patients with personal history of breast cancer, as a supplemental method to mammography, mainly in patients with dense breasts to study the surgical bed and regional nodes.

Screening Breast Ultrasound

Multiple studies (uni- and multicenter) have shown that adding ultrasound to mammography can detect approximately three additional cancers per 1.000 screening studies, occult to mammography. A meta-analysis including 13 studies from 1995 to 2012, with 75,000 women, demonstrates a supplemental cancer detection rate (CDR) of 3.4/1000 exams: 94% invasive, low-grade, and mostly <1.0 cm. The most important of these studies is the ACRIN 6666, a prospective multicenter project

designed to investigate and validate the role of supplemental screening breast ultrasound, in women with dense breasts and increased risk for breast cancer, mainly family history. It included 2637 women considered eligible, with presence of heterogeneously dense tissue in, at least, one quadrant of the breast, submitted to mammography and annual US for three consecutive years. The first-year date confirmed that screening US can, in fact, find an additional cancers, not seen on mammography (4.2 cancers per 1.000 screening studies, mainly invasive, less than 1 cm and node negative).

The major criticism of screening breast ultrasound is its low specificity (large number of negative biopsies), with positive predictive value (PPV) between 6% and 10%, in most of the publications. In later studies, specificity of the method has improved, as in the Yale experience – in the first year of screening breast US, the PPV was 6%, while in the fifth year after US screening, it improved to 29%.

The J-START (Japan Strategic Anti-cancer Randomized Trial), a prospective study published in 2016, evaluated more than 70,000 women with dense breasts and age between 40 and 49, randomized to mammography only (control group) or mammography associated with ultrasonography (investigated group). The authors demonstrated a reduction in the rate of interval cancers in the group screened with mammography and US, in relation to the control group.

Remember that screening breast ultrasound is always supplemental and should be performed after mammography, with correlation of the findings.

Who should get screening breast ultrasound?

1. Women with dense breasts
2. High-risk women who cannot tolerate or do not want yearly MRI (magnetic resonance imaging)

Role of US After Implantation of Tomosynthesis in Screening: Can Tomosynthesis Replace Ultrasonography in Women with Dense Breasts?

Numerous studies have found that ultrasonography, as well as tomosynthesis, detects small invasive cancers not seen in conventional mammography, even retrospectively, in women with dense breasts. Tomosynthesis has the advantage of being only one exam (it is a better mammogram), with a high positive predictive value, but with a high cost of implantation and maintenance. Ultrasonography is a low-cost additional exam, widely available, without radiation, but with low positive predictive value, thus requiring an experienced radiologist to perform it.

There is little information on which exam to choose as a complement to digital mammography in women with dense breasts: ultrasonography, tomosynthesis, or both? The recently published ASTOUND ("Adjunct Screening with Tomosynthesis or Ultrasonography in Women with Mammography-Negative Dense Breasts") study brings a prospective, multicenter study comparing tomosynthesis versus ultrasonography in the supplementary screening of women with dense breasts and negative digital mammography.

The rate of cancer detection was 4/1000 with tomosynthesis and 7/1000 with US, with no significant differences in recall rate or positive predictive value. The authors suggest that, in women with dense breasts, US may be more effective than tomosynthesis. However, these results are preliminary and need to be replicated in other centers. In this study, tomosynthesis detected more than 50% of additional cancers, potentially being the primary mode of screening. In clinical practice, it can be observed that the two modalities complement each other, and women with dense breasts and tomosynthesis can still benefit from screening breast ultrasound.

"Second-Look" Ultrasonography After Magnetic Resonance Imaging (MRI) Findings

MRI is the most sensitive imaging type of exam to detect breast cancer, and it may identify lesions not seen on mammography or US, especially in women at high risk for breast cancer. However, MRI-guided biopsies are expensive and time-consuming, and there is not always a willingness to perform them. Therefore, in most cases, the "second-look" US, aimed at lesions initially identified by MRI, is used. It is not always easy or possible to characterize lesion on US, because they are usually subtle and non-specific, with no typical signs of malignancy. A meta-analysis performed until 2013, which included 17 articles, showed great heterogeneity in the detection rate by the "second-look" US (22.6–82.1%) with a mean of 57.5%. Another systematic review of the literature, with new articles since 2013, presented at the latest European Congress of Radiology (Vienna 2017) confirmed the heterogeneity in the US detection rate, estimated on average by about 64.2%. The conclusion of all the studies is that the "second look" US (after MRI findings) is more likely to detect malignant lesions and lesions that present as mass enhancement. For lesions with non-mass enhancement (which may correspond to CDIS), the US sensitivity is lower, with detection rate around 37.5%. Therefore, negative US after suspected MRI findings does not exclude malignancy, and MRI-guided biopsy should be recommended.

Limitations of Ultrasonography

- Calcifications: although it is possible to visualize calcifications in the US with the current devices, especially if they are associated with dilated masses or ducts, it is not possible to characterize them adequately. Detection and characterization of calcifications continues to be the domain of mammography.
- Architectural distortion: here, too, US is not the best method, and this finding is better characterized in mammography, especially in 3D mammography (tomosynthesis). However, in the presence of focal architectural distortion, seen on 2D or 3D mammography, it is worth to perform ultrasound to look for some findings, such as acoustic shadowing or echotexture changes, in order to do the biopsy by this method.

BI-RADS in Breast Ultrasound

The new US BI-RADS lexicon (second edition – 2013) tries to correct errors, resolve inconsistencies, revise or add terms, and clarify management for selected terms.

Contents of the New BI-RADS®

- General considerations (NEW)
  - Breast anatomy (more detailed in this new edition)
  - Image quality (equipment characteristics and exam technique)
  - Location of the findings (Rt/Lt breast, clockface, and distance from the nipple), orientation of the transducer (sag, transverse, radial, or anti-radial), and lesion measurements
  - Recording the exam (one image of each quadrant and one image of the retroareolar region for a normal exam)
- Lexicon (Table 1)
  - Background echotexture: homogeneous-fat, homogeneous-fibroglandular, and heterogeneous (this is the most frequent in dense breasts: mixed echogenicities of adipose and fibroglandular tissue)
  - Masses: shape, margins, orientation, echo pattern, and posterior acoustic features
  - Calcifications: inside the mass, outside the mass, and intraductal
  - Associated findings: architectural distortion, ductal alterations, skin alterations (thickening or retraction), breast edema, vascularization (present or absent, internal or peripheral), and findings of elastography

Table 1 Lexicon of US

Background echotexture
Homogeneous (fat or fibroglandular) and heterogeneous fibroglandular
Masses
Shape, orientation, margins, echo pattern, posterior acoustic features
Calcifications
Inside of the mass, outside of the mass, intraductal
Associated features
Architectural distortion, ductal changes, skin changes, edema, vascularity, and elasticity assessment
Special cases
Simple cysts, clustered microcysts, complicated cyst, cutaneous lesions, intramammary lymph nodes, foreign body (mammary implants or mammotomy clips)

  - Special cases (including pathognomonic images of lesions): clustered microcysts, simple cysts, cutaneous lesions, foreign body (e.g., mammary implants, clips), axillary lymph nodes, and intramammary lymph nodes

- Description of mass
  - Masses are the most important finding on breast ultrasound. They should be described by:
    - Shape – oval, round, and irregular
    - Margins – circumscribed or not circumscribed (indistinct, angular, microlobulated, or spiculated)
    - Orientation (in relation to skin) – parallel or not parallel
    - Echo pattern (anechoic, hyperechoic, complex, hypoechoic, isoechoic, and heterogeneous)
    - Posterior acoustic features (no posterior features, enhancement, shadowing, combined pattern)
  - They should be measured in three orthogonal axes: length (largest horizontal axis parallel to the skin); height (anteroposterior axis), both in the same scan plane; and width (measured in the scan plane orthogonal to the anterior)
  - It is important to name the images in the film: right or left breast, location of the lesion in hours (face of the clock), and distance of the papilla, anterior, middle, or posterior third

Categories and Recommendation for Appropriate Management

- Category 1:
  - Exam negative for malignancy
- Category 2:
  - Cysts, fat-containing masses, cutaneous masses, intramammary lymph nodes, silicone implants, etc.
  - Multiple and bilateral circumscribed solid masses (at least three masses: one mass in one breast and two masses in the other breast): currently classified as category 2, after work by [5], which found 0% malignancy among 127 lesions with a follow-up period of at least 2 years
- Category 3:
  - Solid mass: classified in BI-RADS® 3 category only if oval, circumscribed, hypoechoic, parallel to the skin, with no associated findings, and with no color Doppler flow (Figs. 2 and 3)

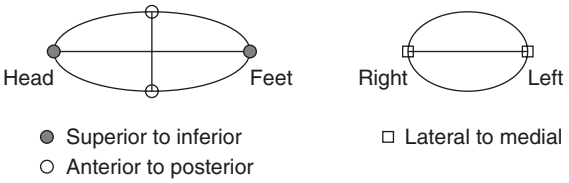

Fig. 2 Measurements of a solid mass by US

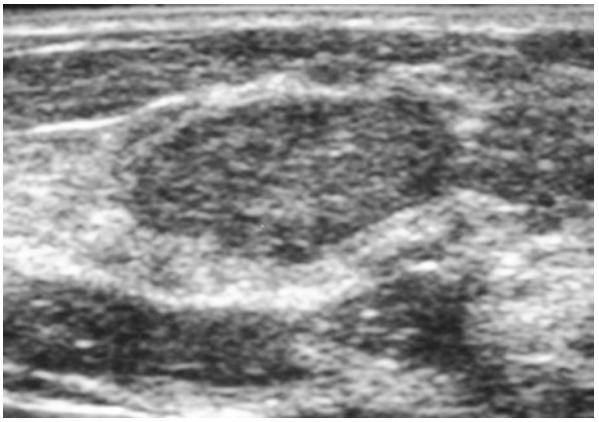

Fig. 3 Example of B3 masses

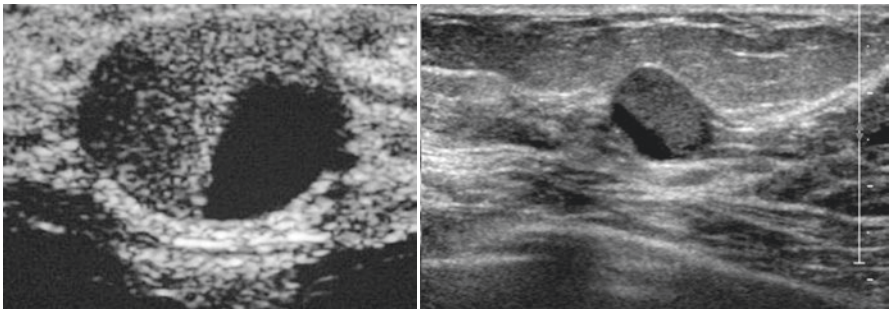

Fig. 4 Examples of thick cysts. Cysts with thick contents, if multiple and bilateral, BI-RADS® 2; if isolated, BI-RADS® 3; if solitary and new in the postmenopausal or high-risk women (BRCA +) or palpable, BI-RADS® 4

– Complicated cysts: classified in BI-RADS® 3 category only if solitary or new, or in high-risk patients, positive BRCA or with a history of lymphoma or melanoma (Berg et al., 2010). The other complicated cysts are classified as category 2, due to the low probability of malignancy of this finding (estimated in 0.3% in the meta-analysis of studies published in the literature – Berg et al. 2010) (Fig. 4)
– Clustered microcysts: classified as BI-RADS® 3 if they are new to mammography or ultrasound and appear in postmenopausal women, especially in those

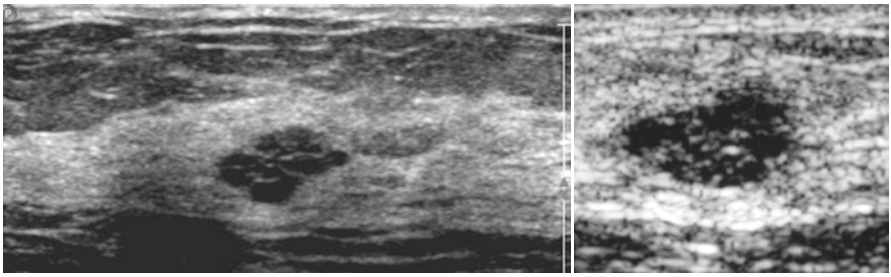

Fig. 5 Clustered microcysts. In general, BI-RADS® 2, except if deep, difficult to characterize or new, in postmenopausal women, without HT; BI-RADS® 3, if non-circumscribed margins or other non-benign characteristic, or if rapid growth or any suspect clinical or imaging findings: BI-RADS® 4

Table 2 Description of solid masses

1. Shape	Oval, round, irregular
2. Margins	Circumscribed, not circumscribed (indistinct, angular, microlobulated, spiculated)
3. Orientation	Parallel, not parallel
4. Echo pattern	Anechoic, hyperechoic, complex cystic and solid, hypoechoic, isoechoic, heterogeneous
5. Posterior acoustic features	No posterior features, enhancement, shadowing, combined pattern

Table 3 Follow-up of category 3 through US

Exam	Time (months)	BI-RADS®
Initial screening and diagnosis		3
Unilateral	6 months	3
Bilateral	12 months	3
Bilateral	24 months	2 or 3
Bilateral	36 months (optional)	2

Attention: Injuries with category 3 imaging criteria, however, new, or with a diameter increase >20% in 6 months = Category 4, and they should be submitted to percutaneous biopsy

without hormone therapy. If it is difficult to characterize them as microcysts, they should be in BI-RADS® 4 category. The other clustered microcysts are classified as category 2, due to the low rate of malignancy found in all published series (0.4%) (Fig. 5) (Tables 2 and 3)

- Category 4
  - Solid masses with lobulated, indistinct, or angled margins
  - Solid masses with nonparallel orientation and non-circumscribed margins

  - Red round hypoechoic masses, other than characteristically cysts with thick contents
  - Solid masses with a diameter increase of 20% or more in 6 months
  - Intraductal solid masses
- Category 5
  - Masses with irregular shape, spiculated or angulated margins, and posterior acoustic shadowing

Novelties in Breast Ultrasonography

- Elastography: a new US acquisition that allows us to compare the elasticity of a mass detected in mode B, assuming that benign masses are "softer" and malignant ones are "hard" masses. There are several types of elastography, which can be handheld compression (qualitative) and others, including shear-wave, which allows quantification of elasticity in kiloPascal or m/s (quantitative) and color scale (qualitative). The benefit of elastography is not the detection of cancer but a better characterization of masses classified as BI-RADS® 3 or 4A in an attempt to avoid unnecessary biopsies and increase the specificity of ultrasonography for malignant lesions when added to the morphology of the mass. It is still an area under study, requiring more work. Lesions characterized in mode B in categories 2, 4B, 4C, and 5 maintain these categories, even if discordant in the elastography.
- Automated US (AWBU – automated whole breast ultrasonography): a computer-based system used for performing and recording the US of the entire breast. The goal is to overcome a major problem of the handheld US, which is the time of the doctor in the exam room, evaluated as 19 minutes in the ACRIN study. In this system, the images are obtained by a transducer connected to a mechanical arm, guided by a computer, and then sent to the monitor where they are stored. The time of the exam is estimated in 10–20 min, and the time of interpretation by the doctor is estimated in 7–10 min.

Recommended Literature

1. Aguillar VLN, Bauab SP, Norma MM. Mama – Diagnóstico por Imagem. Rio de Janeiro: Livraria e Editora Revinter; 2009. *Book on breast imaging, including US*.
2. American College of Radiology. Atlas BI-RADS®. 5th ed; 2013.
3. Barr RG, Zhang Z, Cormack JB, Mendelson EB, Berg WA. Probably benign lesions at screening breast US in a population with elevated risk: prevalence and rate of malignancy in the ACRIN 6666 trial. Radiology. 2013;269:701–12.
4. Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasonography and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA.

2008;299:2151–6. *A multicenter prospective study evaluating the role of complementary ultrasonography in mammography, in women with dense breasts and higher risk for breast cancer*.
5. Berg WA, Zhang Z, Cormack JB, Mendelson EB. Multiple bilateral circumscribed masses at screening breast US: consider annual follow-up. Radiology. 2013;268:673–83. *Review Texts of BI-RADS® on US, fifth edition*.
6. Chae EY, et al. Reassessment and follow-up results of BI-RADS category 3 lesions detected on screening breast ultrasonography. AJR. 2016;206:666–72.
7. Kelly KM, Dean J, Comulada WS, Lee SJ. Breast cancer detection using automated whole breast ultrasonography and mammography in radiographically dense breasts. Eur Radiol. 2010;20:734–42. *A pioneer article in automated US*
8. Spick C, Baltzer P. Diagnostic utility of second-look US for breast lesions identified at MR imaging: systematic review and meta-analysis. Radiology. 2014;273:401–9. *Systematic review of the literature of US "second look" studies after MRI findings*.
9. Stavros AT. Breast ultrasonography. Philadelphia: Lippincott Williams & Wilkins; 2004. *Book on breast imaging, including US*.

Magnetic Resonance Imaging

Alice Coelho Brandão

Definition of the Method

Magnetic resonance imaging (MRI) is an imaging method with several applications in the investigation of breast pathologies, due to the high spatial resolution images, multiplanar capacity (the breast can be observed in several planes), and excellent tissue contrast without exposing the patient to ionizing radiation.

Description of the physical principles of the method is beyond the focus of this work; therefore, for further information about the method, see the book called *Resonance of the Breast*, by this author.

Breast MRI Protocol Making

The protocol includes preparation of the patient before the exam, her positioning, and the examination itself, with the dynamic phase contrasted, and also other sequences.

Preparation of Patient Prior to the Exam

1. Relevant clinical data (Tables 1 and 2):
   - Hormonal: phase of the menstrual cycle and use of hormone therapy. Hormones impact on the impregnation pattern of the breast, which may mimic malignancy or hinder its identification. Therefore, the study should be

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Table 1 Necessary data for the resonance exam

Necessary to the exam		Reason
Previous exams	USG, mammography, resonance, and PET-CT	Comparative report
Regular menstrual cycle	5th–15th day of cycle	Variable impregnation with the menstrual cycle
Avoid the use of deodorant, talcum powder, and cream on breasts and axillae		Artifacts promoted by these materials
Physical exam	Markers in palpable alteration, painful spot, and scars (except mammoplasty)	Correlation with findings in exams
Venous access	Before starting the exam	Contrast medium (gadolinium) required for dynamic study
History of allergy, except to gadolinium	In cases of previous moderate allergy (angioedema) and significant allergy (glottal edema)	Radiologist-oriented antiallergic preparation
Patient relaxed during exam		Artifacts disturb proper interpretation

Table 2 Indispensable elements for adequate MRI

High-field device, 1.5 T or 3 T
Specific coil for the breast
Simultaneous image acquisition of breasts in the contrast dynamic study
Dynamic study with adequate spatial resolution (ability to distinguish nearby objects as different structures): three-dimensional, cut thickness < 2 mm, with resolution at 0.5–0.8 mm
Dynamic study with adequate temporal resolution: < 90 s, so that there is no contamination with background breast enhancement

performed between the 5th and the 15th day of the menstrual cycle. In the therapeutic planning of the neoplasia, an exception can be made to this rule. In patients undergoing hormone replacement therapy, if the test exhibits an abnormality that is not typical of benignity or malignancy, it is recommended to suspend and re-evaluate it within 1 month.

- Clinical condition change: palpable nodule, papillary discharge, surgery, and implant (previous exchange). Skin marker (vitamin E capsule) is positioned at palpable and scarred change (Fig. 1).
- Personal history: previous diagnostic investigation and treatment, biopsy, surgery, radiotherapy, neoadjuvant chemotherapy, and histological and biological tumor data of the current tumor.
- Family history: previous cases of breast neoplasia in the family (male and female) and also of the ovary, uterus, gastrointestinal tube, and thyroid, among other tumors.

Previous exams: important for the correlation with the MRI findings and better definition of the recommendation (which is part of the BI-RADS® tutorial standard), aiming to reduce false-positive and false-negative results.

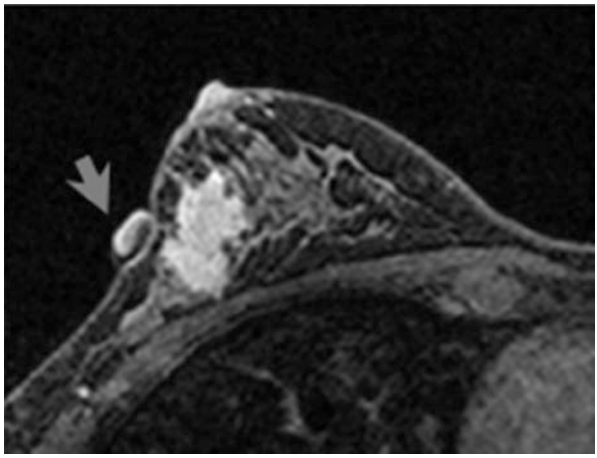


Fig. 1 Clinical change during preparation of patient before the exam

Preparing the breast: the topical use of cream or deodorant in the breasts and axillae should be avoided 24 hours prior to the exam, because it can cause artifacts.

About the Contrast Medium

Pregnant women can undergo MRI (ideally in the second and third trimesters), but the intravenous contrast medium should not be used in this situation. Specifically for the breast, the examination will have rare indications due to the impossibility of performing the study with contrast and difficult positioning depending on the gestational age (see positioning item).

In lactating women, the contrast medium can be used safely, without any harm to the baby, according to the latest guidelines of the American College of Radiology.

Contraindications of Resonance

Some materials may contraindicate the examination, usually due to proximity to a noble structure or loss of function when exposed to the magnetic field (Table 3).

Indications of Resonance

MRI has an extremely high sensitivity (90–95%) for the detection of cancer, greater than the clinical examination, mammography, and ultrasonography. Although the method offers such great potential, because of its high cost, it is reserved for cases

Table 3 Contraindications

Ferromagnetic brain aneurysm clips
Implants and ocular appliances (except intraocular lenses for cataracts)
Otology implants, including cochlear implants
External orthopedic fasteners
Some types of cardiac pacemakers
Firearm projectile near noble structure
Surgically implanted insulin pump

Table 4 Recommended screening of magnetic resonance, by evidence level

Indications of screening with MRI in high-risk patients
1. Annual screening recommendation (based on evidence)
Women with mutations of BRCA1 or 2 genes or first-degree relative with BRCA mutation, but not tested Lifetime risk of developing breast cancer estimated >20–25%, as defined by models such as BRCAPRO, the Tyrer-Cuzick, and BOADICEA
2. Annual screening recommendation (based on expert consensus)
Women undergoing thoracic radiotherapy between 10 and 30 years of age Li-Fraumeni syndrome, Cowden's syndrome, and Bannayan-Riley-Ruvalcaba syndrome and with first-degree relatives with syndromes
Insufficient evidence for recommending or contraindicating
Lifetime risk of developing breast cancer estimated between 15% and 20%, as defined by BRCAPRO or other models Prior diagnosis of lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH) or atypical ductal hyperplasia (ADH) Heterogeneous or extremely dense mammograms Women with a history of breast cancer, including ductal carcinoma in situ (DCIS)
No indication for screening (consensus among specialists)
Lifetime risk of developing breast cancer estimated at <15%

with accurate and evidence-based indications such as screening for breast cancer in high-risk patients, occult neoplasm investigation, and implant evaluation. In the context of surgical planning, there is little evidence that MRI improves patient follow-up, but it may be beneficial in some situations, especially when there is a lesion discrepancy in conventional methods and in certain patients (Tables 4 and 5).

Main Controversies Involving Resonance (Table 6)

BI-RADS® for Resonance

Its main purpose is to standardize the terminology used in mammography radiological reports, facilitating the understanding among radiologists and mastologists as to the clinical significance of radiological findings. It is recommended that the

Table 5 Diagnostic indications of MRI, by evidence level

Indications with high level of evidence
Occult carcinoma: MRI is the exam of choice
Response to adjuvant chemotherapy: better correlation with residual disease and pathology, with decreased contrast uptake before altering tumor size. MRI prior to treatment is fundamental. Accuracy depends on the type of tumor response and drugs used. There is less accuracy in the complete radiological response in the following situations: low-grade tumor, RH and HER2; taxane treatment; response with tumor fragmentation
Implant evaluation: more sensitive examination to evaluate implant integrity
Controversial indications
Evaluation of locoregional recurrence of breast cancer (recurrence "scar"): MRI should not be used as an alternative to biopsy
Staging of cancer and preoperative assessment (multicentricity, "bilateral", multifocality): there is little evidence that preoperative MRI decreases the rate of reoperation, and there is no evidence on the impact of survival. MRI-guided biopsy is required for lesions not identified in the other tests. However, as it is the most sensitive method to detect additional foci, there are patients who may benefit from the examination in this context, such as: DCIS: MRI is more sensitive to determine the extent of the lesion with a worse prognosis, allowing adequate volumetric evaluation of the high-grade lesion Invasive lobular carcinoma: It has an excellent correlation with the extent of the disease High-risk patient: MRI has excellent correlation with the extent of the disease Evaluation of pectoral muscle involvement: In this staging situation, MRI should be used, since it is the more sensitive exam
Papillary flow investigation: it can detect non-visible lesion in conventional methods and aid in therapeutic planning, but there is insufficient evidence for routine recommendation

Table 6 Controversies of indication – points in favor and against the literature

Evaluation of the locoregional recurrence of breast cancer	
In favor	**Against**
It should be used when there is doubt about the conventional methods and physical examination and when it is difficult to differentiate relapse from scar	It should not be used as an alternative to biopsy when the lesion is suspected or highly suspected
Preoperative evaluation of multifocality/multicentricity	
In favor	**Against**
More suitable evaluation for the selection of patients that should be indicated for conservative or nonconservative surgeries Decreased number of relapses	Increased cost Increased number of mastectomies Radiotherapy may be an option for multifocality
Evaluation of contralateral cancer	
In favor	**Against**
Allows simultaneous treatment Prevents reoperation Reduces patient emotional disturbances Prevents disease progression	Cost increase Can be resolved with adjuvant systemic therapy

resonance report should be concise and organized, respecting the systematization of the interpretation of BI-RADS®. It takes into account the following parameters.

Clinical Indication and Technical Aspects

The indication is divided into screening and diagnosis. The latter is understood as evaluation of clinical findings or imaging, implant evaluation, and follow-up of category BI-RADS® 3, among others.

Terminology

Description of the findings should include:

- Breast composition pattern
- Background enhancement pattern of the parenchyma
- Implant and its composition (if present)
- Description of the findings: size and location
- Comparison with previous exams

Breast Composition Pattern (Fig. 2)

Brief description of the breast composition, which is related to the relative amount of adipose and fibroglandular tissue, is divided into four patterns, which are almost entirely fat, scattered fibroglandular tissue, heterogeneous fibroglandular

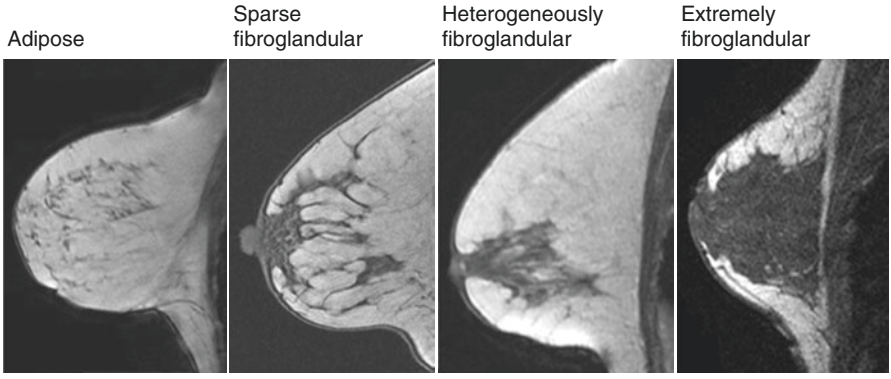


Fig. 2 Breast composition

tissue, and extremely fibroglandular tissue. The pattern of breast composition does not alter the interpretation of MRI, as opposed to mammography.

Background Parenchyma Enhancement

It represents the enhancement of the fibroglandular tissue after the intravenous administration of gadolinium, that is, a response of the parenchyma to the intravenous contrast medium.

It is classified according to the intensity of the parenchyma in the first passage of the contrast medium, relative to the sequence without contrast. The evaluation is qualitative, classified as minimal, mild, moderate, and marked (Fig. 3).

Background enhancement has no correlation with breast density. Extremely dense mammograms may be minimal or mild, and patients with poorly dense breasts may demonstrate markedly background enhanced. As it is most prominent in the luteal phase of the premenopausal menstrual cycle, elective exams should be scheduled in the second week of the cycle, between the 5th and the 12th or the 15th days.

The distribution pattern of parenchyma background enhancement:

- Peripheral or cortical: Typical bilateral, symmetrical, larger in the periphery (lateral quadrants and along the lower breast), due to preferential blood supply (Fig. 4)

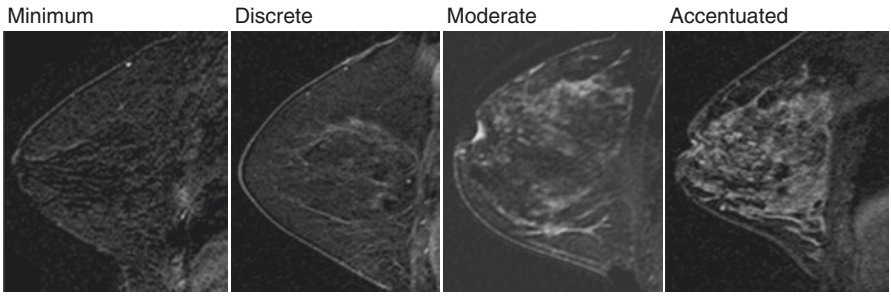


Fig. 3 Classification of the background enhancement pattern of the parenchyma

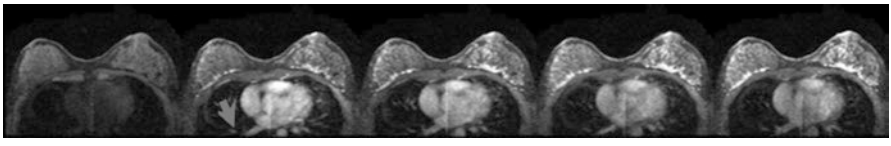


Fig. 4 Typical pattern distribution

Other forms:

- Nodular, symmetrical, more evident in the lateral or medial quadrants
- Multiple "dotted" highlight areas (previous edition – multiple focuses)
- Uniform and diffuse enhancement (Fig. 5)

Description of the Findings

The findings should be described according to the lexicon, which is a specific vocabulary for the description of morphological findings and the kinetic contrast pattern of breast lesions (Table 7), and it includes:

- Morphological findings:

Focus of enhancement:

- Impregnation point less than 5 mm. It is not possible to evaluate clearly shape and margin. Usually, no expression in the pre-contrast images (Fig. 6).
- It can be benign or malignant. Therefore, it should be evaluated in the clinical setting.
- Pattern that favor malignant focus – unique and distinct from Breast parenchyma enhancement, no greasy thread, with washout kinetics, greater or new compared to the previous examination, or adjacent to a previously known tumor or a highly suspicious lesion (Fig. 7).
- Pattern that favors benign focus – high signal in sequences showing high signal liquid content (T2, STIR), possible greasy wire, persistent kinetics, and stable when compared to the previous examination or seen in a first examination (Fig. 8).

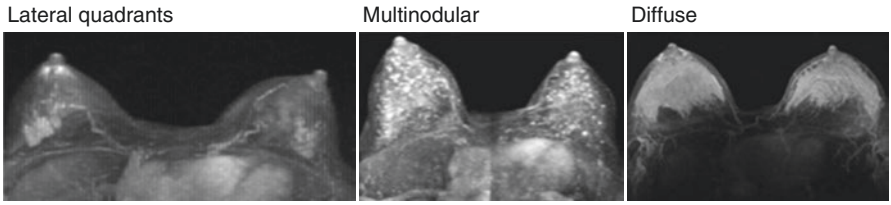


Fig. 5 Other forms of distribution

Table 7 Nodule descriptors

Shape	Margin	Internal enhancement pattern
Round	Circumscribed	Homogeneous
Oval	Irregular	Heterogeneous
Irregular	Spiculated	Internal septations with no enhancement
		Peripheral enhancement

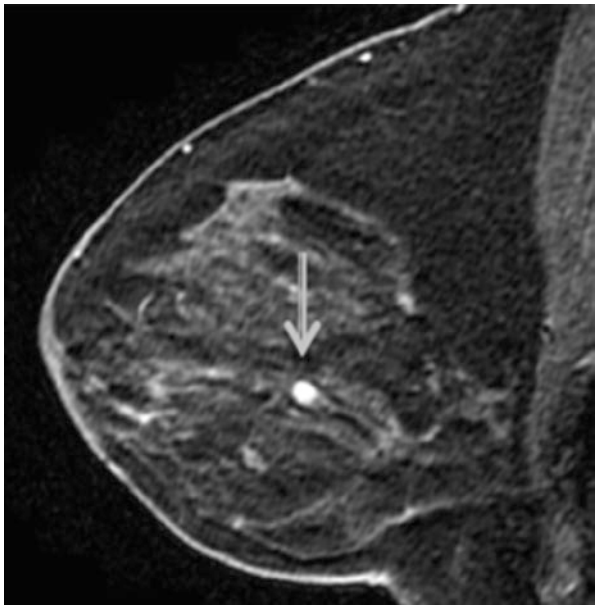


Fig. 6 Morphological finding: impregnation point less than 5 mm

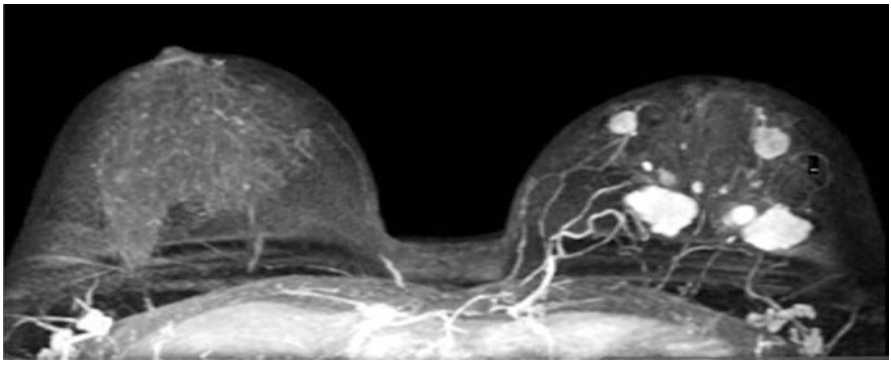


Fig. 7 Focus that favors malignant lesion

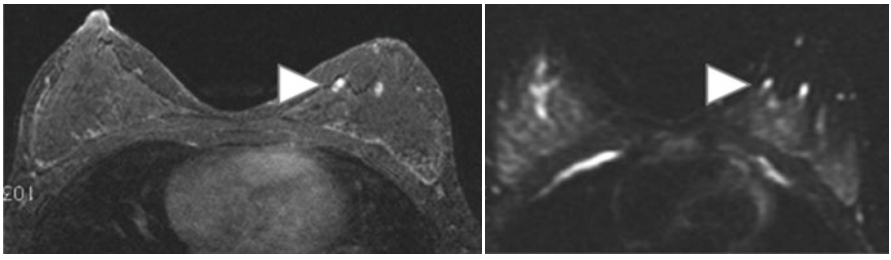


Fig. 8 Focus that favors benign lesion

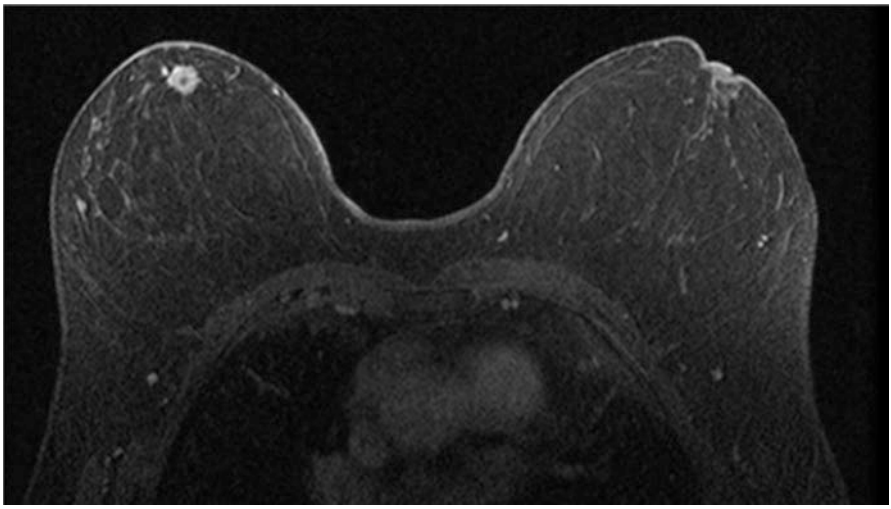


Fig. 9 Three-dimensional enhancement area

Mass, nodule, or nodular enhancement: a three-dimensional enhancement area with the epicenter and convex border that occupies space and can displace or retract the adjacent tissue (Fig. 9). They should be described by:

- Margin and shape: the shape may be round, oval, and irregular; the margin may be circumscribed and not circumscribed (irregular and spiculated); and the internal architecture may be homogeneous or heterogeneous. Lesions that are more suggestive of malignancy include irregular and spiculated nodules, and those more suggestive of benign lesions include circumscribed oval or round nodules (Fig. 10).
- Signal intensity: in T2-weighted images or STIR. Benign lesions may present increased intensity in relation to the parenchyma, particularly fibroadenomas. Malignant lesions tend to be isointense or hypointense. However, very cellular or mucinous necrotic tumors may present a high signal; in such cases, other suspicious features, such as irregular shape, justify the biopsy.
- Internal enhancement pattern: can be characterized as homogeneous and heterogeneous (with non-specific pattern), with non-enhancing dark internal septa and rim enhancement. In general, a dark internal septation that does not enhance indicates a benign process. On the other hand, non-specific heterogeneous enhancement or edge has a greater chance of malignancy (Fig. 11).

Non-mass enhancement: a no space-occupying lesion, with no clear interface/margins. The enhancement is more intense than the rest of the parenchyma, and usually, there is no expression in non-contrast sequences. It may have interposition of normal fibroglandular fat or tissue. Consider if an enhancement does not correspond to the focus or nodule (Fig. 12). The description of terms includes the distribution, the internal enhancement characteristics, T2-weighted signal intensity, and kinetics.

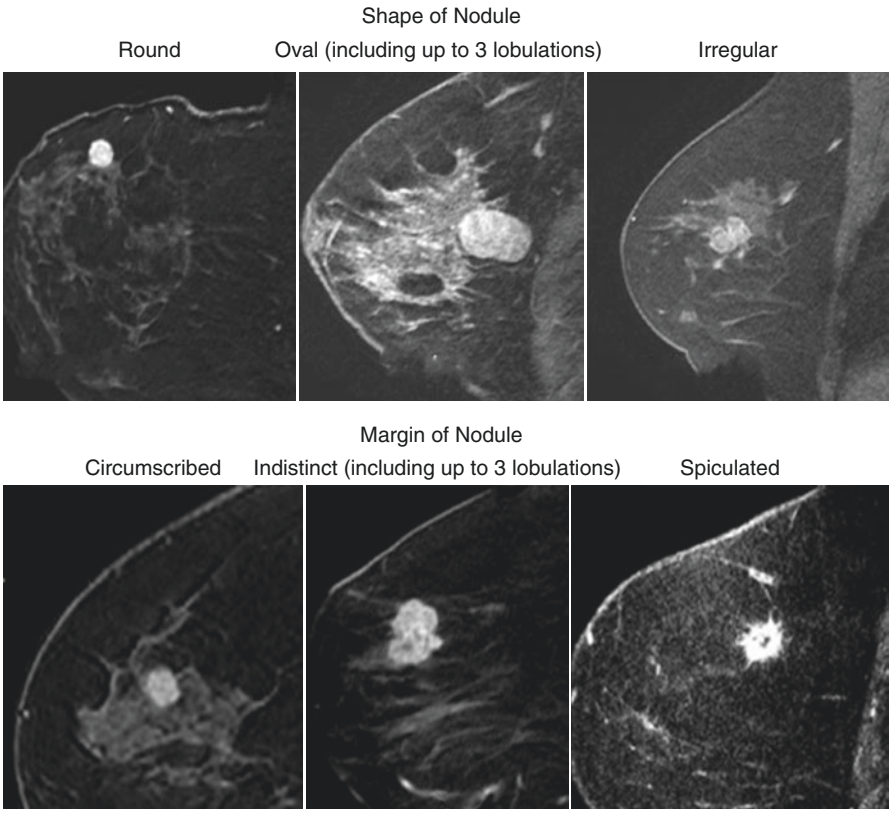


Fig. 10 Shape and nodule margin

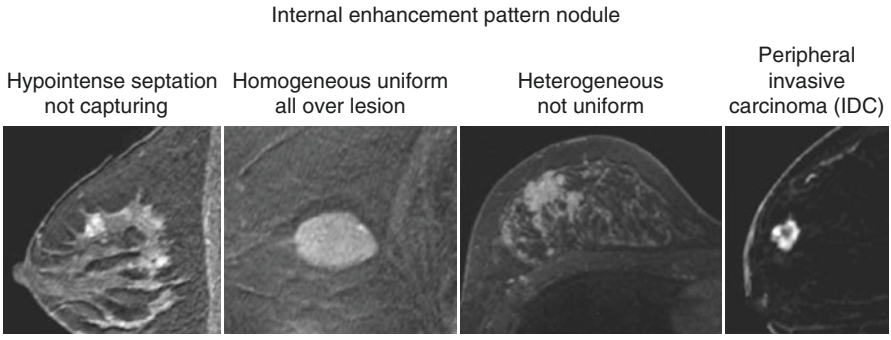


Fig. 11 Internal pattern of nodule enhancement

- Distribution: focal, linear, segmental, regional, diffuse, and multiple:
  - Focal: occupies less than one quadrant (Fig. 13).
  - Linear: linear aspect, which may correspond to a duct. It may have branched appearance (linear branching) (Fig. 14).

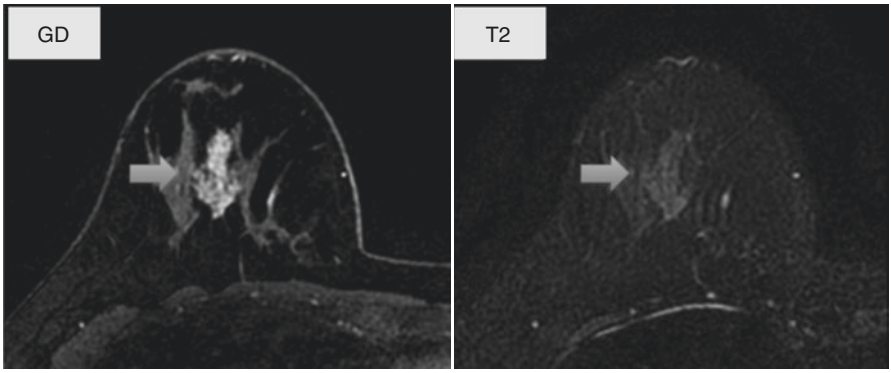
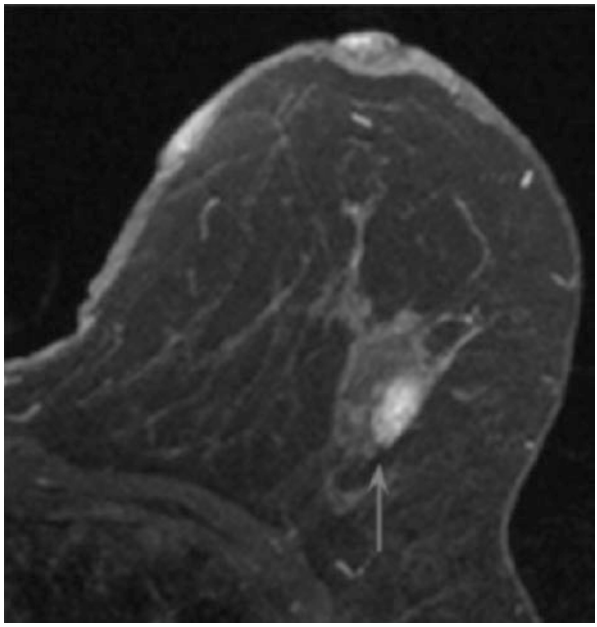


Fig. 12 Nonnodular enhancement

Fig. 13 Focal distribution



- Segmental: triangular shape, with apex pointing to the papilla, suggesting a single duct system involvement (Fig. 15).
- Regional: it comprises an area wider than a single duct system, and it occupies at least one quadrant. It can be geographic, and it does not respect the limits of a quadrant (Fig. 16).
- Multiple regions: it comprises at least two areas, separated by normal tissue, without setting any enhancement pattern described above (Fig. 17).
- Diffuse enhancement: diffuse and uniform in the breast, with similar appearance throughout the fibroglandular tissue.

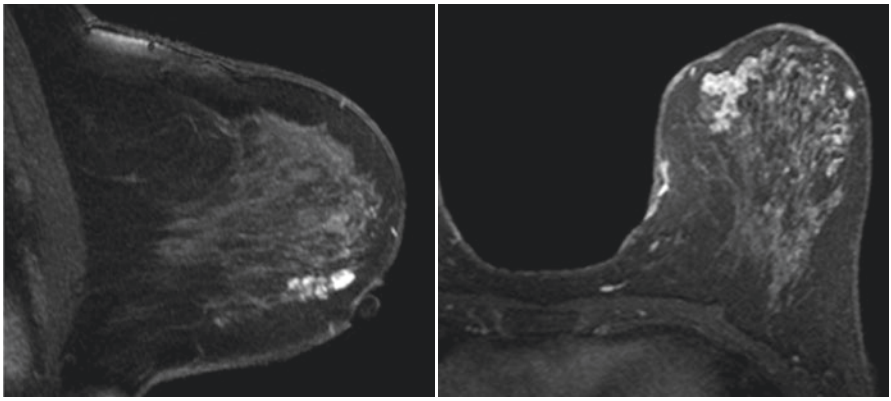


Fig. 14 Linear distribution

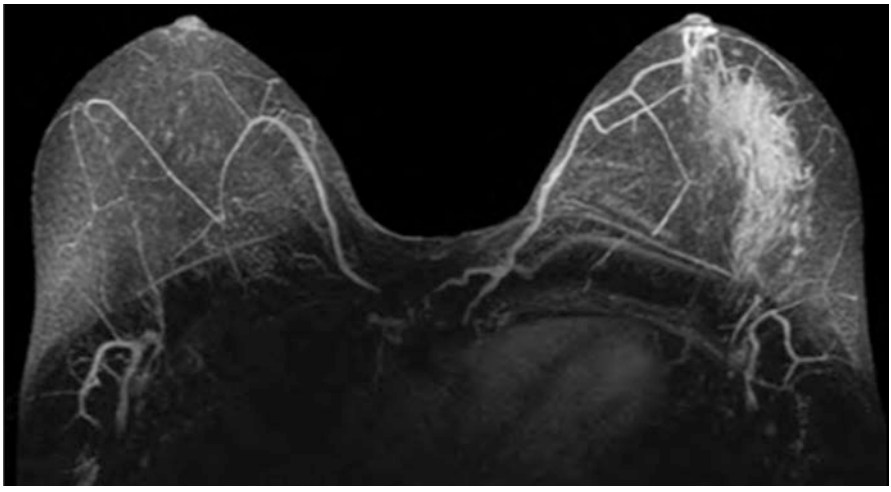


Fig. 15 Segmental distribution

- Internal enhancement pattern (Fig. 18):
  - Homogeneous: uniform enhancement.
  - Heterogeneous: nonuniform enhancement, in a random pattern, separated by normal areas of mammary parenchyma or fat.
  - Clumped: small aggregates of enhancement, variable in size and morphology, similar to "pleomorphic" in mammography, indicating enhancement of shape and varied size.
  - Clustered ring: it may represent dilated neoplastic ducts, forming thin rings of enhancement clustered around the ducts.

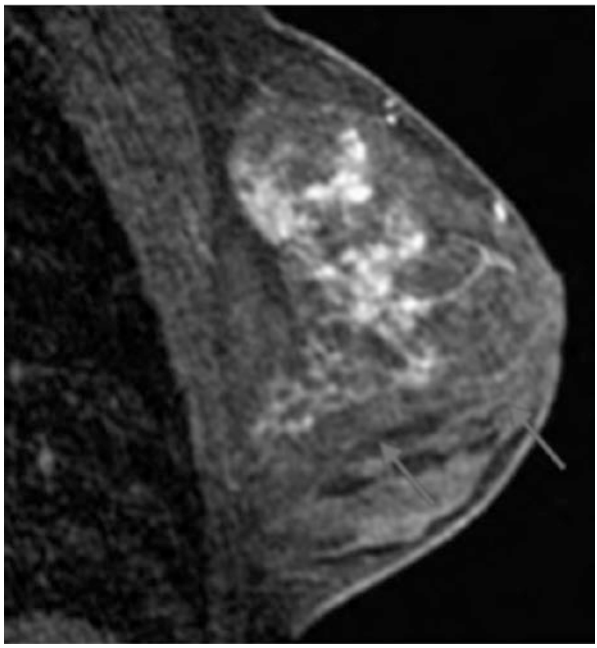


Fig. 16 Regional distribution

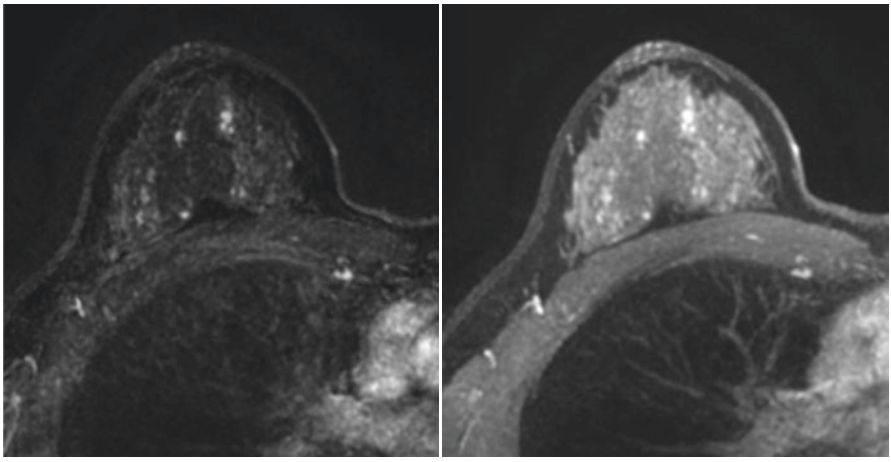


Fig. 17 Multiple highlight areas

- Signal intensity in T2-weighted image or STIR: hypointense, hyperintense, or isointense, in relation to the parenchyma. Intracystic component, hyperintense in T2, suggests a benign lesion.
- Kinetics: they generally present curves of unsuspected enhancement, due to the lower angiogenesis; the distribution and the internal standard are more important.

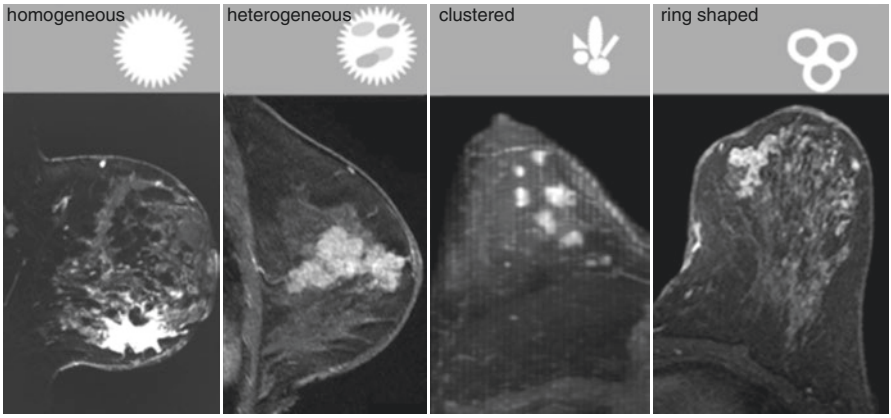


Fig. 18 Internal enhancement pattern

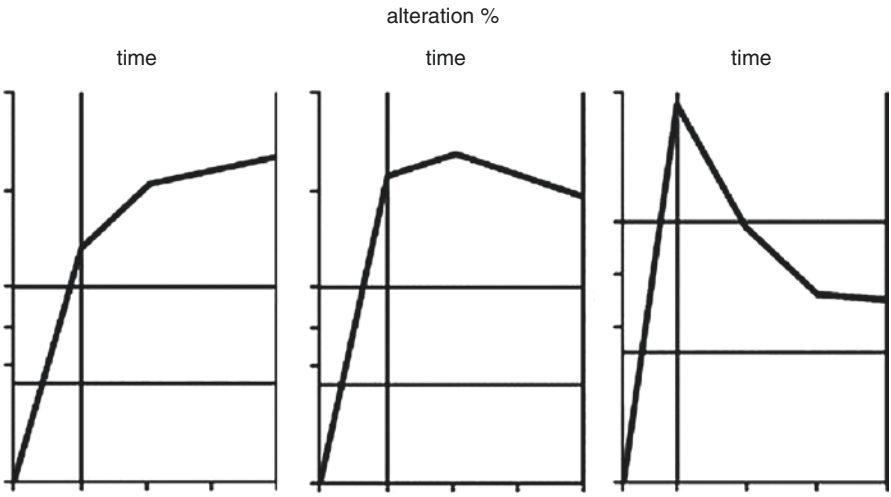


Fig. 19 Pattern of persistent curve (type I), plateau (type II), and washout (type III)

- Kinetic analysis: evaluation of the time versus signal intensity enhancement curve. Divided into:
  - Interpretation of the early phase, the first passage of the contrast medium. Slow, increase in signal intensity less than 50% related to the initial phase; medium, 50% and 100%; and fast, greater than 100%
  - Curve pattern: Persistent curve or type 1, plateau or type 2, and washout or type 3 (Fig. 19)
- Associated findings can be described, such as lymphadenopathy, cutaneous thickening, cutaneous and nipple retraction, and involvement of the thoracic wall.

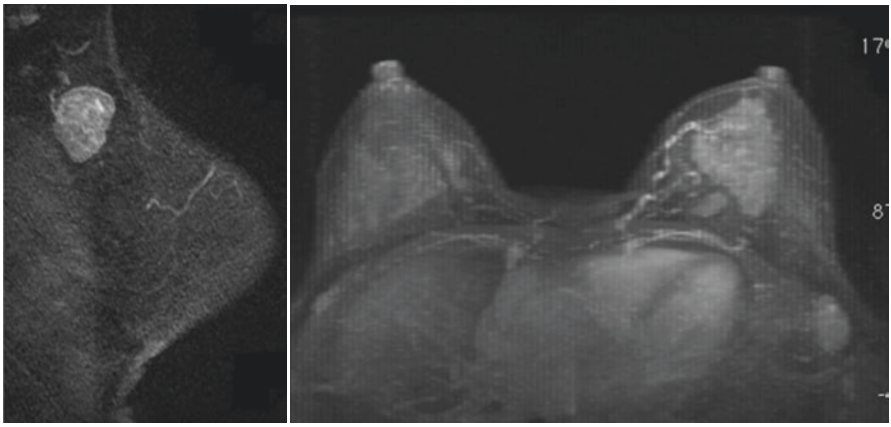


Fig. 20 Signs of infection of the right breast implant

Lymphadenopathy: lymph nodes with round and irregular shape; heterogeneous signal and enhancement, with no fat content. The size of the lymph node and the presence of bilateral or unilaterality should be analyzed within the clinical context of each patient. Therefore, the suspicion will be related to clinical findings. The presence of infectious disease and inflammatory implant changes most likely indicates benignity.

Adenopathy that favors benignity: signs of infection of the right breast implant, which shows thickening and enhancement of the fibrous capsule (Fig. 20).

Adenopathy that favors malignancy: infiltrating lobular carcinoma of the left breast (Fig. 21).

Defining Size and Location of Findings

The following location parameters must be included in the report:

- Laterality
- Quadrant: quadrant, retro-areolar, central, axillary extension, including time
- Depth: anterior, middle, and posterior thirds
- Distance to the papilla, chest wall, or skin surface (Fig. 22)

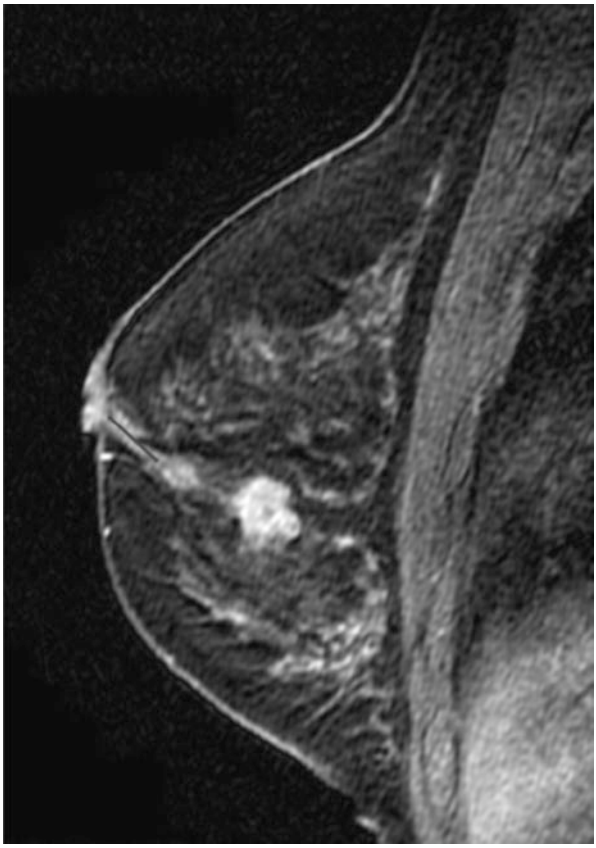


Fig. 21 Infiltrating lobular carcinoma in the left breast, associated with ipsilateral adenopathy

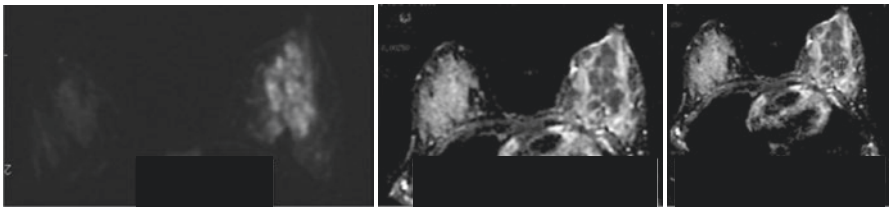


Fig. 22 Retro-areolar nodule distance from the papilla

Diagnostic Impression (Category) and Management Recommendation

This is a summary of findings, including evaluation, incorporating an assessment category into the report. It should preferably be unique for the exam(s) held on the same day.

Description of the categories:

- Category 0: the following are included: technically unsatisfactory images with artifacts related to voluntary movement. They are rarely used, since images considered technically unsatisfactory are usually repeated. Other suggestions would be suspected nodule in MRI, but with possibility of being lymph node, so directed US would avoid biopsy; a finding that probably represents fat necrosis, but which the radiologist would like to correlate with unavailable mammography.
- Category 1: negative examination for malignancy, with no findings. Recommendation: periodic screening.
- Category 2: findings that are worth mentioning, typically benign, such as intramammary lymph node, nodule without enhancement, postsurgical and actinic change, steatonecrosis, postsurgical collection, implant, myocutaneous flap, hamartoma, and cyst. Recommendation: periodic screening.
- Category 3: probably benign lesions with a high probability of being benign, greater than or equal to 98%. No change is expected during the observation period. Included in this category are nodule with benign morphology and kinetics, without suspicion on mammography and ultrasonography; new focus, with benign kinetics and no additional suspected adjacent lesion; patient of childbearing age who has been examined in the suboptimal phase of the cycle; and postmenopausal hormone therapy with probable hormonal enhancement. Recommendation: follow-up of 2–3 years: 6 months, 6 months, 1 year, and optionally one more year to establish stability. To facilitate follow-up, directed ultrasonography may be suggested. For postmenopausal hormone suspension therapy, consider 1-month follow-up.
- Category 4: suspicious findings, with lesions that do not have characteristics typical of the mammary neoplasia, but are likely to be malignant and, therefore, should be investigated with histological correlation. As it includes lesions with variable positive predictive values, the expected histopathological result may be positive or negative. Included in this category are nodule with type III curve, nodule of suspected morphology, and non-mass suspect enhancement. Recommendation: histological analysis, if clinically appropriate. To suggest the best method to guide the biopsy and the modality and follow-up in 6 months with MRI after biopsy to find with benign pathology.
- Category 5: highly suspect findings: lesions that are highly likely to be cancer. The biopsy result is expected to be positive. Included in this category are spiculated nodule, with rim enhancement, irregular nodule with type III curve, and associated finding. Recommendation: histological analysis, if clinically appropriate. It can be recommended as the first method of biopsy directed ultrasonography.

- Category 6: evidence of malignancy: this category includes a patient with a diagnosis of breast cancer, evaluating the extent of the local tumor and contralateral breast or evaluating the response to neoadjuvant chemotherapy.

Novelties and the Future of Resonance

- Multiparametric study (mpMRI): it represents any form of functional image added to the T1- and T2-weighted images and contrast dynamic study. It includes diffusion, spectroscopy, and permeability study. There is evidence that mpMRI can provide additional specificity and information on the biological characteristics of cancer, such as permeability, abnormal cellularity and chemical composition, as well as a qualitative and quantitative image biomarker (Fig. 23).
- Diffusion: it measures the movement of free water, indirectly related to tumor cellularity. The method has 89% sensitivity and specificity of 77%, with potential biopsy reduction of 30% and replace the use of venous contrast medium in the future.
- Spectroscopy: it represents an indirect tissue biopsy, with information on the presence and concentration of the tissue metabolites in a given area. In the

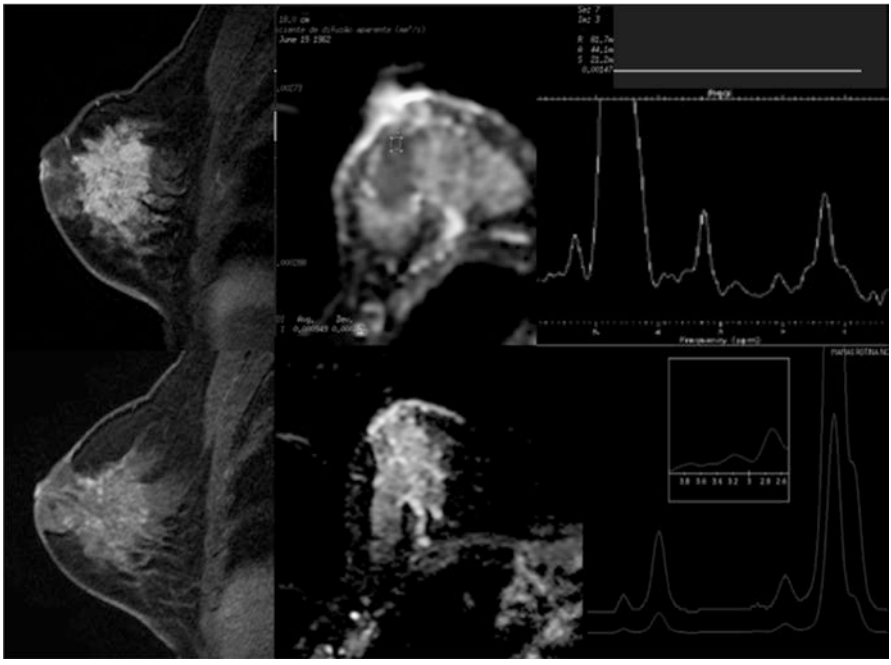


Fig. 23 High-grade intraductal carcinoma in the left breast, with higher cellularity, hyperintense in the diffusion, hypointense in the ADC map, and with ADC value <1

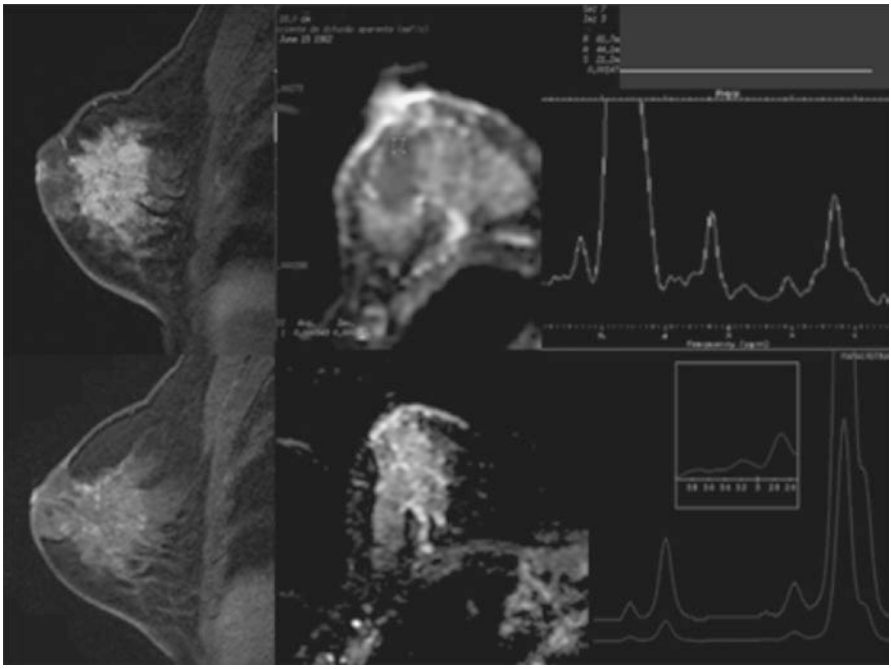


Fig. 24 Pre- and postneoadjuvance infiltrating carcinoma spectroscopy. Note increased choline peak (3.2 ppm) prior to treatment (upper spectral curve) and absence in control (lower curve)

neoplasia, there is an increase in choline concentration due to the greater cell proliferation. The method has specificity around 88% and sensitivity of 73%, and it can be used in the early evaluation of the response to neoadjuvance (Fig. 24).

- Ultrafast or abbreviated protocol: it allows transforming MRI into an economically viable method for screening, as it reduces exam time for up to 5 minutes, and the interpretation time of the radiologist. It maintains adequate sensitivity and negative predictive value.

Recommended Literature

1. ACR BI-RADS Atlas. Breast imaging reporting and data system. 2013.
2. Brandão Alice. Ressonância Magnética da Mama. Editora Revinter. 2010.
3. Pinker A, Helbich TH, Morris EA. The potential of multiparametric MRI of the breast. Published by the British Institute of Radiology. 31 Oct 2016.
4. Sardanelli F, Boetes C, Borisch B, et al. Magnetic resonance imaging of the breast: Recommendations from the EUSOMA working group. Eur J Cancer. 2010;46:1296–316.
5. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, Morris E, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57(3):185.

Nuclear Medicine: Sentinel Lymph Node Detection and Radioguided Occult Lesion Localization (ROLL)

Positron Emission Tomography: PET/CT and PET/MR

Jairo Wagner, Guilherme de Carvalho Campos Neto, Júlio Cesar Silveira Oliveira, and Ricardo Cavalcante Quartim Fonseca

Lymphoscintigraphy and Intraoperative Detection of Sentinel Lymph Node in Breast Cancer

Introduction and Definition

Sentinel lymph node biopsy (SLB) is currently the standard procedure for staging and management of axillary lymph nodes in early-stage breast cancer, with a 95% accuracy and a false-positive rate of 5–15%. Sentinel lymph node (SL) is the first lymph node in the lymphatic drainage chain of the tumor. The rationale for axillary SLB is that due to sequential involvement of lymph nodes by tumor cells, the histology of the first draining lymph node would be representative of all other axillary lymph nodes.

Technique

Lymphoscintigraphy for the characterization of SL is performed at the nuclear medicine department. Thirty to 60 minutes after a small volume injection of a radioactive colloid (e.g., 0.2–0.4 mL of 99mTc-phytate) by intradermal, subareolar, or tumor quadrant projection, scintigraphic images in a planar, tomographic (SPECT), or hybrid (SPECT/CT) gamma camera are obtained. Injected activities range from 0.1 to 3 millicuries (mCi) or 3.7 to 111 megabecquerels (MBq). Time elapsed between radiocolloid injection and intraoperative detection varies from 2 to 24 h.

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Indications and Contraindications

There is consistent evidence suggesting that sentinel lymph node biopsy should replace axillary lymphadenectomy in patients with early-stage breast cancer (T1 or T2 with clinically negative axilla). Several publications have confirmed the effectiveness of the technique and its accuracy for the staging of these cases (the sentinel lymph node is identified and predicts the status of the other lymph nodes in more than 95% of the patients in the main series studied). Prospective studies have also shown that the survival rate of patients undergoing sentinel lymph node biopsy is equivalent to that of patients undergoing lymphadenectomy, but with a significant reduction in complications (especially lymphedema, sensory and motor abnormalities).

For locally advanced (T3 or T4) inflammatory carcinoma, ductal carcinoma in situ (with proposed conservative surgery), previous axillary surgery, and in cases with clinical suspicion of lymph node involvement, the study of the sentinel lymph node is usually contraindicated.

Neoadjuvant chemotherapy, multicentric disease, and pregnancy are not usually contraindications to the procedure.

Radioguided Occult Lesion Localization (ROLL)

For the ROLL (*radioguided occult lesion localization*) technique, a radiopharmaceutical (more often technetium-labeled albumin macroaggregate) is injected intratumorally or adjacent to the lesion under the guidance of some imaging method (ultrasonography, mammography, or magnetic resonance imaging). Like the sentinel lymph node detection, a portable gamma probe detector is used for intraoperative localization of the lesion. Several studies have demonstrated the effectiveness of the technique, with advantages compared to the use of metallic wire localization (Fig. 1).

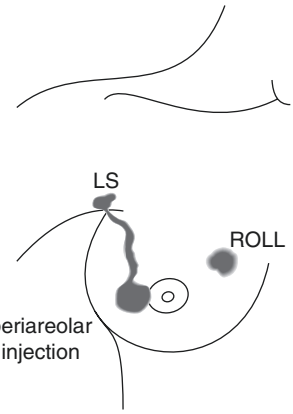

Fig. 1 Example of combined ROLL technique and sentinel lymph node detection. ROLL lesion in the right breast superomedial quadrant and periareolar colloid injection with drainage for the right axillary lymph node

PET/CT and PET/MR

Introduction

PET (positron emission tomography) is a nuclear medicine technique that uses dedicated equipment (PET scanners) and positron-emitting radioisotopes, which labeled to different molecules produce metabolic or functional images of the various organs and systems of the human body. The most widely used PET radiopharmaceutical is ^{18}F-fluorodeoxyglucose (FDG), an analogous molecule of glucose labeled with the positron-emitting radioisotope, ^{18}Fluor, which is avidly captured by cells from a large number of viable malignancies and their metastases.

Malignant neoplasms of the breast with a low replication rate and well differentiated as lobular, tubular, and ductal carcinomas in situ are less avid for FDG when compared to invasive ductal carcinoma. The uptake capacity of this radiopharmaceutical is also related to the tumor grade and the percentage of Ki67. Although there is a strong correlation between the triple-negative tumors, which present unfavorable clinical evolution and high uptake of FDG, when isolated analyzed, the correlation between the expression of estrogen and progesterone receptors and the degree of FDG uptake is still somewhat controversial. In general, luminal B, Her 2-positive, and triple-negative tumors are highly avid for FDG, whereas luminal A tumors are not very avid.

Equipment

PET devices were coupled for more than a decade to multislice tomographs, giving rise to the PET/CT equipment. These allow for the fusion of the metabolic images of PET with the anatomical images of the computed tomography. Recently, with PET devices coupled to magnetic resonance, PET/MR devices have been developed. This technology is already available in Brazil, and it has the advantage of simultaneous acquisition of metabolic images with anatomical and functional magnetic resonance data. They also enable the reduction of the radiation doses to the patient.

Patient preparation for PET/CT or PET/MR studies with FDG must include fasting for 4 hours and restriction of carbohydrate intake 12 hours prior to the examination. The images are obtained about 60–90 minutes after the I.V. administration of 18F-fluorodeoxyglucose.

Indications

Diagnosis (Primary Lesion Detection)

^{18}F-FDG PET/CT and PET/MR scans are not indicated for screening breast cancer. The reasons for this are low sensitivity for lesions smaller than 1.0 cm and low FDG avidity as in lobular carcinoma, ductal carcinoma in situ, and low-grade tumors in

general. On the other hand, the positive predictive value may reach up to 96.6%. Though being less frequent, increased uptake of FDG in benign lesions may occur, such as in areas of fatty necrosis, granulomas, infection, fibroadenomas, intraductal papillomas, and fibrocystic lesions, among others. Correlation with clinical data, breast ultrasound, and mammography may aid in differential diagnosis. In this scenario, PET/MR may have the advantage of the simultaneous acquisition of the metabolic images with the magnetic resonance images.

Positron-emitting isotope detector equipment dedicated to breast imaging (PEM – positron emission mammography) was recently developed with promising results, mainly for the evaluation of inconclusive lesions by traditional screening methods and even in the identification of additional lesions in patients with established diagnosis.

Staging

The use of FDG-PET is not indicated for axillary lymph node evaluation. The negative result does not exclude sentinel lymph node biopsy, since the lesion size resolution of currently available PET/CT systems is about 5–6 mm. On the other hand, the method has a high positive predictive value in the evaluation of axillary lymph nodes. Axillary positivity correlates with worse prognosis and reduction of disease-free survival. Some authors advocate axillary lymphadenectomy when an FDG-PET study is positive; however, the radioguided biopsy of the lymph node should always be encouraged. In addition, FDG studies allow the detection of supra- and infraclavicular metastases and the internal mammary nodes with greater sensitivity than traditional methods.

Due to the low incidence of metastases in early-stage breast cancer, some guidelines do not recommend performing FDG-PET for staging; however, basing the indication on TNM staging alone is a point of great controversy. A recent study of 134 patients under 40 years of age with I to III stage performed FDG-PET for staging. Based on the PET/CT findings, staging was changed to III or IV in 21% of the patients. Metastases (stage IV) were detected in 5% of patients with stage I and IIA, 17% in stage IIB, 31% in stage IIIA, and 50% in stages IIIB and IIIC individually. And, although there is no recommendation for the performance of FDG-PET in stages up to IIIA, its use can be encouraged, especially in patients of greater risk.

Restaging

FDG-PET is the modality of choice in the suspicion of breast cancer recurrence, whether by symptoms, nonspecific findings in other imaging modalities, or increase in tumoral markers Ca15-3 and CEA. Accuracy is superior to the use of chest and abdominal CT associated with bone scintigraphy, added to ultrasound or mammography for local recurrences. The sensitivity of FDG-PET ranges from 85% to 97% and the specificity from 52% to 100%. It is highly relevant that the method leads to

change in the therapeutic strategy in a large number of cases, by detecting earlier the recurrence site in symptomatic or asymptomatic patients who have elevated tumor markers.

Treatment Response Evaluation

Changes in tumor metabolic activity usually precede changes in size or morphology. Therefore, the functional image of FDG-PET has great utility in the evaluation of treatment response, especially in metastatic tumors. The method also helps to identify mixed responses when coexisting responsive and nonresponsive tumor clones can be found in the same patient. Although there is no consensus for the use of PET-CT to evaluate neoadjuvant chemotherapy, several studies have demonstrated its usefulness, especially in the subgroup of triple-negative tumors, by using the method after two treatment cycles to efficiently discriminate patients with an unlikely complete pathological response and greater risk of early recurrence from those with good response.

Another important point is the prognostic factor of the use of FDG-PET in metastatic disease: there is evidence that overall survival was significantly higher in patients with negative FDG-PET after chemotherapy compared to the group in which the lesions remained positive on FDG-PET (24 months vs 10 months, $P < 0.001$).

The evaluation of treatment response of hepatic and bone lesions by FDG-PET should also be highlighted. Bone lesions with good response usually become more sclerotic and significantly reduce FDG uptake.

Follow-Up

PET-CT is not routinely indicated as a follow-up strategy in non-metastatic patients treated satisfactorily, without symptoms and with nonelevation of tumor markers or suspicious findings in conventional images, due to the absence of established cost-effectiveness and exposure to radiation. This reality may change in the future due to the use of PET-MR, since radiation exposure can be reduced by up to 65% when compared to PET-CT.

Recommended Literature

1. Christopher C, Riedl CC, Slobod E, Jochelson M, Morrow M, et al. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med. 2014;55:1578–83. *Retrospective analysis showing PET-CT impact in asymptomatic patients with breast tumors*
2. Duarte C, Bastidas F, De Los Reyes A, Martínez MC, Hurtado G, Gómez MC, et al. Randomized controlled clinical trial comparing radioguided occult lesion localization with

wire-guided lesion localization to assess their efficacy and accuracy in the localization of non-palpable breast lesions. Surg (United States). 2016;159(4):1140–5. *The study demonstrates similar effectiveness between the ROLL technique and the wire-guided lesion localization of non-palpable breast lesions*

3. Groheux D, Giacchetti S, Rubello D, et al. The evolving role of PET/CT in breast cancer. Nucl Med Commun. 2010;31(4):271–3. *General review on the use of PET-CT in breast tumors*
4. Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2017;35(5):561–4. *Recommendations of the American Society of Clinical Oncology for conducting sentinel lymph node biopsy*
5. Tabouret-Viaud C, Botsikas D, Delattre B, et al. PET/MR in breast cancer. Semin Nucl Med. 2015;45:304–21. *Review on the current use of PET-MR in breast tumors and perspectives*

Other Imaging Methods

Fabiola Procaci Kestelman and Clara Fernanda Aguiar Gomes

Introduction

Imaging techniques have significantly developed in recent years. The rather relevant morphological image has evolved into a physiological and functional image capable of providing valuable additional information for a better understanding of disease processes.

Professionals should be aware of these new technologies and their indications and limitations in order to achieve a higher performance in the diagnosis and treatment of breast diseases.

Digital Mammography and Related Techniques

Digital Mammography (DM)

DM represents an evolution of conventional mammography. In this mode, electronic detectors capture and facilitate the display of the X-ray signals on a computer or film to be laser-printed. There are two pieces of technology available: indirect or computerized (CR) and direct, truly digital (DR). In the CR method, an electronic chassis is inserted into the tray in the conventional mammography equipment. This chassis is read in the CR reader, and after the chassis is read, the mammography image is visualized on the screen of the computer or workstation. In the DR method, the image is sent directly from the mammography to the

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workstation. Studies show that this evolution of mammography has shown benefit in dense breasts and young patients.

In the year 2000, the Food and Drug Administration (FDA) approved the use of digital mammography for diagnostic use, with subsequent improvements in image resolution, digital manipulation, and storage. New advances in method performance are expected due to the use of tomosynthesis, which is the evolution of digital mammography.

Digital Tomosynthesis

Mammography presents inherent limitations to the principle of obtaining a two-dimensional (2D) image of the compressed three-dimensional glandular parenchyma, causing overlap of glandular structures. This overlap may make it difficult to visualize a lesion (false negative) or cause a lesion to be identified as suspect, which is actually overlapping glandular parenchyma (false positive).

The tomosynthesis is a mammography device that uses a rotating RX tube, with the angulation ranging from 15° to 45°, and it performs different projections of a static breast. Then the images are reconstructed with a cutoff thickness of 1 mm and can be viewed on the workstation through a specialized software. The radiation dose of a two-incident tomosynthesis exam associated with 2D mammography is within the standards accepted by the Mammography Quality Standards Act (MQSA), although it is slightly higher than that generated by current mammography tungsten tubes.

Most of the recent studies on tomosynthesis show that it improves mammography performance and reduces recall rate. In addition, cancer detection is prevalent for invasive cancer rather than carcinoma in situ, which is important in light of the current concerns of potential cases of overdiagnosis and overtreatment.

Although the FDA has already approved tomosynthesis for clinical use, there are still no clearly established protocols for its use, such as whether it should be used in all patients, whether both projections should be made on each breast, or whether it is possible to use tomosynthesis without 2D mammography. Another issue to be evaluated is the current cost of this exam, which still makes it difficult for screening use in the general population.

Mammography with Contrast

By combining digital mammography with the functional attributes of contrast enhancement, digital mammography offers another potential application. The advantage of digital mammography with contrast (DMC) would be to obtain functional information from the uptake attributed to neovascularization of the malignant lesion associated with information of high anatomical quality, a concept that magnetic resonance imaging (MRI) of the breast has used for years. The potential advantages postulated in

DMC would be greater ease of installation of mammography in the medical units, higher resolution, better patient acceptance (especially in cases of claustrophobia in relation to MRI), and lower potential cost. The disadvantages of such a technique as a screening method are the need for intravenous administration of contrast, adverse consequences to it, higher costs, and increase in the duration of exam.

The potential applications of contrast mammography could be similar to those of MRI, including high-risk patient screening, staging, diagnosis, and treatment response monitoring.

There are two main methods described for digital mammography with contrast: performing serial examinations over time and dual-energy imaging. Both methods use iodinated contrast and are modified units of digital mammography. Serial DMC can be obtained in a single projection, while dual-energy methods allow images of both breasts with unique contrast administration. The first research works demonstrated their technical and clinical feasibility. However, the actual number of patients studied so far is very limited, so the potential future clinical use is uncertain.

Ultrasonography

Elastography

Ultrasonography in breast imaging has always been a low-cost, non-radiation tool that allows for easy access. During the last few years, the use of ultrasonography for screening has increased, particularly in women with dense breasts. Dense breast tissue can obscure small lesions on mammography, and high density may increase the risk of cancer. Recently, some US states have required that women be informed about the density of the breast parenchyma on their mammography to allow the choice of ultrasound screening. Although the use of ultrasonography in breast screening has not yet been well established, some features have been used to improve the characterization of lesions when they are found in ultrasonography.

Elastography is a technique capable of estimating the elasticity of breast tissue by means of measuring tissue tension or tissue displacement during excitation induced by the transducer. The principle is that the applied tension will be lower in more rigid fabrics. Generally, benign lesions tend to be stiffer than normal breast tissue but more susceptible to deforming than malignant lesions.

Currently, there are two types of elastography: compression elastography and share wave elastography. The former evaluates the deformation of tissues as a result of the effect of pressuring the transducer on the skin. This technique is qualitative or semiquantitative, and its results are reflected in the elastogram based on a color scale, which varies depending on the type of equipment. The latter is the most recently developed technique. Share wave elastography is characterized by the use of ultrasound pulses transmitted at high speed without extrinsic compression on the skin, that is, it is not a dependent operator. The tissues generate waves in response to these impulses that allow quantitative evaluation of the lesion studied.

Whatever elastography system is available, this technique should be understood as an added value for B-mode ultrasonography. This may not be relevant for cases of lesions with BI-RADS® 2, 4 (B and C), or 5, that is, lesions with high probability of benignity or malignancy. However, it should be considered in case of more lesions with low suspicion, such as BI-RADS® 3 (probably benign) or BI-RADS® 4A (low suspicion of malignancy). Thus, elastography is a possible complement to B-mode ultrasonography in the study of lesions with indeterminate categories.

Modalities of Molecular Breast Imaging

The modalities of nuclear medicine for molecular breast imaging have evolved over the past decade. These modalities include positron emission mammography (PEM) using 18F-fluorodeoxyglucose (FDG) radionuclide, a high-resolution dedicated positron emission tomography (PET), with the choice of positioning the breast in a manner that is similar to that of mammography, and scintimammography (dual-head gamma or breast-specific gamma imaging – BSGI) using 99 m (Tc99m) technetium.

Traditional molecular imaging involves the exposure of ionizing radiation to the entire body, making these technologies unsuitable for use with the goal of population tracking. The main problem is the risk of cancer induced by radiation in these modalities. Currently, there is no recommendation for use of molecular imaging in screening for breast cancer.

Positron Emission Mammography (PEM)

Due to the limited resolution of PET equipment, small breast tumors are not visible through this technique. The development of a dedicated device for breast PET, the so-called PEM (positron emission mammography), was designed in an attempt to make it easier for the detection of small lesions.

Although PEM is still in early clinical development, a recent multicenter trial has suggested that PEM may assist in the detection and characterization of invasive carcinoma and carcinoma in situ. In this study, Berg et al. evaluated 94 women with known breast cancer or suspected breast lesions and performed PEM with intravenous 18F-fluorodeoxyglucose (FDG) injection. PEM demonstrated sensitivity for detection of cancer at 90%, specificity at 86%, positive predictive value at 88%, negative predictive value at 88%, and accuracy at 88%.

With these results, it is believed that the technique could be used in the surgical planning, in the monitoring of the response to neoadjuvant treatment, as well as in the investigation of cancer recurrence. However, there are some disadvantages related to the cost and technical difficulty due to the manipulation of radiopharmaceuticals. Although PEM devices may, in part, overcome the limitations of 18F-

FDG PET of the whole body for detecting breast cancer, the application of PEM compared to current breast imaging methods does not present validation for clinical use.

Scintimammography

Two other molecular imaging techniques are dedicated dual-head gamma imaging and high-resolution breast-specific gamma imaging (BSGI). They have been investigated for their supporting role in mammography screening. The dedicated dual-head gamma imaging uses a gamma camera system with a cadmium-zinc-telluride (CZT) semiconductor detector instead of a conventional sodium iodide detector. Both use the radiopharmaceutical Tc99m sestamibi. A dual-head gamma prototype showed high sensitivity for malignant lesions smaller than 2 cm, with a sensitivity of 86% for lesions smaller than 1 cm.

An experiment with BSGI in 50 patients showed improvement in the detection of non-palpable lesions and lesions smaller than 1 cm, with some studies showing high sensitivity (96.4%), with moderate specificity (59.5%).

In order to better evaluate the true practical usefulness of these methods, it is necessary that a technical improvement of the cameras dedicated to the breast be achieved, aiming at reducing the dose of radiation, and also that new studies be carried out for determining the clinical impact of these methods.

Other Methods

Electrical Impedance Tomography (EIT)

This is a noninvasive, non-radiation diagnostic technique that uses an electrode on the patient's arm responsible for transmitting a small amount of electrical current that travels through the breast. The basic principle of this technique is that breast cancer cells conduct better electricity (low impedance) than normal breast cells. However, Prasad et al. have not demonstrated any characteristic impedance that differentiates malignant lesions from benign ones.

Thermography

This exam uses infrared camera to detect "hot" areas on the surface of the skin generating heat maps of each breast. The principle of this modality is based on the fact that the skin on the area of breast cancer can be warmer since the tumors

contain fast growth cells and increase the flow of blood, which can generate heat. There is no clinical evidence to justify the use of this technique.

Vibro-Acoustography (VA)

This is an image mode that measures the vibrational-acoustic response of an object to a vibration force. VA uses the propagation force of ultrasound waves. Vibrations produce a sound that can be detected by a hydrophone (a microphone designed to receive sound through water or soft tissues) and produces an image that represents the acoustic characteristics of the object. Preliminary work with an experimental VA system has shown the feasibility of this approach in various tissues. However, further studies are needed on the clinical value of VA in breast imaging.

Conclusion

Imaging methods have been greatly influenced by technological advancement. Exams such as digital mammography and tomosynthesis have led to increased screening performance of breast cancer. However, new technologies should be observed with caution so that increased screening sensitivity is not associated with large numbers of false negatives and significantly increased cost of screening.

Recommended Literature

1. Athanasiou A, Tardivon A, Tanter M, et al. Breast lesions: quantitative elastography with supersonic shear imaging - preliminary results. Radiology. 2010;256(1):297–303. *Forty-eight were analyzed using conventional ultrasonography and shear wave elastography in lesions that had available histopathology. This quantitative technique provided quantitative measures of elasticity, adding complementary information that could potentially help in the characterization of breast lesion*
2. Berg WA, Weinberg IN, Narayanan D, Lobrano ME, Ross E, Amodei L, et al. High-resolution fluorodeoxyglucose positron emission tomography with compression ("positron emission mammography") is highly accurate in depicting primary breast cancer. Breast J. 2006;12(4):309–23. *In this study, we evaluated 94 women with known breast cancer or suspected breast lesions and performed PEM with intravenous injection of 18F-fluorodeoxyglucose (FDG). PEM demonstrated sensitivity for detection of cancer of 90%, specificity of 86%, positive predictive value of 88%, negative predictive value of 88% and accuracy of 88%*
3. Brem RF, Floerke AC, Rapelyea JA, Teal C, Kelly T, Mathur V. Breast-specific gamma imaging as an adjunct imaging modality for the diagnosis of breast cancer. Radiology. 2008;247(3):651–7. *This study retrospectively evaluated the sensitivity and specificity of BSGI scintimammography for the detection of breast cancer; 146 patients were evaluated, 167 lesions were submitted to biopsy, of which 83 were malignant. BSIG demonstrated high sensitivity (96.4%) and moderate specificity (59.5%) in detecting breast cancers*

4. Dromain C, Thibault F, Diekmann F, Fallenberg EM, Jong RA, Koomen M, et al. Dual-energy contrast-enhanced digital mammography: initial clinical results of a multireader, multicase study. Breast Cancer Res. 2012;14(3):R94. *The objective of this study was to compare the accuracy of the diagnosis of dual-energy digital mammography with contrast when associated with mammography and ultrasonography with the precision of the diagnosis of mammography and ultrasonography alone. It was concluded that dual-energy digital mammography with contrast as a complement for mammography and ultrasonography improves diagnostic accuracy in relation to mammography and ultrasonography alone*
5. Wallis M, Moa E, Zanca F, et al. Two-view and single-view tomosynthesis versus full-field digital mammography: high-resolution X-ray imaging observer study. Radiology. 2012;262(3):788–96. *This study with 130 patients demonstrated a higher diagnostic accuracy of 2-position tomosynthesis than 2D digital mammography – mean area under the ROC curve (AUC = 0.772 for 2D, AUC = 0.851 for tomosynthesis)*

Mammographic Screening: General Population

Luciano Fernandes Chala, Paula de Camargo Moraes, and Carlos Shimizu

Definition

Breast cancer screening in the average-risk population is based on periodic mammograms in asymptomatic women aiming the early detection of the disease. Mammographic screening, coupled with therapeutic advances, is associated with the reduction in breast cancer mortality observed in many countries. The detection of small asymptomatic tumors also offers a greater number of therapeutic choices; it increases the chance of conservative treatment and reduces the need for chemotherapy.

History

The dissemination of the population-based screening mammography was based on the results of the following prospective randomized and controlled studies: Health Insurance Plan of New York (HIP), Canadian National Breast Cancer Screening (CNBSS) 1 and 2, Age Trial (UK), Edinburgh Trial (Scotland), and the four Swedish studies (Stockholm, Malmoe I and II, Gothenburg and Swedish Two-County Trial – Ostergotland and Kopparberg).

Except for the two studies conducted in Canada (CNBSS 1 and 2), the others showed a reduction in the relative risk of dying from breast cancer in women aged 40–74 who underwent mammographic screening. The study that showed the greatest reduction in the relative risk of death from breast cancer was the Swedish

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Two-County Trial; after 29 years, the reduction in mortality in the mammographic screening group was 31%. Several meta-analyses with data from these studies were performed. In the meta-analysis performed by the Independent UK Panel, the reduction in breast cancer mortality was estimated at 20%.

Recent observational studies have confirmed the reduction in breast cancer mortality associated with mammographic screening observed in randomized trials. The Euroscreen Working Group conducted a systematic review of observational studies based on the ongoing screening programs in Europe and the United Kingdom and reported that mortality reduction ranged from 25% to 48%.

Relevance of Prospective Randomized and Controlled Randomized Studies

Prospective randomized and controlled studies are the gold standard to demonstrate the impact of mammographic screening on breast cancer mortality. In these studies, women are randomly divided into two groups, one invited to screen and another not-invited (control group) to screen, and both groups are followed for several years. Randomization is an extremely important step in ensuring that the groups, intervention and control, are similar, without bias.

However, this type of study is not free from problems and may, for example, underestimate the impact of mammographic screening. Because of the randomization rule, a participant invited to the mammographic screening group will always belong to it, regardless of whether or not they really attend the screening. If this patient (screening group) chooses not to perform the mammogram and has a death caused by breast cancer, it will be counted in the screening group. If a participant in the control non-screened group decides to perform a mammogram on their own and has a cancer detected at an early stage and life saved by early detection, it continues to belong to the non-screened group. The nonattendance rate for post-invitation mammographic screening in prospective, randomized, and controlled trials ranged from 10 to 39% and that of the non-screened group (participants who chose to undergo mammography on their own) ranged from 13% to 25%.

Current Indications and Controversy

There is no doubt about the benefit in reducing mortality related to mammographic screening, but there is intense controversy regarding the age of onset and end of screening and its frequency. Studies are uniform in showing that the likelihood of mammographic screening to prevent a death from breast cancer increases with age. On the other hand, the adverse effects of mammographic screening remain stable or decrease with age. Thus, the balance between benefit and adverse effects improves with aging.

When Should a Patient Start Mammographic Screening?

There is much debate about the age to start mammographic screening, resulting in different recommendations among medical associations, with starting age ranging from 40, 45, or 50 years (Table 1). The Brazilian College of Radiology, the Brazilian Society of Mastology, and Brazilian Federation of Gynecology and Obstetrics Associations recommend annual mammographic screening beginning at 40.

An important point of the discussion is the balance between benefits and adverse effects of mammographic screening in the 40–49 age group. Until 2009, there was a consensus in recommending the annual mammographic screening to begin at the age of 40, based on the reduction in mortality observed in this age group. In 2009, the US Preventive Services Task Force (USPSTF) introduced the concept of balance between adverse effects and mortality benefit on the decision of when to start the breast cancer screening. As a result, they suggested that the decision to start mammographic screening between the ages of 40 and 49 should be individualized, and women who think that the benefits outweigh the potential adverse effects should consider to start screening before the age 50. It should be noted that the USPSTF does not recommend against screening between the ages of 40 and 49.

However, the introduction of the balance between adverse effects and benefits from mammographic screening on breast cancer mortality introduced by the USPSTF resulted in the loss of consensus in the 40–49-year-old screening group

Table 1 Mammographic screening and recommendations

Mammographic screening – recommendations (2017)			
Entity	Age to start	Interval	Age to stop
BCR; BSM; BRAFESGO	40 years	Annual	As long as a woman is in good health and has a life expectancy of at least 7 years
USPSTF	50 years 40–49 years – the decision must be individualized	Biannual	74 years old. Current evidence is insufficient to assess any benefit or adverse effect in women aged 75 years or older
ACR; SBI	40 years	Annual	As long as a woman is in good health and has a life expectancy of 5–7 years
ACOG	40 years	Annual	75 years (above that the decision to keep screening must be shared decision)
ACS; ASCO	45 years (it may begin at age 40)	Up until 54 years – annual >55 years – biannual or annual	As long as a woman is in good health and has a life expectancy of at least 10 years

Note: *BCR* Brazilian College of Radiology, *BSM* Brazilian Society of Mastology, *BRAFESGO* Brazilian Federation of Gynecology and Obstetrics Associations, *USPSTF* US Preventive Services Task Force, *ACR* American College of Radiology, *SBI* Society of Breast Imaging, *ACOG* American College of Obstetricians and Gynecologists, *ACS* American Cancer Society, *ASCO* American Society of Clinical Oncology

(Table 1). Currently, the screening starting age is a matter of intense discussion by medical entities based on opinions arising from the different evaluation of the same benefits and adverse effects.

The Brazilian College of Radiology, the Brazilian Society of Mastology, and the Brazilian Federation of Gynecology and Obstetrics Associations keep the recommendation to start mammographic screening in the general population at age 40 based on the demonstration that it is associated with the reduction in mortality due to the occurrence of breast cancer in women in the age group from 40 to 49 years. The meta-analysis of the prospective randomized and controlled studies conducted by the USPSTF showed an 8% reduction in the relative risk of death by cancer in women aged 39–49 years submitted to mammographic screening. However, more recent studies have shown a greater reduction in the relative risk of death from breast cancer associated with mammographic screening between the ages of 40 and 49 years. In an observational study, conducted in Sweden and published in 2011, Hellquist et al. observed a 29% reduction in the relative risk of death from breast cancer in women aged 40–49 years who underwent mammographic screening. In a prospective randomized and controlled study conducted in the United Kingdom to evaluate mammographic screening starting at age 40 and published in 2015, Moss et al. observed a 25% reduction in the relative risk of death from breast cancer in the first 10 years after diagnosis in the group that started the mammographic screening at 40 years. Other observational studies specific to this age group showed a reduction of up to 50% in the relative risk of death from breast cancer.

No medical organization recommends screening mammograms in the general population in women younger than 40 years of age.

When Should Mammographic Screening Be Discontinued?

For women aged 70 years and over, especially above 75 years, the available data are scarce and insufficient for definitive conclusions about the benefits and adverse effects of mammographic screening. Breast cancer is a leading cause of death in women over 75 years, but some facts suggest that the benefit of mammographic screening may be lower in this age group due to shorter life expectancy, higher frequency of tumors with good prognosis, higher risk of dying of other diseases, and greater chance of overdiagnosis.

Recommendations regarding mammographic screening in this age group are not homogeneous. Most major medical societies do not establish any specific age at which mammographic screening should be discontinued, suggesting that the decision on their continuity should be made individually considering the overall health and life expectancy of the patient. The Brazilian College of Radiology, the Brazilian Society of Mastology, and the Brazilian Federation of Gynecology and Obstetrics Associations recommend maintaining the mammographic screening while the woman is in good health and has a life expectancy of at least 7 years (Table 1).

What Should Be the Interval Between Mammograms?

There are no studies directly comparing the effect on breast cancer mortality according to different screening intervals. No prospective randomized and controlled study was designed to compare different intervals, and the frequency of screening varied greatly between them (12–33 months). Thus, the relationship between screening interval and breast cancer mortality reduction has been obtained through indirect evidence, including meta-analyses, mathematical models, and observational studies, and the quality of the scientific evidence is therefore low. In a study that used six different mathematical models developed by the Cancer Intervention and Surveillance Modeling Network (CISNET), biannual interval screening strategies retained 79–81% reduction in mortality obtained with the annual interval depending on the age the screening started.

In summary, annual interval mammographic screening ensures a greater reduction in mortality from breast cancer, especially in young women. Also, it increases the likelihood of detecting rapidly growing cancers. On the other hand, it is associated with a greater number of examinations and adverse effects. Proponents of annual interval screening emphasize its benefits in reducing mortality.

Biannual interval screening seems to be associated with lower reduction in mortality, but its proponents argue that it establishes a better balance with adverse effects. It is no coincidence that the defenders of starting screening at 40 years old are the same as those who advocate annual screening, and those who propose of starting screening at 50 years old are the same as those who advocate screening every 2 years.

Adverse Effects

The main adverse effects of mammographic screening are false positives, overdiagnosis, and risks associated with exposure to ionizing radiation. False positives encompass recalls for additional studies, follow-ups, and biopsies with benign results that increase the cost of screening and generate anxiety. Some studies on the subject have shown that most women consider false positives acceptable when the test is associated with a reduction in the risk of dying of breast cancer. However, false positives, while unavoidable, are an unwanted effect of screening for breast cancer. Thus, it is strongly recommended to appropriately employ established diagnostic criteria to reduce their number, as well as to research safe ways to reduce their impact.

Overdiagnosis refers to the screening detection of an invasive or noninvasive carcinoma, which would not cause death or become symptomatic during the life of the patient. This is considered the main adverse effect of the mammographic screening, as it results in overtreatment. It can occur when the cancer diagnosed is not progressive or has slow onset and the patient dies of other causes. The low quality of scientific

evidence about the magnitude of overdiagnosis makes it impossible to provide accurate information and to establish effective screening strategies to reduce it. Until the methodological standards for estimating overdiagnosis are more clearly defined, the correct estimate of this event will be uncertain. No published study has provided universally accepted quantifications about this event. Up to this day, overdiagnosis is considered more of an epidemiological concept than a knowledge that can be used in clinical practice, since it is not possible to determine at the time of diagnosis which tumor corresponds to an overdiagnosis, and all should be treated according to the current protocols. The cancers most likely to correspond to overdiagnosis include ductal carcinomas in situ, small localized invasive carcinomas, and tumors detected in women with reduced life expectancy due to advanced age or, regardless of age, to be carriers of other serious diseases. The risk of overdiagnosis should not be considered a reason for discontinuing the screening. The solution is not to avoid detection but to work toward methods that separate cancers that threaten from those that do not threaten a woman's life and thus employ more appropriate treatments.

Finally, exposure to ionizing radiation increases the risk of breast cancer, but at doses much greater than the ones used in mammography. There are no direct demonstrations that periodic mammograms induce the onset of breast cancer. However, studies with mathematical models indicate that this could occasionally happen, although these same studies indicate that the benefit of mammographic screening for mortality is much higher than this theoretical risk.

Regardless, it is prudent to take measures that minimize women's exposure to unnecessary radiation doses, such as collimate the x-ray beam, decrease the number of additional mammographic incidences, evaluate nodules with ultrasound, and use large detectors to evaluate large breasts.

Should Digital Mammography Be Preferentially Used?

Population studies that showed the benefit of mammographic screening were performed with conventional mammography. Digital mammography can detect some tumors that are not visible in conventional mammography, and it presents some advantages over conventional mammography, since it simplifies the process of archiving, retrieval, and transmission of the images; permits performing a larger number of exams; has a higher contrast resolution; increases diagnostic performance, especially in dense breasts; and reduces the mean glandular dose of radiation. The biggest disadvantage is the higher cost. There are not, and probably there will not be, prospective randomized and controlled population studies comparing the reduction in mortality between women screened with digital mammography and those screened with conventional mammography. The currently available data do not allow us to conclude that population screening with digital mammography is superior to that with conventional mammography in reducing mortality from the disease, nor does it allow us to assess whether the

adverse effects are smaller, equal, or greater. Currently, no medical society recommends the preferential use of digital mammography in screening the general population.

Should Ultrasonography and/or Magnetic Resonance Be Used as Complementary Methods in the Average-Risk Population?

Mammography does not detect all breast cancers. The sensitivity of mammography in screening programs in the United States was 75%. Breast density and age are important predictors of mammographic sensitivity that increases with age and reduction of breast density. The limitations of mammography in relation to sensitivity motivated the evaluation of ultrasonography and magnetic resonance imaging in the screening of breast cancer, especially in women with dense breasts or at high risk for the disease. Ultrasound and magnetic resonance imaging can identify tumors that are not identified by mammography. However, there is no data on the effect on disease mortality of additional use of ultrasonography or MRI in screening for breast cancer in the average-risk population. Therefore, no medical society recommends the further use of these imaging methods in the screening of breast cancer in women of the general population. The exception is women with dense breasts, without other risk factors, when some medical societies suggest that supplementary use of ultrasonography may be considered.

Considerations About Mammary Tomosynthesis

Tomosynthesis is considered an evolution of digital mammography. Prospective studies that included about 200,000 women showed an increase in the detection rate of breast cancer from 27% to 41% and a reduction in recall rates of 13% to 27%. One of the promising aspects regarding tomosynthesis was the increased detection, especially of small invasive carcinomas when compared to digital mammography. The results of these studies stimulated the use of tomosynthesis in the screening scenario.

There are several issues debated around the use of tomosynthesis for breast cancer screening and include the best imaging protocol, economic aspects, impact on breast cancer mortality, and radiation dose. The latter, which was the major initial concern, may be mitigated using the 2D synthesized mammography. Considering all these aspects, in the review of its recommendations in 2017, the Brazilian College of Radiology, the Brazilian Society of Mastology, and the Brazilian Federation of Gynecology and Obstetrics Associations consider that the tomosynthesis with 2D plus 3D protocol, or associated with the synthesized mammography, can be considered for the screening for breast cancer, when available.

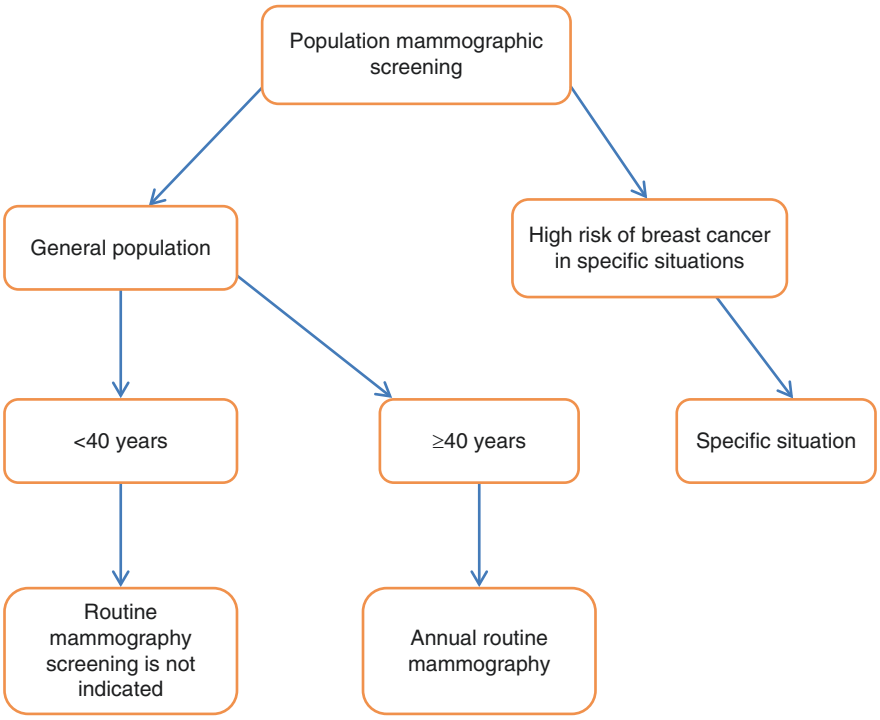

Fig. 1 Recommendations of the Brazilian College of Radiology and the Brazilian Society of Mastology

Flow Chart

The authors of this chapter follow the recommendations of the Brazilian College of Radiology, the Brazilian Society of Mastology, and the Brazilian Federation of Gynecology and Obstetrics Associations, and the flow chart below reflects these recommendations (Fig. 1).

Recommended Literature

1. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. Br J Cancer. 2013;108(11):2205–40. *An extensive and detailed independent systematic review of the literature by the Independent UK Panel commissioned by Cancer Research UK and the Department of Health (England) to assess the benefits and adverse effects of breast cancer screening*
2. Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, et al. Benefits and harms of breast cancer screening: a systematic review. JAMA. 2015;314(15):1615–34. *An extensive systematic review of the literature commissioned by the American Cancer Society*

to synthesize available evidence on the association of mammographic screening and clinical breast examination with breast cancer mortality, overdiagnosis, false positives, and life expectancy. It is used to support its new recommendations (Article 3)

3. Oeffinger KC, Fontham ET, Etzioni R, Herzig A, Michaelson JS, Shih YC, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. JAMA. 2015;314(15):1599–614. *New recommendations for breast cancer screening by the American Cancer Society: the ACS recommends that women in the general population should undergo regular mammographic screening from the age of 45 on (strong recommendation). Between 45 and 54 years old, women should be screened annually (qualified recommendation). Women at age 55 or older should move to biennial screening or have the opportunity to continue their annual screening (qualified recommendation). Women should have the opportunity to initiate annual screening between the ages of 40 and 44 (qualified recommendation). Women should continue screening mammograms provided that their overall health is good and they have a life expectancy of 10 years or more (qualified recommendation). ACS does not recommend clinical breast examination for screening for breast cancer in the general population at any age (qualified recommendation)*
4. Siu AL, U.S. Preventive Services Task Force. Screening for breast cancer: U.S. preventive services task force recommendation statement. Ann Intern Med. 2016;164(4):279–96. *Update of the USPSTF recommendations for the screening of breast cancer. The USPSTF recommends bi-annual mammographic screening for women aged 50–74 (Recommendation B). The decision to initiate mammographic screening in women before age 50 should be individualized. Women who place a greater value on potential benefit than potential adverse effects may choose to start the bi-annual screening between 40 and 49 years old (Recommendation C). The USPSTF concludes that current evidence is insufficient to assess the balance between benefit and adverse effects of mammographic screening in women aged 75 years or older (Statement I). The USPSTF concludes that current evidence is insufficient to assess the benefits and adverse effects of digital breast tomosynthesis as the primary method of screening for breast cancer (Statement I)*
5. Urban LABD, Chala LF, Bauab SP, Schaefer MB, dos Santos RP, Maranhão NMA, et al. Recomendações do Colégio Brasileiro de Radiologia e Diagnóstico por Imagem, da Sociedade Brasileira de Mastologia e da Federação Brasileira de Ginecologia e Obstetrícia para rastreamento do câncer de mama por imagem. Radiol Bras. 2017;50(4):244–9. *Recommendations of the Brazilian College of Radiology and Diagnostic Imaging, the Brazilian Society of Mastology and the Brazilian Federation of Gynecology and Obstetrics for the screening of breast cancer. The authors discuss the risks and benefits according to age range and risk of breast cancer. Annual mammographic screening is recommended for women in the general population aged 40–74 years old. Above 75 years old, it should be reserved for those who have a life expectancy of more than 7 years. Complementary screening with ultrasound should be considered for women with dense breasts. Tomosynthesis is a form of mammography that can be considered for screening for breast cancer when available*

Special Screening Situations

Selma di Pace Bauab and Vera Lucia Nunes Aguillar

Introduction

This chapter discusses special screening situations, predominantly on existing evidence, although some of these situations are not included in the protocols already established. To fill the gaps left by the current guidelines, members of the American College of Radiology (ACR) and the Society of Breast Imaging (SBI) gathered to define recommendations on the multiple modalities of image, based, whenever possible, on published scientific data or on the consensus of specialists of these societies (Table 1).

Some situations were not confronted by these committees, nor commented by the main articles consulted about an individualized screening. The recommendations in the usually omitted situations, addressed in this chapter, are described by articles and books and also evaluated by our own observation.

Table 1 Special screening situations for women

1. Moderate risk
2. High risk
3. Under 40 years
4. Over 74 years
5. Dense breast tissue
6. With prosthesis and breast implants
7. Postoperative breast surgery (without cancer)
8. Postoperative breast surgery (with cancer)
9. Breast reconstruction postoperative surgery

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Recommendations by Risk Factors

There are multiple statistical models to calculate the risk factors based on the woman's family and medical history (Gail, Claus, BRCAPRO, Tyrer-Cuzick) (Tables 2, 3, and 4). Hereafter, we enumerate the current screening recommendations, based on the individualized risk for women, according to the American College of Radiology Appropriateness Criteria (2016 version) and the recommendations of the Brazilian College of Radiology, the Brazilian Society of Mastology, and the Brazilian Federation of Gynecology and Obstetrics guidelines for breast cancer screening (2017 version).

There is no evidence-based data to support further screening with MRI or ultrasonography for women with non-dense breast tissue and average risk for breast cancer (<15%).

Table 2 Typical risk

Women at risk <15% Non-dense breast tissue
Recommendation: mammography preferably with digital technique (tomosynthesis whenever available), annually starting at 40 years of age

Table 3 Intermediate risk

Women with dense breast tissue, risk between 15 and 20%
Recommendation: mammography preferably with digital technique (with tomosynthesis, whenever available), annually starting at 40 years of age Ultrasonography: may be appropriate
Women with personal history of breast cancer[a] **Women with previous biopsy resulting in lobular neoplasia or atypical ductal hyperplasia**[a]
Recommendation: mammography preferably with digital technique (with tomosynthesis, whenever available) annually from diagnosis Ultrasonography: may be appropriate MRI complementary to mammography: usually appropriate[a]

[a]Areas of debate regarding the use of MRI

Table 4 High risk

BRCA1 and BRCA2 mutations carriers, untested first-degree relatives of BRCA mutation carrier **Women with 20% or greater lifetime risk for breast cancer on the basis of family history** **History of chest irradiation received between the ages of 10 and 30 years and genetic syndrome mutation carriers**
Recommendation: mammography preferably with digital technique (tomosynthesis, whenever available), annually starting at the age of 30 years or 10 years before the age that the first-degree relative had breast cancer, or 8 years after the irradiation in the thorax, but not before 30 years old
Mammography and MRI: ought be performed in these patients, being complementary (non-excluding) tests

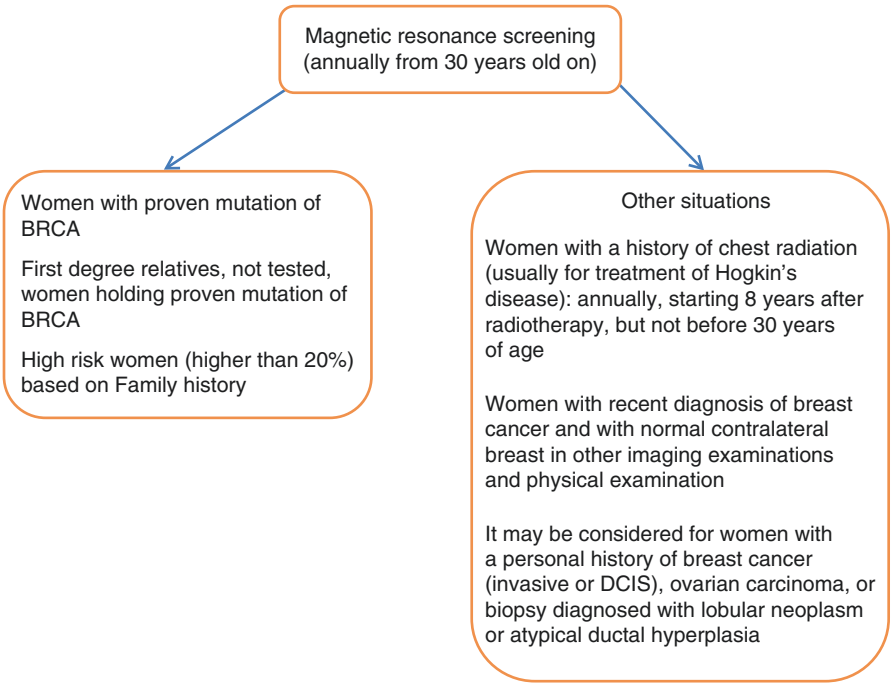

Fig. 1 Indication of magnetic resonance imaging for women with intermediate risk for breast cancer

The most significant area of debate is what to recommend for women at intermediate risk, who do not meet the criteria for further screening with MRI (Fig. 1), but for whom mammography and tomosynthesis may have limited sensitivity. This group includes women at 15 to 20% lifetime risk calculated by one of the mathematical models based on family history and women with a personal history of atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, ductal carcinoma in situ, and invasive carcinoma of the breast.

Atypical ductal hyperplasia and lobular neoplasms (atypical lobular hyperplasia and lobular carcinoma in situ) are precursor lesions and simultaneously risk factors for breast cancer, increasing the relative risk of cancer from four to ten times after diagnosis. The consensus advocates that these women should have mammography annually (with tomosynthesis, whenever possible), from the diagnosis. The question is about magnetic resonance imaging. The American Cancer Society (ACS), in its breast cancer screening updated guidelines, points out that there is no evidence-based data to support standard use of MRI, nor to contraindicate it; therefore, the decision should be individualized. Recent data support screening MRI complementary to mammography (with tomosynthesis, whenever possible) for women with previous history of breast cancer, with an MRI detection rate of 18 cancers/1000 women, and with sensitivity and specificity of 92%

and 82%, respectively. Additionally, scientific-based data advocates in favor of MRI screening for women who have not had preoperative MRI, adjuvant radiotherapy, or hormone therapy, young women with dense breast tissue, and ~~in~~ young women with triple-negative or HER2+ molecular subtypes of breast cancer, especially in the first 3 to 5 years.

Thus, CBR, SBM, and FEBRASGO recommend, for this group of women, similar screening methods to the established criteria for women with BRCA genes 1 or 2 mutation.

Screening for Young Women (<40 Years)

Screening mammography in women under 40 years of age is controversial, owing to the fact that there is no scientific-based data to support it, since the most important randomized controlled studies did not include women in this age group (Fig. 2). Thus, the decision to screen this group is made on the benefits and limitations described in Table 5 and in the level of risk for developing breast cancer.

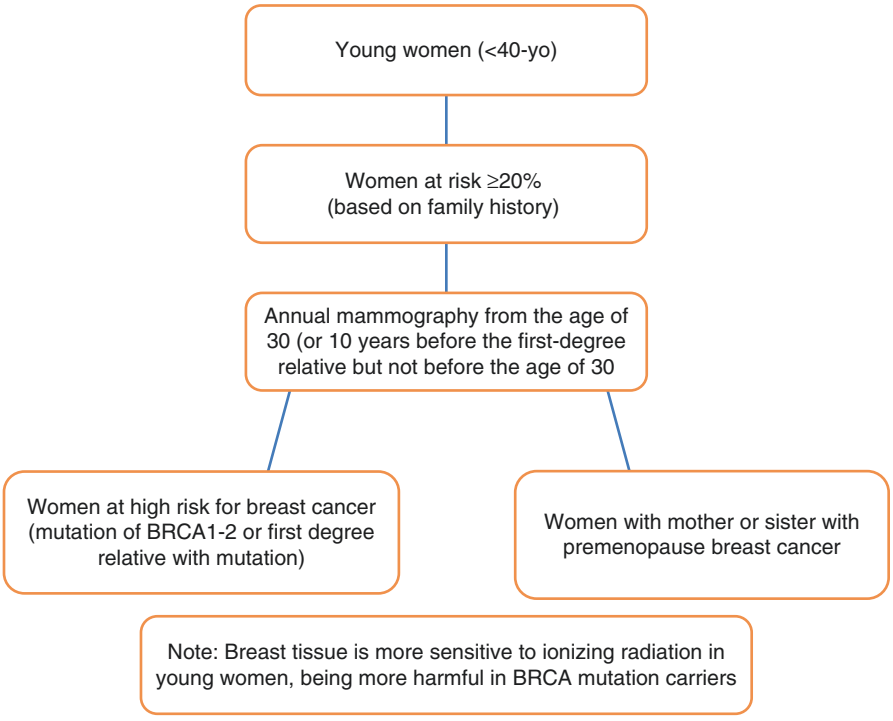

Fig. 2 Recommendations for high-risk young women

Table 5 Benefits and limitations of mammography for young women

Benefits of screening mammography in woman < 40 years
Increased tumor growth
High life expectancy;
Comorbidities are rare in this age group
Limitations of screening mammography in woman < 40 years
Lower incidence of breast cancer
Lower sensitivity of the method
Higher risk of radiation

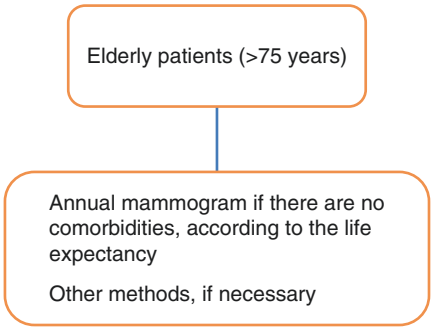

Fig. 3 Recommendations for older women

Screening Elderly Women (>74 Years)

There is no scientific-based data from randomized controlled trials for screening mammography for women over the age of 74 years. However, women's life expectancy has increased, with a progressive incidence of breast cancer in the range aged over 74 years. Currently, about 26% of breast cancer deaths occur in women diagnosed after 74 years. Hartman et al. (AJR 2015) showed that although women 75 years or older accounted for less than 10% of the total screening population during the study time period, the breast cancer (most invasive) cohort was 5.9/1000, which meets ACR's desired goals for medical audit data. The decision to maintain screening in this older age bracket is individualized and relies on the woman's life expectancy. Considering all these factors, many medical organizations recommend the individualization of the decision, which should be considered for healthy women 75 years old or older (Fig. 3). CBR, SBM, and FEBRASGO recommend screening for this group of women, who have a life expectancy of over 7 years.

Women with Dense Breast Tissue (Table 6)

About 43% of women present heterogeneously dense breast tissue, according to the latest reclassification of the BI-RADS ® composition categories. Mammography sensitivity ranges between 30 and 45% in women with dense breast tissue, compared to

Table 6 Women with dense breast tissue

Women with dense breasts tissue as the only risk factor
Adding US to screening mammography may be useful for increasing cancer detection
Women with dense breasts tissue and high risk
Ultrasound may be considered in high-risk women for whom magnetic resonance screening may be appropriate but cannot be performed for some reason

98% in women with non-dense breast tissue, as dense breast tissue may not only obscure lesions but also be an independent risk factor for breast cancer. Interval cancer is more common and has worse prognosis in women with dense breast tissue. In the USA, there are several states whose legislation requires healthcare providers to inform women about their breast density based on the Breast Imaging Reporting and Data System, and to discuss further supplementary screening tests such as ultrasound and MRI in these women, even without evidence of the long-term results.

Breast density is not included in statistical models for cancer risk calculation, although multiple studies have pointed to the impact of adding breast density to Gail's model and demonstrated a significant increase in predictive accuracy.

Several articles have shown that ultrasound can detect invasive cancer, undetectable on mammography, in women with dense breast tissue associated with another risk factor (ACRIN 6666) and also in women with only dense breast tissue.

Recently, the report of J-START (Japan Strategic Anti-cancer Randomized Trial) was published. It is a prospective study that evaluated 72,998 women with dense breast tissue between 40 and 49 years of age. Participants were randomly assigned in 1:1 ratio to undergo exclusively mammography (control group) or mammography associated with ultrasound (intervention group), twice in 2 years. The most relevant data obtained was the demonstration of reduction rate of interval carcinomas in the group double screened with mammography and US, compared to the control group (Fig. 4).

Giger et al. (AJR, 2016), in a multicentric study, compared the use of digital mammography alone and digital mammography associated with automated breast ultrasound (ABUS), demonstrating that this new technique can also increase cancer detection without substantially affecting the specificity.

The major issue to screening ultrasound techniques is its low specificity, as it increases false-positive rates and has a low positive predictive value for biopsies.

Women with Breast Implants (Fig. 5)

- Mammography: Women with implants may have masses not seen on mammography due to dense, compressed, or obscured tissues: Mammography should preferably be digital. Tomosynthesis may add a discrete benefit to the Eklund technique.

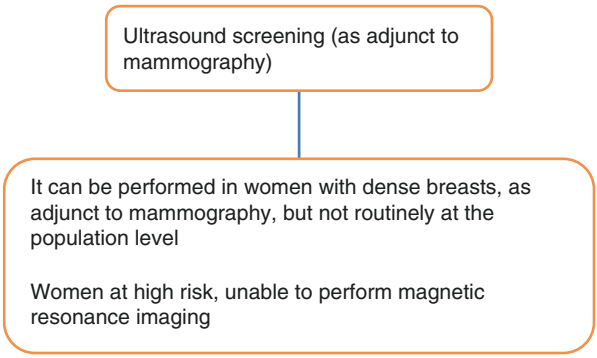

Fig. 4 Recommendations for tracing ultrasound

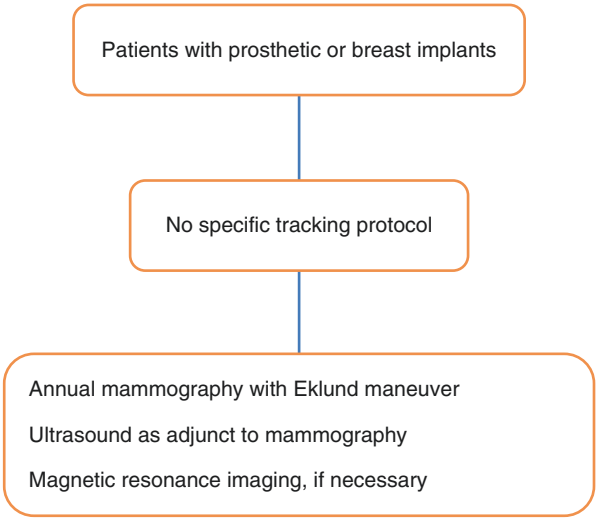

Fig. 5 Recommendations for patients with breast implants

- Ultrasound: It is important to evaluate intracapsular rupture of implants and to detect hematomas and seromas. There is no specific screening protocol, as it may be compared to women with dense breast tissue, in which ultrasound may increase detection of masses obscured by implants.
- Magnetic resonance imaging: It is the gold standard to evaluate the integrity of implants and should be performed whenever there is any doubt at mammography and ultrasound. In 2006, the FDA approved the use of silicone implants for primary breast augmentation and recommended that women with silicone implants should undergo screening MRI for "silent" (asymptomatic) rupture of implants 3 years after implantation and every 2 years thereafter (Margolis et al.). With regard to screening, MRI is used on the same recommendations according to age and risk factors.

Postoperative Women (Reduction Mammoplasty)

- Mammography, ultrasound, and magnetic resonance: Recommendations are the same for women without reduction mammoplasty, according to age ranges and risk factors. There may be an increased number of recalls due to the surgical architectural distortions and to assess possible areas of steatonecrosis which may simulate malignant lesions in these diagnostic methods. Tomosynthesis may decrease the number of recalls in this group.
- MRI may be helpful in dubious cases, but, as a screening exam, it should only be performed following the indications already described in this chapter.
- Pre-mammoplasty period: Mammography should not be used routinely in preoperative care in women younger than 30 years for screening. However, it may be performed on women over 30 years of age who will undergo the procedure, although there is no established protocol. Ultrasound and MRI can be used whenever required. Despite the absence of a specific protocol, young patients in the preoperative period usually undergo breast ultrasound in order to detect the presence of a non-palpable mass.

Screening After Surgery for Breast Cancer

Mastectomy Without Reconstruction (Fig. 6)

- Mammography: Mammography is not recommended, given the difficulty of positioning the patient and because when there are recurrences, most of the time they are detected on clinical exam. Mammography of the contralateral breast should be performed annually.

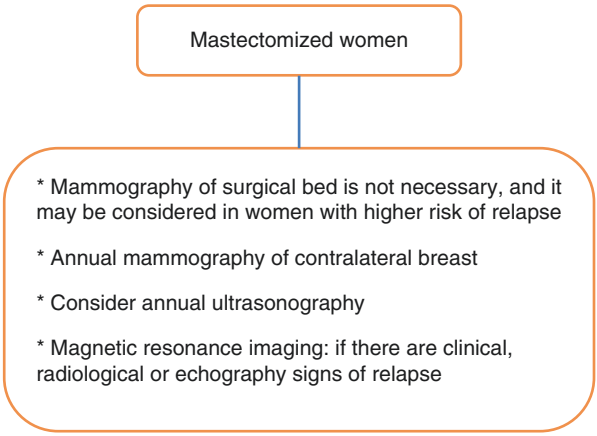

Fig. 6 Screening recommendations after mastectomy

- Ultrasound: It has high sensitivity to detect superficial recurrences, being superior to mammography in these cases. It is also more accurate than the clinical examination in the evaluation of the regional lymph nodes.
- Magnetic resonance imaging: If there are clinical, radiological, or ultrasonographic signs of recurrence, it may be useful to assess the extent of the lesion.

Women with Breast Reconstruction After Mastectomy

Breast reconstruction may be performed with implants, with autologous tissue, or with both. There is no consensus on the imaging follow-up of women with mastectomy and reconstruction, as there are no randomized studies or protocols of NCCN, ACS, or other medical societies. The revised literature shows only reports of cases or series of cases, and the most important issue to guide the recommendation of imaging surveillance in these women seems to be the type of breast reconstruction (Fig. 7).

- Mammography: In women reconstructed with implants, literature does not recommend imaging with mammography, due to the fact that detection of local recurrences (LR) is the role of clinical examination. In these patients, the surgical mastectomy site is pulled anteriorly by the implant, providing the diagnosis of superficial local recurrences (skin and subcutaneous) and deep recurrences (anterior to the pectoral).

If there is an area of concern after the clinical examination, diagnostic mammography should be performed, with supplementary ultrasound and MRI, if necessary. Mammography may be performed to evaluate the amount of residual fibroglandular tissue in the retroareolar region and axillary tail (digital whenever possible, due to the reduced amount of residual tissue) complemented by other methods, if necessary, also considering the risk factors that led to the surgery.

In cases of reconstruction by musculocutaneous flaps, mainly provided by the abdominal rectus (TRAM), the literature is insufficient and controversial, as the current position of medical societies is that there is scant evidence-based data to

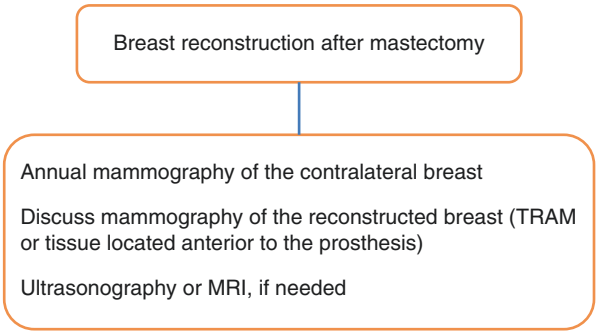

Fig. 7 Screening recommendations for women with mastectomy reconstructed breasts

recommend routinely mammography in women mastectomized and reconstructed by TRAM. However, the examination should be considered in those women with a greater risk of recurrence due to the molecular profile of the tumor or genetic/family risk. In day-to-day practice, it is useful to have a mammography at least in the mediolateral oblique incidence.

- Ultrasound: It allows the detection of palpable and non-palpable lesions and the evaluation of regional lymph nodes. It must be remembered that the LRs occur in the periphery of the flap, between the contact of the native skin and the flap line. The ultrasound exam should evaluate the posterior region of the TRAM; hence, this area may not be included in mammography. However, there is no protocol for performing ultrasound on these women.
- Magnetic resonance imaging: If there are clinical, radiological, or ultrasonographic signs of recurrence, it may be useful to evaluate the extent of the lesion, but there is no indication to routinely follow these patients with MRI. This is an area of debate, as we have mentioned in other topics of this chapter.

Patients Submitted to Conservative Breast Cancer Treatment

Women with personal history of breast cancer present a greater risk of developing another tumor as a local recurrence or a new ipsilateral cancer or contralateral tumor. Early detection of a new tumor has great impact on the patient's life, as it courses with a 17–28% reduction in estimated mortality, according to a systematic review of the literature (Lam et al., 2016). Another article (Houssami et al., 2009) compared the prognosis of asymptomatic recurrences (detected by mammography) with symptomatic recurrences (detected on clinical examination) and found an increase survival rate from 27% to 47% in women with asymptomatic recurrences, with smaller tumors, presenting a more favorable stage and less likelihood of lymph node metastasis (Fig. 8).

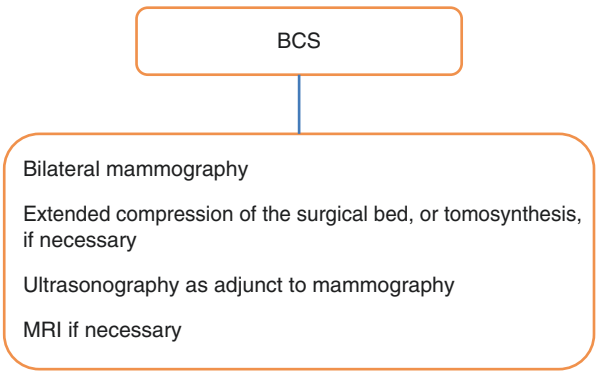

Fig. 8 Screening recommendations for women submitted to conservative surgery

- Mammography: The revision of literature, based on non-randomized studies, supports scientific-based data to encompass the benefits of a mammography follow-up in patients with conservative breast cancer treatment, although there is variability on when to begin, when to end, and what should be the exam interval. The ACS (American Cancer Society) and the NCCN (National Cancer Comprehensive Network) recommend annual digital mammography, starting between 6 and 12 months after the end of radiotherapy (Lam et al.).

Other guidelines supporting semiannual and annual mammography control also advocate in favor to return to annual routine after 2 years or "when the mammographic findings have stabilized". The American College of Radiology pledges "the frequency of imaging exams may vary from institution to institution based on local protocol." The decision of when to finish mammography follow-up is also not present in most guidelines.

The National Institute for Health and Care Excellence (NICE), from the United Kingdom, recommends risk stratification for mammography follow-up after the first 5 years of cancer treatment. The American Cancer Society (ACS) supports the end of the mammography follow-up in the general population if the patient has less than 10 years of life expectancy.

Tomosynthesis associated with conventional digital mammography, or synthesized mammography, shall probably replace conventional digital mammography, as it reduces the number of additional incidences (compression magnification of the surgery site) with shorter examination time and lower dose of radiation. Currently, there is only one prospective, non-randomized study (Sia et al. 2016) about the role of tomosynthesis in women who received treatment for breast cancer (conservative surgery or mastectomy, with or without radiotherapy). The article shows that tomosynthesis reduces the number of indeterminate findings and the rate of recalls when compared to only mammography. In daily practice, whenever available, tomosynthesis is used and presents the same benefits as those observed in general screening, mainly reducing the number of recalls for additional incidences.

- Ultrasound: It may detect hidden recurrences in mammography, especially in women with dense breasts, and is an excellent method for evaluating regional lymph nodes. Although, in practice, ultrasound is widely used as a supplementary method to mammography and clinical examination, most medical societies do not address or recommend its use in post-conservative breast cancer treatment control due to lack of scientific-based data. The ACRIN 6666 Study – which analyzed the value of US supplementary screening in women with dense breast tissue and simultaneously with other risk factor – demonstrated that ultrasound detected 5.3 additional cancers/1000 in the first round of screening, with a positive predictive value for biopsy (VPP3) of 15.3%. Other studies corroborate and reinforce the abovementioned information.

- Mammography + ultrasound + physical examination: This is the most effective approach compared to the same exams singly performed. Although tomosynthesis has been mentioned as a modality to be considered for mammography screening in the NCCN guidelines, the exam has not been suggested separately in any of the current guidelines for monitoring patients who have had breast cancer.
- Magnetic resonance imaging: It is important to differentiate fibrosis from recurrence. It should not be performed before 12–18 months after the conclusion of radiotherapy, as it may induce the false-positive result. Cho N et al. (2017) suggest that the addition of MRI to mammography screening for women <50 years, submitted to conservative treatment for breast cancer, improves the detection of early-stage but biologically aggressive cancer with an acceptable specificity. Lehman et al. (2016) demonstrated that the MRI in patients with previous history of breast cancer presented sensitivity and cancer detection rate similar to those of patients with family history/genetics risk factors, but with higher specificity (lower rate of false positives). However, further studies are required in this regard. Once again, this is an area of debate, as we have already mentioned.

There is no special screening to detect non-mammary recurrences (in the thoracic wall and in the regional lymph nodes); however, it is known that ultrasound is better to diagnose abnormalities in the axillary and supra- and infraclavicular regions (detection of lymphadenopathy) and to supplement the study of the surgical site, especially in women with dense breast tissue.

Summary of the Recommendations in the Postoperative Breast Cancer

- Minimum of annual mammography, with variability for beginning, intervals, and termination. ACS and NCCN recommend the first mammography 6–12 months after the end of radiotherapy. Tomosynthesis may be implanted over time.
- Most guidelines do not approach nor recommend ultrasound as a screening strategy for these women.
- MRI currently provides, in women with previous history of breast cancer, detection rates similar to those of high-risk women and with genetic predisposition.
- Molecular tumor profile, imaging characteristics, and the treatment implemented may contribute to a greater risk of developing a second cancer. Further studies are required to define strategies for specific subgroups of women who have had breast cancer (Table 7).

Table 7 *Guidelines* for image surveillance after conservative treatment for breast cancer

Societies	Mammography	Ultrasound	MRI
ACS, ASCO 2015	Annually, 6 months after RT	Does not address	If risk >20%
NCCN, 2017	Annually, 6–12 months after RT	Does not address	Does not address
NICE	Annually, for 5 years	Does not recommend	Does not recommend
ACR 2014	Institution based	If MRI is contraindicated	After risk stratification
BRC, BMS, BRAFESGO	Annually	If MRI is unavailable	Annually, but not before 30 years

References: NCCN.ORG; NICE.ORG; SBI 2017 CBR, SBM, FEBRASGO 2017
Note: BCR, Brazilian College of Radiology; BSM, Brazilian Society of Mastology; BRAFESGO, Brazilian Federation of Gynecology and Obstetrics Associations; ACR, American College of Radiology; ACS, American Cancer Society; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence

Take-Home Messages

- Women with average risk and moderate risk for breast cancer should start mammography at 40 years of age. The intermediate-risk group must undergo supplementary ultrasound whenever required.
- High-risk women should start the annual mammographic screening, combined with MRI, at the age of 30.
- High-risk women who are not able to perform magnetic resonance imaging for any reason should perform supplementary ultrasound at the age of 30.
- Women with breast implants and postoperative patients of reductive mammoplasty follow the same indication of the age-related screening strategy, based on the risk factors of other women.
- Women subjected to mastectomy, with or without reconstruction, do not require mammographic screening, but may be individually appreciated, especially in cases of reconstruction with TRAM. Ultrasound can be useful. Mammography of the contralateral breast should be performed annually.

Recommended Literature

1. Aguillar V, Bauab S, Mama MN. Diagnóstico por Imagem. Rio de Janeiro: Editora Revinter; 2009.
2. Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to Mammography in women with elevated breast cancer risk. JAMA. 2012;307(13):1394–404. *Prospective study*

conducted between April 2004 and February 2006 to determine the accuracy of ultrasound and magnetic resonance in high-risk women for breast cancer. Recommendations of the Brazilian College of Radiology and Diagnostics by Image, the Brazilian Society of Mastology and the Brazilian Federation of Associations of Gynecology and Obstetrics for screening of breast cancer by imaging methods. Re. Radiol Bras., July, 2017.

3. Lam DL, Houssami N, Lee JM. Imaging surveillance after primary breast cancer treatment. AJR. 2017;208:676–86.
4. Lee CH, Dershaw D, Kopans D, Evans P, Monsees B, Monticciolo D, et al. Breast cancer screening with imaging: recommendations from the society of breast imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. J Am Coll Radiol. 2010;7(1):18–27. *Published consensus by the SBI and ACR on the indications of mammography, ultrasonography and magnetic resonance in the screening of breast cancer.*
5. Schwartz GF, Hughes KS, Lynch HT, Fabian CJ, Fentiman IS, Robson ME, et al. Proceedings of the international consensus conference on breast cancer risk, genetics, & risk management. Breast J. 2009;15(1):4–16. *Review text and consensus on breast cancer and genetic risks, definition and recommendations*.

Percutaneous Biopsies: Clinical and Radiological Aspects

Norma Medicis Maranhão, Selma di Pace Bauab, and Beatriz Maranhão Miranda

Introduction

The applicability of percutaneous biopsies is to define the cytological or histological structure of palpable or impalpable lesions, enabling a non-surgical diagnosis of mammary lesions. The histological result plays a major role in surgical planning, and the complementary immunohistochemical study offers a prominent definition of prognostic factors and adjuvant treatment following the classification of the tumor biology profile.

All mammary lesions, palpable or not, which can be safely accessed by a needle, may be subjected to percutaneous biopsy. The decision relies on the radiologist's discretion to elect the most efficient method to obtain tissue to be analyzed, taking into account factors such as:

1. Sufficient material to be studied
2. Safety to do the procedure
3. Patient comfort
4. Precise correlation among the image and the cytopathology or histopathology

Methods for obtaining the percutaneous tissue:

1. Fine-needle aspiration (FNA)
2. Core biopsy (percutaneous biopsy by a large core needle or fragment biopsy)
3. Vacuum-assisted biopsy (vacuum-assisted fragment biopsy or mammotomy)

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All the aforementioned methods may be guided by ultrasound. Stereotaxic usually guides core biopsy and mammotomy, as magnetic resonance imaging (MRI) may also guide vacuum-assisted biopsy. Whenever the lesion is solely detected by a single method, the procedure must be performed guided by the same imaging exam.

It is mandatory, before the execution of any intervention procedure, to undergo careful analysis of the images which led to the biopsy. Therefore, mammograms must be analyzed to see whether the lesion is consistent or if it corresponds to the overlap of images, which may be elucidated by obtaining additional incidences. Similarly, in the case of a non-spiculated dense nodule, the ultrasound evaluation is required to appreciate the possibility of the lesion being consisted by a cyst, thus avoiding an unnecessary biopsy. The same procedure is adopted in cases of biopsy guided by MRI: findings identified by the resonance should be evaluated by second look ultrasound before performing the biopsy guided by the resonance.

Types of Percutaneous Biopsy

Fine-Needle Aspiration (FNA)

The FNA puncture is guided by ultrasound or even by direct palpation, being performed with a 20/21 G-caliber needle attached to a syringe and allows the retrieve of the cytological sample by push and pull sequenced movements inside the lesion. The exam is a low-cost method and easily executed. However, it presents a high percentage of insufficient material (between 0% and 37%). In order to obtain sufficient tissue from the lesion and, therefore, reducing the percentage of inconclusive results, the procedure must be guided by image methods even in palpable lesions.

Despite the disadvantages, it is a classic technique and should be performed when indicated. First, it is mandatory to have an experienced and dedicated cytopathologist to perform the analysis. The following indications are more objective, being stablished by a critical analysis of the opinions from different authors and using our personal experience with the method, we adopt the following conduct:

FNA Indications (Figs. 1 and 2)

1. Regional adenopathy.
2. Lesions on the mastectomy site.
3. Solid circumscribed lesions in women under the age of 35 years (usually fibroadenomas, which may be a circumscribed carcinoma).
4. Symptomatic cyst.

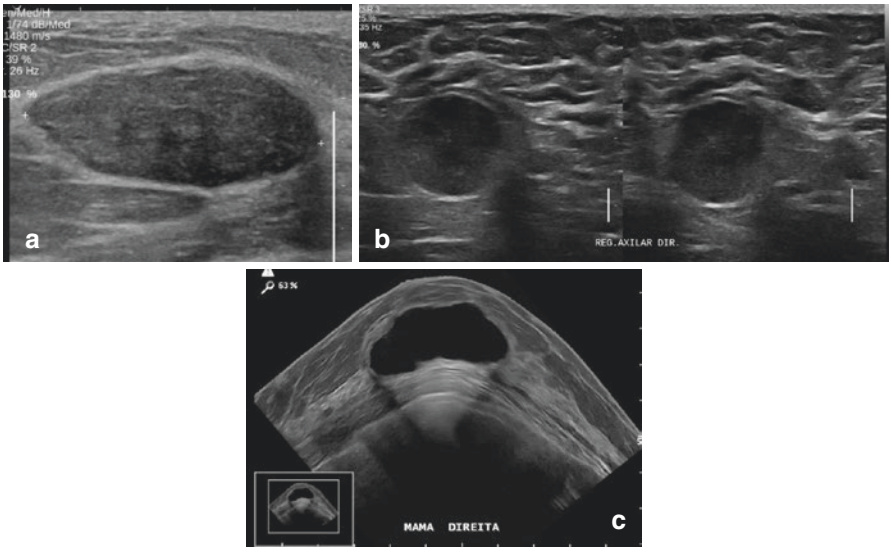

Fig. 1 Indications of FNA. (**a**) Solid circumscribed mass, BI-RADS 3. (**b**) Adenopathy. (**c**) Symptomatic cyst

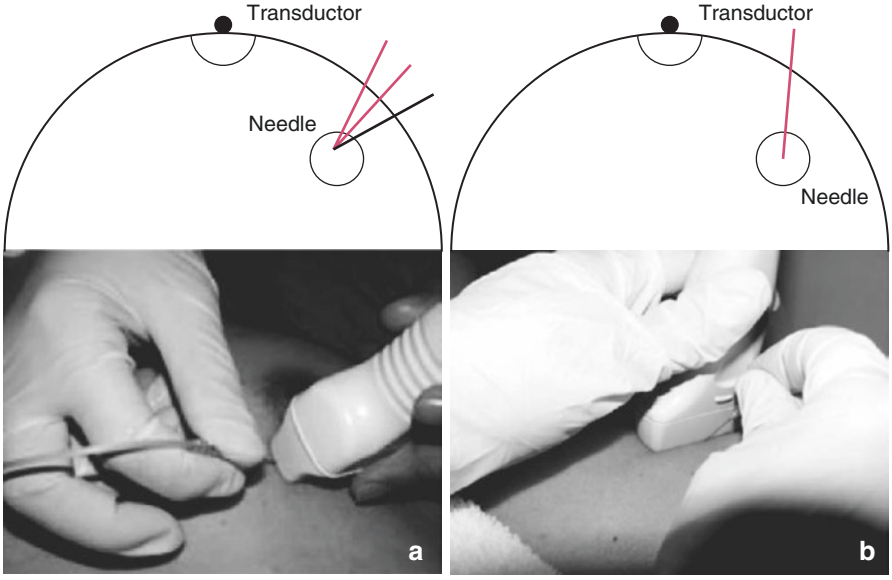

Fig. 2 (**a**) Insertion of the needle parallel to the transducer. (**b**) Insertion of the needle perpendicular to the transducer. (Source: Aguilar V, Bauab S, Maranhão N. Mama: Diagnosis by Image – 1st edition, Retwentyr – Rio de Janeiro, 2009)

FNA Limitations

1. High percentage of insufficient material and false-negative results.
2. Incomplete data on the characteristics of the lesion, as it lacks the capacity to provide the histological and immunohistochemistry classification (because it provides only a "benign" or "malignant" diagnosis, not pursuing the etiology of the lesion nor being capable to distinguish whether it is an in situ tumor or invasive).
3. Spiculated lesions, mainly non-palpable, wich are usually fibrotics and with very little cellular material, providing insufficient sample to the cytological study.
4. In lesions that are suspected to be radiated scleroses and steatonecrosis, usually the result is inconclusive. In the first case (radiated scleroses), surgical biopsy is more appropriate, considering mammotomy as a first step. In the case of steatonecrosis, core biopsy or mammotomy is prefered.
5. Intracystic vegetative lesions, since the liquid portion is usually citology negative (even in the presence of cancer), while the solid portion has great cellularity that may generate a false-positive result. In this case, the surgical biopsy is the best indication, but the core biopsy of the solid portion, or the mammotomy, could also be performed.
6. Microcalcifications: in this case, the core biopsy or mammotomy may provide samples with greater safety and accuracy of results.
7. The requirement of a trained operator and an experienced and dedicated cytopathologist to execute this type of study.

Core Biopsy (Percutaneous Biopsy by a Large Core Needle or Fragment Biopsy)

The mammary percutaneous core biopsy or fragment biopsy is guided by stereotaxic or ultrasound and is a minimally invasive procedure employed to diagnose suspicious non-palpable lesions, by retrieving fragments of the lesion with sufficient proportion and consistency to enable accurate histological analysis and eventually immunohistochemical classification. The material is obtained from the needle, preserved in formaldehyde, and sent to histopathological categorization, being ideally performed with a 14-gauge (ultrasonography) and 12-gauge (stereotaxic) automatically, performed in different ranges (15 and 22 mm), known as core biopsy.

A coaxial needle may be employed, which is previously inserted in the breast, guiding the introduction of the biopsy needle, providing uniformized security through the path in the breast tissue. Axillary adenopathy biopsy may be performed solely in large lymph nodes, ensuring the risk reduction of injuring vessels; the 16-gauge needle supports a 15 mm range, or a special needle. Additionally,

a special needle may be employed, which ensures the method will be restricted to the target tissue.

Core Biopsy Indications

1. Suspicious lesions (BI-RADS® 4 or 5)
2. Microcalcifications that require a biopsy
3. Adenopathy without suspicious mammary lesions (an attempt to diagnose a primary tumor)
4. Lesion with prior atypical cytological diagnosis

Core biopsy advantages compared to FNA:

- A complete histologic diagnosis can be obtained (and not only of "benign" or "malignant" as in the cytology).
- Rarely velds insufficient material.
- The differential diagnosis between in situ and invasive carcinoma is possible and also the immunohistochemical classification.
- Core biopsy may provide tissue from different quadrants of one breast and also bilateral synchronic lesions, providing information of great importance to the treatment.
- Offers greater safety to the physician in the diagnosis of benign lesions than the FNA, especially when the correlation between the image, clinical information, and histopathological result is respected.
- Determines the histology of axillary adenopathy without known mammary lesions.

Core Biopsy Limitations

1. Core biopsy may not be successfully employed in lesions localized close to the thoracic wall, not allowing the complete range of the needle.
2. In superficial lesions, especially in the case of stereotactic core biopsy, because there is a risk of not targeting the lesion or transfixation of the skin.
3. Areas of regional asymmetry or architectural disproportion may not be accessed by core biopsy assisted by two stereotaxic incidences, being exposed to distortions in the Z axis and consequently failing to reach the target tissue.
4. In small breasts, due to the risk of transfixing the breast and reaching the bucky of the device.
5. Patient may not be able to remain immobile while the stereotaxic procedure takes place.
6. Patients treated with anticoagulant must have their medicine discontinued with the physician consent until the biopsy is carried out.

Formerly, scarce microcalcifications localized where they could be entirely removed by core biopsy and consequently impairing future procedures whenever confronting malignant diagnosis were considered to be a limitation of the core biopsy. Currently, a metal clip may be placed in the site of interest after the biopsy, to guide further interventions just like the mammotomy (Figs. 3, 4, and 5).

The literature proves that core biopsy may provide underestimated results, such as atypical epithelial proliferation, radiated sclerosing lesion, and ductal carcinoma in situ. The underestimated nature of these mentioned diagnoses is stablished by mandatory posterior surgical biopsy, consequently enabling the diagnosis of pathologies with greater severity than the aforementioned by the fragment biopsy. Atypical epithelial proliferations may actually consist of a ductal carcinoma in situ whose sampling was insufficient at core biopsy, and radiated sclerosing lesion and ductal carcinoma in situ may represent invasive ductal carcinomas due to an identical reason. According to Jackman et al. (1999), the rate of underrated diagnoses mentioned in the literature from lesions with atypical epithelial proliferation ranges from 31% to 88%, while ductal

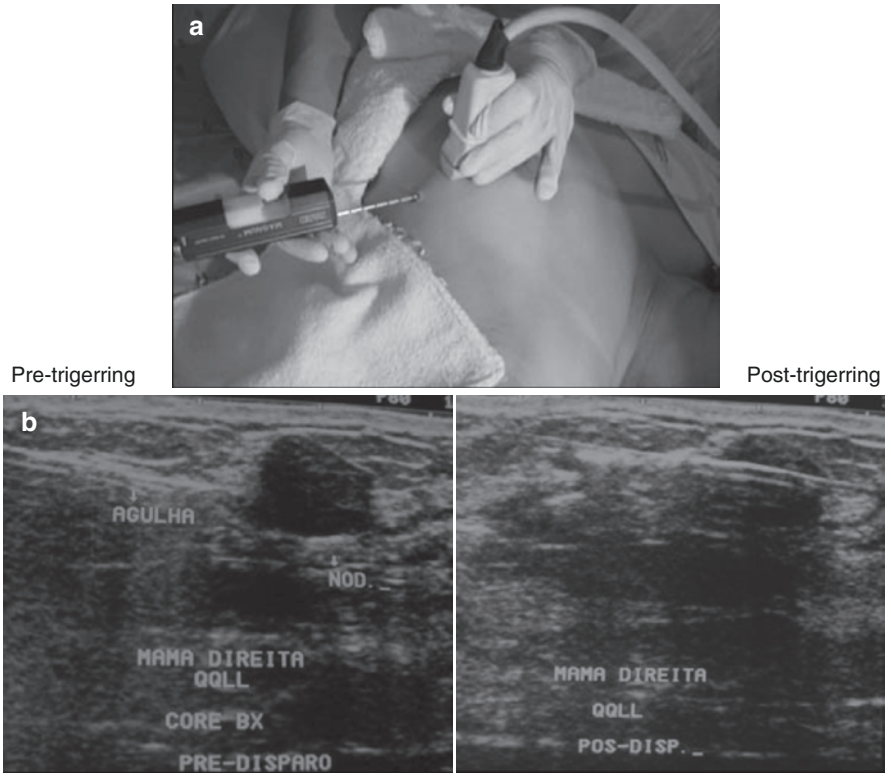

Fig. 3 Ultrasound guided core biopsy. (**a**) Before the procedure, the needle is positioned targeting the nodule. (**b**) After the needle is introduced, the lesion is transfixed. (Source: Aguillar V, Bauab S, Maranhão N. Mama: Diagnostic by Image – 1st edition, Revinter – Rio de Janeiro, 2009)

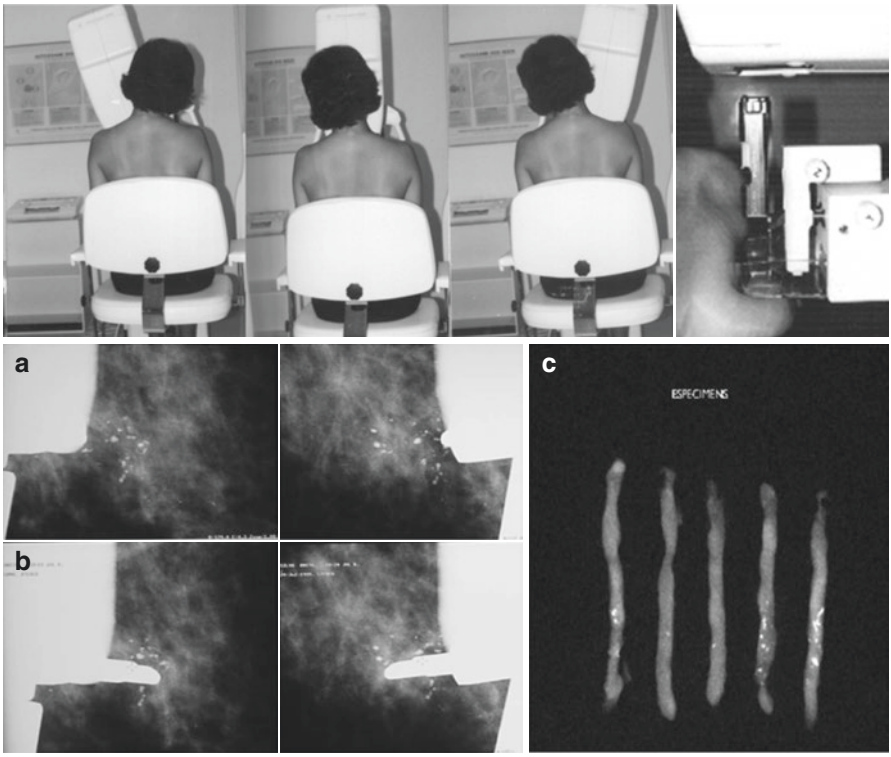

Fig. 4 (**a**)–(**b**) Stereotaxic core biopsy before and after the access to the site of pleomorphic calcifications and (**c**), expanded radiography of the specimens from the core biopsy, demonstrating the presence of calcifications. (Source: Aguillar V, Bauab S, Maranhão N. Mama: Diagnostic by Image – first edition, Revinter – Rio de Janeiro, 2009)

carcinoma in situ ranges between 15% and 36% and the radiated sclerosing lesion configured 25% in our data and 40% in Jackman's research.

The core biopsy was a breakthrough in relation to FNA, enabling diagnoses with greater reliability and reproducibility. However, due to the underestimated diagnostics, mammotomy was created, which retrieves a greater amount of material in an attempt to optimize percutaneous biopsy.

Vacuum-Assisted Percutaneous Biopsy (or Mammotomy)

The mammotomy was created by Parker in 1994, aiming to overcome the limitations of the core biopsy, enabling the retrieval of more tissue and trying to decrease dubious cases of atypical ductal hyperplasia and ductal carcinoma in situ, diagnosed by core biopsy. Through this procedure, lesions with up to 1.5 cm may be fully excised; however, this is not the purpose of the method. It may be stereotaxic,

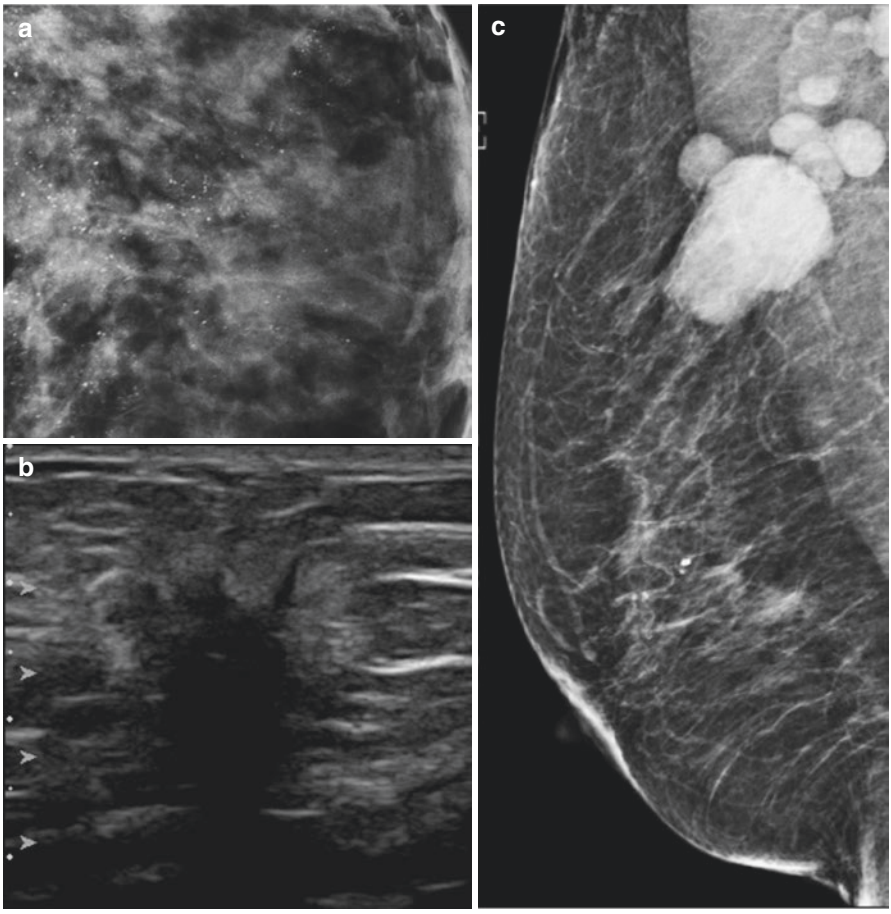

Fig. 5 Core biopsy indications. (**a**) Suspicious microcalcifications. (**b**) Suspicious nodules. (**c**) Axillary lymphadenopathy without known mammary lesion

ultrasonic, or magnetic resonance guided and is performed with an 8-gauge, 9-gauge, or 11-gauge caliber cannula, assisted by a vacuum device.

The major advantages of vacuum biopsy are obtaining larger and more representative fragments, with a smaller amount of blood, and promoting the disposal of a metallic clip in the biopsy site, which is very useful whenever the procedure promotes a complete withdrawal of a malignant lesion, enabling to stablish further presurgical localization, emphasizing that the metal clip may also be employed on the core biopsy.

The disadvantages are it decreases, but doesn't eliminate, the underestimated histological results and presents a much higher operating cost when compared to core biopsy (Fig. 6).

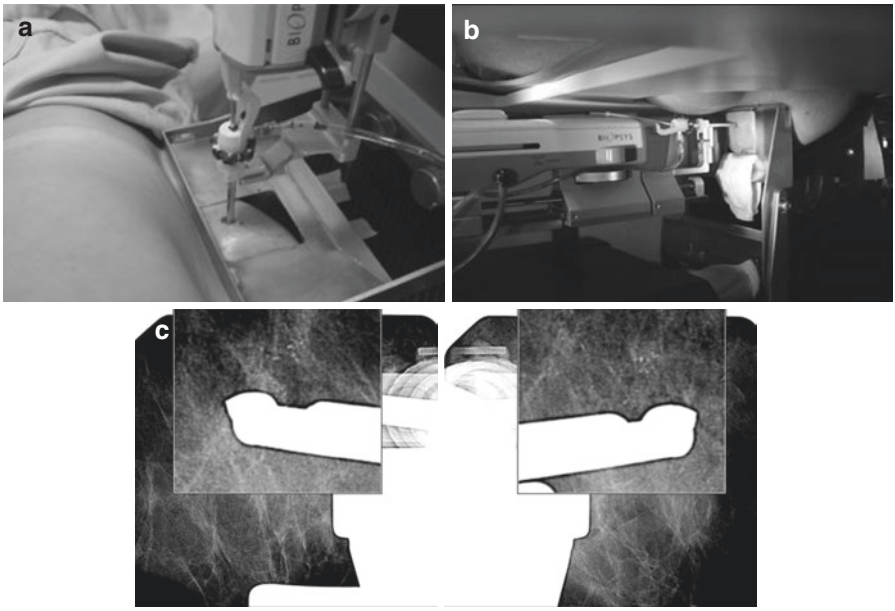

Fig. 6 Stereotaxic mammotomy. The access of the cannula is inserted below, above, or inside the lesion to be biopsied, as the stereotaxic incidences are obtained after the needle firing to make sure that the cannula is positioned properly. (**a)** and (**b**) Patient positioned in decubitus. (**c)** Stereotaxic incidences. (Source: Aguillar V, Bauab S, Maranhão N. Mama: Diagnostic by Image – 1st edition, Revinter – Rio de Janeiro, 2009)

Mammotomy Indications

1. Suspicious small lesions (BI-RADS®4 or 5)
2. Microcalcifications with biopsy indication
3. Lesions identified solely by magnetic resonance
4. Lesion with prior cytological diagnosis
5. Highly likely radial sclerosing lesion

Advantages of Mammotomy in Relation to Core Biopsy

1. Unique incision in the breast, firing the needle just once inside or outside the breast.
2. The amount of sample withdrawn is much higher than the obtained by core biopsy, which may reduce the number underestimated diagnosis.

3. The fragments are contiguously obtained, improving the performance of the pathologist in the analysis of the lesion.
4. The vacuum-assisted system clears the biopsy cavity, harvesting more significant fragments, with a minor amount of blood and clots than in the core biopsy.
5. The device enables the insertion of a metal clip at the biopsy site, whenever the lesion is removed and allows a posterior biopsied localization procedure is required.
6. In breasts with low skin thickness, which are unable to undergo core biopsy, the mammotomy may be preferred.
7. In suspicious microcalcifications, the mammotomy may be more effective than the core biopsy, as the vacuum-assisted technique enables to accurately retrieve a greater quantity of tissue.
8. Alterations suspected to be radial sclerosing lesion (when surgical biopsy is best indicated), in which the percutaneous biopsy is primarily performed, the mammotomy may provide material with greater significance than the core biopsy and may provide more precise diagnosis.

Mammotomy Disadvantages

The great disadvantage of mammotomy is the cost-effective rate. The vacuum-assisted device costs ten times more than the core biopsy. Superficial lesions may locally damage the skin and lesions proximally to the axillary tail and pectoral musculature also present technical limitations. The underestimated results were not totally eliminated, yet considerably decreased, promoting greater reliability. It is important to remember that the biopsy is a diagnostic procedure, not therapeutic.

Conclusion

The percutaneous biopsy of fragments (core biopsy and mammotomy) are indicated to diagnose mammary lesions classified as BI-RADS® 4 (suspected malignancy) and 5 (highly suspected malignancy).

Fragment biopsy is rarely indicated to category 3 (probably benign) lesions, in which image screening may be sufficient. In category 3, percutaneous biopsy may be indicated in some cases, such as to treat patient's anxiety, or due to the preference of the physician, or when the patient intends to get pregnant, or when it presents a high risk for breast cancer, when it will be impossible to provide appropriate follow-up or when the referred patient will be an organ donor.

Scientific data ensures the high capacity of percutaneous biopsy to diagnose carcinoma of the breast with great accuracy, enabling histological classification, in addition to providing efficient diagnosis of benign conditions, classifying their nature, and excluding malignancy.

Size, number, and volume of the fragments present a critical role in the representativity of the samples and may confirm the presence of invasion; however, in the in situ carcinoma, it is not possible to discard the possibility of invasion in an area not sampled in the biopsy.

Benign diagnosis stablished by percutaneous biopsy spares a large number of patients from surgery, and in cases of malignant lesions the procedure avoids surgery for diagnostic purposes, providing essential information on the surgical planning and the biopsy of the sentinel lymph node up-front.

Criteria to Select According to Images or Clinical Features

Briefly, procedures may be performed according to Tables 1 and 2, emphasizing the obligatorily importance of the individualized evaluation.

Table 1 General indications by interventionist method

FNA	Core biopsy	Mammotomy
Aspiration of symptomatic cysts	BI-RADS® 4 or 5 lesions	BI-RADS® 4 or 5 small lesions
BI-RADS® 3 nodules in young patients	Microcalcifications	Solely MRI identifiable lesions
Lymphadenopathy synchronic to suspected mammary lesion	Lymphadenopathy without suspected mammary lesion	Previous diagnosis of cytological atypia
Lesion on mastectomy site	Previous diagnosis of cytological atypia	Probable radial sclerosing lesion

Table 2 Comparison between interventionist methods

FNA	Core biopsy	Mammotomy
Low cost	Medium cost	Elevated cost
Faster	Versatile	Excellent to study microcalcifications
An experienced cytopathologist is mandatory	Worse than mammotomy to: • Low grade DCIS • Papillary lesions • Radial scar	The best option excluding surgical biopsy to lesions with a dubious histological classification
The reliability depends on the cytopathologist		

Source: Aguillar V, Bauab S, Maranhão N. Mama: Diagnostic by Image – first edition, Revinter – Rio de Janeiro, 2009

Take-Home Messages

1. Verify the veracity of the lesion is real before the procedure.
2. Elect the best method to obtain a sufficient sample.
3. The needle must follow the shorter possible path, whether on ultrasound or stereotaxic guided biopsy.
4. To perform core biopsy on a microcalcification the 12-gauge needle is ideal.
5. Whenever the calcifications present a linear or segmental distribuition, the mammotomy is preferable. If unavailable, the core biopsy with a 12-gauge needle must be performed in multiple targets, following the path of the calcifications, requiring several small incisions to introduce the needle in the chosen targets.
6. Percutaneous biopsy of calcifications needs to demonstrate the presence of the calcifications in the radiographed fragments. If the percutaneous biopsy fails to demonstrate the presence of the target tissue, the procedure must be rescheduled or surgical excision may be considered.
7. The number of fragments relies on the quality of the obtained material. If the biopsy targets calcifications, five to nine fragments containing the calcifications are sufficient, ranging up to 20 samples or more. If the biopsy targets a nodule, two to five fragments with the expected consistency and color of the lesion may be sufficient.
8. Macroscopic evaluation of the retrieved material from a nodule, while placing the sample on formaldehyde glass, must contain the following criteria: if the sample remains in the bottom of the glass, the material probably corresponds to the target tissue. If it remains on the surface, it probably corresponds to adipose tissue instead of the desired tissue.
9. Radiological or ultrasound information, such as the lesion description and mammographic and ultrasound category (BI-RADS®), must guide the histopathological examination. It is important to describe the number of retrieved fragments and whether microcalcifications were seen in the radiography of the specimen.
10. Percutaneous biopsy demands medical responsibility before, during, and after the procedure. Imprecise indication leads to unnecessary procedures; the accuracy and the number of the sampling determine the correct diagnosis. The histological results correlated with the images are the gold standard to a successful procedure.

Recommended Literature

1. Abreu and Lima, MCC. The core biopsy in the diagnosis of breast impalpable mammary lesions. An integration of pathological anatomy with high-precision radiology. (PhD) University of Pernambuco; 1997.
2. Aguillar V, Bauab S, Maranhão N. Mama: imaging diagnostics. 1st ed. Rio de Janeiro: Revinter; 2009.
3. Cardenosa G. Mammary imaging. 1st ed. Buenos Aires: Journal; 2005.
4. Dershaw DD. Imaging-guided interventional breast techniques. Springer; 2002.
5. Parker SH, Burbank F. A practical approach to minimally invasive breast biopsy. Radiology. 1996;200:11–20.

Percutaneous Biopsies: Histopathological Aspects

Fernando Nalesso Aguiar and Filomena Marino de Carvalho

Introduction

Percutaneous biopsies with histological sampling enabled the reduction of unnecessary surgeries in benign lesions and enhanced therapeutic planning in cases of malignant neoplasia. However, they require proper interpretation from the clinic, radiologic, and histologic context to minimize false-negative results. Therefore, the following are mandatory:

1. Elect the proper method for the diagnosis of each type of radiological image.
2. Evaluate the radio-pathological correlation.
3. Identify the cases to undergo surgical excision or to repeat the biopsy. In this chapter, we will address items 2 and 3.

Radiologic and Biopsy Context

The medical decision facing a histological diagnosis relies primarily on the verification of its consistency with the image. In this discernment, the synergy between radiologists, pathologists, and mastologists is essential.

In Table 1, the histological findings which may justify different types of images are observed.

Some histological lesions per se do not justify any imaginologic alteration. Among them are:

- Epithelial hyperplasia, usual type
- Lobular intraepithelial neoplasia (LN), classic pattern

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Table 1 Histological findings in different methods of imaging

Image	Histological findings
Circumscribed nodules	Fibroadenoma and phyllodes tumor Hamartoma Apocrine cyst Pseudoangiomatous stromal hyperplasia (PASH) Mammary lymph node Papillary lesions Sarcomas Myofibroblastoma Lymphoma Metastasis Carcinomas (medullary and colloid)
Non-specified nodule	Invasive carcinomas Fibrous scar Sclerosing papillary lesions, including radial scars Mastitis Sclerosing lymphocytic lobulitis Fibromatosis Granular cell tumor Sclerosing adenosis
Solid-cystic lesions	Apocrine microcysts cluster Papillary lesions High-grade carcinomas with necrosis Phyllodes tumor and sarcomas
Microcalcifications	Atypical hyperplasia (ductal, columnar, and apocrine) Lobular intraepithelial neoplasia with microcalcifications Adenosis (microcystic and sclerosing) Ductal carcinoma in situ Mastitis Steatonecrosis Mucocele Carcinomas Hyalinized fibroadenoma Apocrine cysts
Asymmetry	Irregular breast involution with normal breast tissue Adenosis Fibrocystic lesions Mastitis Infiltrative lobular carcinoma
Distortions	Radial scar/sclerosing papillary lesion Fibrous scarring Infiltrating lobular carcinoma Mastitis Mucocele
Enhancements	Invasive and in situ carcinomas Papillary lesions Mastitis Pseudoangiomatous stromal hyperplasia (PASH)

Indications to Repeat the Biopsy

A new biopsy should be considered in radio-pathological discordance due to non-representative sampling. It might be required to decide whether the sampling was representative or not. For instance, a histological sample composed by normal breast tissue may either correspond to the failure of the biopsy to reach the lesion, or hamartoma (nodule), or to irregular involution of the breast parenchyma (density alteration). A sample composed by stroma without glandular elements may correspond to a lipoma or adenolipoma. The indication to repeat the biopsy relies on the multidisciplinary dialogue among radiologists and pathologists and should take place solely if the lesion doesn't require surgical approach.

Indications of Surgical Approach

Histological lesions that deserve surgical excision are those with significant risk of underestimation, even if there is radio-pathological concordance. They feature:

- Atypical ductal hyperplasia
- Lobular intraepithelial neoplasia
- Flat epithelial atypia
- Papillary lesions
- Radial scars
- Fibroepithelial nodular lesions
- Spindle cell lesions
- Mucocele
- Vascular lesions

These lesions are included in the B3 category of the National Health Service Breast Screening Program (NHSBSP) and correspond to about 4% to 9% of the histological diagnosis in percutaneous biopsies. The underestimation rate ranges from 10% to 35%; however, they vary considerably according to the histological type and its extension in the sample obtained. They are also influenced by the size of the image alteration, biopsy method (automated or vacuum-assisted), and number of fragments and size of the needle. Due to the possibility of retrieving a greater amount of tissue by vacuum-assisted biopsy, it has been considered That for small lesions without atypic, only clinical follow-up is required. In Table 2, a summary of underestimation rates and management options is presented. Spindle cell lesions, mucocele lesions, and vascular lesions should always undergo surgical excision because of the difficulty in predicting the risk of underestimation that, when it occurs, is associated with aggressive neoplasias.

Table 2 Mammary benign lesions which generally require surgical approach

Lesions	Underestimation rates	Possible exceptions to surgical excision
Atypical ductal hyperplasia	4–59%	Unifocal lesion with removal of all mammography radiological images by vacuum-assisted biopsy
Flat epithelial atypia	0–20%	No other high-risk lesions, complete image removal, and postmenopausal
Lobular intraepithelial neoplasia	0–38%	Histological and radiological concordance, no high-risk patients, LN classical, incidental finding, and not associated with other risk lesions
Papillary lesion	18–38% (atypia) 0–13% (without atypia)	Complete image removal and absence of atypia
Radiated scar	39% (atypia) 4–9% (no atypia)	Complete image removal and absence of atypia
Nodular fibro-epithelial lesion	2–42%	No clinical, radiological, nor histological suspicion of phyllodes tumor

Recommended Bibliography

1. Marcil G, Wong S, Trabulsi N, Allard-Coutu A, Parsyan A, Omeroglu A, et al. Fibroepithelial breast lesions diagnosed by core needle biopsy demonstrate a moderate rate of upstaging to phyllodes tumors. Am J Surg. 2016. *Retrospective study with 74 percutaneous biopsies diagnosed as nodular fibroepithelial lesion. The surgical excision was performed in 48 (64.9%) and the final diagnoses were fibroadenoma (62.5%), benign Pphyllodes tumor (29.2%) and borderline Pphyllodes tumor (8.3%). The Findings predictive diagnosis of Phyllodes were was stablished by: BIRADS score ≥ 4b, heterogeneous texture and lack of central vascularity by to the ultrasound*
2. Mayer S, Kayser G, Rucker G, Bögner D, Hirschfeld M, Hug C, et al. Absence of epithelial atypia in B3-lesions of the breast is associated with decreased risk for malignancy. Breast. 2017;31:144–9. *Retrospective study with 219 patients subjected to surgical excisional biopsy after diagnosis of histological lesion B3 by percutaneous biopsy. The general underestimation rate was 10%. Atypical lesions had higher rates (24%* vs. *4.8%), as well as in the subgroup of Papillaryuliferous lesions (28.6%* vs. *4.7%).*
3. Mooney KL, Bassett LW, Apple SK. Upgrade rates of high-risk breast lesions diagnosed on core needle biopsy: a single institution experience and literature review. Mod Pathol. 2016;29:1471–84. *Retrospective revisional study of 5750 revised percutaneous biopsies and further analysis of 462 high-risk lesions (epithelial atypia and radial scars). The underestimation rates were 18% for atypical ductal hyperplasia, 11% for flat epithelial atypia, 9% for atypical lobular hyperplasia, 28% for CLIS, and 16% for radialted scarring. Benign nature was indicated by the total excision of microcalcifications, the size < 1 cm and for the CLIS, the as an incidental finding.*
4. Saladin C, Haueisen H, Kampmann G, Oehlschlegel C, Seifert B, Rageth L, et al. Lesions with unclear malignant potential (B3) after minimally invasive breast biopsy: evaluation of vacuum biopsies performed in Switzerland and recommended further management. Acta Radiol. 2016;57:815–21. *Population study including all Mammotomies registered in the Swiss database in the period from 2009 to 2011 (9153 biopsies). The B3 rate was 17.0% and there was 21.5% underestimation (DCIS or invasive), thus distributed: atypical ductal hyperplasia – 25.9%; Flat epithelial atypia – 18.3%; Lobular neoplasiam – 26.4%, radial scarring – 11.1%, and papillary lesions – 3.1%.*

5. Seely JM, Verma R, Kielar A, Smyth KR, Hack K, Taljaard M, et al. Benign papillomas of the breast diagnosed on large – gauge vacuum biopsy compared with 14 gauge core needle biopsy – do they require surgical excision? Breast J. 2017;23:146–53. *Retrospective study including the diagnosis of intraductal benign papilloma, 47 of them diagnosed by core biopsy (14 g) and 60 by Mammotomy (10/12 g). Total underestimation rRates (atypia, DCIS and invasive carcinoma) were 19.1% in the core group and 5% in the Mammotomy group, however the difference was not statistically significant.*

Histopathological Classification of Benign Lesions

Felipe Luzzatto

The majority of benign mammary lesions have their atypical or malignant variant. On certain occasions, the differentiation by the pathologist is difficult, as the histopathological analysis must follow strict diagnostic criteria. The unprecise benign characterization of mammary lesions may lead to inadequate clinical-surgical follow-up and consequently the progression of locoregional disease, causing definitive sequels for patients. The differential diagnosis between benign lesions from malignant neoplasms is fundamental to the appropriate clinical-surgical indication.

The most prevalent benign mammary pathology may be thus divided: intraductal papillary lesions, benign proliferative lesions, fibroepithelial lesions, myoepithelial lesions, mesenchymal lesions, nipple lesions, and gynecomastia. In this chapter, the first three groups will be emphasized, briefly addressing the others.

Papillary Intraductal Lesions

Papillomas are benign tumors consisted by the proliferation of epithelial and myoepithelial cells around fibrovascular axes, and thus creating the aspect of an arborescent structure inside de mammary duct (Fig. 1). They may occur anywhere in the ductal system, i.e. from the nipple to the terminal unit of the lobular duct (TULD). The intraductal papillomas are divided in central or peripheral. The central papillomas occur in the main duct, being normally unique, located in correspondence to the sub-areolar region and associated with papillary discharge. They are rarely palpable and possible mammography abnormalities range from a retro-areolar mass of benign appearance to a solitary retro-areolar dilated duct, almost never with microcalcifications. Peripheral papillomas (microscopic papillomas) originate in TULD, usually multiple and normally without clinical manifestations. The risk to develop

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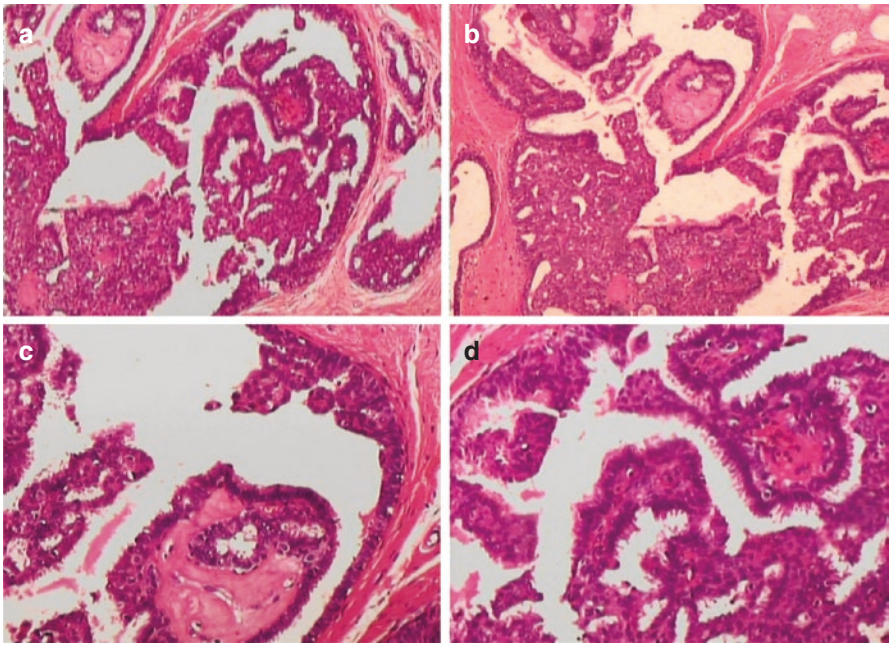

Fig. 1 (**a**)–(**d**) Intraductal papilloma

invasive carcinomas associated with these lesions is usually related to the lesions observed in the adjacent parenchyma; however, benign central papillomas without peripheral atypical lesions present a relative risk (RR) two times greater to develop invasive carcinomas, while peripheral papillomas present RR three times higher. The differential diagnosis among papillary lesions is essential to exclude the association with regional atypical ductal hyperplasia, as studies demonstrate that atypical papillomas may present an RR of up to 7.5 times higher to develop invasive neoplasms. Immunohistochemistry demonstrates the presence of myoepithelial cells (p63 and cytokeratins 5 and 14) and is recommended to perform the differential diagnosis among papillomas without atypical ductal hyperplasia, papillomas with atypical ductal hyperplasia, and papillary carcinoma.

Facing intraductal papillomas diagnosticated by percutaneous biopsies with thick needle, a surgical approach is advised due to the enormous morphological variability in these types of lesions. It is useful to enforce that the intraoperative examination, intended to differentiate between benign and malignant lesions, is extremely challenging. The definitive diagnostic relies on the analysis of paraffin inclusions.

Proliferative Benign Lesions

The majority of proliferative lesions, as well as carcinoma, are originated by the TULD. Addressing the most common benign mammary lesions, we highlight:

Mammary adenoses: Mammary adenoses are a prevalent benign proliferative process, which mainly affects the lobular unit (acinus), occurring particularly in women in their third and fourth decades of age. The most important subtypes feature simple adenoses, sclerosing adenoses, apocrine adenoses, and micro-glandular adenoses. The characterization relies on the disordered proliferation of acinus or tubular structures composed by an epithelial and myoepithelial layer of cells, surrounded by a basal membrane in non-fibrous stroma (simple adenoses; Fig. 2), or eventually fibrous stroma, with compact disposition of the acinus (sclerosing adenoses Fig. 3), or even associated with apocrine metaplasia (apocrine adenoses). The least prevalent presentation is the micro-glandular adenoses, in which it may be observed a disordered proliferation of small glands, marked by a great amount of collagen in the stroma, extended to adjacent adipose tissue, and may simulate an invasive carcinoma. Sclerosing adenoses are associated with a slight increase of risk of mammary carcinoma, similar to usual ductal hyperplasia; however, apocrine adenoses are recognized as a benign process with no known clinical meaning. It

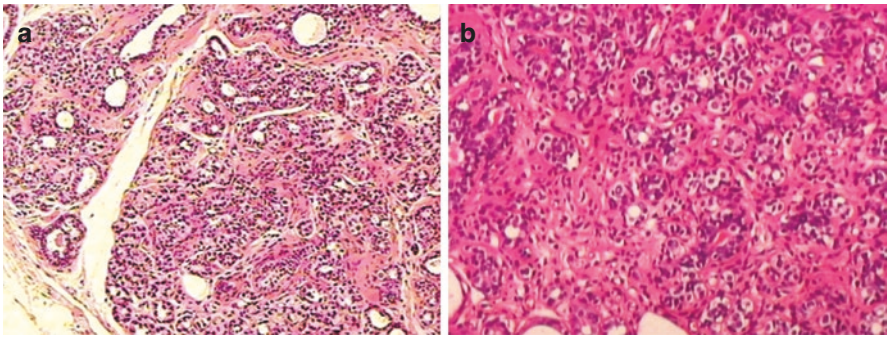

Fig. 2 (**a**)–(**b**) Simple adenoses

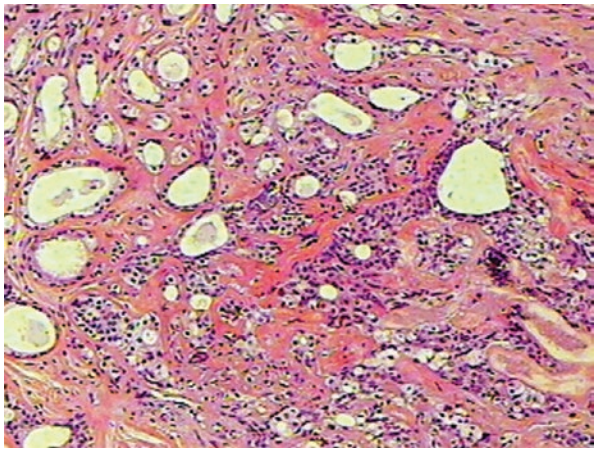

Fig. 3 Sclerosing adenoses

remains unclear whether the micro-glandular adenoses truly consist of a benign proliferation or an indolent lesion, with unknown prognosis and profoundly controversial surgical excision.

Radial scars (RS) and complex sclerosing lesions (CSL): these may be misinterpreted under radiological examination (irregular mammography densities) – macroscopically or microscopically – as invasive carcinomas, due to the disorganization of duct lobular units promoted by stromal elastosis and sclerosis, which are generally trapped in the mammary lobules and ducts (Fig. 4). Usually, the RS terminology is employed to describe minor stellar lesions, while the CSL terminology is usually employed to larger lesions. They are classically associated with adenoses and hyperplasia in varying degrees in the adjacent parenchyma. The differential diagnosis with infiltration neoplasms may be performed by immunohistochemical assays (p63, calponin, heavy myosin chain of smooth muscle), demonstrating the existence of a basal membrane and a layer of myoepithelial cells around the tubular structures. The RR for invasive neoplasms, as with the papillomas, is directly associated with the multiple patterns of ductal hyperplasia observed in adjacent parenchyma, although some studies demonstrate an RR of up to 1.45 times to develop breast carcinoma.

Mammary adenomas: these present clinical and radiological morphologies similar to fibroadenoma. They are constituted by tubular structures of typical epithelial coating and a layer of myoepithelial cells (tubular adenoma), secretions might be associated during pregnancy or lactation (lactate adenoma), or even simultaneously to extensive apocrine metaplasia (apocrine adenoma). It is rarely associated to proliferative mammary lesions, such as pleomorphic adenoma or mixed tumors, whose morphological characteristics are similar to those found in salivary glands and ductal adenoma, which presents glandular proliferations directed to the interior of mammary ducts. Lesions non-related to further recurrences when appropriately excised are considered to be benign.

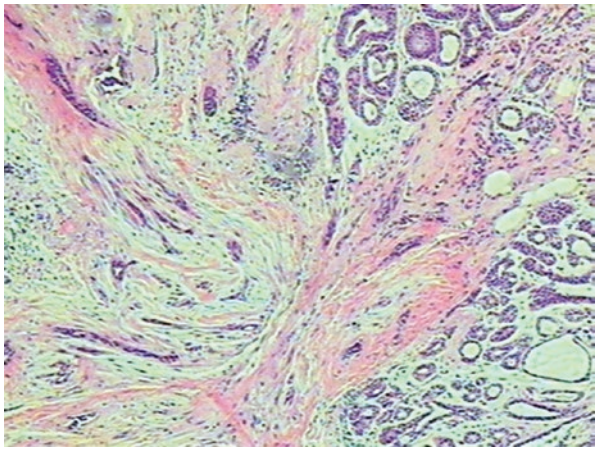

Fig. 4 Radial scars

Fibroepithelial Lesions

These consist of a heterogeneous group of biphasic lesions composed of an epithelial and mesenchymal structure, as the conjunctive is the responsible for the clinical manifestations. They may be divided into fibroadenomatoid mastopathy, fibroadenoma, phyllode tumor, and hamartoma.

Fibroadenomatoid mastopathy (sclerosing lobular hyperplasia): limited lesion of up to 8.0 cm in diameter, usually non-related to clinical manifestations, however easily radiologically identifiable. Microscopically, increased interlobular collagenous are observed in the lobules stroma, similar to micro fibroadenomas. The lesions' appropriate therapy consists of surgical excision, and recurrences are infrequent.

Fibroadenoma: it is a biphasic tumor, which occurs mainly in women under the age of 30 years, consisted by an epithelial component (canalicular or tubular), associated to varying degrees of hyperplasia, and involved by collagenous or mixed stroma (Fig. 5). It is manifested by a single, mobile, slow-growth nodular lesion, and less commonly as multiple lesions, which may reach up to 20 cm (giant fibroadenomas). Homogeneous, oval, circumscribed nodules are observed in mammography. Juvenile fibroadenoma usually presents hypercellular stroma, occurring mainly in young women (under 20 years) and should be considered as a differential diagnosis of phyllodes tumor. Most excised fibroadenomas do not present recurrences, and the risk to develop cancer from fibroadenomas – or in breasts previously treated for them – is low.

Phyllodes tumor: this denotes a group of circumscribed biphasic tumors analogous to fibroadenoma, however composed by a notoriously greater amount of hypercellular stroma and epithelial structures, organized on a foliate arrangement. They are regularly benign but may also be divided into borderline and malignant variants, being usually unique, solid, and painless lesions, measuring from 4.0 to 5.0 cm of diameter in general (ranging from 1.0 to 20.0 cm). Multifocal or bilateral lesions are rare. Radiological methods present a rounded image, containing cysts,

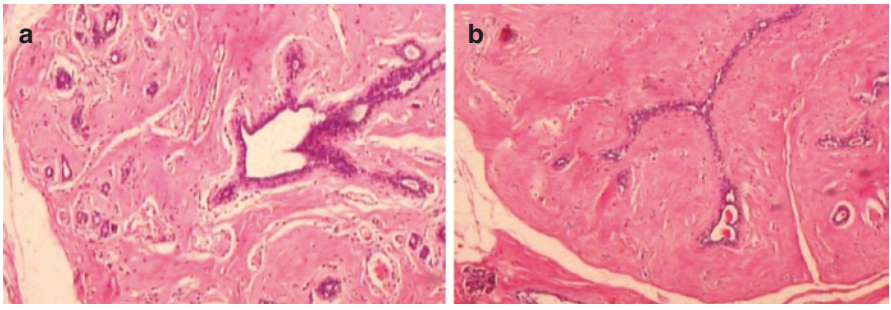

Fig. 5 (**a**)–(**b**) Fibroadenoma

fissures, or calcifications, and may also present well-defined or irregular margins. Recurrences are common after simple excisions, mainly when compromised margins and critical lesions are present.

Hamartoma (fibroblast lipoma, adenolipofibroma, condrolipoma): these circumscribed lesions are composed of a disorderly growth of mature and benign mammary tissue. They are usually asymptomatic, detected solely on mammography, presenting a benign nature, non-related to recurrences, dispensing further treatment most of the times, and may be surgically excised when associated to symptoms or related to suspicious radiological findings.

Myoepithelial Lesions

Originated in myoepithelial cells and related to myoepithelial proliferation, they are capable to invade mammary ducts or to grow in the adjacent tissue. The adenomyoepithelioma is predominantly composed of a solid proliferation of myoepithelial cells, disposed in a fusiform, lobular, or tubular pattern. Most of these lesions are benign, and their recurrence may be due to multinodular growth into the interior of the duct.

Mesenchymal Lesions

Related to this category, it is relevant to highlight the pseudo angiomatous stromal hyperplasia (PASH), which is a benign lesion consisting of pseudo vascular anastomosing spaces, being diagnosed in about 25% of mammary biopsies, and which may eventually present their clinical manifestation concretized by a nodule. Additional mesenchymal lesions may be mentioned as hemangioma, fibromatosis, lipoma, granular tumor, and inflammatory myofibroblastic tumor (Fig. 6).

Lesions on the Nipple

Addressing lesions of the nipples, it is relevant to emphasize the nipple adenoma (nipple papillomatosis, papillomatosis of sub-areolar ducts), which is constituted of a compact proliferation of small tubules, coated by epithelial and myoepithelial cells simultaneously to sclerosis and adenosis. It is clinically associated with nipple discharge composed by blood and serous liquid, leading to nipple erosion. Recurrences after its resection have been described, but it is rarely related to carcinoma. Paget's disease will be described in the following chapters, as it is a malignant lesion of the glandular epithelium present inside the nipple epithelium.

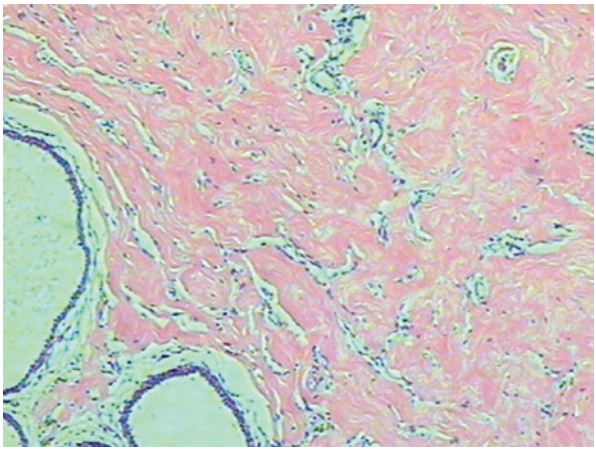

Fig. 6 Pseudoangiomatous stromal hyperplasia (PASH)

Gynecomastia

Gynecomastia consists of a normally reversible, non-neoplastic, unilateral, or bilateral increase of the male breast, associated with the formation of a palpable retroareolar mass, due to epithelium and stroma hyperplasia, due to the proliferation of the connective periductal tissue, edema, inflammation, and micro-papillae formation. It is generated by the oscillating ratio between free androgen and the estrogen and may occur from childhood to adulthood, regressive, most of the time in about 2 years, not being considered as a risk factor for breast cancer.

Summarizing: Table 1.

Table 1 The most frequent group of benign lesions described by clinical, radiological, pathological aspects and their relative risk (RR) to develop invasive carcinoma

Lesions	Clinical findings	Radiological findings	Pathological findings	RR (invase carcinoma)
Papillomas	Central: papillary discharge, rarely palpable Peripheral: usually nonspecific	Solidly and delimitated nodule and hypoechoic Cystic lesions composed of flat walls, lobuled, constituted by a solid component	Arborescent structures with vascular axis, constituted by dual cellularity (epithelium and myoepithelium)	Central: 2x RR Peripheral: 3x RR Atypical papilloma: 7.5x RR depending on the lesions of the adjacent parenchyma
Adenoses	Usually unspecific	Usually unspecific (except microcalcifications)	Hyperplasic ducts with irregular secondary lumens, peripherally distributed and disorganized central cells	Similar to the usual ductal sclerosing hyperplasia

(continued)

Table 1 (continued)

Lesions	Clinical findings	Radiological findings	Pathological findings	RR (invase carcinoma)
Complex sclerosing lesions/radial scar	Unspecific and rarely palpable	Irregular stellar density associated to a dense or radiolucent center	Stellar aspect. Tubules, trapped amid collagen	Relying on the adjacent parenchyma lesions
Fibroadenoma	Single nodular lesion, rarely multiple, palpable, mobile, and slow-growing	Homogeneous, oval, circumscribed nodule	Nodule with epithelial component (canalicular or tubular), with varying degrees of hyperplasia, amid collagenous or mixed stroma	Very low
Phyllodes tumor	Single, firm, and painless mass, usually measuring a diameter of 4.0–5.0 cm. Rarely multiple Fast growth	Rounded image, containing cysts, calcifications, or fissures, well-defined or irregular margins	Nodule composed by stromal hypercellular and fissured epithelial tissues, also presenting foliate arrangement	Depends on the classification of the lesion (benign, borderline, or malignant)

Recommended Reading

1. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, editors. WHO classification of tumours of the breast. Lyon: IARC; 2012. *Pathological, clinical and radiological findings related to the prognosis of the different types of lesions in mammary pathology, according to the most recent classification of the World Health Organization (WHO)*
2. Lewis JT, Hartmann LC, Vierkant RA, Maloney SD, Shane Pankratz V, Allers TM, Frost MH, Visscher DW. An analysis of breast cancer risk in women with single, multiple and atypical papilloma. Am J Surg Pathol. 2006;30:665–72. *Cohort study in patients diagnosed with fibrocystic mammary alteration. The RR for breast carcinoma in single papillomas (RR 2.04) was greater when compared to the non-proliferative mammary alteration (RR 1.28), but similar to the proliferative mammary alteration without atypia (RR 1.90). The RR for single papilloma carcinoma with atypia (RR 5.11) was not substantially different from atypical ductal hyperplasia/atypical lobular hyperplasia (RR 4.17). Patients with multiple papillomas present RR for carcinoma of 3.01, which is increased compared to the proliferative alteration without atypia or to the unique papillomas, and even greater in multiple papillomas with atypia (RR of 7.01). Therefore, multiple papillomas represent a proliferative mammary alteration with unique biological and clinical behavior*
3. Nakhlis F, Lester S, Denison C, Wong SM, Mongiu A, Golshan M. Complex sclerosing lesions and radial sclerosing lesions on core needle biopsy: Low risk of carcinoma on excision in cases with clinical and imaging concordance. Breast J. 2017. *Radiant sclerosing lesions (RSL) and complex lesions (CEL) are found to be unusual in biopsies, associated to divergent diagnoses obtained by surgical specimens, ranging between 0% and 23%, presenting, therefore, controversial management. In this study, it was sought to determine the risk of malignancy ratio between RSL/CEL, diagnosed in biopsies, aiming the evaluating the risk of future can-*

cer when performed solely by clinical follow-ups of these lesions, without surgical excision. Retrospectively, 118 cases of RSL/CEL in biopsies between 2005 and 2014 were analyzed. Among the 98 patients evaluated, in 34 cases (35%) surgical excisions were performed and in 64 (65%) clinical follow-up was performed. A malignancy rate of 9% was observed in surgical specimens of BIRADS lesions > 4c characterized as RSL/CEL in biopsies. In patients with concordant biopsies and BIRADS 4a, or in lesions weakly suspicioned, subjected to observation, a low subsequent rate of ipsilateral carcinoma was found. Despite this data, further studies are needed to confirm that clinical accompaniment may be a reasonable alternative to surgical excision whenever facing a RSL/CEL diagnosis in concordant biopsies, in BIRADS 4a or in non-palpable lesions less likely to be suspicioned.

4. Page DL, Salhany KE, Jensen RA, Dupont WD. Subsequent breast carcinoma risk after biopsy with atypia in a breast papilloma. Cancer. 1996;78(2):258–66. *Study demonstrates that the relative risk of atypical and non-atypical papillary lesions to develop invasive carcinoma is proportional to the lesions observed in the adjacent breast parenchyma. The carcinoma RR in women with papillomas, with atypical hyperplasia in adjacent parenchyma was 4 times higher than that observed in papillomas without atypia, being the risk particularly increased in the sites where the original papilloma was excised.*
5. Spruill L. Benign mimickers of malignant breast lesions. Semin Diagn Pathol. 2016;33(1):2–12. *Revision article in which some of the most common benign lesions (usual ductal hyperplasia, sclerosing, and radiation) are described and the malignant lesions that may simulate those benign diagnosis. The histopathological aspects are emphasized, aiming to identify characteristics that will lead to their correct diagnosis, either by biopsy, with partial representation of the lesion, or by the obtaining surgical specimens, representing the lesions. entirety*

Breast Lump

BBSG – Brazilian Breast Study Group

Introduction

A breast lump refers to every tumor present in the mammary gland. It may present cystic or solid content, might be palpable to the clinical examination or not, and is considered one of the most common reasons to access medical aid and may reach 60% of the specialist consultations. Most patients will present benign pathologies (70–75% of diagnoses).

Epidemiology and Physiopathology

Breast histology undergoes notorious changes during female ageing, markedly amid menarche and menopause. It begins with a clear predominance of ducts, lobules, and intralobular and interlobular stroma observed during women's reproductive life until the fibrotic changes and cystic formations, currently called fibrocystic changes, which are benign functional changes of the breasts. About 60–70% of women with no mammary pathology present this histological alteration (usually transient and related to menstrual status). Lastly, after menopause, the breast undergoes a lipo-substitution process, which occurs in 75% of cases, or fibro-substitution, present in the remaining 25% of women.

After menarche, the lobules and the breast stroma may respond in an exaggerated manner to physiological hormonal stimuli, forming fibroadenoma. They are nodules of limited growth and, in general, do not exceed 2 cm, involuting after menopause. Approximately 50% of fibroadenomas contain other proliferative lesions, such as sclerosing processes, adenoses, typical ductal hyperplasia, and epithelial microcalcifications. These are called complex fibroadenomas. Some variations,

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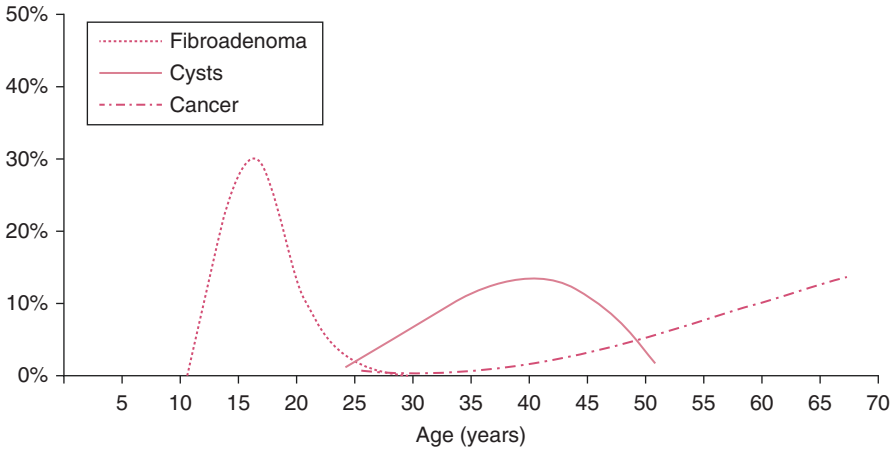


Fig. 1 Age-based breast mass epidemiology

such as the phyllodes tumor and the giant fibroadenoma, present greater cellularity than the regular stroma and usually reach larger sizes. In autopsy studies, 15–23% of women close to 20 years presented multiple fibroadenomas, with epidemiological data pointing to only 2.2% of clinical incidence. With the routine use of ultrasound in young women, the diagnosis of fibroadenoma becomes more frequent.

In the third and fourth decades of age, the proportion of palpable breast mass increases. In histological terms, this increase is due to the augmentation of normal lobular tissue. The stroma may also exhibit hypertrophy, resulting in palpable areas, of non-defined characteristics, overall in the superior-lateral quadrants of the breasts. In women between the fourth decade and the beginning of menopause, the glandular tissue may suffer hypertrophy in association with an increase of stromal tissue. At this stage, there is an increase in the incidence of breast fibrocystic changes, especially in women who undergo hormonal therapy (Fig. 1).

Histologically the cysts are originated in the terminal lobular duct unit. Most of the time, the internal epithelial layer is absent or atrophied. The majority are subclinical, called microcysts. Complex cysts correspond to 5% of the cysts. The diagnosis is performed through ultrasound, as they present a solid area inside. The rate of malignancy of this type of cyst is low, but it should be considered suspicious for neoplasia and thus investigated with histological or cytological methods.

Clinical Pattern

Currently, due to the stricter guidelines addressing breast imaging exams (mammography and ultrasound), plenty of mass are diagnosed without clinical manifestation.

The best time to perform the physical examination of the breasts is after menstruation. Physical examination must be complete, including static and dynamic inspection, palpation and evaluation of the axillary, supraclavicular, and infraclavicular area

for masses or adenopathy. The evaluation of the contralateral breast is indispensable to the definition of small tumors.

Following the identification of the mass, the main characteristics that must be described are consistency (i.e., hard or soft, smooth or irregular), mobility (whether it feels freely mobile or fixed to the skin or chest wall), size, and location. In cases of follow-up being required, these characteristics must be compared retrospectively.

Differential Diagnosis

Fibroadenoma

The fibroadenomas are firm and elastic tumors, presenting regular and smooth limits. They are bilateralism and consist of multiple tumors in 10% and 10–15% of the cases, respectively. The lesion does not present cutaneous alteration or reactional adenomegalies. They may vary in size according to the menstrual cycle phase, usually increase in gestation and breastfeeding, and involute in menopause.

Phyllodes Tumor

They present similar clinical features to the fibroadenoma but with superior dimensions and faster growth.

Juvenile Fibroadenoma

They present the same clinical nature of phyllodes tumor; however, they may be diagnosed in women after menopause.

Hamartoma

Also known as fibroadenolipoma, it is an infrequent benign lesion. It is usually diagnosed by imaging methods; but whenever palpable, it corresponds to well-delimited tumors of precise boundaries. Histologically, it is described as “breast in a breast” (normal area of breast encapsulated tissue).

Cysts

They are presented as softened nodules of smooth and well-defined boundaries. They may cause pain when they grow up suddenly.

Functional Benign Breast Alterations

Patients refer localized pain, usually in superolateral quadrant of the breasts, and under clinical examination are fibro-elastic thickening, movable, which involute after menstruation.

Malignant Neoplasia or Neoplasms

There are solid masses composed by indefinite boundaries and adhered to adjacent structures. The following factors may be found: cutaneous alteration, suspicious capillary flow, and axillary and supraclavicular adenomegalies. They're usually painless.

Steatonecrosis

This presents similar characteristics to cancer but is secondary to trauma or to prior surgical procedures.

Ductal Ectasia

The clinical manifestation of this entity corresponds to the solid retro-areolar nodule, commonly associated with pain during palpation, inversion of nipple, and papillary flow. It affects women in the fourth decade of life and in perimenopause. It may simulate cancer.

Papilloma

The lesion usually addresses women between 30 and 50 years, presenting a bloody nipple discharge associated with nodules close to the areola. Most of the time it is small sized, but they may form cysts up to 10 cm.

Propaedeutics

Firstly, the anamneses is of great value in diagnosing breast mass. Age (evaluation of the incidence of masses according to age group), hormonal status, associated

factors (pain, cutaneous alteration, axillary and supraclavicular adenomegalies), and the sustained usage of medicaments (contraceptives, hormone therapy) must be included in the clinical history. Complimentarily regarding medical history, the doctor should identify risk factors involved on the development of breast cancer, requiring invasive propaedeutics. It is important to emphasize that 80% of women diagnosed with breast cancer present few or no risk factors.

Mammary propaedeutics, whenever facing the discovery of breast nodules, is based on three axis: clinical, radiological, and cyto-/histological examination.

In palpable masses, the ultrasound has proven to be a more effective method when compared to mammography, although it has no screening indication. The ultrasound is harmless, mandatory to differentiate among solid and cystic lesions, and generally well tolerated by women.

The ultrasonographic features of benign lesions are listed in Table 1.

The continuous execution of mammograms is vital to screen other lesions and may be capable to diagnose alterations such as lipomas and calcified fibroadenomas.

The MRI has a high sensitivity, but it has a reduced specificity. It does not usually compose the propaedeutics routine but may be employed in special situations.

Whenever facing non-palpable or palpable lesions, ultrasound may be performed, which is an easier and cheaper method. The fine needle aspiration, which may undergo cytological evaluation, should be performed in ambulatory regime, not requiring local anesthesia, and is the gold standard in the differentiation of solid and cystic lesions. Cystic lesions may be entirely drained, therefore accomplishing curing status. Solid lesions require a percutaneous core biopsy for a histological sample, in order to achieve satisfactory indices of sensitivity and specificity and in cases of neoplastic lesions, is capable to provide material for immunohistochemical analysis.

Patients with a standard triple evaluation (clinical, image, and biopsy) are submitted to discrete risk of malignant findings.

Incisional surgical biopsy (retrieves part of the lesion) should always be avoided. Contrarily, excisional biopsy (retrieves all the lesion) may be performed in some cases of reduced risk as it is both diagnostic and curative. In such cases, the patient should be informed of the theoretical risk of carcinoma.

Table 1 Ultrasonographic characteristics of benign lesions. (Adapted from Chala L et al., J Clin Ultrasound, 2007; 35(1): 9–19.)

Characteristics	Benign features
Morphology	Rounded, ellipsoid, or with up to three lobulations
Boundaries	Well defined
Architectural distortions	Not present
Height/width ratio duvida	Smaller than one
Acoustic shadow	Not present
Size	Smaller than one

Treatment

Cysts

Simple non-palpable cysts, diagnosed solely by ultrasound, should not be approached nor monitored, and the patient should be tranquilized.

Facing palpable cysts, fine needle aspiration is an option, being both diagnostic and therapeutic. Cytology is not of great appliance, as it presents reduced validity and the sample is usually inapplicable, but may be required in suspicious cases such as in the presence of blood, bulky cysts (above 50 ml), or cysts that recur in a short time. Control must be performed within 6 months.

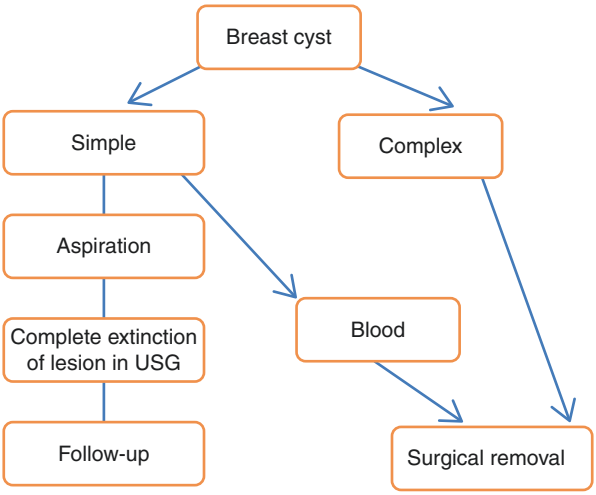
Surgical excision should be indicated facing cases of cysts with solid content. Cysts with thick content, thin septum, or clustered microcysts are associated with little risk of malignancy and may be accompanied clinically.

Solid Masses

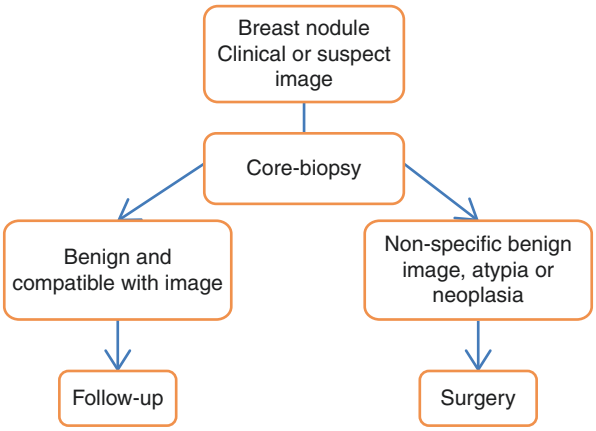
All nodules with suspicious image must undergo percutaneous biopsy, regardless of age. The need to surgically approach those patients should be determined according to the biopsy result.

Patients under 30 years of age present little risk of breast cancer; therefore biopsy may be avoided if the clinical examination and image are absolutely suggestive of a benign lesion. In such cases, the indication of surgery depends on the patient's desire and is usually performed whenever injuries cause deformity due to their sizes.

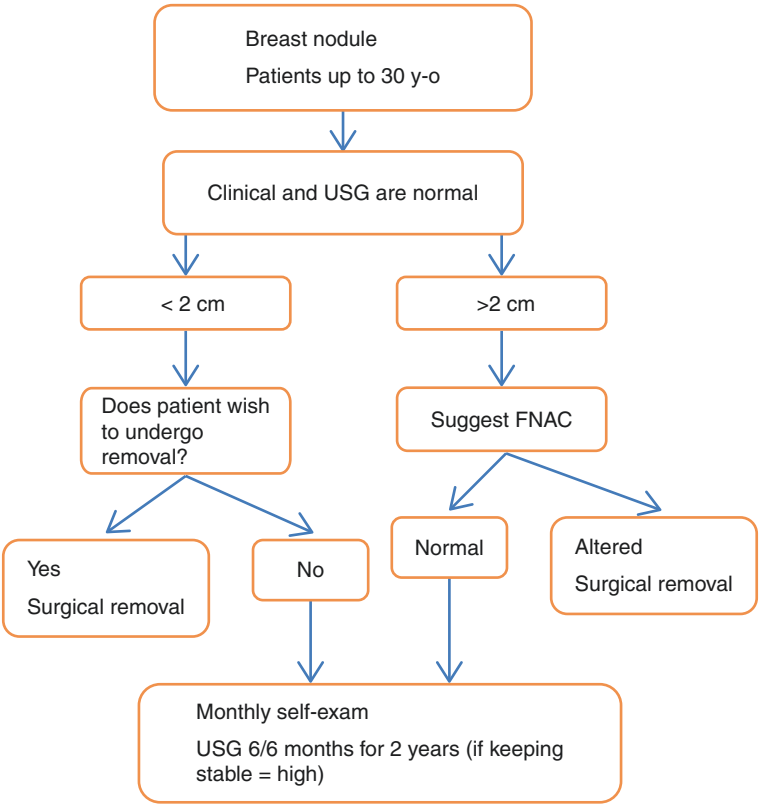
Flowcharts



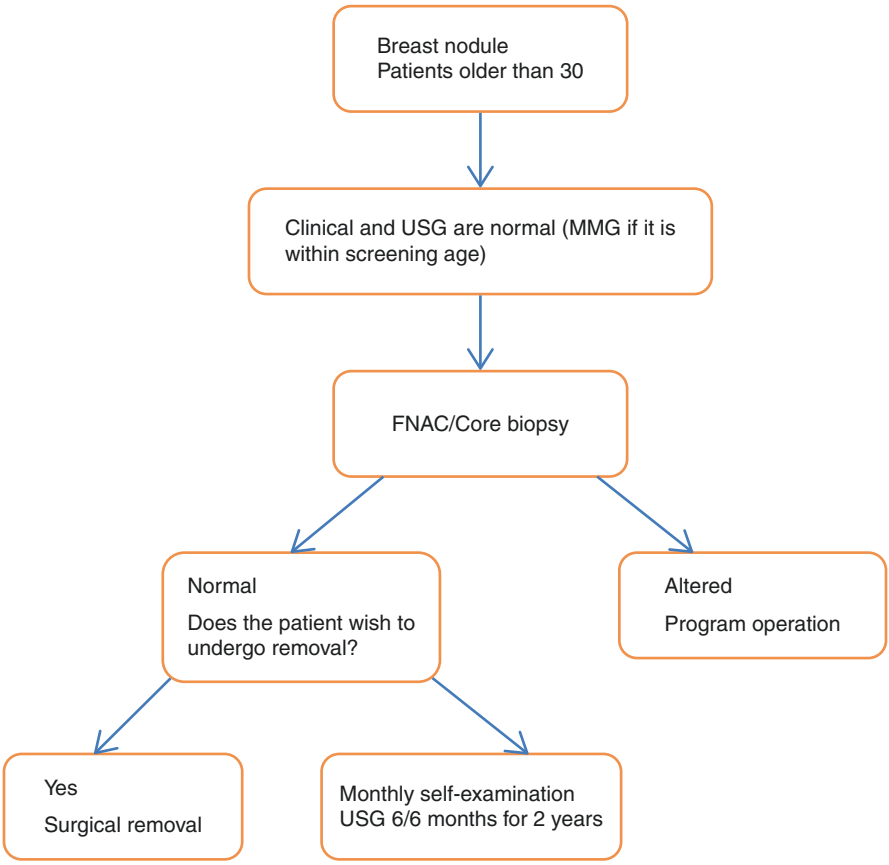
Flowchart 1: Breast cyst



Flowchart 2: Breast mass with abnormal imaging



Flowchart 3: Propably benign breast mass before 30 years-old



Flowchart 4: Probably benign breast mass after 30 years-old

Recommended Reading

1. El-Wakeel H, Umpleby HC. Systematic review of fibroadenoma as a risk factor for breast cancer. Breast. 2003;12(5):302–7. *7 cohort and control case studies were evaluated. Two studies pointed in favor to the relative risk of breast cancer in fibroadenomas without hyperplasia between 1.48 and 1.7, fibroadenoma with hyperplasia between 3.47 and 3.7 and fibroadenoma with hyperplasia and atypia between 6.9 and 7.29, as the risk remains for more than 20 years after diagnosis. It suggests to improve the concern directed for patients with fibroadenoma associated with hyperplasia, with or without atypia.*
2. Hartmenn LC, et al. Benign breast disease and the risk of breast cancer. N Engl J Med. 2005;353:229–37. *The presence of proliferative lesions in biopsies, patients' age and family history are determinant factors to evaluate the risk of breast cancer. Apparently, there was no association between the presence of atypia and family history in determining the risk*

3. Mary Ann Kosir, MD, Professor of Surgery and Oncology, Wayne State UniversitySchool of Medicine, Karmanos Cancer Center/Gynecology and Obstetrics – MSD Manual Professional Edition. *Breast Masses (Breast Lumps).*
4. Oyama T, Koibuchi Y, McKee G. Core needle biopsy (CNB) as a diagnostic method for breast lesions: comparison with fine needle aspiration cytology (FNA). Breast Cancer. 2004;11(4):339–42. *The vacuum-assisted puncture for non-palpable nodules has shown to be less specific when compared to percutaneous biopsy. In tangible lesions, the specificity of the vacuum-assisted puncture increases when the triple diagnosis is associated: physical examination, image and cytology*
5. Román M, Quintana MJ, Ferrer J, Sala M. Castells. Cumulative risk of breast cancer screening outcomes according to the presence of previous benign breast disease and family history of breast cancer: supporting personalized screening. Br J Cancer. 2017;116(11):1480–5. *Screening follow-up of 42,928 women for 15 years, demonstrating the excess of exams in women with benign pathologies.*
6. Smith GE, Burrows P. Ultrasound diagnosis of fibroadenoma – is biopsy always necessary? Clin Radiol. 2008;63(5):511–5. *Retrospective study with 347 women under the age of 25 who presented nodules with benign characteristics and were still subjected to biopsy by coarse needle. Divergence was present in just one case, in which invasive carcinoma was diagnosed. It concludes that in young women with nodules whose ultrasonographic analysis is benign, do not require histological diagnosis.*

Breast Pain

BBSG – Brazilian Breast Study Group

Breast pain or mastalgia is a frequent complaint among women and may interfere directly with the emotional, social, and professional life. It brings anguish and anxiety because women frequently related it to breast cancer.

Epidemiology

Breast cancer is poorly associated with mastalgia (0.8% to 2% of cases), usually appearing as an acyclic and persistent and focal pain in the breast. Epidemiological data show that approximately 65–70% of women will present mastalgia at some stage of life, being more common in early adolescence and during menacme, with subsequent premenopausal attenuation and disappearance during gestations and postmenopausal period. It can be divided into cyclic, when related to the menstrual cycle, or acyclic, when attributed to a non-hormonal causes.

Anamnesis should assess the onset; duration; location; intensity; triggering, relieving, aggravating, or associated factors; and, especially, relation to the menstrual cycle. The psychological condition of the patient must also be perceived in order to exclude any association with psychosomatic origin.

During the physical examination, the chest wall should be carefully examined in order to exclude extramammary causes (Table 1). The palpation of the costal arches, as well as joints, are fundamental for the diagnosis of osteochondritis.

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Table 1 Causes of extramammary pain

Muscular pain
Costochondritis (Tietze syndrome)
Intercostal neuritis
Scapular bursitis
Cervical radiculopathy
Chest wall trauma/rib fracture
Herpes zoster
Pericarditis
Gastroesophageal reflux
Peptic ulcer
Coronary diseases

Pathophysiology of Cyclic Mastalgia

The pathophysiology is not completely understood, but it may be related to an imbalance in the E/P ratio at the end of the second phase of the menstrual cycle. This imbalance occurs at the central level (dopaminergic system) and it may lead to increased prolactin release. Also, excessive stress, which releases endogenous opioids (serotonin) reducing dopamine, facilitates the release of prolactin, which may justify the consequent increase in breast tissue sensitivity.

Clinical Presentation of Cyclic Mastalgia

Women with cyclic mastalgia will have pain often associated with pre-menstrual or periovulatory breast swelling with remission of symptoms after menstruation. In more severe cases, pain may persist throughout the menstrual cycle. It affects both breasts, being more common in the superolateral quadrant, usually in stabbing and of acute manifestation.

Etiology of Cyclic Mastalgia

There are several causes of cyclic mastalgia, as listed below in Table 2.

Clinical Presentation of Non-cyclic Mastalgia

Non-cyclic mastalgia presents discomfort usually located at one point of the breast, but it can radiate to the armpit, the arm, the shoulder, and the hand. The primary factor is nonconformity with the menstrual cycle.

Table 2 Causes of cyclic mastalgia

Breast hypertrophy
Macrocysts
Thrombophlebitis (Mondor syndrome)
Previous breast surgery
Ductal ectasia
Mastitis
Trauma
Pregnancy
Large nodules
Medication
Cancer

Propedeutics

Clinical evaluation is usually sufficient to elucidate the condition. Breast Image present limited value and should be restricted to patients requiring screening or suspected focal lesions, but exclusion of breast neoplasm is essential in the investigation of breast pain. In cases of suspected extramammary pain, specific examinations may be required to evaluate other organs or regions of the body.

Treatment

After excluding the presence of neoplasia, the main treatment is reassurance. Simple information about the self-limiting nature of the symptom and also about the lack of relation with breast cancer is enough to reassure 85% to 90% of the women. There are behavioral measures that are not proven but are reported as beneficial and harmless: the use of sports bra, fat-free diet, and physical exercise are the most notable ones. Other drugs have efficacy in the treatment of pain but are not specific for mastalgia, such as anti-inflammatories and analgesics in general, but prolonged use is at risk of side effects. Topical anti-inflammatory drugs in gel form have satisfactory results and fewer side effects and may be an alternative to musculoskeletal pain. Anxiolytic medications or antidepressants have a global effect on pain relief and treat cases that may exacerbate it. Unfortunately, there are no randomized trials evaluating mastalgia response to these medications (Table 3).

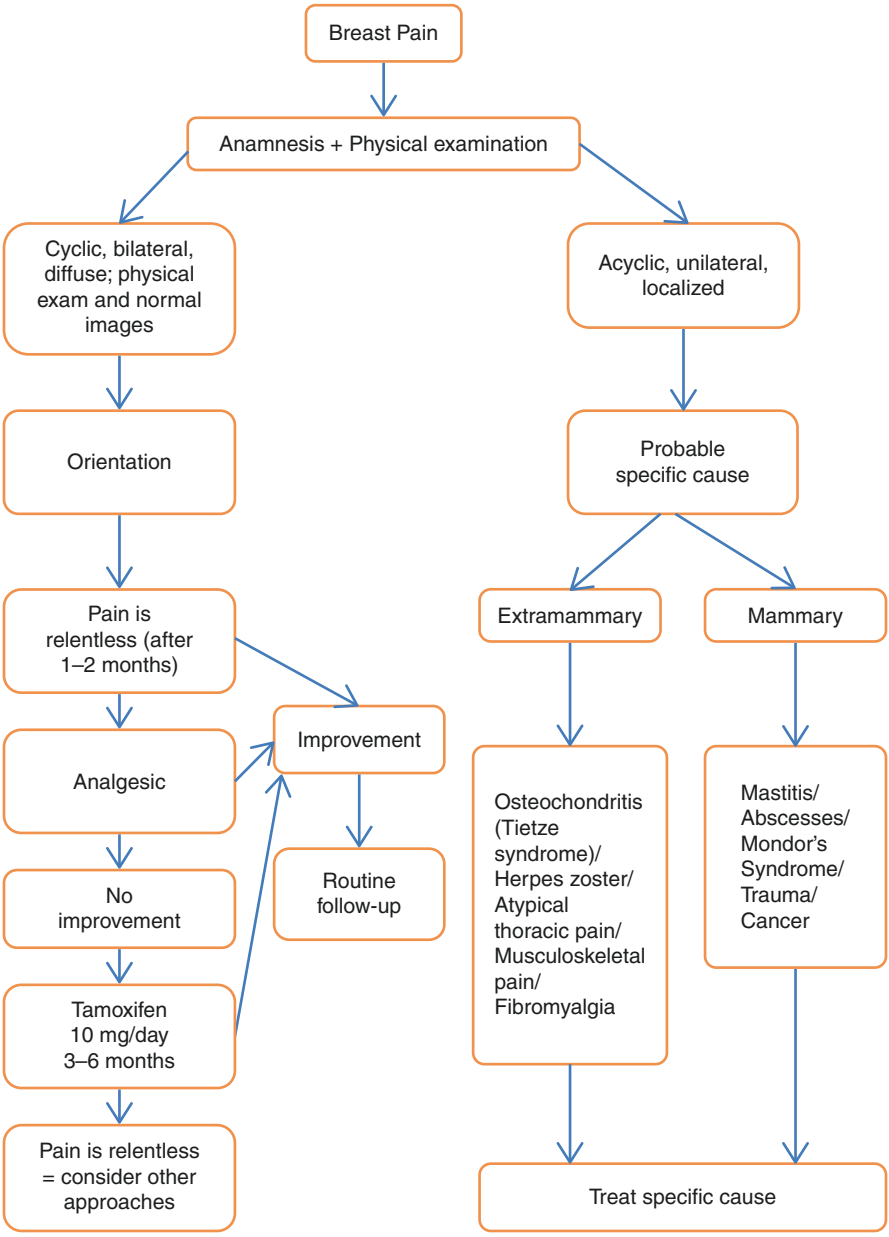
As patients have high response to reassurance, any drug, even placebo, appears to have high success rates. Unfortunately, these drugs are widely used in clinical practice, leading to unnecessary cost and risk, and they include diuretics, a diet free of xanthine and progestogens. The pharmacological treatment of choice for cyclic mastalgia is hormonal blockade. Inhibitors of estrogen and prolactin act in the improvement of the condition, even in the absence of elevated levels of these hormones. Srivastava et al. performed a meta-analysis with the four drugs most commonly used

Table 3 Drugs that can potentially cause non-cyclic mastalgia

Hormone medications (estrogen, progesterone, clomiphene, cyproterone)
Antidepressants, anxiolytics, antipsychotics (sertraline, venlafaxine, amitriptyline, haloperidol)
Antihypertensive/cardiac (spironolactone, methyldopa, digoxin)
Antimicrobials (ketoconazole, metronidazole)
Miscellaneous (cimetidine, domperidone, cyclosporine)

in the treatment of breast pain: tamoxifen, danazol, bromocriptine, and primrose oil derivatives (herbal medicines with high gamma-oleic acid concentration), and although there were no studies using a good methodology, some conclusions were obtained: the results indicated that primrose oil, vitamins, or gamma-linoleic acid did not demonstrate efficacy in the treatment of mastalgia, whereas hormonal drugs presented positive results in relief of symptoms, with tamoxifen being the one with the least side effects at a dose of 10 mg per day, orally, for 3 to 6 months.

Flow Chart



Flowchart 1 Approach of patient with mastalgia

Recommended Reading

1. Gong C, et al. A double-blind randomized controlled trial of toremifen therapy for Mastalgia. Arch Surg. 2006;141:43–7. *Toremifen citrate has been shown to be effective in relieving the moderate and severe symptoms of cyclic mastalgia, in addition to improving non-cyclic breast pain. Its highest favorable point, relative to tamoxifen, is the lowest rate of side effects*
2. Goyal A, Mansel RE. A randomized multicenter study of gamolenic acid (Efamast) with and without antioxidant vitamins and minerals in the management of mastalgia. Breast J. 2005;11(1):41–7. *555 women with moderate to severe symptoms of cyclic mastalgia were randomized into four treatment groups: gamma-Linolenic acid and antioxidants, fatty acids and antioxidants, gamma-Linolenic acid and placebo, fatty acids and placebo. There was similar reduction of symptoms in the four groups. This study observed that the use of gamma-Linolenic acid did not differ in efficacy when compared to the use of placebos.*
3. Mansel R, Goyal A, Le Nestour E, Marsini-Etévé V, O'Connell K, Afimoxifene (4-OHT) Breast Pain Research Group. A phase II trial of Afimoxifene (4-hydroxytamoxifen gel) for cyclical mastalgia in premenopausal women. Breast Cancer Res Treat. 2007;106(3):389–97. *Afimoxifene is a new antiestrogenic agent with a unique metabolic effect, and with a significant reduction of the mammary symptomatology. An attractive characteristic it presents is decrease of the side effects in relation to tamoxifen, since it does not undergo metabolism of the first hepatic passage.*
4. Srivastava A, Mansel RE, Arvind N, Prasad K, Dhar A, Chabra A. Evidence-based management of Mastalgia: a meta-analysis of randomised trials. Breast. 2007;16:503–12. *Danazol, bromocriptine and tamoxifen are drugs that offer relative relief from the symptoms of mastalgia. No study compared the efficacy of the drugs to each other, but tamoxifen in small doses is the drug of choice. The use of gamma-Linolenic acid derivatives still lacks reliable studies.*

Nipple Discharge

BBSG – Brazilian Breast Study Group

Definition and Epidemiology

Nipple discharge is a drainage of intraductal fluid through the nipple outside puerperal pregnant cycle. It's responsible for almost 5–10% of breast complaints in out patient clinic. Milk secretion is called galactorrhea and non-milk secretion is called telorrhea.

Between 60% and 80% of women will have papillary flow throughout their life, more common during menacme, but when it is present in elderly patients, the probability of neoplastic origin increases. About 90–95% of cases have benign origin.

Pathophysiology

It can be caused by factors that are specific to the mammary gland, both intraductal and extraductal, or by extramammary factors related to the control of milk production (Tables 1 and 2).

1. Intraductal: inherent to the inner wall of the duct
   Epithelial proliferations (papillomas, adenomas, hyperplasia, etc.)
   Intraductal infections (galactophoritis)
   Intraductal neoplasm with necrosis
2. Extraductal: pathologies that can partially disrupt the intra ductal epithelium and cause nipple discharge
   Malignant neoplasms
   Infections
   Other pathologies

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Table 1 Main medicines associated to galactorrhea

Pharmacological class	Medicines
Hormones	Estrogens, oral contraceptives, thyroid hormones
Psychotropic	Risperidone, clomipramine, nortriptyline, serotonin reuptake inhibitors, phenothiazine, tricyclic antidepressants, opioids, codeine, heroin, cocaine, sulpiride
Antiemetic	Metoclopramide, domperidone
Anti-hypertensive	Verapamil, methyldopa, reserpine
H2 blockers	Cimetidine, ranitidine, omeprazole

Table 2 Pathologies that may cause an increase in prolactin

Origin	Pathology
Lesions in NCS	Prolactinomas, acromegaly, craniopharyngioma, encephalitis, pituitary tumor, surgical transection, pituitary trauma
Lesions in thoracic wall	Herpes zoster neuritis, thoracotomy, mastectomy, burns, dermatitis, and traumatisms
Systemic diseases	Chronic renal failure, Addison's disease, Cushing's disease, adrenal hyperplasia, primary hypothyroidism, diabetes, liver disease
Ectopic production	Bronchogenic carcinoma, hypernephroma
Varied causes	Anovulation, coitus, dilatation and curettage, breast stimulation, hysterectomy, IUD, pseudocyesis, neck surgeries

- Galactorrhea: caused by non-mammary factors, usually by changes that cause hyperprolactinemia. Some patients, however, may present galactorrhea without increasing prolactin levels. The most common cause of increased prolactin levels is the use of dopamine suppressive drugs.

Diagnosis

Anamnesis

In routine gynecological anamnesis, the physician should seek information on family history, use of hormone therapy, use of medications, excessive manipulation of the papilla or trauma, and age, in addition to other signs or symptoms of breast and secretion characteristics. It is also advisable to define the characteristics of the papillary flow, which can indeed determine what should be investigated:

- Laterality (unilateral or bilateral)
- Number of orifices (single or multiple)
- Uprising (spontaneous or provoked to expression)
- Macroscopic aspect (milky; purulent; multicolored, greenish, brown, or yellowish; viscous; crystalline; serous; hemorrhagic)

Physical Examination

At inspection, is important confirm the date of anamnesis and aspects of fluid discharge. Palpation should be oriented in order to promote secretion and establish the location or mammary segment that is causing the effusion ("trigger point").

The characteristics of the flow that present suspicions to the physical examination are:

- Unilateral
- Spontaneous
- Single ductal
- Hemorrhagic, serohemorrhagic, crystalline, serous
- Presence of associated tumor
- Elderly patients
- Male

Differences in the Effusion Aspect

- Serous (fibrocystic mastopathy, cancer, papilloma, papillomatosis)
- Crystalline (papilloma, papillomatosis, cancer)
- Multicolor (ductal ectasia)
- Viscous (comedomastitis)
- Purulent (galactophoritis)
- Serohemorrhagic, hemorrhagic (papilloma, cancer)

Cytology

There is no benefit in the cytology of this test, since the sensitivity assessed in several studies was very low, ranging from 6% to 17%.

Mammography and Ultrasonography

They have low sensitivity in the diagnosis of the alterations, but their accomplishment is mandatory to evaluate possible concomitant lesions. The sensitivity and specificity of mammography in cancer or high-risk lesions are 10% and 94–100%, respectively.

Ultrasonography can detect some intraductal lesions, such as ductal ectasia, papilloma, and abscesses, in addition to guiding possible percutaneous biopsies.

Magnetic Resonance Imaging

In recent years there has been a progressive increase in the use of magnetic resonance imaging in the papillary flow propaedeutics: despite having a relevant role in the differentiation of benign and malignant lesions, the false-positive rates and the limitation of biopsies make it difficult to perform this exam.

Ductography or Galactography

It consists of catheterization of the duct and water-soluble contrast injection, with sequential mammograms to evaluate the ductal tree and to observe filling or blocking faults. It may be useful in peripheral lesions, but have little applicability due to the discomfort the technique produces, to be unspecific and, mainly due to the advent and evolution of the ultrasound technique, especially when performed by experienced professionals.

Ductoscopy

Is micro endoscope fiber optic, inserted into the duct that allows visualization, biopsy and citologica analysis. with high prdictive positive value, but with low sensitivity and painful. This technique is widely used in Japan and China, and there is also a classification system based on the appearance of the lesions, developed by the Japanese Association of Breast Ductoscopy, with reports of experience in other countries. Still, a learning curve and special care handling it are required, and there are no scientific reports of experience in Brazil.

Ductal Lavage

This technique was very promising in the beginning; however, it presents the same drawbacks of the cytological evaluation of the flow; in addition, a benign result does not detract from the continuation of the investigation and positivity does not determine the location of the disease.

Differential Diagnosis

Situations that cause an exudate on the papillary surface, that is, a false effusion are as follows (Figs. 1 and 2):

- Papillary inversion
- Eczematous lesions

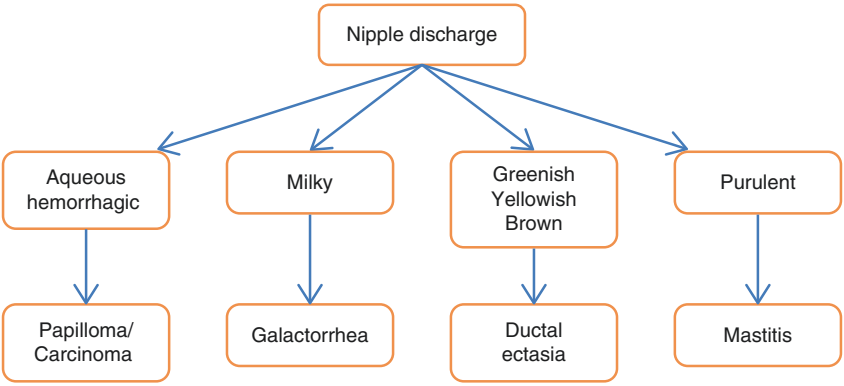

Fig. 1 Flowchart of the characteristics of effusion and possible diagnoses

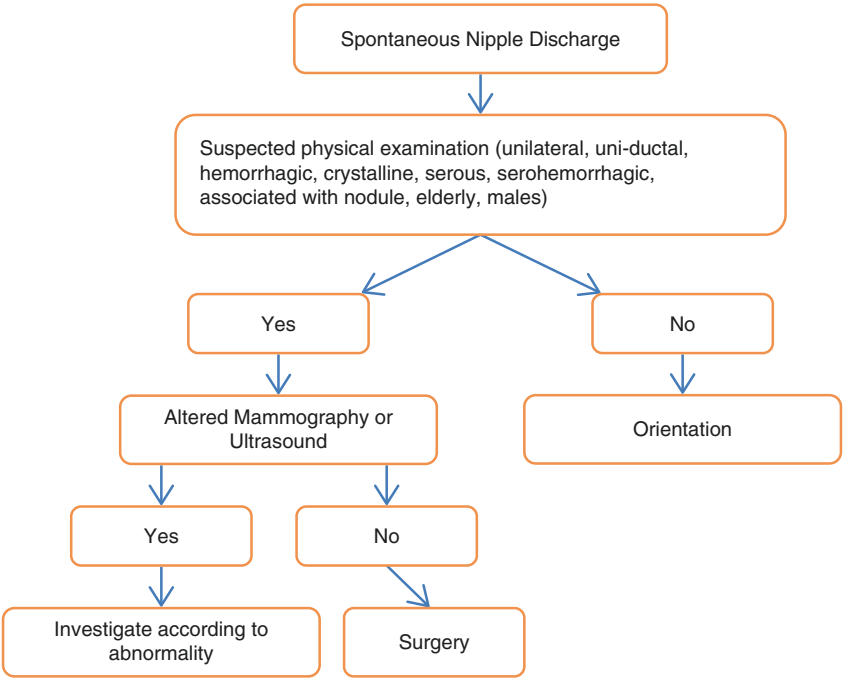

Fig. 2 Flowchart of management of spontaneous papillary effusion

- Traumatic injuries
- Herpes simplex
- Infections
- Ductal fistulas
- Recurrent chronic subareolar abscess

Only excision can provide a definitive histological diagnosis, and it remains the gold standard in suspicious lesions.

Treatment

It will depend on the characteristics of the flow. Most will only need guidance and reassurance, the purulent are treated with antibiotic therapy, and the suspect ones are operated.

Some patients with unsuspected flow (multidrug, bilateral) may require surgery because of the excessive discomfort caused by the continuous effusion.

In the patient who still wants to breastfeed, a selective resection of the affected duct is performed, guided by the "trigger point," while in women without breastfeeding or postmenopausal desire, selective resection can be replaced by resection of the main ducts. The intraoperative examination has little value in the diagnosis of papillary lesions.

The main anatomopathological findings of patients submitted to surgery due to papillary flow are:

- Papilloma: this is the most common cause of hyaline, serohematic, or bloody secretion. It usually affects the subareolar main ducts, with a diameter varying from a few millimeters to 4.0 cm, a soft and friable consistency, being present in about 35–50% of the operated cases. In the absence of evident lesion on clinical examination or imaging methods, papilloma is the most frequent cause of pathological papillary effusion in more than 95% of patients;
- Ductal ectasia: loss of elastin from the ductal walls and chronic inflammatory infiltration, being evidenced in 15–30% of the operated cases;
- Carcinoma: confirmed in around 5–20% of the operated cases. When there is suspected palpable lesion, or visible by imaging methods, the presence of bleeding effusion is almost pathognomonic of malignant neoplasm.

Recommended Reading

1. Alcock C, Layer GT. Predicting occult malignancy in nipple discharge. ANZ J Surg. 2010;80(9):646–9. *It corroborates with most of the published studies that the gold standard diagnosis-treatment for suspected papillary flow is microductectomy.*

2. Liu M, Guo G, Xie F, et al. Mammary ductoscopy and follow-up avoid unnecessary duct excision in patients with pathologic nipple discharge. J Surg Oncol. 2015;112(2):139–43. *It shows that ductoscopy, in specialized services, is an excellent diagnostic method for suspicious papillary flow.*
3. Sanders LM, Daigle M. The rightful role of MRI after negative conventional imaging in the management of bloody nipple discharge. Breast J. 2016;22(2):209–12. *In patients with suspected papillary flow and conventional negative tests (mammography and ultrasonography), magnetic resonance imaging is indicated by high negative predictive value.*
4. Simmons R, Adamovich T, Brennan M, et al. Nonsurgical evaluation of pathologic nipple discharge. Ann Surg Oncol. 2003;10(2):113–6. *Cytological evaluation of 108 patients with suspicious papillary flow, showing low specificity. It concludes that it should not be part of the diagnostic arsenal.*
5. Wong Chung JE, Jeuriens-van de Ven SA, van Helmond N, et al. Does nipple discharge color predict (pre-) malignant breast pathology? Breast J. 2016;22(2):202–8. *Evaluation of 184 patients with unilateral and uniductal papillary flow with bloody appearance. Twenty cases of carcinoma and twenty-one cases of atypical lesions were found. It was concluded that the presence of blood secretion should guide the surgical investigation.*

Gynecomastia

BBSG – Brazilian Breast Study Group

Introduction

Gynecomastia is the benign proliferation of glandular tissue in males, more frequent in adolescents and the elderly. In most cases, it is a physiological and transient condition, but an in-depth clinical investigation may be necessary to rule out pathological causes. Differential diagnosis should be made between true gynecomastia and lipomastia, which consists of the accumulation of adipose tissue in the prepectoral region.

Epidemiology

The incidence in the general population is unknown, but three known peaks of incidence are the following: in the newborns (secondary to the maternal hyper estrogenic state), during adolescence, and in senescence (between the sixth and the seventh decades of life).

Pathophysiology

Gynecomastia occurs due to an imbalance between the concentration of estrogen and free circulating testosterone, but its cause is usually idiopathic. The association with external and pathological causes should always be discarded, such as those described in Table 1.

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Table 1 Causes of gynecomastia

Pathologies	Klinefelter syndrome; neoplasms (lung/adrenal/prostate/testis); Parkinson's disease; cirrhosis, hepatoma; chronic renal failure; malnutrition; hyperthyroidism
Medicines	Amphetamines; captopril; ketoconazole; anabolic steroids; spironolactone; haloperidol; nifedipine; prednisone; zoladex; diazepam; metronidazole; flutamide; verapamil; amiodarone; antiretrovirals; cyproterone acetate; metoclopramide; antipsychotics; finasteride; omeprazole; cyclophosphamide; theophylline
Drugs	Marijuana; alcohol; heroin

Diagnostic Investigation

It is important to consider previous pathologies, medications in use, and drug abuse. In the physical examination, the characteristic finding is a discoid-shaped nodule, elastic consistency, and well-delimited borders, not adhered to deep planes and with concentric growth in relation to the nipple, presenting bilaterally in approximately half the patients, while papillary flow is very unusual. Differentiation with lipomastia or pseudogynecomastia is necessary, especially in obese patients, when the increase in breast volume is due to adipose tissue, not an actual increase of the mammary gland. Imaging tests can aid in diagnosis or therapeutic planning. Laboratory investigation consists mainly in the serum levels of the following hormones: human chorionic gonadotrophin (HCG), estradiol (E2), testosterone (T), and luteinizing hormone (LH). No specific cause is usually identified, and most cases are considered idiopathic.

Treatment

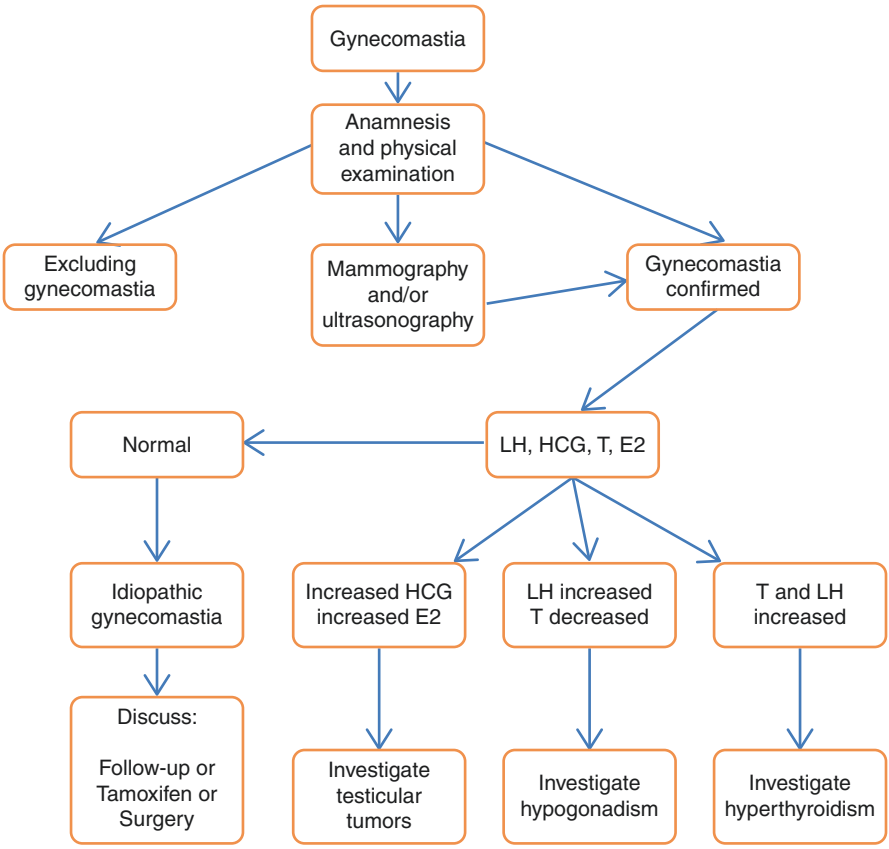
When etiology gynecomastia is known, its management consists in the treatment of the primary cause. Obese patients, for example, should be encouraged to lose weight; also, those who use medicines associated with the development of gynecomastia are recommended to change them when possible. Abandonment of substance use, such as alcohol, marijuana, and heroin, should be recommended. In suspected cases of neoplasia, treatment of the primary tumor should be the priority. In newborns, spontaneous involution occurs when maternal estrogenic stimulus ceases. In adolescents, the conduct is expectant, since in most cases spontaneous regression occurs.

Surgical treatment can be considered in cases of social and psychological discomfort. Men, without physical or psychological discomfort, or those with a surgical contraindication, may have expectant behavior, and annual clinical follow-up is recommended. Surgery may be considered in cases of idiopathic gynecomastia without spontaneous regression. The techniques are variable, but usually discrete incisions, such as partial or complete periareolar, should be considered. Bulky gynecomastia may require the use of reductive mammoplasty techniques, while

liposuction is a method chosen in cases of lipomastia or those associated with open surgery techniques. The aesthetic result is generally favorable, but caution with the vascularization of cutaneous flaps and nipple-areola complex is important to avoid necrosis.

Medicine treatment is controversal. There are no randomized trials of drug use in gynecomastia. Tamoxifen at a dose of 10–20 mg/day for 3–6 months has shown some favorable results; however, randomized clinical studies are still needed to establish the true efficacy of tamoxifen in the treatment of gynecomastia, as well as the optimal dose, duration of treatment and the actual rate of recurrence. And it is also important to consider the increase in thromboembolic events.

Flowchart



Flowchart 1 Approach of patient with gynecomastia

Recommended Reading

1. Braunstein GD. Gynecomastia. NEJM. 2007;357(12):1229–37. *A review article on investigation (imaging and laboratory tests) management of gynecomastia and postoperative results*
2. Deepinder F, Braunstein GD. Drug-induced gynecomastia: na evidence-based review. Expert Opin Drug Saf. 2012;11(5):779–95. *An article about medicines inducing gynecomastia*
3. James R, Ahmed F, Cunnick G. The efficacy of tamoxifen in the treatment of primary gynecomastia: an observational study of tamoxifen versus observation alone. Breast J. 2012;18(6):620–1. *Use of tamoxifen to manage gynecomastia*
4. Lee JH, Kim IK, Kim TG, Kim YH. Surgical correction of gynecomastia with minimal scarring. Aesthet Plast Surg. 2012;36(6):1302–6. *Surgical treatment of gynecomastia*

Infectious Breast Diseases

BBSG – Brazilian Breast Study Group

Introduction

Inflammatory processes of the breast, also called mastitis, are, by concept, infections that are installed in the breast tissue. Performing the differential diagnosis between the various types of mastitis can be complicated, especially with the low incidence types. In addition, confusion of diagnosis between infectious processes and breast carcinoma may occur, leading to delayed treatment of breast neoplasia. Recognizing the clinical picture and performing the differential diagnosis between acute mastitis and inflammatory carcinoma are fundamental in patient management (Fig. 1).

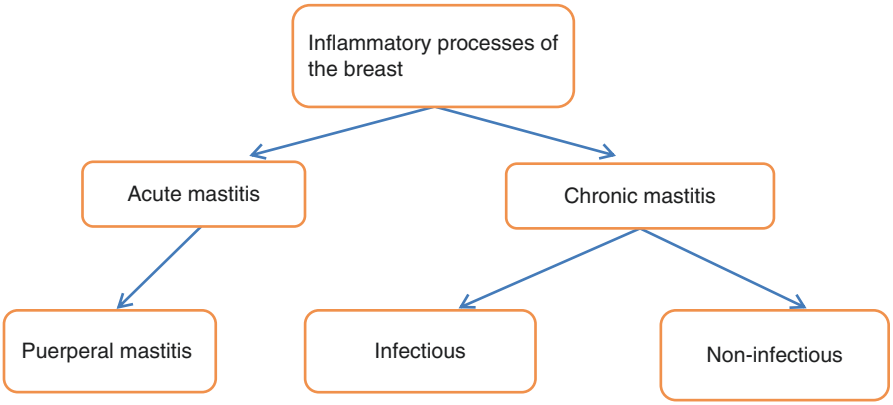


Fig. 1 Flowchart of the inflammatory processes of the breast

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The incidence of mastitis is inversely proportional to the quality of basic health care, since it is dependent on hygiene, sanitation, and dietary factors of the population. Although it can be found in any age group and in all phases of a woman's life, it is more common in the age group between 18 and 50 years.

Mastitis is classified into acute or chronic and infectious or non-infectious.

Acute Mastitis

It presents a clinical evolution lasting less than 30 days. Infection of the mammary parenchyma in the puerperium is the most common acute mastitis.

Puerperal (or Lactation) Mastitis

It occurs in the period of breastfeeding, more commonly from the second to the fifth week of the puerperium. The incidence is higher in primigravidae and after elective cesarean sections. The main "port of entry" is fissures in the nipple arising from breastfeeding. Milk stasis and the practice of poor hygiene with the nipple-areolar complex are predisposing factors. They are usually flat or umbilicated nipples, with thin skin and little elasticity. The germs most related to infection are *Staphylococcus aureus* and *Staphylococcus epidermidis* and *Streptococcus* species. Bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus mirabillis* may also be responsible for the infectious condition.

Clinically, it presents as edema, erythema, and increased breast temperature. The upper lateral quadrant of the breast (site with higher milk production) is the most affected by the infectious condition. When there is a floating area, always suspect an abscess associated with mastitis. There may also be systemic symptoms such as high fever, anorexia, nausea, and vomiting. The most common forms of presentation, caused by staphylococcus, usually culminate in the formation of multilocular abscesses with large amounts of pus. Streptococcal mastitis develops as cellulites, while anaerobes can produce large areas of tissue necrosis, especially in patients with immunosuppression or diabetes.

The treatment consists of maintaining breastfeeding, delicate manual milking of the breasts (avoiding breast engorgement), use of a bra or braces to properly support the breasts, and use of analgesics, antipyretics, and antibiotics. The most indicated analgesics and antipyretics for safe use during breastfeeding are paracetamol and dipyrone. The antibiotics may initially be administered orally (Table 1). If there is clinical worsening (greater breast area affected by infectious symptoms, fever, or fluctuation areas), intravenous antibiotic should be initiated. In the presence of breast abscess, surgical drainage is mandatory (Fig. 2). Breast ultrasound can be useful in evaluating breast abscesses, quantifying the extent of the purulent collection, especially in cases of deeply localized abscesses. Doppler is an interesting parameter of therapeutic response. In bulky abscesses, the surgeon should consider

Table 1 Antibiotics used for the treatment of infectious breast processes: drugs and posology

Drug	Posology	Observations
Cephalexin	500 mg 6/6 h orally 7–14 days	First choice for non-complex infectious processes
Cefadroxil	500 mg 12/12 h orally 7–14 days	More comfortable posology
Amoxicillin/ clavulanate	875 mg 12/12 h orally 7–14 days	
Ciprofloxacin	500 mg 12/12 h orally 7–14 days	First-line drug for gonococcal mastitis
Trimethoprim /sulfamethoxazole	160/800 mg 12/12 h orally 7–14 days	
Metronidazole and cephalexin	500 mg 8/8 orally 7–10 days 500 mg 6/6 orally 7–10 days	Chronic recurrent subareolar abscess
Oxacillin	2 g intravenous 4/4 h	Option when there is no response to orally. Begin treatment orally 48 h afebrile
Cefoxitin and clindamycin	1 g intravenous 6/6 h and 600 mg intravenous 8/8 h	Mastitis due to anaerobic drugs with no response to treatment orally. Begin treatment orally 48 h afebrile

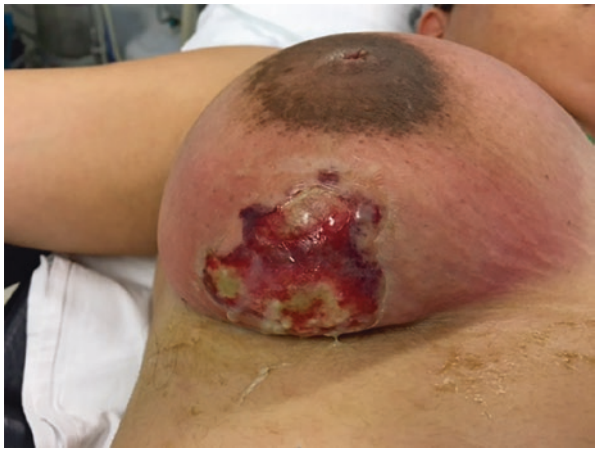

Fig. 2 Puerperal mastitis with abscess and skin necrosis

placing penrose drain for 48/72 h. Purulent secretion drained from the abscess should be referred for culture and antibiogram. With the result of the antibiogram, the tested antibiotic can be adjusted.

To perform the prophylaxis of puerperal mastitis, hygiene measures and exercises with the nipples should be taught during the prenatal period to increase elasticity and thus reduce the appearance of cracks. During breastfeeding, milk stasis (breast engorgement), considered a culture broth for bacterial growth, should be avoided.

Chronic Mastitis

The main characteristic is the time of evolution greater than 30 days or by recurrence after treatment. They are usually slow in evolution and may or may not be preceded by an acute infection. More common in young women (30–40 years), hardly occur in postmenopausal women. They can be classified as infectious (where there is an identified infectious agent) and non-infectious.

Infectious Chronic Mastitis

Chronic Recurrent Subareolar Breast Abscess (CRSBA)

Recurrent and chronic infection of the subareolar region (Fig. 3) is strongly associated with smoking, diabetes, and obesity. It is a common disease in young women with a pathogenesis that is not well established and develops outside the pregnancy-puerperal cycle. Usually it is unilateral, but it can be bilateral. It begins as an inflammation of a well-located subareolar area, which evolves into a small abscess that tends to drain spontaneously with the formation of a fistula that heals later. It is clinically repeated several times, with intervals of months to years, from where the chronic and recurrent denomination derives. At the site of the abscess a cavity is formed and it reopens with each activation of the infectious process.

The treatment with antibiotics (with aerobic and anaerobic coverage) orally presents a good response. When fistula formation occurs, the surgical treatment

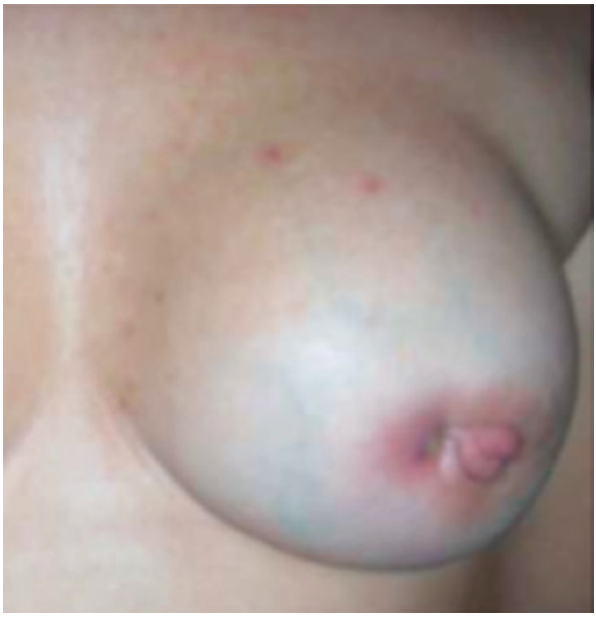

Fig. 3 Chronic recurrent subareolar breast abscess (CRSBA)

with resection of the involved ductal system can be performed. The resected tissue should be sent for histological study in order to rule out breast neoplasia and other infectious types. It is recommended to stop smoking for treatment success. If the patient does not want pregnancy, it is recommended, besides the removal of the involved ductal system, to excise the other main ducts to reduce the risk of relapse.

Mastitis Caused by Tuberculosis

Clinically, it manifests through several slowly developing abscesses or multiple peripheral fistulas, with a personal or family history of treatment for tuberculosis. Palpable axillary lymph nodes can be found. In the diagnosis, tuberculin skin test and chest radiography should be performed with the aim of evaluating primary pulmonary focus. The definitive diagnosis of tuberculosis is obtained by biopsy of the lesion, identifying caseous granulomas. The culture can identify the bacillus acid resistant alcohol (BAAR). The treatment is performed with tuberculostatic agents and follow-up of the infectologist also important.

Mastitis Caused by Mycobacterium

They are infectious processes in the breasts of extremely slow evolution. They occur more frequently in HIV-positive patients with CD4 lower than 50/mm3. The diagnosis can be made by blood culture and/or culture of material removed from the breast (tissue or secretions) that identifies atypical mycobacteria. The treatment is usually performed through the combination of clarithromycin, ethambutol, and rifabutin for 6 months. There is a description of the identification of *Mycobacterium avium-intracellulare* (MAC) in the culture of silicone implant users in immunocompetent women. Treatment included withdrawal of the silicone implant and use of clarithromycin for 6 months.

Viral Mastitis

Infectious breast processes can also be caused by viruses, specifically herpes simplex or herpes zoster. It is usually associated with genital and/or oral herpes. The diagnosis is clinical, by noticing lesions on the skin of the breast with painful and recurrent vesicles. The duration of the infectious process is usually self-limiting, with resolution in seven to ten days. The use of oral acyclovir 400 mg 8/8 h for 5 to 7 days may reduce the symptoms. Herpes zoster (Varicella zoster) causes rashes with vesicles, very painful, following the line of a dermatome on the breast. In the history of the disease, systemic symptoms of fever, malaise, and exanthema usually occur 24–48 h before the onset of skin lesions. It occurs more frequently in patients with some immunodeficiency, especially in HIV-positive women, or in those that do chronic use of corticosteroids, or in chemotherapeutic treatment. Oral acyclovir is

recommended for milder cases, and intravenous for severe forms. Potent analgesics with codeine in the acute phase, or even anesthetic blockade of the affected nerve to control pain, are recommended. Antiseptic dressings are useful in the prevention of secondary bacterial infections.

Lymphocytic Mastitis or Syphilis of the Breast

It is first presented as cutaneous lesions in the areola-nipple complex, caused by the inoculation of the treponema. In the secondary form, there are macular skin lesions that develop into papules, and in the tertiary form, there is a hardened nodule that softens undergoing ulceration or fistulization. The most important differential diagnosis includes Paget's disease. The laboratory diagnosis is based on treponemal antigens (VDRL and FTA-ABS) and/or the presence of treponema in dark field microscopy. The treatment is performed with Penicillin G Benzathine 2.4 million intramuscular injection (1.2 million in each buttock), repeated in seven days (total of 4.8 million).

We can mention some other rare infectious chronic mastitides such as actinomycosis, mammary leprosy, gonococcal mastitis, helminth, and fungal mastitis.

Chronic Non-infectious Mastitis

Periductal Mastitis

Periductal mastitis affects non-lactating women during their reproductive life. It may also be called plasmacytic mastitis. Etiologically, it is related to bacterial infection and smoking. It occurs more often in multiparous women who breastfeed. Clinically, it presents with unilateral acyclic mastalgia, mammary secretion (dark green or serous coloration), nipple retraction, subareolar mass with or without inflammation of the overlying breast, and even nipple fistula. It can mimic other serious diseases, including breast carcinoma. For the differential diagnosis, mammography and mammographic ultrasound are essential. Cytology of papillary effusion can be performed; however, it is important to remember that the absence of malignant neoplastic cells does not definitively exclude mammary carcinoma. The biopsy and culture of the material removed from the breast are important in the differential diagnosis. Effective antibiotics against organisms isolated in the culture should be used during infection. There is indication of surgery for correction of the nipple fistulas or in the cases of spontaneous papillary effusion that clinically bothers the patient. It is important to remember that in women in the menacme aiming to have children, the exeresis of the ducts can hinder future breastfeeding.

Idiopathic Granulomatous Mastitis

A rare chronic disease in which an inflammatory process is observed with granulomatous changes occurring around the lobes and mammary ducts, in the absence of specific infection, trauma, foreign body, or evidence of sarcoidosis. It can mimic carcinoma (Fig. 4). The recurrence rate ranges from 16% to 50%, usually keeping the patient under medical care for long periods of time. They occur in women aged between 20 and 50 years, with an average of 30 years. The variability in clinical presentation and duration of symptoms reflect the heterogeneity of this entity. A hallmark of this inflammatory pathology is lobular involvement, allowing it to be differentiated from sarcoidosis. An autoimmune phenomenon has been suggested but has not been proven. There is no consistent relationship with breastfeeding, parity and oral contraceptive, or use of hormones. Local manifestations of this pathology may mimic malignant lesions, especially when associated with an irregularly shaped mass or when the nipple is retracted. The findings in breast imaging tests are usually non-specific. The process is more diffuse, and the amount of pus is minimal and always present in multiple small loci that communicate through small channels.

In the literature there is no consensus on the best treatment. Broad excision of the entire inflammatory mass is not indicated and may be impossible due to poor aesthetic outcome, especially when the disease involves more than one quadrant. The treatment should be adapted to each case according to the clinical presentation. High-dose corticosteroids may be used as 60 mg/day (0.8 mg/kg/day in the first week with gradual reduction to completion of 8 weeks) or methotrexate. Although they present high recurrence rates in the literature (up to 50%), it is not yet established how long these patients need to be followed, since the time of recurrence is unknown.

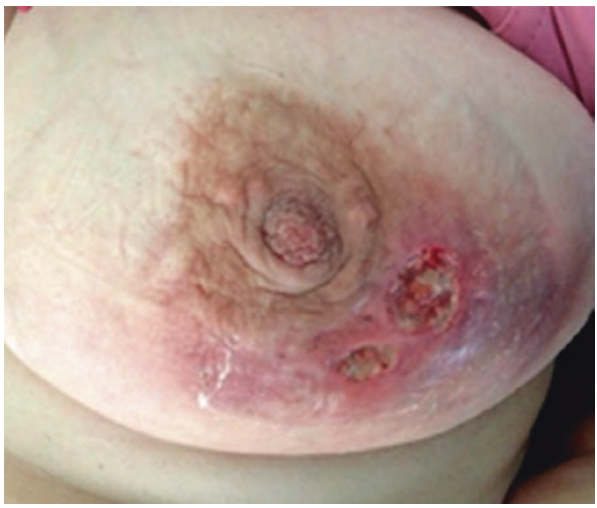

Fig. 4 Idiopathic granulomatous mastitis

Mondor's Disease

The main characteristic of this disease is thrombophlebitis of the superficial veins of the breast (thoracoepigastric vein and/or its tributaries). The disease is self-limiting, and pathophysiology is not fully known yet. It presents as a fibrous and painful cord in the subcutaneous that corresponds to the committed venous path. It most frequently affects women with bulky and pendulous breasts and after trauma, including surgery. Due to increased vascularization and breast volume, pregnant women are at greater risk. This disease is a cause of unilateral acyclic mastalgia. The diagnosis is basically clinical. It is treated conservatively, prescribing anti-inflammatories and analgesics for pain relief. Antibiotics and anticoagulants are not indicated.

Breast Sarcoidosis

It is characterized by non-caseous epithelioid granulomas, and its etiology is unknown. The breast is involved in less than 1% of cases. In most cases other organs are already involved, although breast involvement may be the initial site of the disease. Clinically, it may present as a non-painful and mobile mass, with smooth or irregular edges. At mammography, the lesion may appear well defined or spiculated. It may exist as a single mass or as multiple lesions. On ultrasonography, a hypoechoic mass may show indistinct margins that cannot be differentiated from malignant lesions. On the other hand, it may present as an intramammary lymph node or a granuloma. Histological diagnosis confirms non-caseous granuloma, with negative PPD and positive Kveim test. The treatment is clinical and directed to the systemic symptoms of the disease. Total resection of the breast lesion is not necessary.

Conclusion

The inflammatory processes of the breast present several causative agents. Performing the differential diagnosis of the various types of mastitis can be difficult, especially in cases of low incidence. The use of imaging and biopsy methods of the compromised breast tissue is essential for cases with a complicated differential diagnosis, especially to exclude mammary carcinoma. In most cases, adequate clinical management is sufficient for mastitis treatment. Surgery is indicated in cases of abscess and/or failure of clinical treatment.

Recommended Reading

1. Crepinsek MA, Crowe L, Michener K, Smart NA. Interventions for preventing mastitis after childbirth. Cochrane Database Syst Rev. 2010;8(4):290.
2. Cullinane M, Amir LH, Donath SM, Garland SM, Tabrizi SN, Payne MS, et al. Determinants of mastitis in women in the CASTLE study: a cohort study. BMC Fam Pract. 2015;16:181.
3. Dixon JM, Khan LR. Treatment of breast infection. BMJ. 2011;342:d396.
4. Kamal RM, Hamed ST, Salem DS. Classification of inflammatory breast disorders and step by step diagnosis. Breast J. 2009;15(4):367–80.
5. Rungruang B, Kelley JL 3rd. Benign breast diseases: epidemiology, evaluation, and management. Clin Obstet Gynecol. 2011;54(1):110–24.
6. Taffurelli M, Pellegrini A, Santini D, Zanotti S, Di Simone D, Serra M. Recurrent periductal mastitis: surgical treatment. Surgery. 2016;160(6):1689–92.
7. Viegas JF, Zerwes F, Vollbrecht B, Santos MM, Souza ABA, Frasson AL. Mastites. In: Boff RA, et al., editors. Compêndio de Mastologia: Abordagem Multidisciplinar, vol. I. Caxias do Sul: Lorigraf; 2015. p. 359–66.
8. Zerwes F, Vollbrecht B, Viegas JF, Frasson AL. Processos inflamatórios da mama. In: Urbanetz AA, Luz SH, editors. PROAGO Ciclo 9, vol. 3. Porto Alegre: Artmed/Panamericana; 2012. p. 9–34.

Classification of Intraductal Precursor and Proliferative Lesions

Helenice Gobbi

Concept, Nomenclature, and Classification

Proliferative epithelial lesions or mammary epithelial hyperplasia comprises a heterogeneous spectrum of alterations confined to the ductal-lobular system. These lesions are divided into two major categories, ductal and lobular, based on cytological and architectural criteria, meaning no specific origin in ducts or lobules. The new Classification of Breast Tumors of the World Health Organization (WHO) 2012 (Table 1) adopted the classic or traditional terminology of intraductal proliferative

Table 1 Histopathologic classifications of proliferative mammary lesions

Dupont and Page (1985)	Tavassoli (1998)	WHO (2012)
Mild ductal hyperplasia	Usual ductal hyperplasia	Usual ductal hyperplasia
Moderate ductal hyperplasia with no atypia		
	Ductal intraepithelial neoplasia grade 1A (DIN 1A)	Columnar cell lesions: Alterations in the columnar cells with no atypia Hyperplasia of columnar cells with no atypia Flat epithelial atypia
Atypical ductal hyperplasia	Ductal intraepithelial neoplasia grade 1B (DIN 1B)	Atypical ductal hyperplasia
Low-grade ductal carcinoma in situ	Ductal intraepithelial neoplasia grade 1C (DIN 1C)	Low-grade ductal carcinoma in situ
Intermediate-grade ductal carcinoma in situ	Ductal intraepithelial neoplasia grade 2 (DIN 2)	Intermediate-grade ductal carcinoma in situ
High-grade ductal carcinoma in situ	Ductal intraepithelial neoplasia grade 3 (DIN 3)	High-grade ductal carcinoma in situ

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lesions and did not recommend the nomenclature of "mammary intraductal neoplasia"proposed by Tavassoli. According to WHO, the concept and terminology of intraductal proliferative lesions should be viewed as an evolving process, which may be modified when new molecular and genetic data are incorporated into the classification of these lesions.

Pathology and Clinic

Intraductal proliferative lesions of the breast (IPLB) are classified under microscopy in usual ductal hyperplasias, columnar cell lesions, flat epithelial atypia, and atypical ductal hyperplasias (Table 1). Precursor lesions include ductal carcinoma in situ (DCIS) and lobular neoplasia, which includes lobular carcinoma in situ and atypical lobular hyperplasia (Table 2). Intraductal proliferative lesions are generally asymptomatic and occur in a wide age range, ranging from 20 to 80 years. DCIS is more common among patients between 50 and 59 years.

Atypical ductal hyperplasias (ADH) are proliferative lesions similar to ductal carcinomas in situ of low grade, but small (<2 to 3 mm) and do not completely fill two ducts or spaces (Fig. 1). The cells are monomorphic, with well-defined borders, with regular and slightly atypical nuclei, and form architectural patterns similar to those described in ductal carcinoma in situ (solid, cribriform, and micropapillary). Molecular studies have provided contributions to the understanding of the biological nature and evolution of ADH, but are not yet validated for routine clinical use. ADH is associated with relative risk for development of invasive carcinoma of 3-5x. For women in the perimenopause (between 40 and 55 years) stage, the risk is about 4X, and the absolute risk is 10%. The presence of ADH is a risk indicator for any location in the breast, and 3.7–22% of women with this diagnosis develop invasive carcinoma. If there is a family history of breast cancer in first-degree relative (mother, sister, or daughter), the relative risk doubles and will be around 8–10′ (Table 3).

Ductal carcinoma in situ is a neoplastic proliferation confined to the ductal-lobular system, characterized by cytological atypia and inherent tendency, but not mandatory for progression to invasive carcinoma. Before mammographic screening programs were applied, DCIS corresponded to 2–3% of palpable breast tumors.

Table 2 Histopathological classification of precursor lesions

Precursor lesions
Ductal carcinoma in situ
Lobular neoplasia
Lobular carcinoma in situ
Carcinoma lobular in situ
Pleomorphic lobular carcinoma in situ
Atypical lobular hyperplasia

Source: Classification of Breast Tumors by the World Health Organization (2012) – 4th edition

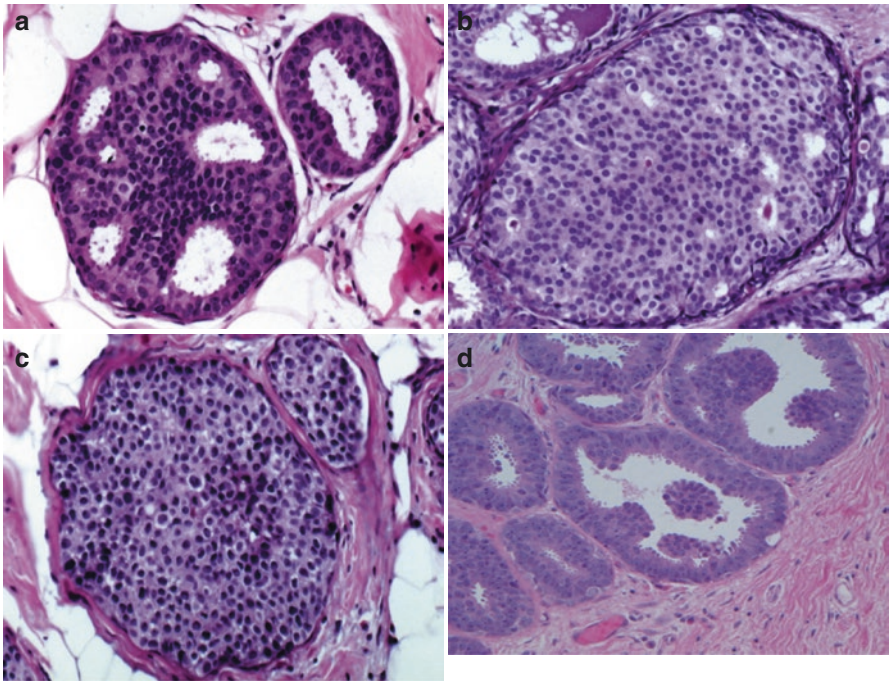

Fig. 1 (**a**) Atypical ductal hyperplasia (**b**) Ductal carcinoma in situ (**c**) Lobular carcinoma in situ (**d**) Flat epithelial atypia

Table 3 Intraductal proliferative lesions and precursor lesions and their respective risks (both relative and absolute) for evolution to invasive carcinoma risk lesion breast

Lesion	Relative risk[a]	Absolute risk[b]	Risk lesion breast
Usual ductal hyperplasia	1.5–2.0′	5–7%	Both breasts
Atypical ductal or lobular hyperplasia	4.0–5.0′	13–17%	Both breasts
Carcinoma in situ Lobular carcinoma in situ Ductal carcinoma in situ[c]	8–10′	25–30%	Both beasts Ipsilateral breast

[a]Relative risk is the risk compared to women without any other risk factor

[b]Absolute lifetime risk is the percentage of women who are expected to develop invasive carcinoma if they are not treated

[c]This risk applies to low-grade ductal carcinoma in situ, originally misdiagnosed as a benign lesion, whose patients were followed up without treatment. The risk for progression of high-grade ductal carcinoma in situ is presumably higher than this

Currently, 80–85% of DCIS are detected by mammography. The DCIS can be classified according to the architectural pattern in solid, cribriform, micropapillary, and comedo types. The histological grade of DCIS is based on nuclear grade and on the presence and extent of necrosis, dividing into low (Fig. 1b), intermediate, and high grades. In addition to histological type and degree, pathologists should include the

presence and type of necrosis (focal or comedo), size and extent of the lesion, location of microcalcifications (if DCIS only, if associated with other lesions, or both), and the state of the surgical margins. Currently, estrogen receptor research is the only molecular marker validated for routine clinical use in DCIS for selection of patients for antiestrogen therapy. Some studies indicate that young patients, large lesions, high nuclear grade, comedo-like necrosis, and positive margins are associated with a higher risk of local recurrence and progression to invasive carcinoma.

Lobular neoplasia refers to the entire spectrum of atypical epithelial lesions involving the terminal duct-lobular unit, characterized by the proliferation of small, uniform cells, without cell cohesion, with or without pagetoid extension to terminal ducts. The WHO Consensus of 2012 considered it important to distinguish atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) based on the extent of involvement of lobular units. Lobular neoplasia is multicentric in up to 85% of patients and bilateral in 30–67%. Classical LCIS has mild to moderate nuclear atypia (Fig. 1c). The pleomorphic variant of LCIS, usually associated with microcalcifications detected at mammography, is characterized by loss of cell cohesion, contains areas of comedo-like necrosis and marked nuclear pleomorphism similar to high-grade DCIS with or without apocrine characteristics (referred to as pleomorphic LCIS). The loss of immunohistochemical expression of E-cadherin may be useful in the differentiation between ductal carcinoma in situ and pleomorphic LCIS. However, the diagnosis should not be based solely on the immunophenotype and loss of expression of E-cadherin, but on the careful analysis of the immunolocations allied to the evaluation of the topographic distribution of the lesions, since up to 15% of the lobular lesions express E-cadherin. Although LCIS has a very slow evolution, it gives patients a relative risk of progression to major invasive carcinoma (about 8–10') than ALH (about four times), and for this reason some authors prefer to continue to designate these two lesions in a stratified form, such as ALH and LCIS.

Columnar cell lesions (CCL) encompass the alteration of columnar cells and hyperplasia of columnar cells without atypia. They affect the terminal duct-lobular units, which are enlarged, with dilated acini, covered by tall columnar cells. There are frequent luminal secretions and microcalcifications and therefore these lesions have been more frequently diagnosed in mammographic screening programs. Lesions with one to two layers of columnar cells lining the spaces are referred to as "columnar cell alteration"; lesions with more than two layers of cells or formation of cell tufts are termed "columnar cell hyperplasia". Flat epithelial atypia (FEA) was defined by the WHO Consensus (2012) as a neoplastic alteration of terminal duct-lobular units characterized by the replacement of native cells by one or more layers of monomorphic cells, with a low degree of atypia (Fig. 1d). The term "clinging monomorphic type carcinoma" has already been employed for lesions now referred to as FEA. However, the WHO Consensus Committee 2012 recommends that "flat" proliferative lesions with a high nuclear grade be referred to as ductal carcinoma in situ and did not recommend the terminology "clinging carcinoma."

CCLs and FEAs are asymptomatic and can be usually found as a result of microcalcifications detected at mammography. CCLs and FEAs are frequently

associated with cysts, epithelial proliferative lesions, atypical ductal hyperplasia, and lobular neoplasia. From a prognostic point of view, FEA has more scientific interest as an initial lesion in the evolutionary pathway of low grade neoplasms than a lesion of clinical importance as a precursor or risk marker. Few data are available, from small series, with very limited clinical follow-up, suggesting that some cases of FEA may progress to invasive carcinoma. Despite the presence of "atypia" in the name, FEA should not be considered equivalent to atypical ductal or lobular hyperplasia from the point of view of clinical management of the patient. Results from small series of retrospective studies show that up to 30% of patients with FEA in needle biopsy have more advanced lesions on the excisional biopsy. However, due to the limitations of the studies and the great variation in the follow-up times after the initial biopsy, it is still uncertain whether there is a need to indicate surgical excision after diagnosis of FEA in needle biopsy. Radiological and pathological correlation is recommended for determination of the subsequent conduct. Until now, in the presence of a diagnosis of CCL without atypia, no additional measures are required. In cases of FEA, the most recommended has been to accompany the patients.

Recommended Reading

1. Boulos FI, Dupont WD, Schuyler PA, Sanders ME, Page DL, Fedda FA, Simpson JF. Clinicopathologic characteristics of carcinomas that develop after a biopsy containing columnar cell lesions: evidence against a precursor role. Cancer. 2012;118(9):2372–7. *Invasive carcinomas subsequent to previous biopsy with columnar cell lesions occurred in both breasts; they were histologically varied and had no relation to the type of lesion (with or without flat atypia). The authors concluded that these facts speak against a precursor role for columnar cell lesions.*
2. Collins LC, Aroner SA, Connolly JL, Colditz GA, Schnitt SJ, Tamimi RM. Breast cancer risk by extent and type of atypical hyperplasia: an update from the Nurses' Health Studies. Cancer. 2016;122(4):515–20. *This study (part of the project that has accompanied American nurses for many years as to several risk factors), evaluated the risk for breast cancer based on the type and number of outbreaks of atypical hyperplasia in the initial biopsy*
3. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast--risk assessment and management options. N Engl J Med. 2015;372(1):78–89. *Excellent review on morphological, molecular, epidemiological aspects, risk related to different types of lesions and options for clinical management of atypical breast hyperplasias*
4. King TA, Pilewskie M, Muhsen S, Patil S, Mautner SK, Park A, et al. Lobular carcinoma in situ: a 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk. J Clin Oncol. 2015;33(33):3945–52. *Study of clinical-pathological characteristics of cases of lobular carcinoma* in situ *followed for a long time. A 2% incidence of invasive carcinoma was observed annually – 63% in the ipsilateral breast and of varied histological types. The risk of invasive carcinoma increased with the number of foci of LCIS and reduced with the use of chemoprophylaxis*
5. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, editors. WHO Classification of Tumours of the Breast. 4th ed. Lyon: IARC; 2012. *This is the most recent Classification of Breast Tumors of the World Health Organization and it contains a description of the criteria for histopathological diagnosis, epidemiology, clinical and molecular aspects of the intraductal and precursor proliferative lesions.*

Procedure for Cases of Intraductal and Proliferative Lesions

BBSG – Brazilian Breast Study Group

Introduction

The adequate classification of proliferative lesions is important because of its association with the risk of developing invasive breast carcinoma, especially when diagnosed between 35 and 55 years of age. Several criteria have already been described for the classification of atypical hyperplasias of ductal and lobular patterns, without a definite consensus among the authors, although there is common agreement that they share similar risks for the development of invasive breast carcinoma. The importance of histopathological differentiation of atypical ductal hyperplasias with low-grade ductal carcinoma in situ (DCIS) is emphasized, which requires a completely different treatment.

Definitions

Three main criteria are important in the classification of these lesions according to Page: cytology, histological pattern, and extent (size) of the lesion.

The main representative lesions of this group include atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma in situ. Flat epithelial atypia (FEA) is also considered in the spectrum of intraductal proliferative lesions.

The diagnostic criteria for the classification of atypical ductal hyperplasia (ADH) are imperfect and are characterized more by the absence of criteria for DCIS than proper characters. It is characterized by the dilation of the actin of the duct-lobular terminal units (DLTU) with stratification of more than two layers of monomorphic cells, sometimes with the presence of intraluminal calcifications in the area < 2 mm.

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Page defines that the morphological changes of the DCIS may be present in the ADH, but occupy less than two separate ductal spaces. Larger areas should be classified as DCIS. Larger lesions can be classified as ADH if present in association with radial scar or complex sclerosing lesions. Biologically, they are characterized by the frequent expression of estrogen and progesterone receptors (ER/PR), cyclin D-1 variable expression, and low Ki-67 expression, demonstrating low proliferative activity of these lesions.

Lobular neoplasia (LN) is classified into the group of lesions represented by atypical proliferation of uniform small cells with loss of cohesiveness around the duct-lobular terminal unit (DLTU).

Included in this group are atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). It is considered that this group of lesions are multicentric and of increased risk for the development of invasive carcinoma in both breasts. Despite the different criteria proposed for its differentiation, there is a low concordance in the diagnostic classification of these entities among experienced pathologists.

Pleomorphic lobular carcinoma in situ presents a greater nuclear pleomorphism rather than the uniform proliferation usually described in these lesions. Areas of central necrosis of the comedo type and higher frequency of Ki-67 and p-53 expression also show the presence of this carcinoma. Negativity for E-cadherin allows differentiation of DCIS, especially the comedo-carcinoma subtype.

The differential diagnosis between lobular carcinoma in situ and DCIS cannot always be performed based only on morphological criteria. A greater cohesiveness of the cells and better structural organization in the DCIS have been observed. Immunohistochemistry, through E-cadherin, allows this differentiation by the demonstration of positivity found in the cell membrane of ductal lesions and because there is no impregnation of this in lobular neoplasms.

Alterations of atypical columnar cells and atypical columnar cell hyperplasia are usually grouped in the spectrum of flat epithelial atypia (FEA). These lesions may coexist frequently with DCIS, LCIS, and invasive forms, but their biological progression to one of these forms seems very slow. As a consequence, the finding of FEA in percutaneous biopsy products may be associated with higher grade lesions (DCIS, invasive ductal carcinoma, IDC; invasive lobular carcinoma, ILC), and surgical resection of the area of interest should be indicated. Its presence in the surgical margins of parts diagnosed with DCIS, IDC, and ILC seems not to be associated with a greater risk of recurrence, and therefore no indication is considered.

The new classification of breast tumors by the World Health Organization (WHO 2012) has adopted the classic or traditional terminology of intraductal proliferative lesions. The terminologies, intraductal neoplasms (IDN) and intralobular neoplasms (ILN) proposed by Tavassoli, were not recommended in this last review.

Epidemiology

The incidence of atypical ductal hyperplasia is around 4% of the biopsies of benign symptomatic lesions of the breast, although its incidental finding associated with lesions detected in mammographic screening is more common. Its incidence continues to increase even after 10–20 years of menopause, an important differential factor of lobular neoplasia that presents a lower incidence in postmenopausal women.

The true incidence of lobular neoplasms is not known to date, and it is estimated in about 1 to 3.8% of breast biopsy specimens. Up to 30% bilaterality and up to 85% multicentricity are described for these lesions.

Clinical Propaedeutics and Subsidiary Exams

Lobular neoplasias manifest as an incidental finding of biopsies and usually lack clinical and radiological manifestations. The pleomorphic variant is frequently found in association with dystrophic microcalcifications observed on mammography, similar to those of the comedo subtype DCIS.

Likewise, the differential diagnosis of ductal proliferative lesions can be performed through the evaluation of microcalcifications suspected on mammography.

Treatment

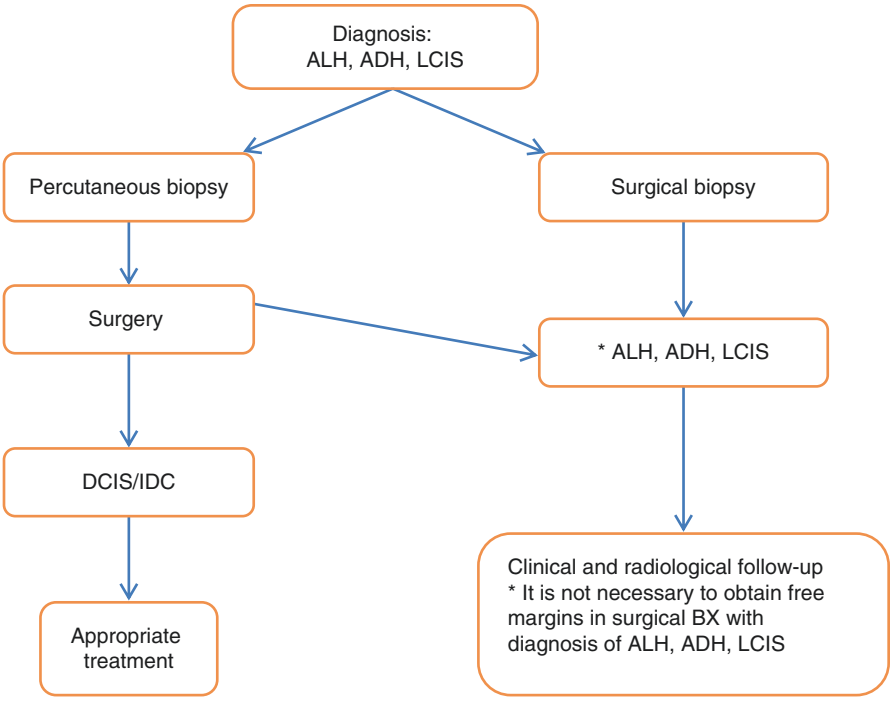
Surgical

Atypical proliferative lesions present the same treatment algorithm. In the lesions diagnosed by means of percutaneous biopsy, surgical excision of the area of interest must be carried out due to the risk of 15–30% of underestimation (DCIS, IDC, and ILC). With the increased use of percutaneous vacuum biopsies (which remove larger diameter fragments), some highly selected patients with complete removal of the lesion (confirmed by examination following biopsy) may be followed up with periodic examinations. When resulting from a surgical biopsy, there is no need to enlarge the margins if they are compromised by one of these lesions. The conduct to be adopted in the pleomorphic LCIS is controversial, since biologically it resembles more to the DCIS, but there are no prospective clinical studies that have proven their greater aggressiveness. Some authors suggest the expansion of the surgical margins, when these are positive for the pleomorphic variant of lobular carcinoma.

SERMS

The use of SERMS (Tamoxifen 20 mg/day or Raloxifene 60 mg/day) for 5 consecutive years shows a reduction of at least 50% in the subsequent risk of invasive carcinoma. Tamoxifen has the advantage of reducing the incidence of DCIS, not observed with Raloxifene. Studies with aromatase inhibitors have also shown benefits.

Flowchart



Flowchart 1 Management

Recommended Reading

1. Ellis IO. Intraductal proliferative lesions of the breast: morphology, associated risk and molecular biology. Modern Pathology. 2010;23:S1–7. *Review of the main morphological aspects of ductal proliferative lesions, and suggestion of management of these lesions*
2. Fisher ER, Land S, Fisher B, Mamounas E, Gilarski L, Wolmark N. Pathologic findings from the national surgical adjuvant breast and bowel project. Twelve-year observations concerning lobular carcinoma in situ. Cancer. 2004;15(100):238–44. *Study of 182 patients with LN. After 12 years, 10.5% of invasive carcinoma (contralateral: 5.0%, ipsilateral: 5.5%). All local invasive relapses occurred at the site of the primary lesion. Interpretation: LN is a precursor lesion of breast cancer, but quite indolent*
3. Ho CSB, Tan PH. Atypical hiperplasia and in situ breast carcinona – lobular neoplasia of the breast: 68 years on. Pathology. 2009;41(1):28–5. *The adoption of different classifications represents the difficulty in choosing the correct classification of these lesions and the interobserver variability described*
4. O'Malley FP. Lobular neoplasia: morphology, biological potential and management in core biopsies. Mod Pathol. 2010;23:S14–25. *Review of the main morphological aspects of ductal proliferative lesions, and suggestion of management of these lesions*

Ductal Carcinoma in Situ

BBSG – Brazilian Breast Study Group

Introduction

Ductal carcinoma in situ (DCIS) is part of the group of precursor lesions of breast cancer. It is characterized by proliferation of neoplastic cells within the mammary ducts, without rupture of the basal membrane.

Definition and Pathophysiology

DCIS is an intraductal neoplasm with the potential to become invasive carcinoma. It may be classified according to its histological grade as low, intermediate, or high grade. The histopathological alteration is similar to atypical ductal hyperplasia, but with a greater extension (the differentiation between low-grade DCIS and atypical ductal hyperplasia is not always easy).

Low-grade DCIS has a low proliferative index—it does not completely obstruct the lumen of the duct—and it usually occurs in discontinuous portions. In contrast, high-grade DCIS usually presents continuity of the lesion, and obstruction of ductal lumen may occur, with necrosis of the central portion (comedo-necrosis) (Fig. 1).

The percentage of cases progressing to invasive carcinoma in 10 years, if untreated, is 14%–46% depending on the studies. Despite the suspicion that high-grade lesions are at higher risk, no study or test can predict the behavior of the different types of DCIS in an objective and safe way. Consequently, all cases are dealt with in an aggressive approach.

Local recurrences (LR) have particular importance in DCIS, since about 30–50% of them are invasive tumors.

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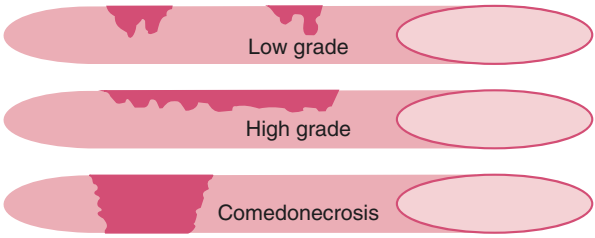


Fig. 1 Schemes of the types of DCIS

As with invasive carcinoma, DCIS appears to have a different prognosis, according to its molecular profile. Luminal A tumors have a much lower recurrence rate than the other subtypes, with a percentage of invasive relapse in 10 years of less than 2%.

The main risk factors for relapse include young age, black race, positive margins, high grade, and presence of comedo-necrosis.

Epidemiology

The estimated incidence of breast cancer in the USA in 2015 was 292,130 cases, out of which 60,290 (20.6%) were diagnosed as DCIS. There has been a continuous annual increase since the 1960s, but since 2004 the incidence of DCIS in the USA has been stable. Also in the USA, necropsy studies have found the presence of DCIS in 10–15% of patients deceased for other causes.

Data from 108,000 American women treated by DCIS between 1988 and 2011 showed specific mortality from breast cancer of 3.3% in 20 years of follow-up. Patients younger than 35 years and black race individuals had higher rates, around 7%. The limitations of this study are the absence of information on margins, use of tamoxifen, and diagnostic method (clinical or radiological). The type of surgery (conservative or mastectomy) does not modify mortality.

Diagnosis

Currently, 80% of cases of DCIS are diagnosed in radiological screening tests, and the most common presentation is the presence of a grouping of irregular microcalcifications. In tests classified as BI-RADS™ 4 that result positive, most of the lesions are DCIS (65%) or DCIS with microinvasion (30%).

It is not possible to determine the presence of invasion only with clinical and imaging examination. However, palpable lesions and extensive (up to 4 cm) or linear microcalcifications indicate a higher risk of invasive disease.

Despite the routine use of magnetic resonance imaging (MRI), its indication in DCIS is still controversial. Some studies have shown that MRI detects more outbreaks of multicentricity, microinvasion, or residual disease than mammography. In 2007, Kuhl et al. observed that breast screening with this method detected about

50% more DCIS than mammography, mainly of the high-grade and comedo-necrosis types.

The remaining question is what the malignant potential of these new DCIS is. The great fear would be to increase the excessive diagnosis, increasing the number and size of procedures but without reducing the incidence of invasive carcinomas.

Whenever possible, percutaneous biopsies are indicated on imaging alterations (BI-RADS™ 4 and 5). The percutaneous vacuum biopsy showed higher sensitivity (85–97%) and specificity (99%) in the histopathological diagnosis of these lesions. It is particularly important in very small lesions, where the risk of not removing the lesion in a core biopsy is inversely proportional to the size of the lesion.

Even if this procedure reveals the presence of DCIS, there is an average risk of underestimation of invasive disease of 20%. The presence of comedo-necrosis (besides palpable lesions and microcalcifications longer than 4 cm) is predictive of invasive lesion.

Surgical Treatment

Every DCIS must be removed surgically. It is intended primarily to prevent invasive cancer and, in a secondary way, to prevent local recurrence of DCIS.

Classically, total mastectomy was considered gold standard in the treatment of DCIS, with a cure rate of 99%. The evolution of conservative surgery provided a new possibility of treatment, being considered the current gold standard, whenever the lesion size/breast size ratio favors resection of the lesion with free margin and an acceptable esthetic result.

Conservative treatment alone results in a local recurrence rate of around 25% at 10 years of follow-up (30% to 50% of these in invasive form).

With the addition of radiotherapy, the rates of local recurrence in 15 years are between 10 and 20%.

The surgical technique is similar to that for invasive carcinomas, and the ideal margin in patients submitted to radiotherapy, according to the Consensus published in 2016, is at least 2 mm.

In cases with that the margin is below 2 mm (but not positive), some factors should be considered in the subsequent surgical decision: presence of residual calcifications, extension of the DCIS near the margin, which margin is close (deep margins should not be considered), cosmetic impact of re-excision, and life expectancy. Margins below 2 mm should not be an isolated indication for mastectomy, and before thinking about mastectomy, a new approach with conservative margin expansion should be considered.

The rate of recurrence of mastectomies in 10 years is around 1%.

In St. Gallen, in 2017, the follow-up of 96 months of 282 patients with DCIS who underwent nipple sparing mastectomy at the European Institute of Oncology was presented. General local recurrence was 4.3%, with 2.5% of invasive carcinoma.

Sentinel lymph node biopsy (SLNB) should be reserved for cases of mastectomy and may be discussed in cases where there is strong suspicion of invasive carcinoma, such as tumors larger than 4 cm, palpable lesions, and comedo-necrosis. Failure to perform the SLNB can be discussed with the patient until a proven diagnosis of invasion is made, leaving the patient's indication only for cases of real need.

Radiation Therapy

The four randomized trials that evaluated the impact of radiotherapy on DCIS treatment allocated 3729 patients with an average follow-up of 8.9 years.

In all studies, there was a 50% reduction in the risk of relapse (Fig. 2), with no statistical difference between DCIS subgroups. In patients submitted to radiotherapy (RT), 47% of recurrences presented invasive carcinoma, and in the group not submitted to radiotherapy, this event occurred in 48% of relapses.

Other studies have attempted to identify groups of patients who could do without radiotherapy. The most well-known model is the Van Nuys Prognostic Index (VNPI), which assigns scores according to the nuclear grade, lesion size, margins distance, and age of the patient. According to the authors, the relapse in low-risk cases without radiotherapy was 3% in 12 years in the 93 patients studied. However, these results were not obtained in other studies that used the same forms of selection. The VNPI authors themselves reported a 13.9% recurrence in the 12-year review of 212 patients.

A specific genomic signature was developed for patients with CDIS, the *Oncotype DX Breast DCIS Score test*, which, through the analysis of 12 genes, classifies the

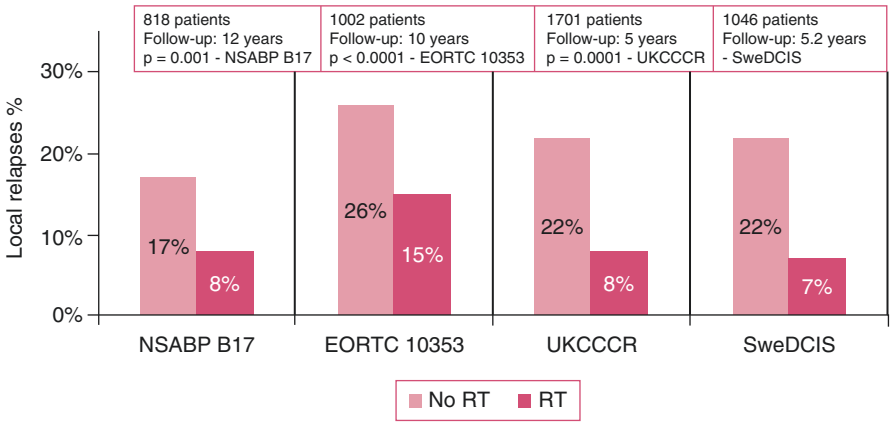


Fig. 2 Results of randomized studies of conservative surgery with or without radiotherapy for DCIS

patients into three risk groups. Low-risk patients would have little benefit from using radiotherapy. This strategy is little used in practice because it considers a minimum risk of 10% in the lowest score. In addition, the high cost and the possibility of selecting these low-risk patients using clinical-pathological criteria make the test poorly used.

The RTOG 9804 randomized study was designed to evaluate the benefit of radiotherapy in 629 patients with lesions considered low risk (low and intermediate grade, dimension smaller than 2.5 cm, 3 mm, or wider margins). In 5 years of follow-up, the percentage of local recurrence was 0.4% in the RT group versus 3.5% in the non-RT group.

Therefore, radiotherapy should routinely be part of the conservative treatment of DCIS. Obviously, some clinical situations may have an absolute risk of very low LR and in these cases the decision to irradiate the breast can be individualized.

Systemic Treatment

The only systemic therapy for DCIS is hormone therapy.

Two studies evaluated the impact of tamoxifen on local recurrence and mortality reduction, with conflicting results due to patient selection. Apparently, there is a benefit in reducing local and contralateral recurrences, especially in premenopausal, positive margin, and comedo-necrosis patients. In other patients, it is not possible to quantify this benefit. With regard to overall survival, preliminary data show an annual survival gain of 1–2% after 15 years.

Tamoxifen is used in patients at high risk of local recurrence and who are not contraindicated for this therapy (history of thromboembolic phenomena, endometrial carcinoma, and cataract).

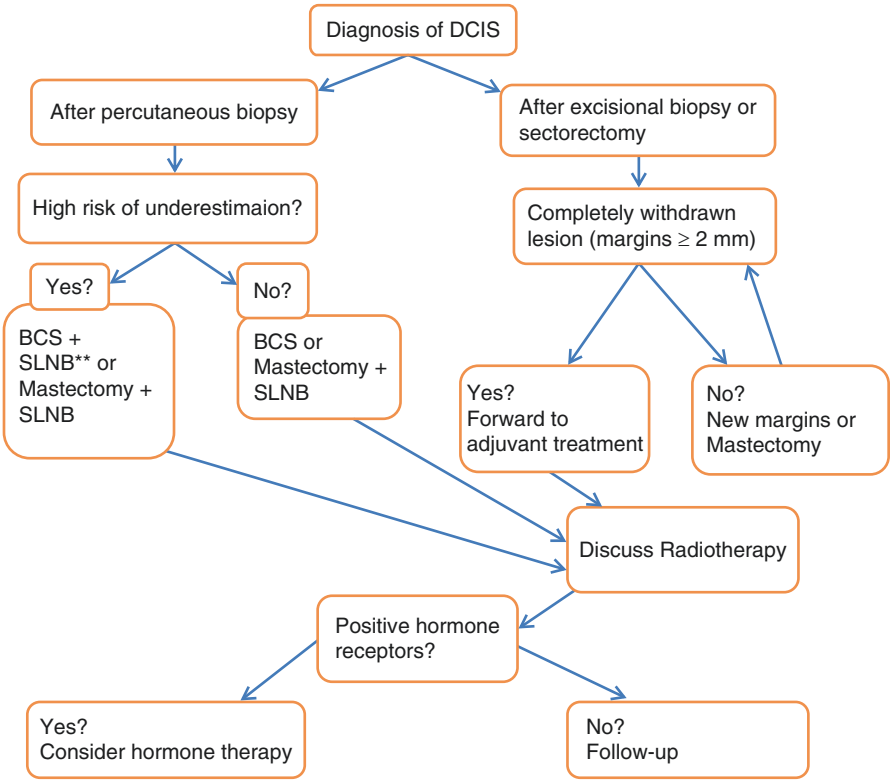
Aromatase inhibitors have been tested in randomized trials in postmenopausal DCIS patients and have shown similar results to tamoxifen.

The NSABP B43 study is evaluating the use of trastuzumab in patients with DCIS and HER2 positive.

No Treatment

Three randomized trials are currently evaluating the absence of surgery in selected patients. COMET, LORD, and LORIS studies intend to randomize 3000 women with DCIS considered at low risk for standard treatment (surgery, radiotherapy, and possibly, hormone therapy) versus radiological follow-up. This option should not be encouraged outside clinical study.

Flowchart



Observations:

* Exceptions can be made by analyzing the risk-benefit of therapy.

** In cases that mastectomy is not scheduled, it should be preferred to perform the BLS when evidence of invasion is provided.

Flowchart 1 Management

Recommended Reading

1. Davis KL, Barth RJ, Gui J, et al. Use of MRI in preoperative planning for women with newly diagnosed DCIS: risk or benefit? Ann Surg Oncol. 2012;19:3270–4. *Retrospective assessment of 218 patients who underwent surgical treatment for DCIS, in which 154 patients underwent preoperative magnetic resonance imaging and 64 did not. There were no differences between the size of the resected area, neither a decrease in the rates of re-excision and conversion to mastectomy in patients who underwent preoperative MRI. It is also important to point out that there was a significant increase in costs and a delay in starting treatment in the MRI group.*

2. Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database Syst Rev. 2009; 1:Art.No.:CD000563. *Systematic review of the four randomized studies on RT in DCIS: NSABP B17, EORTC 10353, UKCCCR and SweDCIS. Reduction in total relapses: 51% (95% IC, 0.41-0.59), benefit in all subgroups of patients and negligible side effects. Interpretation: RT should always be used after BCS.*
3. Morrow M, Van Zee K, Solin L, et al. Society of Surgical Oncology – American Society of Radiation Oncology – American Society of Clinical Oncology guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. J Clin Oncol. 2016;34:4040–6. *Consensus of the American Societies (ASCO, ASTRO, SSO) evidencing the minimum necessary margin in patients submitted to conservative surgery and radiotherapy. The use of margins greater than 2 mm did not bring benefit in relation to the decrease of local recurrence*
4. Staley H, McCallum I, Bruce J. Postoperative tamoxifen for ductal carcinoma in situ. Cochrane Database Syst Rev. 2012;10:CD007847. *A retrospective study of 174 patients with DCIS who underwent magnetic resonance imaging before surgery. There was an increase in costs and a delay in starting treatment. On the other hand, there was no reduction in the number of re-interventions and did not reduce the risk of conversion from conservative surgery to radical surgery.*
5. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24. Randomized clinical trials for DCIS. J Natl Cancer Inst. 2011;103:478–88. *The NSABP B-17 and B24 trials are the most important prospective studies related to conservative surgery in the treatment of DCIS. At 15 years of follow-up, the local recurrence rate was 19.4% in patients who underwent conservative surgery alone, compared to 8.5% in patients receiving Tamoxifen and Radiotherapy.*

Identifying High-Risk Female Patients

BBSG – Brazilian Breast Study Group

Introduction

It is estimated that 75–80% of breast cancer cases originate in women with no risk factors for the disease. Only 10% of tumors are considered hereditary, and 10–15% have a positive family history (family cancer). However, identifying higher-risk patients is useful, as it allows selecting those cases that benefit from interventions while also reassuring those at low risk.

Definition of High Risk

Figures 1 and 2 show lifetime risk and risk within 5 years for a general population.

Women considered to be at high risk for developing breast cancer have a lifetime risk ≥ 20% (RR > 2.5) and those at moderate risk between 15% and 20% (RR: 1.6 to 2.5).

Subjective Risk Analysis

A careful analysis of the clinical and family history is carried out. In addition to age and sex (female), multiple risk factors for breast cancer should be investigated during the visit (Table 1).

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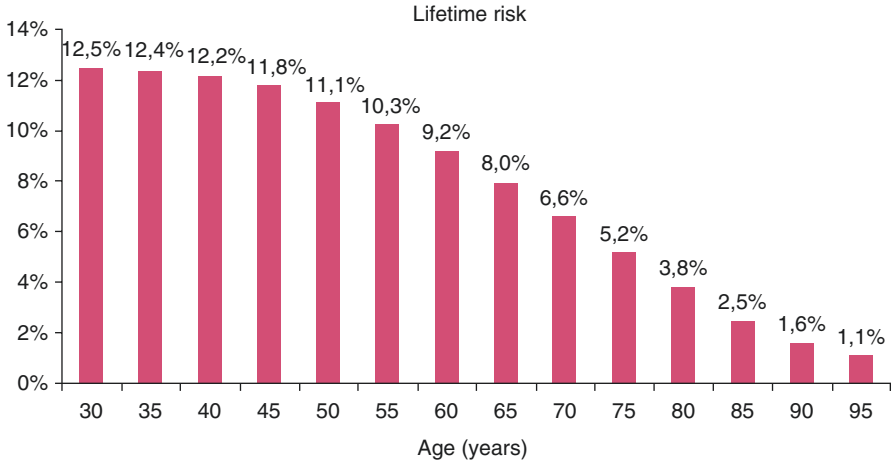


Fig. 1 Lifetime risk of breast cancer for the general population (SEER data, NCI)

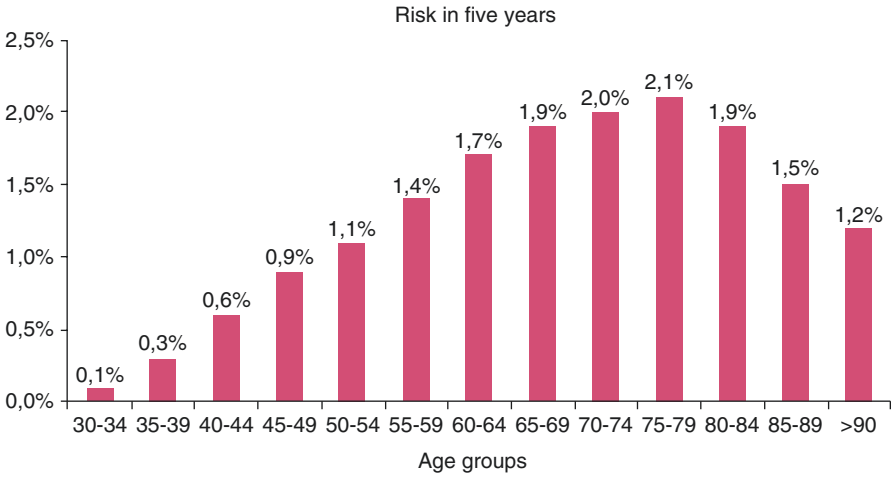


Fig. 2 Risk within 5 years according to age range (SEER, NCI data)

Quantitative Risk Analysis

Mathematical models, validated mainly for the white American population, can be used to quantify the risk of breast cancer. The most used ones are Gail, Claus, BRCAPRO, and Tyrer-Cuzick, all of which are available online (Table 2).

Gail's model is best known and focuses primarily on personal history, but it is limited as to family background. On the other hand, Claus and BRCAPRO models focus almost exclusively on family history. The model that covers more information

Table 1 Risk factors for breast cancer

Family history	RR
Breast or ovary cancer (1 relative at first degree >50 years)	1.8
Breast or ovary cancer (1 relative at first degree <50 years)	3.3
Breast or ovary cancer (1 relative at second degree)	1.5
Breast or ovary cancer (2 relatives at first degree >50 years)	3.6
Bilateral breast cancer	3.2
Breast and ovary cancer in the same individual	3
Breast cancer in males	3–5
Known genetic mutation	4–8
Individual history	**RR**
Previous breast biopsy showing atypia or carcinoma	4
Thoracic irradiation before age 30	3
Ashkenazi Jewish origin	4–8
Menarche at early age	1.3
Late menopause	1.2–1.5
Nuliparity or first pregnancy after age 30	1.7–1.9
No breast-feeding	1.2
Use of HT (E + P or tibolone) post menopause	1.2
High breast density post menopause	5.23
Obesity post menopause	1.2–1.9
High levels of circulating estrogen	5
Continuous consumption of alcohol (> 2 glasses/day)	1.24

Table 2 Websites of the main models for risk assessment

Model	Virtual address
Gail	www.cancer.gov/bcrisktool
Claus	www.cyrillicsoftware.com
BRCAPRO	www.cyrillicsoftware.com
Tyrer-Cuzick	www.ems-trials.org/riskevaluator/

is that of Tyrer-Cuzick, which gives satisfactory importance to all data (Table 3). Some studies have compared the efficacy of these programs in high- and low-risk populations. The conclusion is that the model proposed by Tyrer-Cuzick is the one that presents less risk of underestimation for both groups.

To improve accuracy in predicting risk, other factors have been introduced in current models, such as breast density, hormonal dosages, and lifestyle.

A meta-analysis of 42 studies, comparing breast density as a risk factor for breast cancer, indicated a relative risk of breast cancer of 4.64 in patients with more than 70% of dense breast tissue compared to breasts lower than 5% density at mammography.

Table 3 Variables analyzed in the main models for risk assessment

Analyzed variables		Gail	Claus	BRCAPRO	Tyrer-Cuzick
Personal	Age	Yes	Yes	Yes	Yes
	BMI	No	No	No	Yes
	Menarche	Yes	No	No	Yes
	1st delivery	Yes	No	No	Yes
	Menopause	No	No	No	Yes
	Previous biopsies	Yes	No	No	Yes
	Hyperplasia with atypia	Yes	No	No	Yes
	Lobular neoplasia	No	No	No	Yes
Family	1st-degree relative	Yes	Yes	Yes	Yes
	2nd-degree relative	No	Yes	Yes	Yes
	Cancer age	No	Yes	Yes	Yes
	Bilateral breast cancer	No	No	Yes	Yes
	Ovary cancer	No	No	Yes	Yes
	Breast cancer in males	No	No	Yes	No

Hereditary Genetic Syndromes

Among the known genetic syndromes for breast cancer, the most frequent and studied is the mutation of BRCA 1 and 2, with a lifetime risk of about 70%.

The best known specific statistical models for calculating the risk of presenting this mutation:

- BRCAPRO (Parmigiani et al. 1997)
- Myriad (Frank et al.)
- BOADICEA
- Manchester score

The use of these models is important because it allows selecting which cases actually need the genetic test. Apparently, the most effective one is BRCAPRO, but Myriad has been validated in a larger number of patients.

The other genetic syndromes are less common and do not have commercially available diagnostic tests. The main features of these changes can be seen in Table 4.

Conclusion

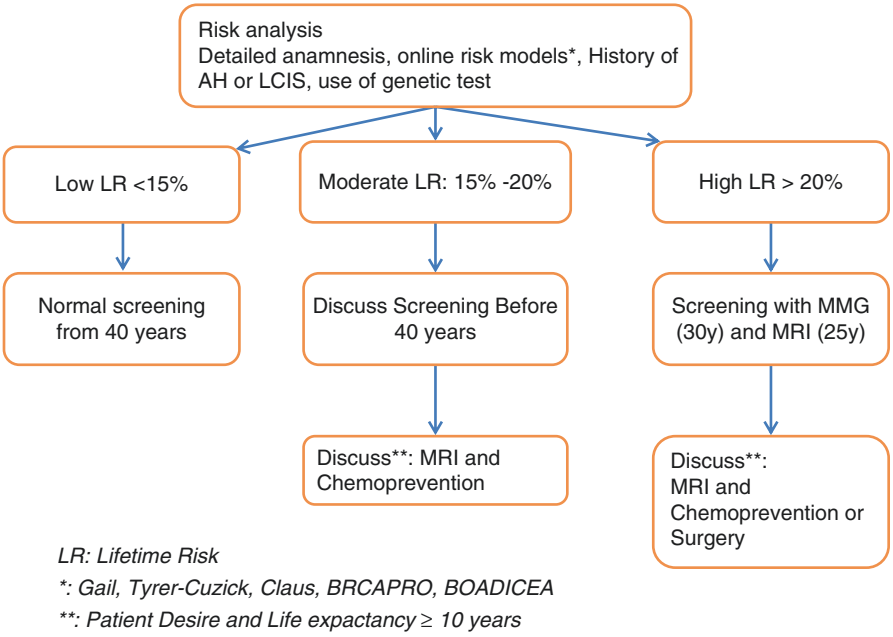
The definition of individual risk is important in today's medicine. The use of statistical models helps to define which patients require intervention to lessen the onset of cancer and who should do the genetic test. However, if these resources are not available, adequate and careful anamnesis is sufficient for this evaluation.

Table 4 Characteristics of the most known genetic syndromes

Syndrome	Gene	Risk at age 70	Associated tumors
HBOC	BRCA 1	55%	Ovary and pancreas
HBOC	BRCA 2	47%	Ovary, prostate, and pancreas
Li-Fraumeni	p53	>90%	Sarcoma of soft tissues, osteosarcoma, SNC, adrenal, leukemia, and colon
Cowden	PTEN	25–50%	Thyroid, endometrium, and genitourinary
Peutz-Jeghers	STK11/ LKB1	45–54%	Intestine, uterus, testicle, and sexual cords
Hereditary diffuse gastric carcinoma	CDH1	39%	Lobular carcinoma and diffuse gastric cancer
Ataxia-telangiectasia	ATM	RR: 3–4	Not defined
Li-Fraumeni variant	CHEK2	RR: 2	Not defined

HBOC, Hereditary Breast and Ovarian Cancer

Flowchart



Flowchart 1 Risk analysis and Management

Recommended Reading

1. Berry DA, Parmigiani G, Sanchez J, Schildkraut J, Winer E. Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. J Natl Cancer Inst. 1997;89(3):227–38. *BRCAPRO. Mathematical model with Bayesian theorem that calculates the risk of the proband to be a carrier of genetic mutation in the BRCA, later validated by diagnostic studies*
2. Brentnall A, et al. Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening. Breast Cancer Res. 2015;17:147. *A prospective study in the United Kingdom that analyzed breast density to improve the accuracy of Gail and Cuzick's risk models. The study included 50,628 patients with a follow-up of 3.2 years. In the univariate analysis, breast density impacted on the best accuracy of the Tyrer-Cuzick and Gail models in predicting cancer risk.*
3. Evans DG, Howell A. Breast cancer risk-assessment models. Breast Cancer Res. 2007;9:213–21. *A review study comparing the efficacy of the major risk assessment models to calculate the onset of disease and the risk of BRCA mutation. In the first category, the best model was Tyrer-Cuzick (81%), followed by Claus (56%), BRCAPRO (49%) and Gail (48%). In the second, BRCAPRO is the most effective for BRCA 1 and Manchester for BRCA 2.*
4. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81(24):1879–86. *First report of Gail's model; case-control report in North American patients participating in a prevention study. Subsequently, Chlebowski et al. observed that it only predicted tumors with positive receptors. Another model for African Americans is suggested.*
5. NICE. 2013 – current UK guidance on the management of patients at high risk of breast cancer due to their family history. *Guidelines on management and identification of high-risk patient for breast cancer.*
6. Santen RJ, Boyd NF, Chlebowski RT, Cummings S, Cuzick J, Dowsett M, et al. Critical assessment of new risk factors for breast câncer: considerations for development of as improved risk prediction model. Endocr Relat Cancer. 2007;14:169–87. *Review article that updates the main risk factors for breast cancer, mainly analyzing hormonal influence: dense breasts and plasma levels of free estrogen. It also includes personal factors (atypia and radiotherapy) and genetic factors.*
7. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004;23(7):1111–30. *Model of Tyrer-Cuzick. Bayesian theorem that evaluates most known risks of breast cancer and calculates the risk for the disease and for being a mutation carrier in BRCA*

Practical Aspects of Genetic Counseling: Genetic Tests to Identify Risks

Bernardo Garicochea and Rodrigo Santa Cruz Guindalini

Definition

Germline mutations in hereditary predisposition genes to cancer account for about 5–10% of all diagnosed cases of breast cancer. The loss of function of about 30 different genes presents a clear correlation with patterns of heredity, i.e., individuals with germ mutation in one of these genes are more likely to develop breast cancer, as well as other types of cancer throughout their lives, in comparison with the general population. These mutation-bearing patients have what is called hereditary breast cancer. Currently, the identification of individuals with these genetic alterations is fundamental, as it can not only be extremely useful for guiding the clinical-surgical treatment of patients affected by neoplasias, but it can also guide personalized prevention and risk-reduction strategies for asymptomatic patients who are part of the same family. It is important to note that, once a proband mutation is identified in the test, there is a 50% chance that first-degree relatives (children, siblings, and parents) have this mutation and are at increased risk of developing cancer. Further, distant relatives may also have this genetic variant and therefore, this risk should be evaluated individually.

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Hereditary Syndromes That May Lead to Breast Cancer: Clinical Aspects

The suspicion that a certain family or individual has mutations in genes that predispose to cancer can be estimated from individual characteristics and family history that should be actively searched in the anamnesis. The most common findings of suspected heredity for breast cancer are presented in Table 1. It is often important to look closely at the composition of the maternal or paternal family. So one should ask the following, for instance: did the woman's father have male siblings, the same occurring with the woman's grandfather? In this case, the mutation may have been silently transmitted by two generations without identifiable phenotype, revealing itself as the first woman to be the carrier after several generations. In addition, attention is required with very small families (limited family structure = absence of two first, second, or third female relatives in one of the lineages—maternal or paternal—who have lived longer than 45 years) or in cases that the patient does not seem to be safe to report on diseases that affected her relatives.

Table 1 Most usual hereditary suspicion of breast cancer

Individual affected by 1 or more of the following	Individual not affected but with family history of 1 or more of the following
Early breast cancer (<35 years∗)	≥2 primary breast tumors, in 1 individual or in different individuals on the same side of the family
Triple negative breast cancer (<60 years∗)	≥1 ovarian cancer on the same side of the family
Breast cancer at age ≤ 50 years and 1 second primary breast tumor∗ ≥1 relative with breast and/or ovary cancer∗	1st or second degree relative with breast cancer ≤45 years
Breast cancer at any age and ≥1 relative with breast cancer ≤50 years∗ ≥1 relative with breast cancer in male;∗ ≥1 relative with ovary cancer∗ ≥2 relatives with breast, prostate, or pancreatic cancer∗ From a high-risk population (Ashkenazi Jews)∗	Combination of breast cancer with 1 or more of the following: thyroid, endometrial, diffuse gastric cancers, adrenocortical, cerebral, sarcoma, dermatological alterations and/or macrocephaly, or leukemia/lymphoma on the same side of the family
Combination of breast cancer with 1 or more of the following: ovarian, thyroid, endometrial, diffuse gastric, adrenocortical, brain, sarcoma, dermatologic and/or macrocephalic, or leukemia/lymphoma cancers on the same side of the family	Known mutation in the gene in family susceptible to breast cancer
	Breast cancer in men

Symbol ∗: criteria for mandatory coverage by genetic testing health plans for BRCA1 and BRCA2 according to the Health Procedures and Events Schedule of the National Health Agency published in 2016

In order to optimize the research strategy, the team responsible for the genetic counseling of the patient must identify the best member of the family to offer the genetic test. In general, the most suitable individual is the adult with a diagnosis of cancer at an earlier age related to the clinical suspicion in question.

Genes Associated with Hereditary Breast Cancer

Genes associated with heredity for breast cancer are very different from each other, both in the function they exert in the normal cell and in the associated cancer pattern (phenotype). Thus, when such a gene has its chemical structure modified, the reflection that will be produced in the protein may affect certain tissues more intensely to the detriment of others. Thus, certain mutations are associated only to breast cancer, while others are associated to cancer in several organs, including the breast.

Dozens of genes have had mutations described and correlated with the breast cancer phenotype. These genes can be grouped into three groups: genes whose mutations have high penetrance (> fivefold increased risk of cancer, i.e., the correlation between mutation and breast cancer is very strong), genes with moderate penetrance (2–5′ > risk of cancer), and low penetrance genes (1–2′ > risk of cancer). This classification allows the individualization of prevention programs.

High-Penetrance Genes

Mutation carriers in these genes have more than 50% chance of having breast cancer during life (up to 90 years). BRCA1 and BRCA2 harbor about 50% of the mutations associated with hereditary breast cancer to date and account for approximately 5% of all breast neoplasms. Other genes with less frequent mutations are PALB2, PTEN (Cowden's syndrome), STK11 (Peutz-Jeghers syndrome), TP53 (Li-Fraumeni syndrome), and homozygosity/composite heterozygosity in CHEK2. The TP53 gene is rarely mutated in the human species, but in the Brazilian population, a specific mutation is quite prevalent (R337H) and should always be considered in genetic panels for breast cancer.

Moderate-Penetrance Genes

The risk of breast cancer in carriers of heterozygous mutation in these genes generally does not exceed 25–50%. The most frequent genes are ATM, heterozygous in CHEK2, NBN, BARD1, and NF1.

Low-Penetrance Genes

Mutations or variants (polymorphisms) in these genes slightly increase the risk for breast cancer, and these changes are not evaluable by commercial genetic testing currently available. The combination of multiple low-penetrance variants (polygenic risk) can certainly cause a substantial increase in the risk of breast cancer, but to understand how these genes are articulated, more time for observation and clinical research will be needed.

Genetic Tests

Historically, clinical criteria such as personal and family history of cancer combined with some phenotypic characteristics of an individual were used to indicate the investigation of mutations in genes most likely related to the clinical condition of interest. Molecular tests were targeted at 1 or 2 most commonly involved genes, and the research turned to less likely genes only when the clinical suspicion was too high. With this type of strategy, over the past two decades progressively, molecular tests for cancer risk assessment have spread, and guidelines to guide the request for evidence-based genetic testing have been created for hereditary breast cancer.

More recently, genetic testing for hereditary cancer syndromes has been transformed by the advent of Next Generation Sequencing Platforms (NGS), which enabled the reading of multiple genes in depth (i.e. several times the same stretch) into a single reaction. By improving the technology and the speed and breadth to read multiple genes, it is now possible to approach multiple genetic syndromes simultaneously. In addition, the price of these tests has fallen sharply, which makes them affordable for many patients. Considering clinical practice, such tests are preferably performed from the saliva or blood of an individual having breast cancer and are commercially available through multigenic panels associated with breast cancer.

After the mutation is detected, in most cases it is possible to estimate the risk of other cancers that this individual possesses and, therefore, to plan personalized cancer screening and prevention strategies for certain organs. The other family members do not need to repeat the comprehensive genetic mapping with the research of dozens of genes. As the mutated gene has already been identified, it is enough to study only the point mutation discovered in this gene on a much simpler platform in the family at risk.

Variants of Unknown Significance

A disadvantage of testing a larger number of genes, especially those that are not well characterized, is the potential to identify a greater number of variants of unknown significance (VUS), thus greatly increasing the percentage of patients

with inconclusive results. The presence of a VUS means that the effect of this variant on the function of the gene product is still unknown. Therefore, the set of scientific evidence available to date does not allow us to conclude whether or not this variant causes an increased risk of cancer. Until this uncertainty can be resolved, caution should be taken before using this result to guide clinical-surgical management decisions. In fact, most VUSs are unlikely to be pathogenic mutations, but some will be. Historically, most VUSs are later reclassified as benign variants. However, reclassification can take years. In this scenario, recommendations for prevention, screening, and risk reduction of cancer based on personal risk factors and family history for both the patient and his or her relatives should be made. In general, it is not recommended to test family members for a VUS, except within the context of academic research. However, in some rare cases, understanding the inheritance pattern of a variant may be useful for genetic counseling.

Genetic Syndromes Associated to Breast Cancer

The main genetic syndromes associated with high risk of developing breast cancer are hereditary predisposition syndrome to breast and ovarian cancer (mutations in the BRCA1 and BRCA2 genes), Li-Fraumeni syndrome (mutation in the TP53 gene), Cowden's syndrome (mutation in the PTEN gene), hereditary diffuse gastric cancer (mutation in the CDH1 gene), and Peutz-Jeghers syndrome (mutation in the STK11 gene). Among these, deleterious mutations in BRCA 1/2 are the most prevalent and cause approximately 5% of all breast neoplasms.

Hereditary Predisposition Syndrome to Breast and Ovarian Cancer

Deleterious mutations in the BRCA1 and BRCA2 genes cause hereditary predisposition syndrome to breast and ovarian cancer, which is an autosomal dominant syndrome. BRCA1 mutation carriers have a cumulative risk of 72% for breast cancer (up to 80 years), 44% for ovarian cancer (up to 80 years) and 40% for contralateral breast cancer (up to 20 years after diagnosis of previous breast cancer). Patients with BRCA2 mutation present a cumulative risk of 69% for breast cancer (up to 80 years), 17% for ovarian cancer (up to 80 years) and 26% for contralateral breast cancer (up to 20 years after breast cancer). It is important to highlight that the risk of breast cancer practically doubles with the presence of ≥2 relatives of first and/or second degree with a history of breast cancer. In addition, mutations located outside the c.2282-c.4071 regions of the BRCA1 gene and c.2831-c.6401 of the BRCA2 gene have shown to increase the risk for breast cancer significantly (Fig. 1 and Table 2).

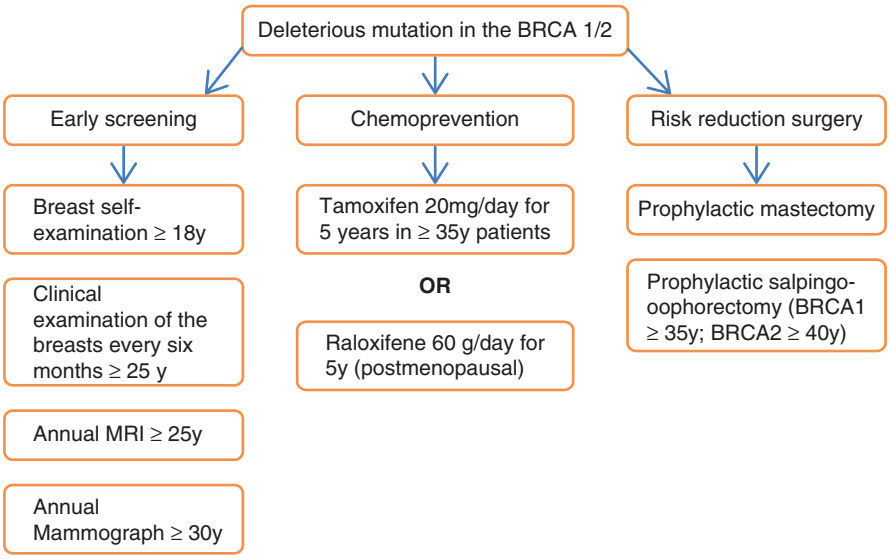

Fig. 1 Flowchart to guide patients with deleterious mutation in BRCA1/2

Table 2 Proposal of clinical surgical handling based on findings from the genetic test

Gene	Risk of breast cancer	Prophylactic resection of breast tissue	Annual breast screening with NMR	Prophylactic bilateral salpingo-oophorectomy
BRCA1	72%	Yes	≥20–25y	≥ 35y
BRCA2	69%	Yes	≥20–25y	≥ 40y
TP53	90%	Yes	≥20–25y	No
CDH1	40%	BFH	≥ 30y	No
STK11	~50%	BFH	≥25y	No
PTEN	~50%	BFH	≥30y	No
PALB2	35%	BFH	≥30y	BFH
ATM	RR 2.8	BFH	≥40y	BFH
CHEK2	RR 1.5–3.0	No	≥40y	BFH
NBN	RR 2.7	No	≥40y	BFH
BRIP1/ RAD51C/ RAD51D	ID	No	BFH	≥50–55y

y years, *BFH* based on family history, *ID* insufficient data, *NMR* nuclear magnetic resonance, *RR* relative risk

Recommended Reading

1. Kuchenbaeker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast Cancer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;317(23):2402–16. *A prospective study with approximately 10,000 BRCA1/2 mutation carriers that established cumulative risk of breast cancer, ovarian cancer, and contralateral breast cancer. In addition, we evaluated the influence of the family and local history of the mutation as to the risk of breast cancer. Interpretation: identified that family history is a strong risk factor for those with mutation and that the risk of breast cancer varies according to the location of the mutation*.
2. Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev. Clin Oncol. 2016;13(9):581–8. *A consensus of specialists that proposes differentiated clinical and surgical management for mutation carriers in genes of moderate penetrance. Interpretation: there is still a lack of studies to validate breast cancer screening and prevention interventions for carriers of mutations in moderate penetrance genes.*
3. Valencia OM, Samuel SE, Viscusi RK, Riall TS, Neumayer LA, Aziz H. The role of genetic testing in patients with breast cancer: a review. JAMA Surg. 2017;152(6):589–94. *A practical and concise review of the major genes involved with hereditary breast cancer. Interpretation: useful for quick and targeted queries*
4. Villani A, Tabori U, Schiffman J, Shlien A, Beyene J, Druker H, Novokmet A, Finlay J, Malkin D. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol. 2011;12(6):559. *The first prospective study to demonstrate in Li-Fraumeni syndrome that a rigorous follow-up can detect tumors earlier. Interpretation: accurate early screening is effective.*
5. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med. 2008;148(9):671. *A systematic review of 11 studies demonstrating that breast resonance in conjunction with mammography has a sensitivity of 94% and specificity of 77% in patients at high risk for developing breast cancer. Interpretation: it is currently recommended to add the annual breast resonance in the early screening scheme.*

Prevention: Behavioral Measures and Habits

BBSG – Brazilian Breast Study Group

Introduction

Breast cancer causes great distress in women because of the high incidence, mortality, and risk of mutilation. In addition to screening, patients want to know what other measures can be taken to reduce risks. Among the most questioned issues are the habits of a person's life and environmental factors.

Since the mid-1990s, the amount of scientific literature on this subject has increased significantly. The report called *Food, Nutrition and Cancer Prevention: A Global Perspective produced by the World Cancer Research Fund* (WCRF) along with the American Institute for Cancer Research has been one of the most authoritative documents on the subject over the last 10 years.

In May 2017, following a systematic global review of 119 publications, the new Cancer Prevention Recommendations were launched. The studies evaluated data from more than 12 million women and more than 260,000 cases of breast cancer. The report assesses the relationship between diet, weight, physical activity, and breast cancer and also which of these factors increase or decrease the risk of developing the disease.

In summary, the authors concluded that…

- Premenopausal breast cancer – there is strong evidence that:
  - Drinking alcohol increases risk.
  - Performing regular physical activity lowers risk.
  - Breastfeeding lowers risk.
  - Overweight or obesity between adolescence and adulthood until before menopause does not raise the risk, and it may even decrease it

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- Postmenopausal breast cancer – there is a strong evidence that:
  - Drinking alcohol increases risk.
  - Being physically active (including regular, and even intense, physical activity) lowers risk.
  - Overweight or obesity increases risk.
  - Breastfeeding lowers risk.

Following this introductory section, some topics related to this subject will be discussed.

Body Mass Index

An overweight BMI influences differently on risk according to the hormonal condition.

Postmenopausal

Research has shown that postmenopausal obese women are at a higher risk for breast cancer than those with normal weight. Two are the most accepted hypotheses: increase of circulating sex steroids due to the greater peripheral conversion of androstenedione to estrone in the subcutaneous tissue and a chronic inflammatory environment favoring the performance of mitogenic and anti-apoptotic agents. In a cohort of 337,000 participants, BMI > 28 kg/m^2 caused 26% more breast tumors. Another study found that the gain of 20–29 kg increased the risk by 56% and the gain of 40–49 kg doubled the odds. Weight loss has a protective effect, especially in women who do not use hormonal therapy. In another cohort, the sustained loss of at least 10 kg reduced the risk by 57%.

The impact of weight gain after 40 years of age was evaluated in the European Prospective Investigation into Cancer and Nutrition study, which included more than 200,000 women. In this study, high weight gain (0.83 to 4.98 kg/year) was associated with a small but significant increased risk of breast cancer (HR 1.09, CI 1.01–1.18).

Premenopausal

Contrary to previous results, high body weight represents a protective effect in premenopausal women. The mechanisms of this effect are not clear. The main hypothesis is the anovulation caused by obesity, which can lead to lower circulating

hormone levels. Other hypotheses would be earlier cell differentiation or lower levels of growth factors.

In a combined analysis of cohort studies, there was a 14% decrease in risk for each 5 kg/m^2 increase in BMI.

A study presented in December 2016 (Chlebowski, Aragaki, Anderson et al. SABCS 2016 S5–04 – WHI DM Trial) has shown that women diagnosed with breast cancer and those who adopt a low-fat diet have a lower risk of relapse and death from the disease although that was not statistically significant. The results from WHI and others do not provide definitive evidence to guide women's choices about the ideal diet to prevent breast cancer. However, there was a suggestion in the study that low-fat intake could help reduce the risk of developing the disease.

Physical Exercising

Different measures are used to collect data on physical activity, and it is difficult to standardize all types of activities and to perform a specific study on each type of practice. However, the categorization in low or high intensity activities allows some conclusions.

In the premenopausal period, there is no increase in benefit when we compare the intensity of the exercise performed: in this phase, the periodicity seems to be more relevant. In the postmenopausal period, the most recent meta-analysis (Breast Cancer Report 2017) evaluated eight studies (n = 11,798) regarding the impact of physical exercise intensity and concluded that there is a 13% reduction in the risk of developing (RR: 0.87, CI95%: 0.79–0.96) in the group that performed more vigorous exercises.

Some observational studies have suggested that four to 7 h of weekly physical exercise can reduce the onset of breast cancer by up to 20% regardless of the menopausal status.

In a cohort study by Howard et al. (2009), with more than 45,000 women, differentiating the type and amount of exercise, it was concluded that more than 10 h of walking (week) has protective effects. Other types of exercise or less walking time did not present significant results. Another point observed that the protective effect of exercise was in premenopausal or postmenopausal women who have never used menopausal hormone therapy (HT).

Several studies conducted around the world have observed an average risk reduction of 30 to 40% in women who practice regular physical activity. Physical activity reduces levels of sex hormones and the production of estrogens and androgens, as well as increasing the amount of sex hormone-binding globulin, thus reducing the ability of hormones to act on target tissues and interfering with the risk of developing hormone-dependents. In addition, there is a significant reduction in insulin levels, interfering with insulin-like growth factor (IGFs) that are associated with increased risk of breast cancer.

Alcohol Intake

Alcohol consumption is associated with increased risk in both epidemiological and animal models. The main hypothesis is the carcinogenic effect of alcohol metabolites, but other theories suggest interference in estrogen metabolism or nutritional deficiencies.

According to NCCN 2016, alcohol consumption should be limited to 1 drink per day (equivalent to 29 ml of liquor, or 177 ml of wine, or 236 ml of beer). Meta-analysis of ten studies (n = 4.227) evaluated daily alcohol intake and risk of premenopausal breast cancer: a significant increase of 5% per 10 grams of ethanol/day (RR: 1.05, 95% CI, 1.02–1.08) (Fig. 1).

Regarding alcohol consumption and the risk of postmenopausal breast cancer, a meta-analysis with 22 studies (n = 35.221) showed a significant increase of 9% per 10 grams of alcohol/day (RR: 1.09, 95% CI %: 1.07–1.12) (Fig. 2).

The type of drink does not seem to influence, but the folic acid supplement appears to reduce or eliminate the risk caused by alcohol.

Phytoestrogens

Prevention through functional foods emerges as an additional tool (probable mechanisms of anticancer action, antioxidants, antiinflammatory, antiestrogenic, and anti-angiogenic). Among the food compounds studied for their preventive action, the

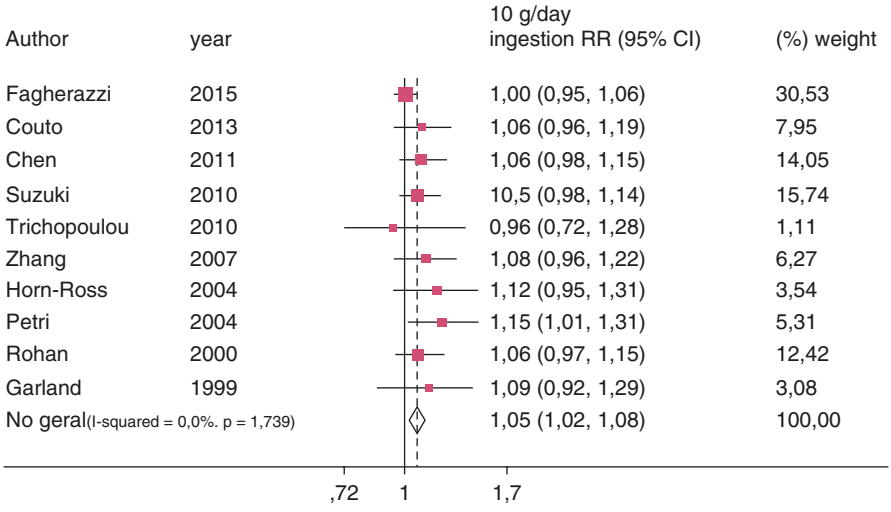

Fig. 1 Alcohol dose-response (ethanol) meta-analysis and premenopausal breast cancer, 10 g/day

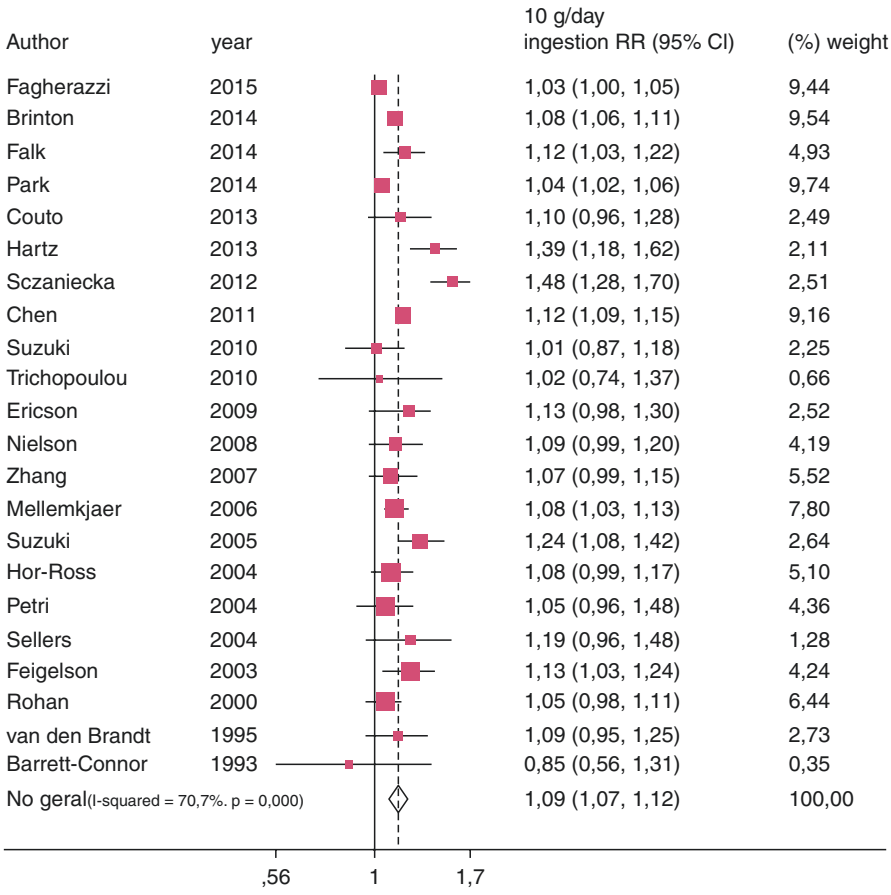

Fig. 2 Alcohol dose-response (ethanol) meta-analysis and postmenopausal breast cancer, 10 g/day

main ones are conjugated linoleic acid (CLA), n-3 polyunsaturated fatty acids, phytoestrogens (isoflavones), vitamins, and minerals.

High levels of isoflavanoids are associated with low risk for breast cancer, found in soybean derivatives, lignans, *cimicifuga racemosa* and *trifolium pratense*.

The consumption of foods rich in phytoestrogens such as fresh fruit, fresh vegetables, and vegetable oils has been reported as a protector of breast cancer and can reduce the risk of breast cancer by 33–45%.

However, the effect of these substances still lacks consistent clinical studies. After all, there are several factors that can interfere with the analysis, such as patient selection and weight loss in the vegetable-rich diet group.

Food Intake

A healthy diet is critical to maintaining a good quality of life, allowing for greater weight control and fewer cardiovascular diseases. There has been a growing interest in research evaluating the eating patterns of adolescents and young adults versus the risk of breast cancer. The types of foods consumed, their frequency and their proportion in the diet have been analyzed in several countries. In the United States, a large population study involving more than 95,000 women concluded that consumption of certain dietary fibers (fruits, vegetables, and whole grains) is associated with a significantly lower risk of breast cancer: 13% lower per 10 g/day of fiber increase during early adulthood and 14% risk reduction per 10 g/day of fiber increase during adolescence. Other studies estimated a more modest risk reduction – 5% for every 10 g/day increase in fiber intake – but still significant.

Previous studies were almost nonsignificant, but it is noteworthy that none of them examined the diet during adolescence, a period in which risk factors for the development of neoplasia appear to be particularly important since breast tissue has a higher rate of proliferation.

The effect of the main food types on the risk can be seen in Table 1.

Table 1 Effect of main food types on the risk

Food/Nutrient	Effect on risk	Evidence
Total fat	No association	9 cohorts and 1 clinical trial
Fat type	Inconsistent association (apparent worsening with animal fat)	9 cohorts and 1 clinical trial
Total carbohydrates	No association	1 observational cohort
Carbohydrate type	No association	3 observational cohorts
Fibers	No association	1 observational cohort
Red meat	Inconsistent association	1 observational cohort and systemic analysis of 8 prospective cohorts
Milk and dairy products	No association	Systematic analysis of 13 prospective cohorts
Fruit and vegetables	No association	Systematic analysis of 8 prospective cohorts
Caffeine	No association	1 observational cohort
Vitamins A, C, and E	No association	1 observational cohort
Folic acid	No association	1 observational cohort
Carotenes	Apparent reduction	1 observational cohort

Smoking

Although the results are not rather regular, several studies suggest that there is a modest increase in the risk of breast cancer among smokers. The increased risk was more consistent in studies evaluating early onset of smoking, long duration and/or high pack rate/year.

Breastfeeding

A protective effect of breastfeeding has been shown in several studies and its magnitude depends on the duration of breastfeeding. A meta-analysis estimated that for every 12 months of breastfeeding there is a relative reduction of 4.3% risk of cancer. The mechanism that would explain this protective factor is that breastfeeding provides anovulatory cycles to women, thus less time exposed to endogenous estrogen.

Conclusions

Importantly, risk factors and protective factors potentially modify the risk of developing breast cancer. Among them, some factors that deserve mention are postmenopausal obesity and excessive alcohol consumption. Risk-reducing factors, such as regular physical activity, weight loss or normal BMI, and breastfeeding deserve mention.

Recommended Reading

1. Assaf AR, Beresford SA, Risica PM, Aragaki A, Brunner RL, Bowen DJ, et al. Low-fat dietary pattern intervention and health-related quality of life: the women's health initiative randomized controlled dietary modification trial. J Acad Nutr Diet. 2016;116(2):259–71. *DM Trial investigated the effect of a low-fat diet, high fruit, vegetable, and grain intake on breast cancer, colorectal cancer, and heart disease in postmenopausal women. The intervention goals were to reduce fat intake to 20% of calories, increase fruit/vegetables to five or more servings daily and increase portions of grains to six or more daily. 48,835 postmenopausal women of multiple races and ethnicities and varied ages participated in the trial. Overall, there was a non-significant breast cancer rate of 9% lower in women in the dietary intervention group compared to women in the control group.*

2. Cummings SR, Tice JA, Bauer S, Browner WS, Cuzick J, Ziv E, et al. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. J Natl Cancer Inst. 2009;101(6):384–98. *In this study, the authors found that the regular practice of postmenopausal physical activity was associated with a lower risk of developing the disease (RR: 0.80; 95% CI: 0.69–0.94).*
3. Diet, Nutrition, Physical Activity and Breast Cancer. 2017. In http://www.aicr.org/continuous-update-project/reports/breast-cancer-report-2017.pdf. *The Food, Nutrition and Cancer Prevention Report: A Global Perspective Produced by the World Cancer Research Fund (WCRF) together with the American Institute for Cancer Research. The studies looked at data on more than 12 million women and more than 260,000 cases of breast cancer. The report assesses the relationship between diet, weight, physical activity and breast cancer and which of these factors increase or decrease the risk of developing the disease.*
4. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA. 2006;296(2):193–201. *The study showed that postmenopausal weight gain, more specifically a 10 kg gain, increased the relative risk of developing breast cancer (RR 1.18, 95% CI 1.03–1.35, p = 0.002).*
5. Harris HR, Willett WC, Vaidya RL, Michels KB. An adolescent and early adulthood dietary pattern associated with inflammation and the incidence of breast cancer. Cancer Res. 2017;77(5):1179–87. *This is a study investigating an "inflammatory" dietary pattern in women and their association with breast cancer among 45,204 women at the Nurses' Health Study II. Participants completed a 1998 food frequency questionnaire on the high school diet and one in 1991, when they were between 27 and 44 years old. A food pattern characterized by inflammation was associated with an increased incidence of premenopausal and postmenopausal breast cancer. Overall, the findings support the notion that an adolescent and adult diet characterized by high intake of sugar-sweetened sodas and diet, refined grains, processed red meat and margarine, and low intake of green leafy vegetables increase the incidence of premenopausal breast cancer.*

Prevention: Chemoprevention (Primary Prevention of Breast Cancer)

BBSG – Brazilian Breast Study Group

Definition

In 1976, Sporn defined chemoprevention as the use of natural or pharmacological agents that inhibit the development of invasive breast carcinoma by blocking changes in DNA that would initiate carcinogenesis or by preventing and reversing the progression of already present precursor lesions. Proven and well-established methods block estrogenic action in the breast through the use of SERMs (Selective Estrogen Receptor Modulators) or aromatase inhibitors.

SERMs

SERMs (tamoxifen and raloxifene) are compounds that act on estrogen receptors (ER). The characteristics that differentiate these substances from the pure agonists or antagonists is that their action in the different tissues is variable (Table 1).

Aromatase Inhibitors (AI)

In the postmenopausal women, E1 is converted to estradiol (E2) by the 17-ß-hydroxysteroid dehydrogenase type 1 (17bHSD1). Testosterone, in turn, is converted to E2 by the enzyme aromatase. The predominant sources of aromatase in postmenopausal women are peripheral tissues such as muscle, skin, and especially adipose tissue. The mammary adipose tissue can also form estrogens from the

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Table 1 Variations of action of tamoxifen and raloxifene

Place of action	Tamoxifen	Raloxifene
Bone	↓ (Premenopausal)	↓ (Premenopausal)
	↑ (Postmenopausal)	↑↑ (Postmenopausal)
Breast	↓↓	↓
Cholesterol	↓	↓
Coagulation	↑↑	↑
Endometrium	↑↑	↑

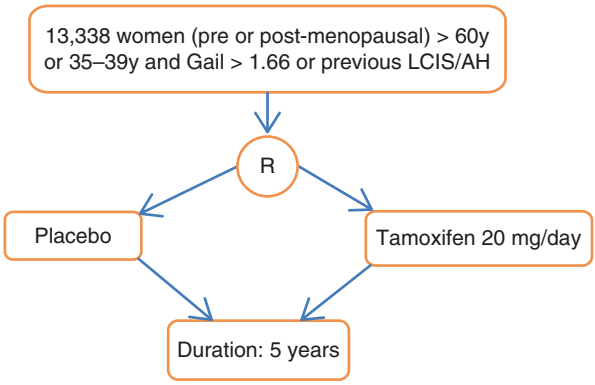


Fig. 1 Drawing of NSABP-P1 study

aromatization of circulating androgens. The rate of estrogenic suppression of aromatase inhibitors ranges from 85% to 95%.

Background Facts

In 1895, Beatson performed the first bilateral oophorectomy due to locally advanced breast cancer and observed regression of recurrence of the disease on the chest wall in a premenopausal patient. The effectiveness of estrogenic blockade for breast cancer control has been known since the mid-nineteenth century. Numerous drugs were involved in ovarian suppression: these have evolved over the years and tamoxifen (TMX) has become the drug of choice.

Some studies on hormone therapy in breast cancer have reported reduction in the incidence of contralateral breast cancer. Such information led to the first randomized study on the use of tamoxifen in primary breast cancer prevention: NSABP-P1 (Fig. 1).

In parallel, the action of raloxifene (RAL) was proposed in primary prevention. Research data on osteoporosis (MORE and CORE Studies) showed favorable results. The NSABP-P2 or STAR study (Study of Tamoxifen and Raloxifene) compared raloxifene with tamoxifen (Fig. 2).

Following studies with SERMs, Goss et al. [3] (MAP.3), published a randomized clinical trial comparing aromatase inhibitor (exemestane) with placebo (Fig. 3).

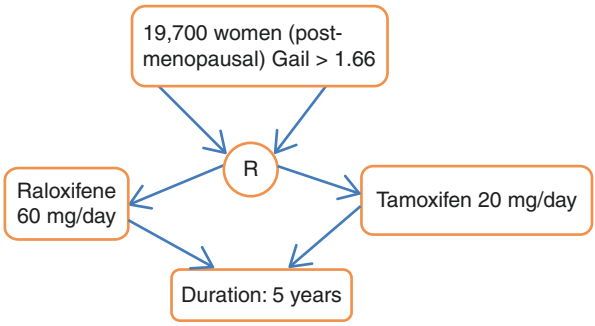


Fig. 2 Drawing of STAR study

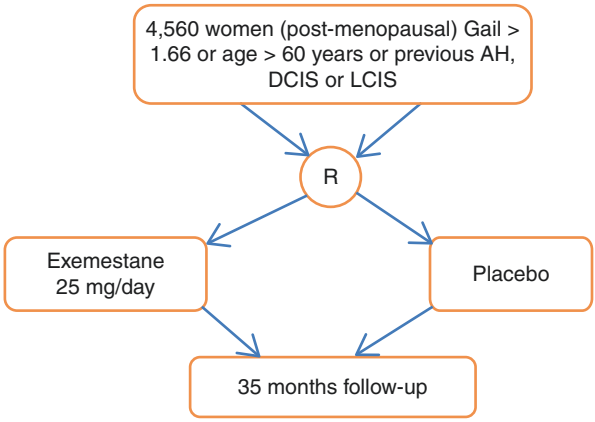


Fig. 3 Drawing of chemoprevention study with exemestane (MAP.3)

In 2014 [1], Cuzik et al. published a randomized clinical study called IBIS II, comparing another class of aromatase inhibitor (anastrozole) with placebo (Fig. 4).

Efficacy

NSABP-P1 results demonstrated a 49% reduction in the risk of invasive breast carcinoma and 50% reduction of carcinoma in situ (Fig. 5). In patients with a history of atypical hyperplasia, this reduction was up to 86%.

This benefit was also observed in the meta-analysis of the main studies that evaluated tamoxifen and raloxifene as risk reducing agents, but only for tumors with hormone receptor (HR) expression (Fig. 6). Subgroup analysis of BRCA1/2 mutation patients from the NSABP-P1 trial showed that there was no risk reduction in patients with BRCA 1 mutation, probably because most of these patients develop negative RH tumors, even in patients with mutation of BRCA 2, there was a reduction in risk in 68%, a result corroborated by a cohort study. Therefore, the use of SERM chemoprevention appears to be ineffective in women with BRCA-1 mutation, and data are limited for BRCA 2.

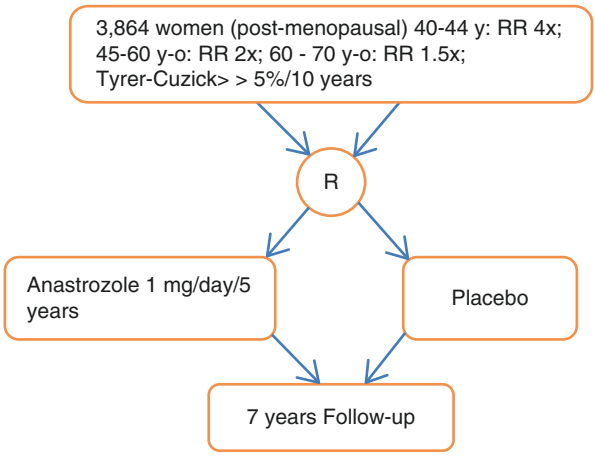


Fig. 4 Drawing of chemoprevention study with anastrozole (IBIS II)

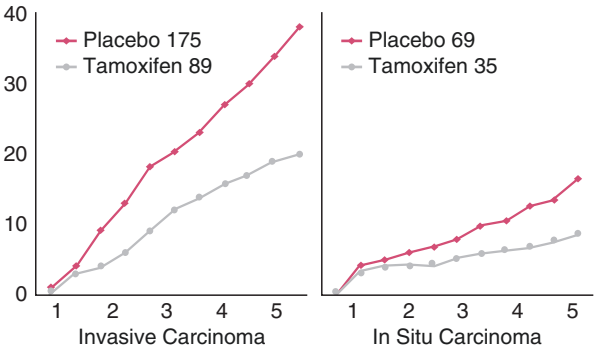


Fig. 5 Number of invasive carcinoma and carcinoma in situ events in the NSABP-P1 study after 5 years. (Adapted from Fisher B et al. [2])

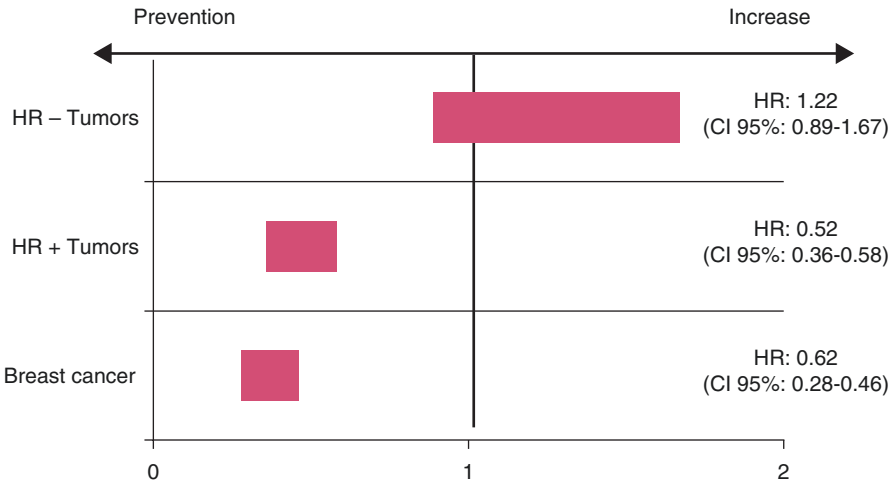


Fig. 6 Meta-analysis of the main studies on chemoprevention with TMX (NSABP-P1, IBIS-1, Royal Marsden and Milan) demonstrating risk reduction only in RH + tumors. (Adapted from Cuzick et al. 2003)

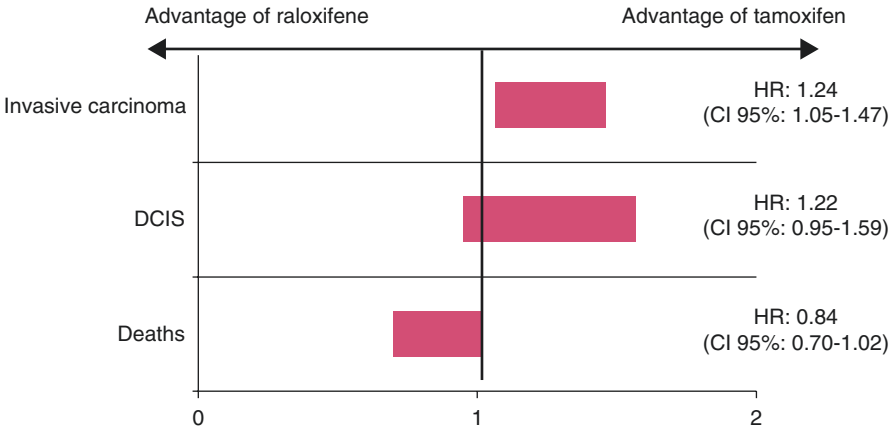


Fig. 7 Results of the comparison between TMX and RAL after 81 months of follow-up. (Adapted from Vogel et al. [6])

The STAR study, evaluating the effect of RAL, demonstrated an inferiority of this drug compared to TMX in the prevention of invasive carcinoma and carcinoma in situ after 81 months of follow-up (Fig. 7).

AI studies showed a reduced risk of developing breast cancer compared to placebo. The study with exemestane demonstrated a 65% reduction in the risk of developing invasive breast carcinoma (95% IC: 0.18–0.70; p 0.002) and 35% in the risk of developing carcinoma in situ, but with no statistical difference in the latter (95% IC: 0.28–1.5, p 0.31).

The anastrozole study demonstrated a 50% reduction in the risk of developing invasive carcinoma (95% IC: 0.32–0.76, p 0.001) and 53% carcinoma in situ (95% IC: 0.32–0.68; $p < 0.0001$).

Side Effects

The main side effects of TMX and RAL can be seen in Figs. 8, 9, and 10.

Analyses of the use of aromatase inhibitors showed safe in relation to thromboembolic and endometrial phenomena. However, the use of these medications increased osteoporosis, muscle and joint pain, and elevation of systemic arterial levels with the use of anastrozole.

Drug Interactions

Tamoxifen can be considered a classic "prodrug", requiring metabolic activation to elicit pharmacologic activity. Both genetic and pharmacologic factors that alter

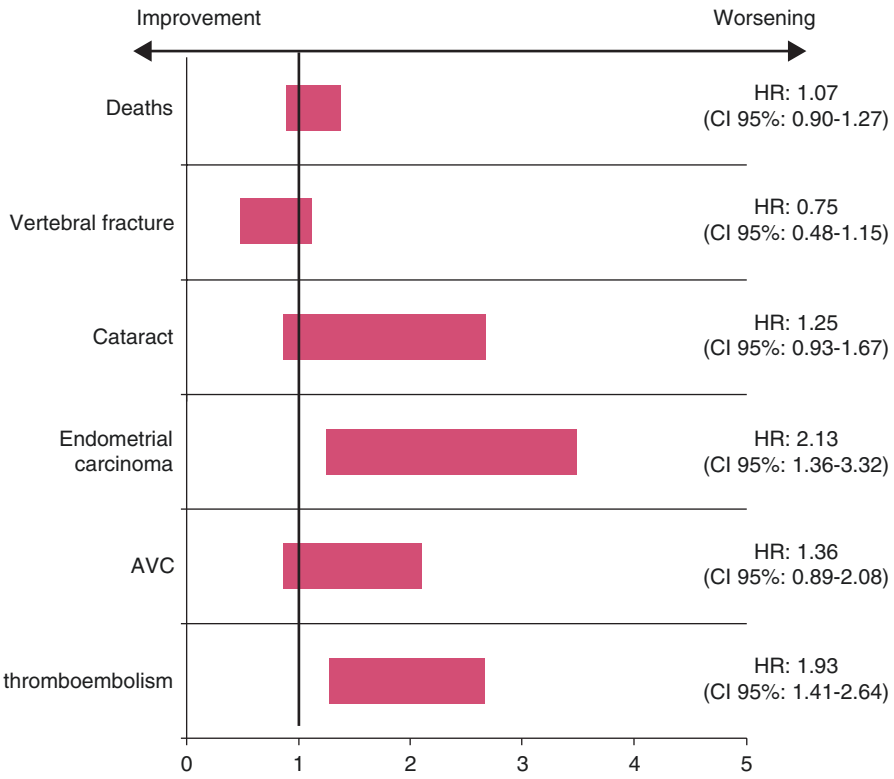


Fig. 8 Meta-analysis of the main side effects of the studies comparing TMX with placebo. (Adapted from Nelson et al. [5])

CYP2D6 enzyme activity directly affect the concentrations of the active tamoxifen metabolites and the outcomes of patients receiving adjuvant tamoxifen. The main drugs in this condition are antidepressant that inhibit serotonin and noradrenaline reuptake, especially paroxetine, fluoxetine, and bupropion, which are considered to be strong inhibitors.

Indications

Based on scientific evidence and international recommendations such as the *National Comprehensive Cancer Network* (NCCN), indications of chemoprophylaxis and its agents for patients who wish to perform it are as follows:

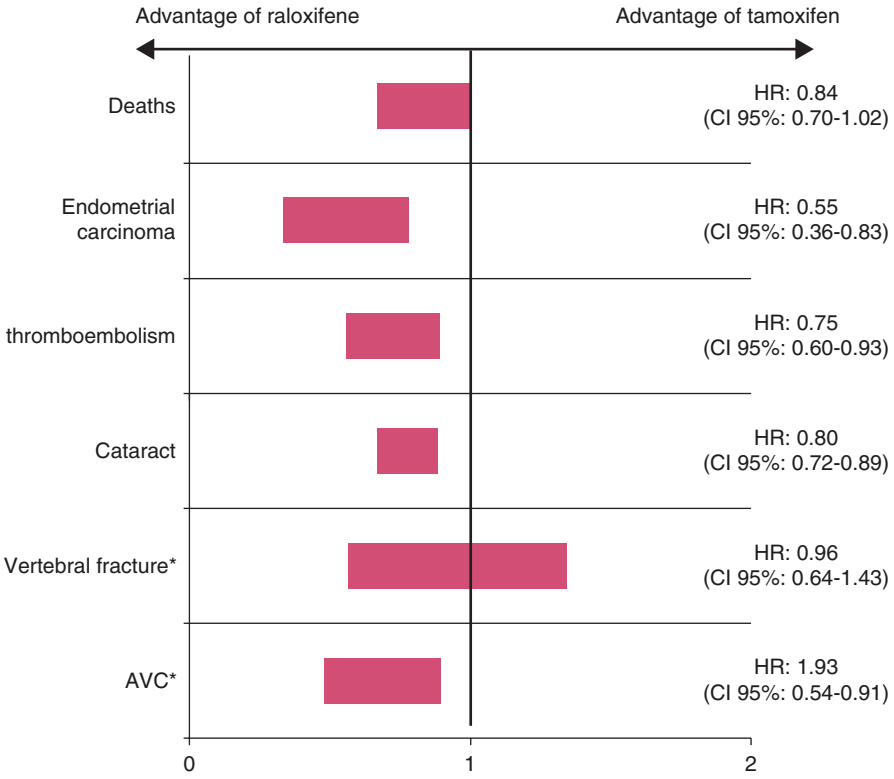


Fig. 9 Results of the STAR study, comparing RAL with TMX. (Adapted from Vogel et al. [6] and 2006∗)

- Tamoxifen 20 mg/day for 5 years: Premenopausal and postmenopausal patients considered to be at high risk (Gail index ≥1.7); personal history of lobular carcinoma in situ or hyperplasia with previous atypia. Evidence is limited, but with some benefit for BRCA 2 gene mutation carriers.
- Raloxifene 60 mg/day for 5 years: Postmenopausal patients considered to be at high risk (Gail score ≥ 1.7); personal history of lobular carcinoma in situ or hyperplasia with previous atypia.
- Exemestane 25 mg/day or anastrozole 1 mg/day for 5 years: Postmenopausal patients with indication for chemoprophylaxis but with contraindication or intolerance to TMX and RL.

Always take these issues into account before the prescription of the medicines the contraindications.

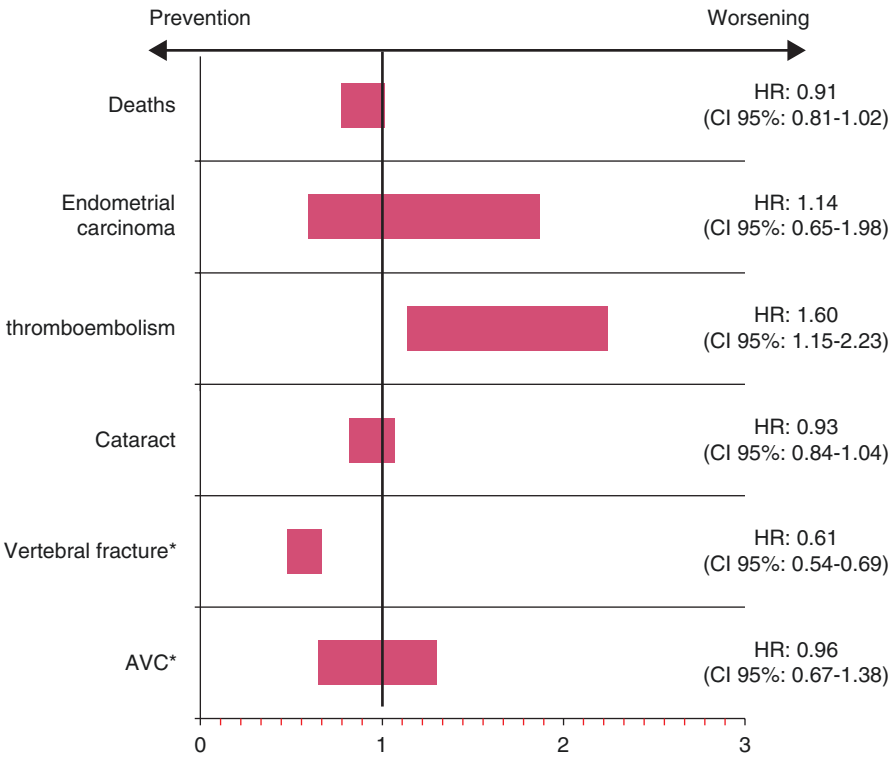
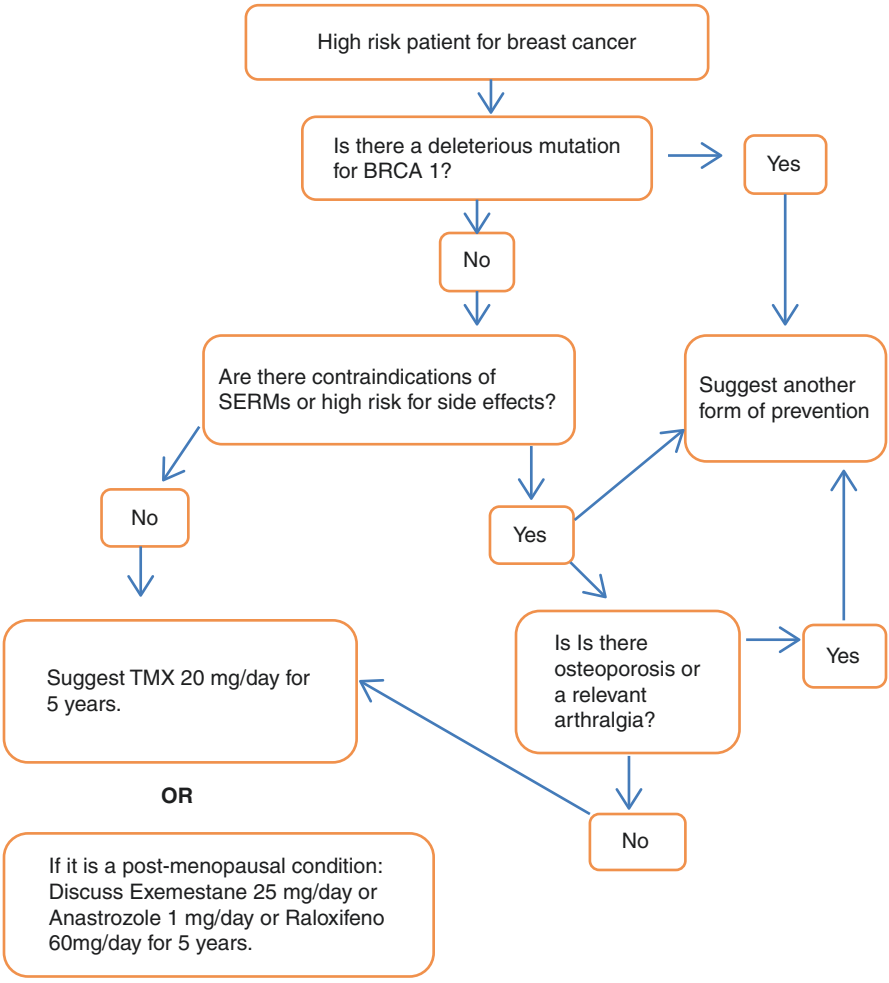


Fig. 10 Meta-analysis of the main side effects of the studies comparing RAL with placebo. (Adapted from Nelson et al. [5])

Conclusion

Chemotherapy with SERMs (TMX and RL) or aromatase inhibitors (exemestane or anastrozole) are options for women at high risk for developing breast cancer (in situ or invasive). The analysis that the benefits of drug use outweigh the risks of its side effects should always be considered for decision-making. It will be up to the patient to make the final decision to use them or to look for other ways to reduce risk.

Flowchart



Flowchart 1 High-risk patient for breast cancer

Leitura Recomendada

1. Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 2014;383:1041–8. *A randomized, double-blind study of 3864 high-risk postmenopausal women randomized for anastrozole or placebo use for five years. After a seven-year follow-up, 50% reduction in breast cancer was observed in the experimental group. The main side effects were related to the osteoarticular system.*
2. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90(18):1371–88. *1st randomized placebo-controlled clinical trial of chemoprevention. The study evaluated 13,338 women, mainly at high risk. After five years, a 48% reduction in the incidence of breast cancer was observed, but there was no reduction in mortality. Increased endometrial carcinoma, cataract, and DVT /PET were observed.*
3. Goss PE, Ingle JN, Alés-Martínez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. NCIC CTG MAP.3 Study Investigators. N Engl J Med. 2011;364(25):2381–91. *A randomized, double-blind study of 4560 high-risk postmenopausal women randomized to take exemestane or placebo for five years. After a mean follow-up of 35 months, a 65% reduction in breast cancer was observed in the experimental group. The main side effects were related to the locomotor system.*
4. King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA. 2001;286(18):2251–6. *Analysis of a small group of NSABP-P1 patients who had a proven BRCA mutation. In the 19 studied women, there was a non-significant reduction in the incidence of breast cancer only in the BRCA-2 mutation group (RR: 0.38, 95% CI: 0.06–1.56). No benefit was observed in BRCA-1 patients (RR: 1.67, 95% IC: 0.32–10.7).*
5. Nelson HD, Fu R, Griffin JC, Nygren P, Smith B, Humphrey L. Systematic review: comparative effectiveness of medications to reduce risk for primary breast cancer. Ann Int Med. 2009;151:703–15. *Systematic review with chemoprevention studies: TMX (4 studies) and ADR (2 studies). Both medications reduced the risk of invasive and* in situ *breast cancer, but only in HR + tumors. Fractures were also reduced, but there was an increase in thromboembolic problems and endometrial carcinoma (mainly with TMX).*
6. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Update of the national surgical adjuvant breast and bowel project study of tamoxifen and raloxifene (STAR) P-2 trial: preventing breast cancer. Cancer Prev Res. 2010;3(6):OF1–11. *A randomized clinical trial of 19,747 patients comparing the use of tamoxifen with raloxifene for five years. Follow-up of 81 months. Tamoxifen was more efficient in invasive cancer chemoprevention (95% IC, 1.05–1.47) and borderline for DCIS (95% IC, 0.95–1.59), but the side effects of ADR were lower, especially in the endometrium and coagulation*

Prevention: Risk-Reducing Surgery

BBSG – Brazilian Breast Study Group

Definition

Risk-reducing surgical procedures are also wrongly referred to as "prophylactic surgery." This second term should be avoided as it suggests the false idea that there is total cancer prevention. The surgical procedures are bilateral prophylactic mastectomy and bilateral salpingo-oophorectomy. These are strategies that can be used in patients at high risk for breast cancer, but their role is much better defined in women with deleterious mutations associated with breast cancer, especially BRCA-1 and BRCA-2. These procedures have high complexity and considerable risk of complications and should be reserved for exceptional situations and after careful evaluation of risks and benefits.

Selection of Patients

Among all forms of prevention, the most effective in reducing the incidence of cancer is the surgical one, although data on benefit in relation to survival are quite controversial.

There is no consensus as to which patient group should undergo the procedure. It appears that young women with a mutation proven in BRCA-1 are the best candidates, since the benefits of chemoprevention are questionable because most of these tumors are negative hormone receptors. BRCA-2 mutation carriers also benefit from risk-reducing surgery, but because most of these tumors are hormone-positive receptors, it is possible that chemoprevention is an effective measure as well. The

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great discussion is whether it would be as effective as the risk-reducing surgery, and up until now there is no data to confirm such benefit.

Some guidelines, such as the national comprehensive cancer network (NCCN) in its 2019 version, contemplate the possibility of risk-reducing mastectomy (RRM) for women with mutations in other genes such as TP53, ATM, PTEN, and PALB2 and salpingo-oophorectomy (SOB) for those in mutations of RAD51C, RAD51D, and BRIP1.

Patients with precursor lesions and high-risk patients without genetic mutation may benefit from chemoprevention, and the role of surgery should be well discussed and individualized.

There are two very distinct scenarios in the indication of risk-reducing surgeries:

- Patients with no personal history of cancer.
- Patients with a previous history of breast/ovarian cancer, where the benefit of surgery should take into account the staging of the disease

Surgery Technique

Risk-Reducing Mastectomies (RRM)

The studies on risk-reducing mastectomies are heterogeneous, using different surgical techniques, from total mastectomy, skin preservation mastectomy, and nipple-sparing mastectomy (adenomastectomy). There is no data demonstrating more or less efficacy between one technique and another.

The best esthetic results are obtained with adenomastectomy; however, that is not always feasible, because it depends a lot on the volume, shape, and degree of ptosis. The most commonly used type of reconstruction is that with definitive prostheses or expanders and only in cases of exception with myocutaneous flap. In patients without suspected breast lesions, sentinel lymph node biopsy (SLB) should not be performed (Table 1).

Table 1 Mathematical model based on the main studies on the risk of incidental carcinoma, SLB, and ALND. By demonstrating that the systematic use of SLB in a population causes more damage than the axillary emptying of incidental case findings

	Results in the medical literature		
Probability/risk	Base	Minimum	Maximum
Incidental carcinoma (average)	1.9%	0.1%	3.5%
Complications from SLB (average)	6.8%	0%	22%
Complications from routine use of ALND (average)	31.4%	12%	69%
Complications from ALND only from cases of incidental carcinoma	0.5%	0.01%	2.4%

Adapted from Boughey et al. [1]

Bilateral Salpingo-Oophorectomy (SOB)

This procedure may or may not be associated with breast surgery. In cases of BRCA-1 and BRCA-2 mutation carriers, the presentation of tubal/ovarian cancer usually occurs later than breast cancer, so mastectomy is preferred between 25 and 40 years and the SOB between 40 and 45 years. This also avoids the consequences of early castration in young women, with all its consequences in terms of bone health and quality of life.

The procedure itself is simple, and it is important that the entire uterine tube is withdrawn along with the ovary, from its uterine portion to the fimbriae.

Efficacy for Prevention

Risk-Reducing Surgery: Patients Without Cancer

The first consistent data regarding the benefit of RRM in women at high risk for breast cancer are derived from the Hartmann study. Risk reduction after 14 years of follow-up was 90%, and there was an estimate of mortality reduction with the procedure (Figs. 1 and 2). One of the publications of the PROSE (Prevention and Observation of Surgical End Points Study Group) showed an average follow-up of 6.4 years, 105 cases of RRM in mutation carriers in the BRCA-1 and BRCA-2 genes compared to 378 control cases; the incidence of breast cancer was 1.9% and 48.7%, respectively (OR, 0.05; 95% CI, 0.01–0.22).

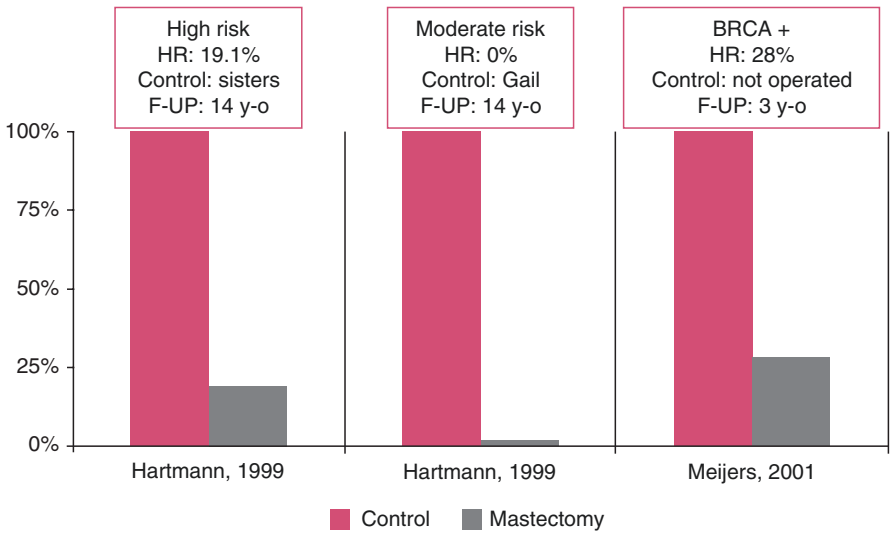

Fig. 1 Specific mortality in bilateral mastectomy studies

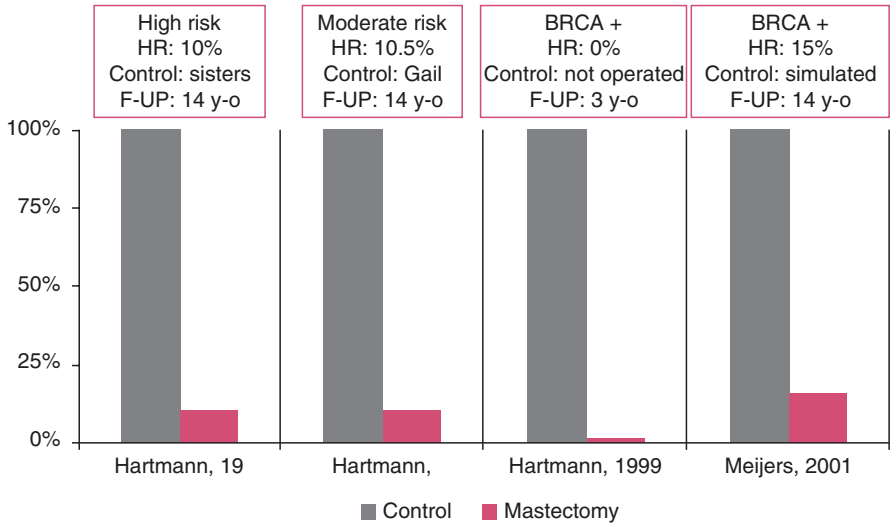

Fig. 2 Incidence of breast cancer in bilateral mastectomy studies

In a prospective cohort with 22 centers in the United States and Europe, Domcheck et al. evaluated 2482 women with BRCA-1 and BRCA-2 mutations, 15% of whom were submitted to RRM and 40% were submitted to SOB. No patient undergoing RRM developed breast cancer versus 7% in the non-RRM group. SOB was associated with reduction of all-cause mortality (OR, 0.40; 95% CI, 0.26–0.61), reduction of specific mortality for breast cancer (OR, 0.44; 95% CI, 26–0.76), and reduction of specific mortality for ovarian cancer (OR, 0.25; 95% CI, 0.08–0.75).

To date, the literature has failed to present robust data associating RRM with increased survival in women at high risk for breast cancer. The only prospective cohort study that was able to demonstrate such association is the Dutch one, and it evaluated 570 healthy and mutated BRCA-1 or BRCA-2 women, of whom 212 underwent MRR. Despite a relatively short follow-up to assess mortality, the authors were able to demonstrate increased survival in the surgery group.

Regarding SOB, the efficacy of this surgery in reducing the risk of breast and ovarian cancer in patients with BRCA mutation has been demonstrated in numerous studies. In a prospective, multicenter study, Kauff et al. studied 170 BRCA-1 and BRCA-2 mutation carriers over 35 years of age followed prospectively for 2 years. Rates of tubal cancer, carcinomatosis, or ovarian cancer were reported in 1/98 (1%) in patients undergoing BMS and 5/83 (6%) in those who had not undergone surgery. In a recent publication of the same group and with a longer follow-up, SOB significantly reduced the chance of developing breast/gynecological cancer by 88%. The benefit was most evident in BRCA-2 mutation carriers and in those with hormone receptor-positive tumors (Fig. 3).

In the meta-analysis published by Rebbeck et al. [6], published in 2009, a meta-analysis, which included 10 studies of women with BRCA-1 or BRCA-2 mutation submitted to SOB, and respective outcomes in relation to breast and gynecological cancer were studied. The data show a risk reduction of about 80% for ovarian/tubal cancer and 50% for breast cancer with SOB (Fig. 4).

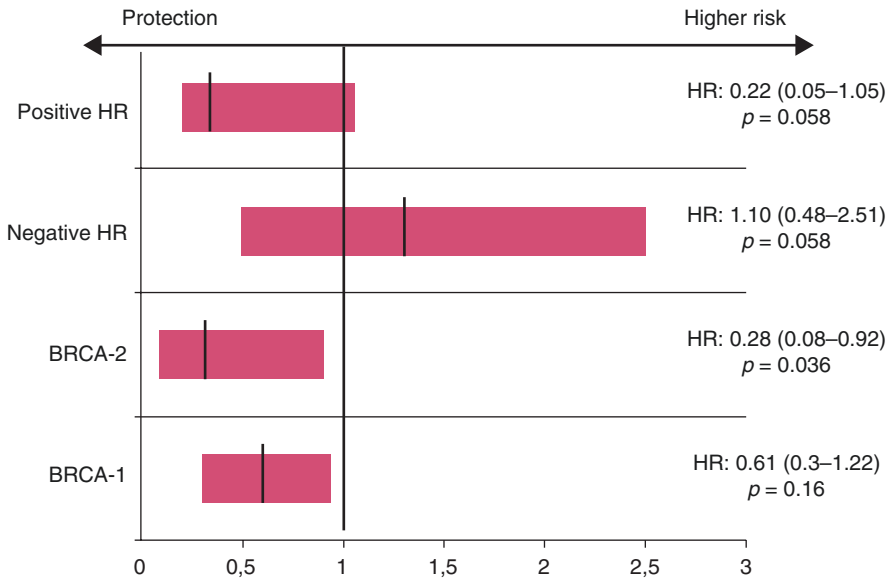

Fig. 3 Prospective cohort study with 325 women with BRCA-1 and 185 BRCA-2 mutation, followed by 36 months and compared with 283 controls (Adapted from Kauff ND et al. 2008)

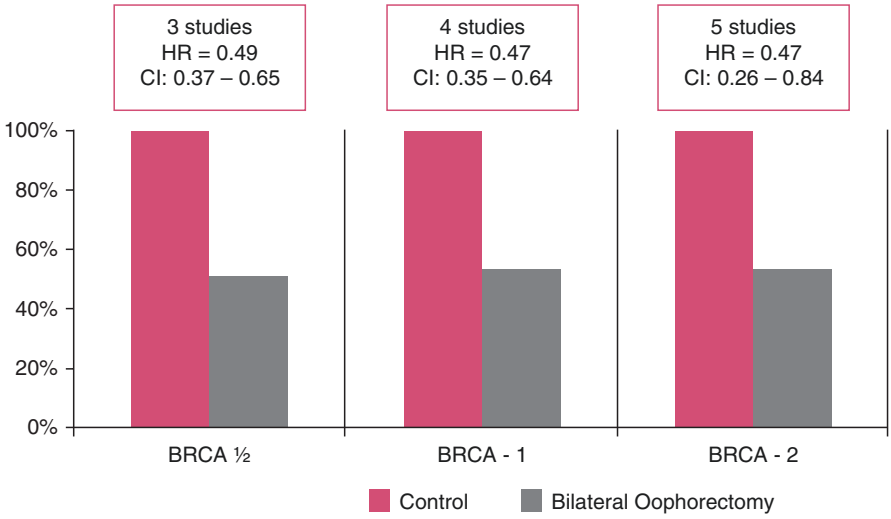

Fig. 4 Meta-analysis of SOB studies in patients with genetic mutation (Adapted from Rebbeck et al. [6])

In summary, there is evidence that RRM and especially SOB should be included among cancer prevention strategies in women with BRCA-1 and BRCA-2 mutation. Data on mutations of other genes are still rather scarce.

Risk-Reducing Surgery: Patients with Cancer

The benefit of this procedure is also debatable. Studies of conservative surgery (without contralateral surgery) for carcinoma in patients with mutation in BRCA-1 or BRCA-2 demonstrated similar survival to the general population, despite an increase in local recurrence and contralateral cancer.

The primary prognostic factor of breast cancer patients is tumor characteristics and staging. Therefore, contralateral RRM may be beneficial in cases with a low risk for recurrence, metastasis, or death. The limitations of the studies also prevent the evaluation of the true impact of surgery in reducing mortality.

Boughey et al. [1] compared 385 women of high familial risk (without a determined mutation) and stage I and II breast cancer and submitted to mastectomy for cancer and contralateral RRM with 385 others submitted only to mastectomy. After 17 years, there was an increase in SLD (FSG?) and GS in the group submitted to contralateral RRM. While for women with BRCA mutation and breast cancer, Metcalfe et al. studied 390 American women, stages I and II, 181 being submitted to contralateral RRM and followed-up over 20 years. The survival rate was 88% in the contralateral RRM group (95% CI, 83–93) and 66% in the unilateral mastectomy group (95% CI, 59–73), representing a 48% reduction in mortality (OR, 0.52; 95% CI, 0.29–0.93). In this study, 94% of contralateral RRMs were performed in the first 10 years after diagnosis.

Studies evaluating the role of SOB in women with BRCA mutation and personal history of breast cancer treated with surgery only in the affected breast showed a positive impact in reducing the risk for contralateral breast cancer. Metcalfe et al. showed that the risk of these women who had already developed breast cancer was 12.7% for BRCA-1 mutation and 6.8% for BRCA-2 mutation (the difference being significant) carriers. It was important to note that 25% of the deaths in patients with stage I breast cancer were due to ovarian cancer.

Therefore, there is also evidence that both RRM and SOB may offer survival benefits for women with BRCA mutation and cancer already diagnosed.

Complications

The complications after mastectomy with reconstruction due to cancer and RRM are similar, for it is all about a non-esthetic procedure. These data must be clearly informed, since it is not uncommon for patients' expectations to be overestimated (Table 2).

Table 2 Compilation of rates for complications from mastectomy /reconstruction

Complications from mastectomy	
Seroma	25–60%
Wound infection	2.8–15%
Skin necrosis	1.0–22%
Hematoma	2%
Complications from reconstruction with implant	
Prosthesis infection	0.5–5%
Capsular contracture	5.0–50%
Exposition to ruptures that need procedure	10–25%
Complications from reconstructions with grafts	
Skin necrosis	1–6%
Wound infection	4–12%
Abdominal hernias (TRAM)	20%
Other functional limitations	Up to15%

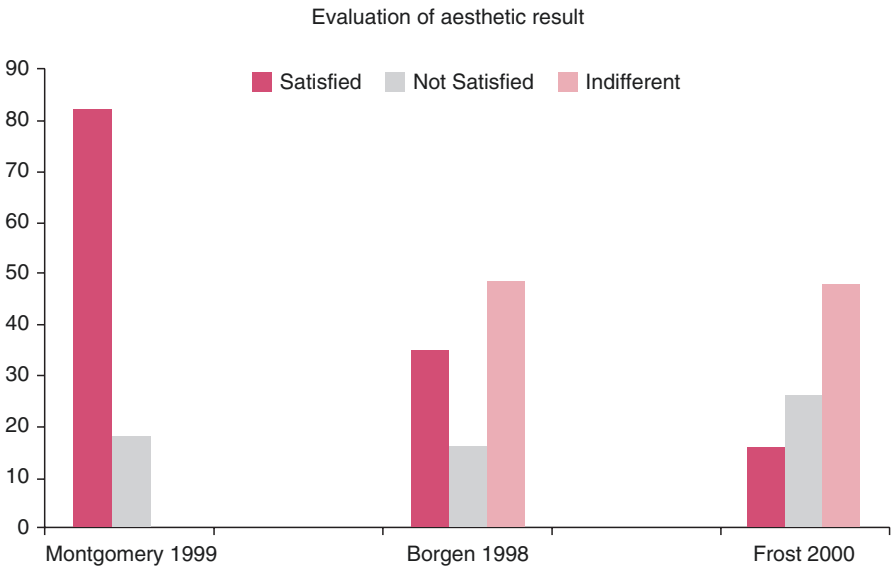

Fig. 5 Patient assessment of the esthetic result of the risk-reducing mastectomy (Modified from Lostumbo et al. [4])

In addition, the psychological problems resulting from the procedure are also noticed in a considerable number of women. There are studies that show an increase in cancerophobia, worsening of femininity, lower self-esteem, and also sexuality in about 20% to 25% of patients. In a Cochrane database review made by Lostumbo et al. [4] in 2010, it was shown that the majority of patients were satisfied with the surgery option; however, there was no unanimity regarding satisfaction with the esthetic result (Figs. 5 and 6).

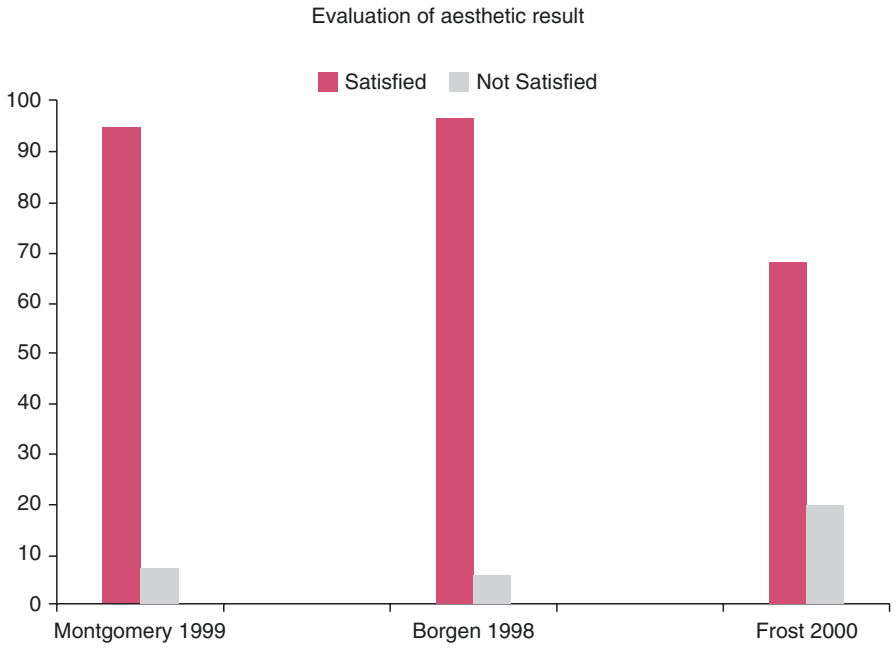

Fig. 6 Patient satisfaction by choice of risk-reducing mastectomy (Modified from Lostumbo et al. [4])

SOB causes infertility and early menopause. The use of replacement therapy may reduce climacteric symptoms but should be used in exceptional situations as there are no clinical safety studies.

Conclusion

Risk-reducing surgery should be adopted after a careful analysis of each case, without the need for urgency, and care should be multidisciplinary. Existing risks and lack of conclusive protection studies should always be reported.

Recommended Reading

1. Boughey J, Hoskin TL, Degnim AC, et al. Contralateral prophylactic mastectomy is associated with a survival advantage in high-risk women with a personal history of breast cancer. Ann Surg Oncol. 2010;17:2702–9. *A retrospective study evaluating the role of contralateral risk-reducing mastectomy in high risk women with breast cancer EC I and II. After 17 years, there was an increase in SLD and SG in the group submitted to contralateral RRM.*

2. Domcheck SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA 1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304:967–75. *Evaluation of 2482 women with BRCA mutation 1 and 2, 15% of whom were submitted to RRM and 40% were submitted to SOB. No patient undergoing RRM developed breast cancer,* versus *7% in the non-RRM group, and SOB was associated with reduction of all-cause mortality, reduction of specific mortality for breast cancer, and reduction of specific mortality for ovarian cancer.*
3. Heemskerk-Gerritsen BA, Rookus MA, Aalfs CM, et al. Improved overall survival after contralateral risk-reducing mastectomy in BRCA ½ mutation carriers with a history of unilateral breast cancer: a prospective analysis. Int J Cancer. 2015;136:668–77. *A study with 583 women with cancer and BRCA mutation was evaluated at 11-year follow-up. The incidence of breast cancer was 2% in the contralateral RRM group* versus *19% in the mastectomy only group, and there was a 50% reduction in mortality in the contralateral RRM group.*
4. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev. 2010;(10, 11):CD002748. *Systematic review written initially in 2004 and revised in 2010. It evaluates the main studies on bilateral and contralateral mastectomy.*
5. Metcalfe K, Gershman S, Ghadirian P. Contralateral mastectomy and survival after breast cancer in carriers of BRCA 1 and BRCA 2 mutations: retrospective analysis. BMJ. 2014;348. *A study with women at stage I and II breast cancer and mutation in BRCA 1 and 2, submitted to unilateral surgery. In this sample, the risk of developing contralateral cancer was 40% in 10 years and the factors associated with the reduction of this risk were the use of tamoxifen and oophorectomy. The risk of these women who already had breast cancer to develop ovarian cancer was 12.7% ratio for BRCA 1 mutation carriers and 6.8% for BRCA 2 mutation.*
6. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingooophorectomy in *BRCA1* or *BRCA2* mutation carriers. J Nat Cancer Inst. 2009;101(2):80–7. *A meta-analysis of 10 studies on the benefit of SOB in reducing breast cancer risk.The benefit was observed in all mutated patients: BRCA-1 (HR: 0.47 CI: 0.35–0.64) and BRCA-2 (HR: 0.47; CI: 0.265–0.85).*

Carcinogenesis and Natural History of Breast Cancer

José Cláudio Casali da Rocha

Introduction to the Development of Breast Invasive Carcinoma

The clinical presentation of breast cancer can range from microinvasive to highly metastatic. The vast majority of breast cancers belong to the class of carcinomas originating from the epithelium of the lobules and ducts of the gland, more specifically luminal cells (potentially secreting milk). Basal-like subtype breast adenocarcinomas – often negative for estrogen receptor (ER) and progesterone (PR) and HER2 receptor expression – have a genetic signature similar to myoepithelial cells that line tubules and lobules and are typical of tumors with BRCA1 deficiency [1, 7]. Invasive carcinoma is often associated with outbreaks of carcinoma in situ and with atypical hyperplastic lesions, suggesting that these premalignant lesions may represent precursor lesions of cancer. The less branched and more cellularized nulliparous type I lobes are more amenable to malignant transformation compared to the more differentiated multiparous type III lobe.

Although several risk factors for breast cancer such as aging, family history, ionizing radiation, diet, and reproductive history are already well known, the genetic mechanisms of malignant transformation have only recently been unraveled with large epidemiological studies and genomic sequencing of tumors. The current perception that the environment external to the individual (exposures, habits, diet, wellness) relates to the tissue microenvironment (genetic and epigenetic modifications) reveals a true tumor ecosystem with immuno-psycho-endocrine and genetic interactions between the tumor and the individual and why not say between the primary tumor and its metastases. Epidemiological and experimental investigations have identified protective factors related to diet that influence the stages of initiation and promotion of cancer. Some foods and nutrients (garlic, selenium) and hormones

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(phytoestrogens, vitamin D) have a protective effect against cancer, acting as antioxidants (preventing the formation of DNA adducts) and as antiproliferative. Recently, the role of breastfeeding as a risk modifier was explored in women of high genetic risk, being protective for carriers of family mutation in BRCA1 gene (risk reduction in 32%), but without influence for BRCA2 mutants [4].

Mammary Carcinogenesis

Cancer is a chronic, degenerative, genetic-based disease caused by a series of structural (genetic) and chemical (epigenetic) events that drive the process of transforming a normal cell into malignancy. Genome sequencing of hundreds of breast cancers has shown that only four mutations in key genes are sufficient for this transformation, the so-called driver mutations. Much of the breast cancers present genomic instability leading to the accumulation of apparently irrelevant genomic changes, called passenger mutations. When a conductive mutation is inherited and can be passed on to the offspring, thus significantly increasing its risk, the cancer is designated as hereditary or family. The concept of carcinogenesis as a multistage process that precedes the uprising of neoplasms has generated the concept of preneoplasm, which would be characterized by stages prior to benign and malignant neoplasms [8].

Didactically, the carcinogenesis process can be divided into three stages as follows:

- Initiation: characterized by mutations in a mammary stem cell caused by chemical, physical (ultraviolet and ionizing radiation), and biological (virus) factors or inherited (heredity), usually irreparable and permanent, affecting cell proliferation and programmed cell death (apoptosis). The process starts with the inactivation of tumor suppressor genes (e.g., TP53, PTEN, CDKN2A, cyclin D, and caspase 8) or the activation of proto-oncogenes in oncogenes (HER2, MYC). The clonal accumulation of cells leads histologically to ductal hyperplasia, initially without atypia.
- Promotion: in this phase, there is expansion of mutation clones formed by phenotypically modified cells (FABER; SARMA, 1987) by stimulating the cellular proliferation of autocrine growth factors in which the cell that is undergoing transformation secretes its own growth factor (EGF, IGF, VEGF, PDGF, TGF-alpha, and HIF, among others) or it recruits inflammatory and stromal cells to produce these factors. The cell evolves mechanisms to evade the immune system, not only neutralizing lymphocytes and macrophages but also recruiting them as true allies. Histologically, nuclear atypia and rare mitoses appear, as well as lymphocytic infiltration and markers of vascular proliferation.
- Progression: the process of transformation reaches its climax, with immortal mutant cells, capable of proliferating indefinitely, destroying the lamina propria

and invading tissues, lymphatics till it gets to the blood flow. Genes linked to glucose metabolism, angiogenesis, and adhesion molecules are reprogrammed so that the cell can survive in inhospitable situations of extreme acidosis and hypoxia. Phenotypically, they are carcinomas in situ and invasive carcinomas.

At the time of diagnosis, breast cancer is composed of heterogeneous populations of tumor cells with distinct biological behaviors and not infrequently with different responses to systemic treatments. Two models of clonal evolution are recognized (Fig. 1):

1. The stochastic model of clonal evolution postulates that the tumor originates from a single cell that undergoes selective pressures through randomly acquired genetic aberrations leading to expansion of the most advantageous clones;
2. The clonal evolution model from the so-called cancer stem cells suggests that the population of tumor cells originates from auto-regenerative cells capable of deriving all the cellular components of the tumor. We know from experiments that about 1% of malignant tumor cells consist of tumor stem cells capable of regenerating all tumor components when they are recruited and remain in the quiescent state (G0 phase of the cell cycle) for long periods of hibernation. On the other hand, the already differentiated malignant tumor cells (i.e., 99% of the tumor) are not sufficient to regenerate new tumors alone.

A number of cytogenetic changes can be observed in breast cancer; the vast majority of them are due to genomic instability and are not functional. The genomic instability of the most proliferative tumors leads to a disorganization of the genome, with enormous structural changes such as multiple chromosomal copies and complex translocations between them (Fig. 2).

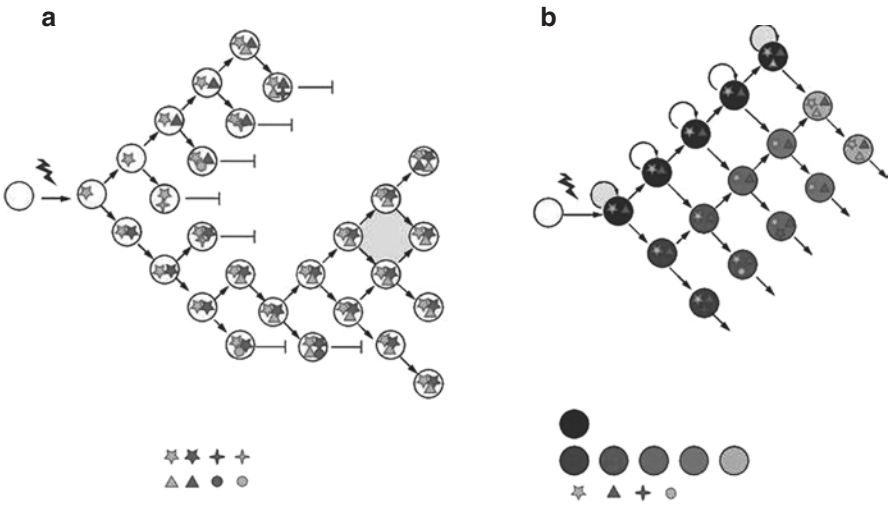

Fig. 1 Carcinogenesis models. (**a**) The stochastic model. (**b**) The cancer stem cell model

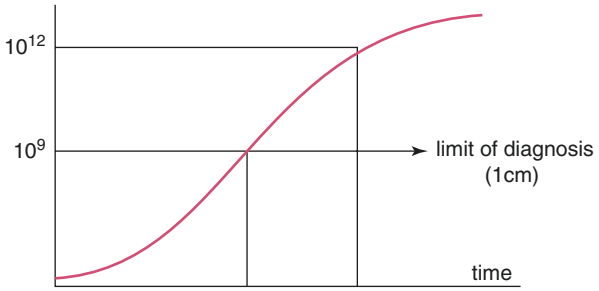

Fig. 2 Genetic advances with representation of the structural changes observed in a breast cancer cell line. (**a**) Spectral karyotype (SKY), where each chromosome is identified by distinct colors, revealing extensive aneuploidy (pseudo-tetraploid cell, ~ 4n) with multiple breaks and chromosomal rearrangements. Notice the chromosomes of multiple colors. (**b**) Graphic result of the broad genomic sequencing of this same cell. The chromosomes are shown as clockwise (outer ring), and translocations are indicated by the lilac lines connecting chromosomes

Comparative genomic sequencing of breast tumors revealed the major genetic mutations and aberrations found in the four major molecular subtypes (luminal A, luminal B, HER2 enriched, and basal-like), revealing differences that explain their distinct biological behavior and prognosis (Table 1).

Natural History of Breast Cancer: Development and Dissemination

Starting with the malignant transformation, the tumor cells grow in number, accumulating and forming tumors. The pattern of malignant cell growth, a result of the balance between proliferation and tumor cell death, follows a Gompertzian sigmoid curve (Fig. 3). Once the mitotic proliferation index (measured by the Ki67 marker) correlates directly with the histological grade of the tumor and its biological behavior, it seems obvious that in order for an adequate detection of more proliferative tumors to occur, the more intense the preventive screening should be, as recommended for women with hereditary breast cancer syndromes (e.g., hereditary breast and ovarian cancer and Li-Fraumeni syndrome).

Hanahan and Weinberg recently updated their carcinogenesis model with a total of ten biological capabilities acquired by human tumor cells. Figure 4 schematically shows these biological processes [2].

The process of disseminating cancer locally and to sites away from the primary site thus depends on a multi-capacity of the tumor cell. Reprogramming the gene expression of tumor cells results from:

- The production of transcription factors that stimulate the production of proteins favorable to proliferation and tumor survival
- Point and/or structural mutations that activate or inactivate genes

Table 1 Major mutations and aberrations by molecular subtypes of breast cancer – ER+, estrogen receptor expression; HER2-, without cErbB2/HER2 expression; TN, triple-negative; mut, mutation; del, deletion; amp, amplification; between parentheses, the frequency

Subtype	Luminal A	Luminal B	Basal-like	HER2
ER+/HER2 (%)	87	82	10	20
HER2+ (%)	7	15	2	68
TNs (%)	2	1	80	9
Via TP53	Mut TP53 (12%); gain MDM2 (14%)	Mut TP53 (32%); gain MDM2 (31%)	Mut TP53 (84%); gain MDM2 (14%)	Mut TP53 (75%); gain MDM2 (30%)
Via PIK3CA/ PTEN	Mut PIK3CA (49%); Mut/del PTEN (13%); del INPP4B (9%)	Mut PIK3CA (32%); Mut/del PTEN (24%); del INPP4B (16%)	Mut PIK3CA (7%); Mut/del PTEN (35%); del INPP4B (30%)	Mut PIK3CA (42%); Mut/ del PTEN (19%); del INPP4B (30%)
Via RB1	Amp cyclin D1 (29%); gain CDK4 (14%); hypo expression CDKN2C; hyperexpression RB1	Amp cyclin D1 (58%); gain CDK4 (25%)	Mut/del RB1 (20%); amp cyclin E1 (9%); hyperexpression CDKN2A; hypo expression RB1	Amp cyclin D1 (38%); gain CDK4 (24%)
Proliferation	Low	High	High	High
Chromosomic alterations (numerical and structural)	Predominantly diploid; mostly with no genomic instability; gain 1q, 8q, 8p11; 8p, del 16q; amp 11q13.3 (24%)	Mostly aneuploid; frequent focal amp; gain 1q, 8q, 8p11; del 8p, 16q; amp 11q13.3 (51%); amp 8p11.23 (28%)	Mostly aneuploid; high genomic instability; gain 1q, 10p; del 8p, 5q; focal gain focal MYC (40%)	Mostly aneuploid; high genomic instability; gain 1q, 8q; del 8p; focal amp HER2 (71%)
DNA mutations	PIK3CA (49%); TP53 (12%); GATA3 (14%); MAP3K1 (14%)	TP53 (32%); PIK3CA (32%); MAP3K1 (5%)	TP53 (84%); PIK3CA (7%)	TP53 (75%); PIK3CA (42%); PIK3R1 (8%)
DNA methylation (epigenetic)	–	Hyper methylated phenotype	Hypo methylated	–
Protein expression.	High expression via estrogen; high expression MYB; subtypes RPPA	High expression via estrogen; high expression FOXM1 and MYC	High expression of proteins for DNA repair, with no expression of PTEN and INPP4B (pAKT)	High expression of EGFR and HER2

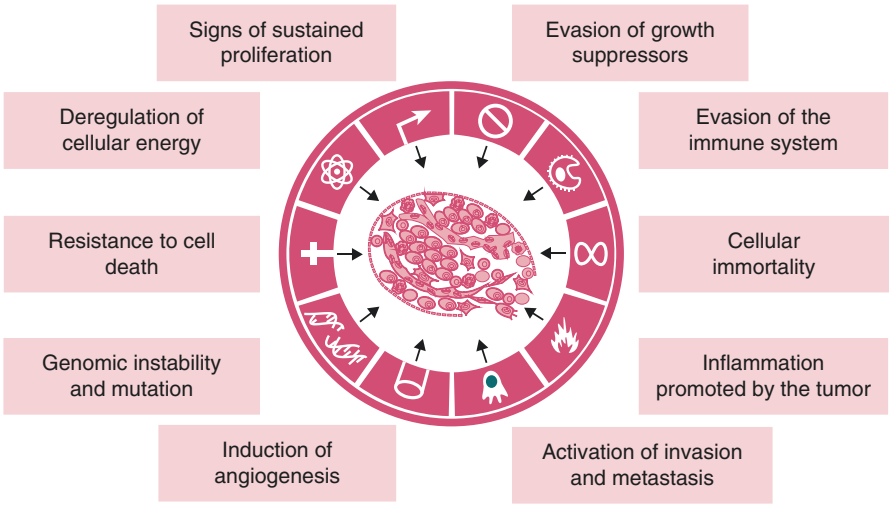

Fig. 3 Gompertzian curve of tumor growth. Cell growth reaches maximal proliferative capacity to about 1 cm^3 with approximately one billion cells

- "Epimutations" (such as methylation and acetylation) that bind or deactivate genes
- Interference of micro-RNAs from miRNA interference, such as miR-155 and self-regulatory miR-21, which do not encode proteins but which intercept and block target gene RNAs [5].

Locorregional Dissemination

A group of intercellular adhesion molecules in between the basement membrane cell histologically form, respectively, the desmosomes and the adherent junctions. They reprogrammed in the malignant cell to allow their displacement, as lytic enzymes are released locally to make room for locorregional tumor invasion. The tumor cell breaks the basement membrane and invades the stroma, reaches the tiny lymphatic capillaries, and is drained to the regional lymph nodes, where it is retained (Fig. 5).

Recently, it has been discovered that tumor stem cells circulate freely through the blood and the lymphatic system even in the early clinical stages, putting down the hypothesis of late secondary dissemination and defined breast cancer as a systemic disease. The quantification of the number of circulating stem cells (CTCs) by molecular methods can be used clinically to define tumor burden and guide systemic therapies.

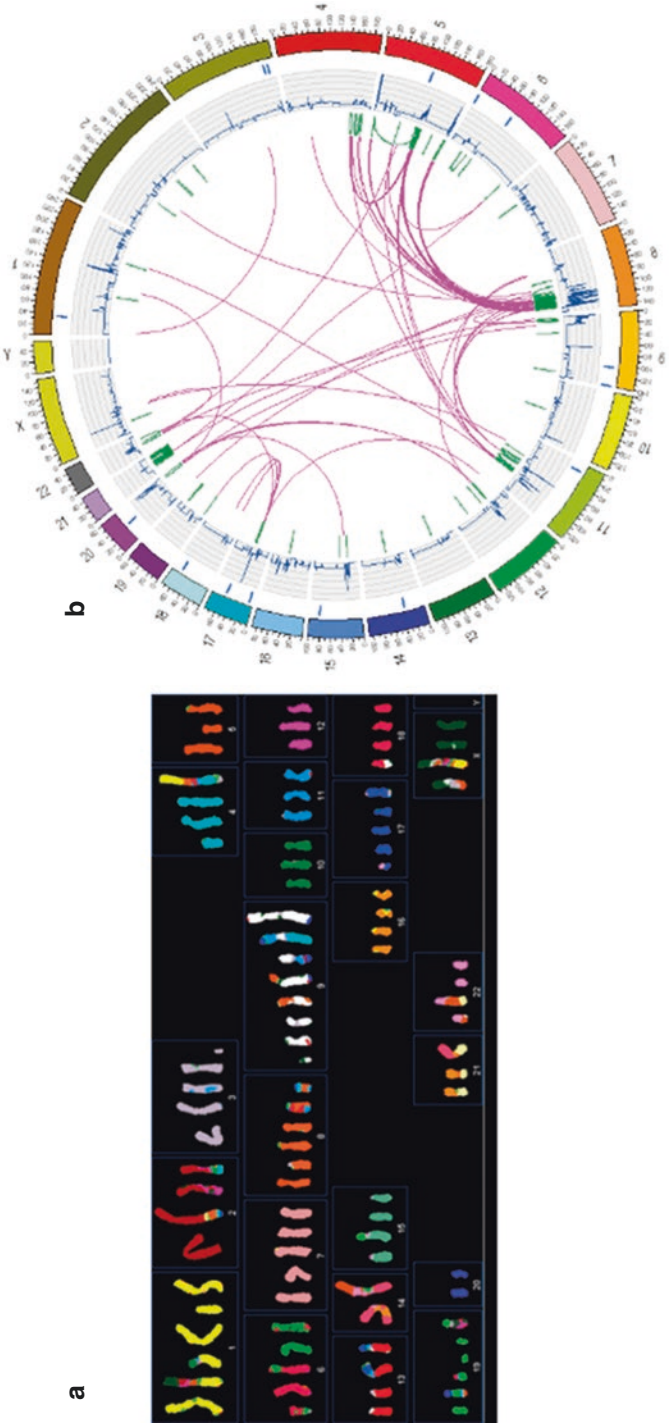

Fig. 4 Biological abilities acquired by the malignant cell, as updated by Hanahan and Weinberg [2]

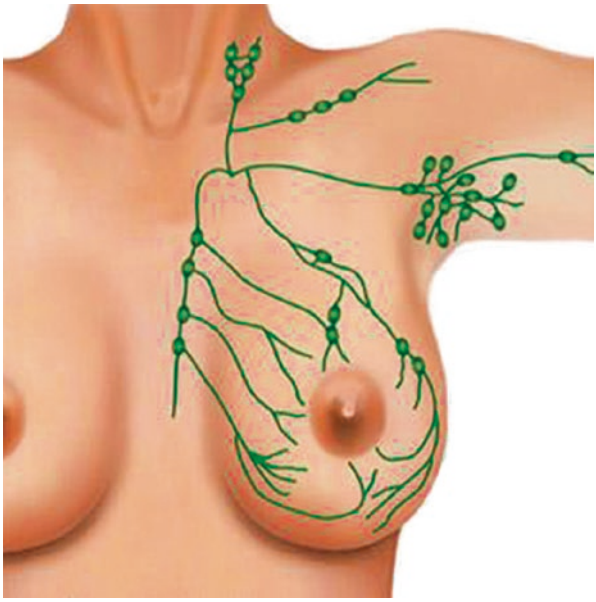

Fig. 5 Lymphatic drainage of the breast

Dissemination Through Metastasis

It is already clear that systemic metastases can originate from the primary site, but also from other metastases. Tumor cells seeded in the bloodstream may attach to distal organs randomly by tumor embolization, but the tendency of tumors to attach to preferred secondary sites has long been known. Bones are the major site of metastasis in all molecular subtypes except basal-like and the first site of recurrence in patients who fail systemic treatment. Especially, those tumors in which bone is the only metastasis (bone-only metastasis), corresponding to 15% of breast cancers, the prognosis is relatively good, with a good response to systemic treatments and longer survival; these tumors usually express hormonal receptors (ER + and PR +) in more than 85% of the cases, and most of those with recurrence (in the first 36 months of surgery) occur in young women, being tumors of higher histological and nuclear level involving the column [6]. On the other hand, the basal-like subtype is associated with predilection for cerebral and visceral sites and few for bone sites. Table 2 shows the frequency of the major preferred metastasis sites of each molecular subtype of breast cancer.

Table 2 Differences in staging patterns of tumor and dissemination according to the molecular subtypes of breast cancer

Phenotype of breast cancer	Luminal A	Luminal B	Luminal/ HER2+	Enriched HER2	Basal-like	Non-basal triple negative	P value
Do tumor (T) %							0.002
T0–2	86.4	83	80.7	80.5	81.5	78.9	
T3–4	4	5	8.2	7.9	6	7.9	
n.a.	9.6	12	11.1	11.7	12.5	13.2	
Locorregional (N) %							<0.001
N0	55.5	49.9	42	42.9	59.4	56.3	
N1	38.5	42	49.4	48.5	33.5	36.2	
N2–3	1.2	2.7	3.7	1.9	1.1	2.5	
n.a.	4.8	5.4	4.9	6.9	6	5	
Brain	2.2	4.7	7.9	14.3	10.9	7.2	<0.001
Liver	7.9	13.8	21.3	23.3	9.3	10.7	<0.001
Lung	6.7	13.4	17.7	24.1	18.5	12.5	<0.001
Bone	18.7	30.4	30.9	30.1	16.6	15.1	<0.001
Distant lymph node	4.5	9.6	10.5	13	17.2	12.3	<0.001
Peritoneum/ pleura	7.8	14.7	16	16.2	12.8	9.2	<0.001

Adapted from Nielsen [3]

Recommended Reading

1. Casali-da-Rocha JC, Cocramo S, Ramirez R. Aspectos moleculares das neoplasias: câncer de mama. Em: Oncologia Molecular. Editora Atheneu. In: 2ª Edição; 2010.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–67.
3. Kennecke H, Yerushalmi R, Woods R, Cheang MCU, Voduc D, Speers CH, Nielsen TO, Gelmon K. Metastatic behavior of breast cancer subtypes. J Clin Oncol. 2010;28(20):3271–7.
4. Kotsopoulos J, Lubinski J, Salmena L, Lynch HT, Kim-Sing C, Foulkes WD, Ghadirian P, Neuhausen SL, Demsky R, Tung N, Ainsworth P, Senter L, Eisen A, Eng C, Singer C, Ginsburg O, Blum J, Huzarski T, Poll A, Sun P, Narod SA. Breastfeeding and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res. 2012;14(2):R42.
5. Krell J, Frampton AE, Jacob J, Castellano L, Stebbing J. miRNAs in breast cancer: ready for real time? Pharmacogenomics. 2012;13(6):709–19.
6. Lee SJ, Park S, Ahn HK, Yi JH, Cho EY, Sun JM, Lee JE, Nam SJ, Yang J, Park YH, Ahn JS, Im Y. Implications of bone-only metastases in breast cancer: favorable preference with excellent outcomes of hormone receptor positive breast cancer. Cancer Res Treat. 2011;43(2):89–95.
7. Rakha EA, Reis-Filho e IO Ellis JS. Basal-like breast cancer: a critical review. J Clin Oncol. 2008;26(15):2568–81.
8. Sapkota Y, Ghosh S, Lai R, Coe BP, Cass CE, Yasui Y, Mackey JR, Damaraju S. Germline DNA Copy Number Aberrations Identified as Potential Prognostic Factors for Breast Cancer Recurrence. PlosOne. 2013;8(1):e53850.

Histopathological and Immunohistochemical Classification of Invasive Breast Carcinomas

Carlos E. Bacchi and Cristiano Ribeiro Viana

Introduction

Breast carcinomas are divided into two major groups: carcinomas in situ and invasive carcinomas. Carcinomas in situ are defined as a proliferation of malignant epithelial cells confined to the ductal acinar system of the breast, with no evidence of stromal invasion. In contrast, invasive carcinomas are those in which tumor cells invade tissues adjacent to the mammary ducts and have a tendency to metastasize to regional lymph nodes and distant anatomical sites. In this chapter, only invasive carcinomas will be considered.

The majority of invasive tumors of the breast are represented by carcinomas that probably originate from the cells of the terminal ductal-lobular unit (TDLU). Breast carcinomas exhibit a broad spectrum of morphological phenotypes, with specific histological types, which present prognostic differences and, sometimes, their own clinical characteristics. Table 1 presents the main histological types of invasive breast carcinomas according to the latest classification of the World Health Organization [3]. The main histological types are discussed below.

Nonspecial Invasive Carcinoma (Ductal Invasive Carcinoma, SOE)

Nonspecial invasive carcinoma, also known as invasive ductal carcinoma, is the most common histological type, accounting for 40% to 75% of cases of breast cancer, depending on the series evaluated. They are probably a heterogeneous group of

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Table 1 Histopathological classification of invasive breast carcinomas according to the WHO [3]

A. Nonspecial invasive carcinoma (synonym: ductal invasive carcinoma SOE)
B. Invasive carcinomas, special types
b1. Invasive lobular carcinoma
b2. Tubular carcinoma
b3. Cribriform carcinoma
b4. Mucinous carcinoma
b5. Carcinoma with medullary findings
b6. Carcinoma with apocrine differentiation
b7. Carcinoma with cell differentiation without signet ring
b8. Invasive micropapillary carcinoma
b9. Metaplastic carcinoma, no special type
b10. Inflammatory carcinoma
b11. Bilateral nonsynchronic breast carcinoma
C. Rare types
c1. Neuroendocrine carcinoma
c2. Secretory carcinoma
c3. Invasive papillary carcinoma
c4. Acinic cell carcinoma
c5. Muco-epidermoid carcinoma
c6. Polymorphic carcinoma
c7. Oncocyclic carcinoma
c8. Lipid-rich carcinoma
c9. Glycogen-rich carcinoma
c10. Sebaceous carcinoma
c11. Salivary gland tumors

tumors and are thus designated because they do not exhibit characteristic morphological findings to be classified as special type, for example, tubular carcinoma or lobular carcinoma.

This sort of carcinoma rarely occurs before a person is aged 40. The size is in the spectrum that ranges between 10 and 100 mm. These carcinomas present, at the imaging examination, spiked or irregular borders more than 90% of the times, followed by a nodular pattern, which overlaps with the findings of the macroscopic examination, being hard palpation.

Microscopic features vary from case to case, and the diagnosis of invasive nonspecial type carcinoma is obtained by excluding all special types of breast carcinoma. In general, neoplastic cells form cords; irregular clusters of cells, often interconnected with each other; as well as trabeculae. Depending on the degree of differentiation of carcinomas, neoplastic glandular formations are found (Fig. 1), even with well-formed lumens. The cytoplasm is abundant and eosinophilic. The nuclei range from regular and uniform to pleomorphic, with prominent nucleoli. Figures of mitoses, in some cases, are numerous while in others are scarce.

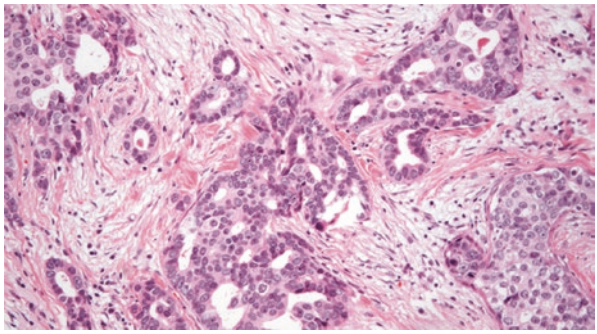

Fig. 1 Nonspecial invasive carcinoma. Proliferation of ducal-glandular malignant structures with stromal invasion

Microcalcifications may or may not be present, as well as areas of necrosis of variable dimensions, that is, with focal pattern, or of geographic necrosis.

According to the WHO classification, 2012, variants of nonspecial-type invasive carcinoma are described, namely, mixed-type carcinoma, pleomorphic carcinoma, giant cell-type stroma of the osteoclast type, carcinoma with choriocarcinomatous findings, and carcinoma with melanocyte findings, the last four being very rare.

The prognosis is similar to that of other subtypes of breast carcinoma and depends fundamentally on the following prognostic factors: histological grade, tumor size (macroscopic measure), regional lymph node status, and vascular invasion and angioinvasion. The survival of this type of carcinoma is also influenced by biological-predictive factors, namely, expression of hormonal receptors (estrogen and progesterone) and HER2.

The following are some of the breast carcinomas of special types, which make up about 25% of the total number of mammary carcinomas.

Tubular Carcinoma

Tubular carcinoma in its pure form accounts for only 2% of breast carcinomas. This type of carcinoma usually presents a good prognosis. The morphological findings are characterized by the presence of neoplastic tubular structures, with very clear lumens and covered by a single layer of cells. This morphological pattern should be present in more than 90% of the lesion so that the carcinoma is designated as tubular. About 60–70% of these carcinomas are non-palpable masses and mammography findings, being identifiable because of their spiculated appearance and the highly cellular stroma. There is a tendency for this carcinoma to occur in an older age group when compared to nonspecial-type carcinoma. In addition, most of them do not present lymph node involvement. Due to these characteristics, tubular carcinoma presents an excellent prognosis. Even in some series, the survival of women with tubular carcinoma is similar to those without breast carcinoma.

Carcinoma with Medullary Findings

According to the new definition of the WHO [3], the special type of carcinoma with medullary findings includes the following types of carcinomas previously diagnosed separately: medullary carcinoma, atypical medullary carcinoma, and a nonspecial-type invasive carcinoma subtype with medullary findings. These tumors should present some of the following findings to be qualified as carcinomas with medullary findings: the interface between carcinoma and adjacent nonneoplastic and noninfiltrative tissue, that is, the tumor pushes more than infiltrates the neighboring tissue, a syncytial pattern growth, cells with high nuclear grade, and prominent inflammatory infiltrate.

Classical medullary carcinoma accounts for about 1% of all breast carcinomas. The average age ranges from 45 to 52 years. From the clinical point of view, as well as the imaging studies, carcinoma with medullary findings is well-circumscribed and may even be confused with a benign tumor in mammographic findings.

The macroscopic characteristics of the carcinoma with medullary findings reflect clinical and imaging findings, which means it is a well-defined, rounded, oval, or lobed tumor with a softer consistency and may have foci of necrosis and hemorrhage and measuring between 2 and 3 cm. Microscopically, it is composed of large, slightly differentiated neoplastic cells, arranged in large sheets, without the presence of glandular structures, with scarce stroma and presence of associated prominent lymphoplasmacytic infiltrate.

In general, the medullary carcinoma presents negativity of expression for hormonal receptors and HER2, making, therefore, part of the group of triple-negative carcinomas. There is a high frequency of this type of carcinoma among BRAC1-positive patients. Although this concept has been questioned in recent years, medullary carcinoma has been considered a tumor of better prognosis when compared to nonspecial invasive carcinoma, especially those with dense lymphocytic infiltrate and high mitotic activity, since they respond better to chemotherapy.

Mucinous Carcinoma (Colloid)

Mucinous or colloid carcinoma is a variety of breast tumor in which there is large production of intra- and/or extracellular mucin. In its characteristic microscopic presentation, mucinous carcinoma reveals small, uniform neoplastic cells trapped in mucus lakes (Fig. 2).

In its pure form, where more than 90% of the tumor is rich in mucin, mucinous carcinoma accounts for 2% of invasive tumors of the breast. The mean age of patients with this type of carcinoma is usually around 66 years, higher than that of patients with infiltrative ductal carcinoma, NOS. The mammographic findings show a well-defined tumor. Macroscopy reveals typical characteristics, namely, gelati-

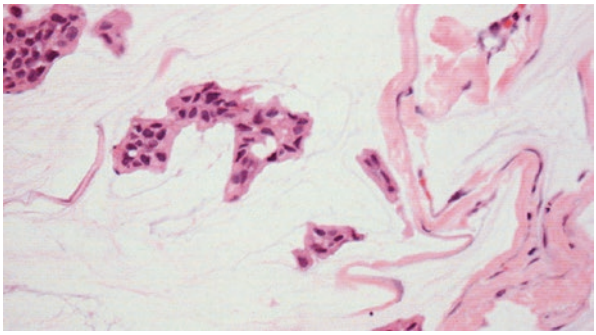

Fig. 2 Mucinous carcinoma (colloid). Clusters of neoplastic cells are found among abundant mucin-rich stroma

nous and bosselated appearance, with a very soft consistency. About 95% of them are positive for estrogen receptor and only 5% for HER2. The prognosis of mucinous carcinoma is also dependent on the prognostic factors mentioned for nonspecial-type invasive carcinoma. It is important to note, however, that, in general, pure mucinous carcinomas tend to present a good prognosis (80 to 100% survival in 10 years).

It should be noted that in the WHO classification, 2012, two subtypes of mucinous carcinomas are described. The type A mucinous carcinoma, considered as the classic type, which under microscopy represents a large quantity of mucin (mucus lakes), tumor cells with low degree of atypia, and low index of mitotic figures. On the other hand, mucinous carcinoma presenting large cell groups is designated as hypercellular or mucinous type B carcinoma. This type of mucinous carcinoma, in particular, usually exhibits neuroendocrine differentiation demonstrated by the expression of chromogranin A and synaptophysin.

Carcinoma with Apocrine Differentiation (Invasive Apocrine Carcinoma)

According to the WHO, 2012, carcinoma with apocrine differentiation is a carcinoma that demonstrates cytological findings of apocrine cells in more than 90% of the population of neoplastic cells. Classically these cells are large, with round nuclei, evident nucleoli, and finely granular eosinophilic cytoplasm. Its incidence varies from 1% to 4%. They demonstrate androgen receptor expression, in combination with hormone receptor negativity and HER2 expression in about 50% of cases. The immunohistochemical marker GCDFP-15 (gross cystic disease fluid protein-15) is classically expressed in these carcinomas. There are no differences in the clinical, mammographic, and macroscopic presentation between apocrine and non-apocrine carcinomas. This similarity also seems to occur in relation to the prognosis.

Metaplastic Carcinoma

Metaplastic carcinoma is rare, accounting for less than 1% of invasive breast carcinomas. They comprise a heterogeneous group of tumors consisting entirely or in part of a component that has no histological appearance of nonspecial (classical)-type invasive carcinoma. Among the main subtypes, we have spindle cell carcinoma (Fig. 3); squamous cell carcinoma; low-grade adenosquamous carcinoma; metaplastic carcinoma with mesenchymal differentiation, which may be benign (carcinoma producing bone or chondroid matrix) or malignant (carcinoma with osteosarcomatous differentiation, for instance); and mixed metaplastic carcinoma. The immunohistochemical expression of high molecular weight cytokeratin should be present but may be focal. Usually the clinical findings show great palpable masses, and the metastases are preferentially hematogenous. Metaplastic carcinoma also belongs to the group of triple-negative carcinomas. The prognosis is generally poor except for some subtypes, such as low-grade adenosquamous carcinoma.

Secretory Carcinoma

Secretory carcinoma is a rare, low-grade carcinoma, representing less than 0.2% of all invasive mammary carcinomas. This type of carcinoma is commonly found in young people (mean age 25 years), including children, hence the alternate name for juvenile carcinoma. It is important to emphasize that in 50% of the cases, this carcinoma has a subareolar location, especially when it occurs in men and children. It presents abundant amount of eosinophilic secretion in the cytoplasm of the cells and tumor lumens, exhibiting characteristically solid and microcystic growth patterns, in addition to areas with tubular components. Secretory carcinoma usually presents an excellent prognosis, mainly in children, being more aggressive in women. In general, there is no expression of hormone receptors, so it is another example of triple-negative carcinoma of the breast.

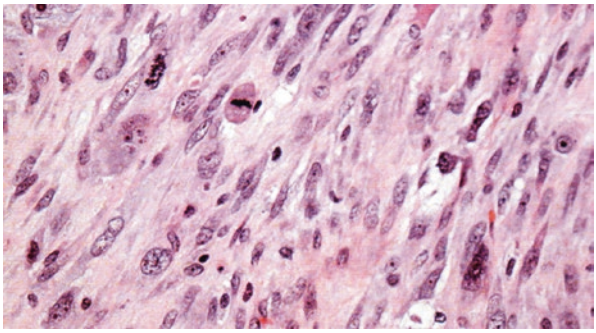

Fig. 3 Metaplastic carcinoma, sarcomatoid variant (fusocellular). Proliferation of neoplastic fusocellular cells with intense atypia, pleomorphism, and numerous mitosis figures

Inflammatory Carcinoma

Inflammatory carcinoma is defined as a breast carcinoma with peculiar clinical presentation (more than a third of the skin with erythema, edema, heat, and peau d'orange) due to the important lymphatic obstruction caused by the dissemination of carcinoma that affects the breast. The vast majority of cases present an important neoplastic obstruction of the dermal lymphatic vessels. There is no association with true inflammation. Clinically, it can be mistaken for mastitis or cellulitis. It is considered a type of advanced mammary carcinoma, and the diagnosis must always be anatomo-clinical. The frequency of inflammatory carcinoma varies between 1 and 10%, according to the diagnostic criteria used for this type of carcinoma. The use of systemic chemotherapy has improved the survival (25 to 50% in 5 years) of patients affected by this type of carcinoma. In general, it presents absence of expression for hormonal receptors and HER2, that is, it is a triple-negative carcinoma.

Lobular Invasive Carcinoma

Lobular invasive carcinoma, usually associated with lobular carcinoma in situ, represents 5–15% of mammary carcinomas. It performs with multicentricity and bilaterality, at a frequency higher than nonspecial-type invasive carcinoma. Macroscopic examination usually reveals a poorly delimited tumor mass, which is irregular and difficult to identify by the pathologist. Microscopic findings reveal noncohesive tumor cells, individually arranged and infiltrating the stroma ("Indian row" pattern), characterizing the classic and more frequent type (Fig. 4). There are other morphological variants such as solid, alveolar, pleomorphic, lobule-lobular, and mixed type. About 85% of them lose expression of E-cadherin (cell adhesion molecule), and approximately 70–95% of them have hormone receptor expression and negativity for HER2. The pleomorphic subtype (Fig. 5) shows a more aggressive biological behavior, with negativity to estrogen and progesterone receptors and HER2 expression. The classic and other subtypes of invasive lobular carcinoma present a lower

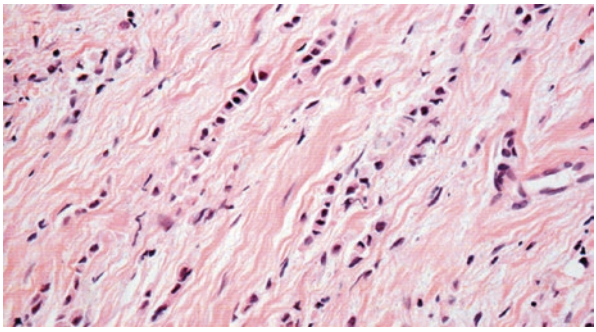

Fig. 4 Invasive, classic lobular carcinoma. Proliferation of neoplastic cells with discrete atypia and with eosinophilic cytoplasm and "Indian rank" growth pattern

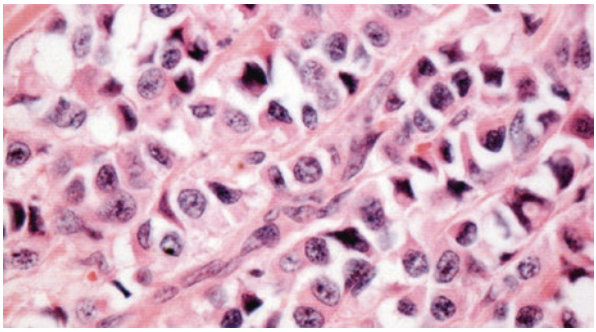

Fig. 5 Invasive lobular carcinoma, pleomorphic variant. Presence of cells of epithelioid pattern, unrelated to each other, with atypia and pleomorphism

index of lymph node metastases when compared with nonspecial-type invasive carcinoma, but usually give more distant metastases, including unusual sites such as serous surfaces of the gastrointestinal and gynecological tract, besides leptomeninges and bone.

Other Sorts of Breast Carcinoma

There are other breast carcinomas that, due to their lower frequency, are not discussed in detail in this chapter, being only mentioned as invasive cribriform carcinoma, neuroendocrine carcinoma, invasive papillary carcinoma, invasive micropapillary carcinoma, differentiated carcinoma in signet ring cells, lipid-rich carcinoma, oncocytic carcinoma, adenoid cystic carcinoma, acinar cell carcinoma, mucoepidermoid carcinoma, polymorphous carcinoma, clear cell carcinoma rich in glycogen, and sebaceous carcinoma.

Molecular Classification of Breast Cancer

Breast carcinoma is a heterogeneous neoplasm with morphological findings, clinical behavior, and variable response to therapeutic regimens. Some researchers have hypothesized that this heterogeneity may be related to the cellular origin or to the differentiation pathway of tumor cells. The normal breast contains two cell layers: luminal or internal cells and the layer of myoepithelial or basal-external cells. By the analysis of the gene expression profile, using the DNA microarray methodology, Sorlie et al. [4] (basal-like, HER2+, normal breast type, luminal B, and luminal A) had a worse prognosis in the basal-like group. The basal-like designation is due to the gene expression profile of these tumors, which is similar to that of basal cells of the breast, precursors of glandular epithelial cells and myoepithelial cells. In the analysis of more than 300 tumors for the expression of gene profiles and correlation

with clinical follow-up, data from three individual and independent studies have demonstrated that basal-like mammary carcinomas comprise 19% of these tumors and present a close association with poor prognosis, evaluated for disease-free survival. Subsequent studies that have attempted to evaluate the immunohistochemical profile of the basal-like group have revealed that these tumors are typically negative for estrogen and progesterone receptors and for HER2 protein product. Due to the negativity for these three markers, this group of breast carcinoma has been termed triple-negative. Other markers commonly expressed in the group are the basal cytokeratin 5 and 6, epidermal growth factor receptor (EGFR) or HER1, KIT, and vimentin. In addition to the distinct immunohistochemical profile, the basal-like phenotype has been related to the BRCA1 mutation and is reported to be more frequent in premenopausal women, which indicates a probable higher frequency in young patients.

Table 2 summarizes the main features of gene expression and clinical findings of molecular subtypes of breast cancer.

Another molecular group characterized by the DNA microarray methodology, in 2005, is the apocrine molecular group. Carcinomas belonging to the apocrine molecular group had strong evidence and were positive for androgen receptor, but negative for estrogen and progesterone receptors by immunohistochemistry, in addition to frequently expressing HER2. It is possible that the apocrine molecular group presents super positions to the HER2 group originally described.

In 2007, another molecular type of breast cancer was described: the claudin-low subtype. The molecular characteristic of this group of carcinomas is the low expression of genes encoding the cell adhesion proteins, namely, claudins 3, 4, and 7 and e-cadherin. In addition, they are triple-negative and have an intense associated immune response.

Table 2 Molecular subtypes of breast cancer and its characteristics of genetic and clinical expression

	Molecular subtypes		
	Luminal	HER2	Basal
Genetic expression pattern	High expression of genes from hormone receptors and associate genes	High expression of HER2 gene and amplicon gene Low expression of hormone receptor genes	High expression of basal cell genes; expression of genes from basal cytokeratin
Clinical findings	70% of invasive cancers Positive estrogen and progesterone receptors Luminal B presents tendency for higher nuclear degree than Lumina A Some of them may express HER2 (hybrid luminal)	15% of invasive cancers; estrogen receptors and progesterone negative receptors More probability to appear with a high nuclear degree and lymph nodal metastasis	15% of invasive cancers Mostly triple-negative BRCA1 dysfunction Particularly common in Afro-American women

Immunohistochemical Parameters in the Molecular Classification of Breast Cancer

Cheang et al. [1] have suggested that the application of a selected panel of antibodies in formalin-fixed and paraffin-embedded tissue has the ability to classify breast carcinomas in a manner that is very close to molecular classification (luminal, HER2, and basal-simile). Table 3 summarizes the use of six immunohistochemical markers that can be used routinely in pathology laboratories to classify breast carcinomas into approximate molecular groups. It is worth mentioning that tumor samples from core biopsy should be fixed in 10% buffered formalin for a period of 6 to 48 h and that the surgical specimens should be painted and sliced as soon as they are removed from the patients and then be fixed for a period of 12 to 72 h. These procedures will prevent autolysis and facilitate morphological analysis of neoplasia, as well as avoid false-negative results in immunohistochemical and molecular studies.

The apocrine molecular group apparently demonstrates its own immunophenotype, i.e., androgen receptor and HER2 receptor positivity, and hormone receptor (estrogen and progesterone) or triple-negative receptor positivity (negativity for estrogen, progesterone, and HER2).

ER, estrogen receptor; PR, progesterone receptor; CK, cytokeratin

Final Words

1. Invasive breast carcinomas exhibit broad morphological spectrum and are divided into nonspecial type and special types.
2. Nonspecial invasive carcinoma (invasive ductal carcinoma, SOE) is the most common histological type (70% of cases).

Table 3 Use of immunohistochemical parameters in the molecular classification of breast cancer

Molecular subtype	Immunohistochemical profile
Luminal A	RE+ an/or RP+, HER2-, and Ki-67 (<14%)
Luminal B	RE+ and/or RP+, HER2-, and Ki-67 (≥14%)
Hybrid luminal	RE+ and/or RP+, HER2+, and any Ki-67 level
HER2	RE-, RP-, HER2+
Basal-simile	RE-, RP-, HER2-, and CK5/6 and/or EGFR+

3. The molecular classification of breast cancer includes these subgroups: luminal A, luminal B, HER2, and basal-simile. Other well-characterized molecular groups are the apocrine and claudin-low.
4. With a panel of six biomarkers, it is possible to classify breast cancer in molecular subtypes through immunohistochemistry.

Recommended Reading

1. Cheang MC, Chia SK, Voduc D, et al. Ki67 index, HER2 status and prognosis in patients with luminal B breast cancer. J Natl Cancer Inst. 2009;101:736–50. *The authors evaluated the gene expression to determine the molecular subtype of breast cancer. Subsequently, the positive hormone receptor group was evaluated with a panel of four markers (Ki-67, HER2, estrogen receptor and progesterone receptor). The results showed that patients with positive receptors could be separated into two distinct groups (luminal A and luminal B) with repercussion on survival. The main contribution of this study was to demonstrate that these markers may be useful in separating the luminal A and luminal B groups similar to the molecular evaluation.*
2. Hicks DG, Lester SC. Diagnostic pathology breast. 2nd ed. Canada: Amirsys/Elsevier; 2016. *An excellent book in which the authors describe the main topics of mammary pathology. In the chapter about carcinoma, they correlate clinical and imaging findings with those of macroscopy. In addition, they also correlate microscopic, immunohistochemical and molecular findings with the prognosis and survival of patients with breast carcinomas.*
3. Lakahni SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, editors. World Health Organization Classification of Tumours of the Breast. Lyon: IARC Press; 2012. *This publication refers to the issue of the World Health Organization on classification of breast tumors and it reflects the views of the Consensus Group of breast cancer experts who met in September 2011 in Lyon, France. Among the invasive carcinomas, the alternative of using the term "invasive carcinoma" is proposed only in cases of breast carcinoma when they do not belong to a special subtype.*
4. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Eystein Lonning P, Borresen-Dale AL. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001;98:10869–74. *In a prospective study, the survival analysis of patients with locally advanced and uniformly treated breast disease showed significant differences for patients belonging to different molecular groups. The basal-simile group correlated with worse prognosis and there was a difference between the two positive receptor groups, with the luminal group A presenting a better prognosis than luminal group B.*

Staging and Prognostic Factors

Felipe Luzzatto

Breast Cancer Staging

Breast cancer staging has an essential significance, as it offers a bottom line to further approaches, standardizes and directs the prognosis definition, predicts the evolution of the disease whenever diagnosed, and subsidizes the determination of the best treatment approach of the cancer.

Breast cancer staging is employed to invasive carcinomas and also to in situ carcinomas, with or without microinvasion. However, neoplasms such as breast sarcomas, phyllodes tumors, and breast lymphomas will be classified, respectively, regarding the staging of sarcomas originated in soft tissue from either torso or extremities and sarcomas with non-usual topography and histology, not complying with the guidelines recommended to stage breast carcinomas.

The Union for International Cancer Control (UICC) associated with the American Joint Committee on Cancer (AJCC) in its 8th edition emphasizes some modifications provided in relation to previous editions of the TNM (tumor, nodes, metastasis) of breast cancer and its prognosis factors, which will be presented in this chapter.

Topography Codes

- Nipple (C 50.0)
- Central breast region (C 50.1)
- Upper inner breast quadrant (C50.2)
- Lower inner breast quadrant (C50.3)

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- Upper external breast quadrant (C50.4)
- Lower external breast quadrant (C50.5)
- Spence's axillary tail (C50.6)
- Overlapping breast lesion (C50.8)
- Non-specified breast alterations (C50.9)

Clinical and Pathological Definition of Primary Breast Cancer (cT/pT)

The T-category of primary tumors is equally defined, regardless of the application of clinical and/or pathological criteria. The classification of the primary tumor ought to be indicated as "C" or "P", when originated from clinical or pathological suspicion, respectively. Additionally, the pathological classification must be the definitive to quantify the size of the lesion.

Lobular carcinoma in situ (LCIS) was replaced from the PTs category to enhance the characterization of the tumor (T), since it is considered a benign entity.

Tumors larger than 1.0 mm and smaller than 2.0 mm should be considered as measuring 2.0 mm, not fulfilling the microinvasive neoplasms criteria (pT1mi), which are defined as invasive neoplasms dimensioned with less than 1.0 mm.

Microscopic satellite tumors peripheral to larger tumors do not significantly impact the main tumor volume and thus are not added to the largest tumor dimension (T).

Multiple concomitant tumors, clinically or macroscopically identified, are yet considered to be referred as (m) after the T-category – exactly as in the previous editions – as solely the measures of the largest tumor are employed to define T-category (multiple tumor dimension is not added).

Cutaneous satellite nodules should be particularized from the primary tumor and macroscopically identifiable to categorize pT4b. Microscopic findings of dermal or cutaneous satellite tumors, in the absence of ulceration or cutaneous edema (clinical *peau d'orange*), do not qualify with pT4b.

T (Category)	T (Criteria)
TX	Primary tumor may not be evaluated
T0	No evidence to support a primary tumor suspicion
Tis (CDIS)*	Carcinoma ductal in situ
Tis (Paget)	Paget's nipple disease non-associated with invasive or in situ carcinoma (DCIS) of the subjacent mammary tissue. Impaired mammary tissue by carcinomas associated with Paget's disease are classified accordingly to their measures and histological characteristics, not diminishing the importance of emphasizing Paget's disease
T1	Largest tumor ≤20 mm
T1mi	Largest tumor ≤1 mm (microinvasive)

T (Category)	T (Criteria)
T1a	Largest tumor between 1 mm and 5 mm
T1b	Largest tumor between 5 mm and 10 mm
T1c	Largest tumor between 10 mm and 20 mm
T2	Largest tumor between 20 mm and 50 mm
T3	Largest tumor beyond 50 mm
T4	Tumors of any size with direct impairment of the thoracic wall or skin ulceration/ macroscopic nodules. Note: solely the dermal invasion does not meet the T4 criteria
T4a	Thoracic wall impairment Note: invasion or adhesion to pectoral muscle in the absence of thoracic wall structures invasion do not characterize a T4
T4b	Ulceration and/or macroscopic ipsilateral satellite nodules and/or skin edema (including peau d'orange), which do not fulfill inflammatory carcinoma criteria.
T4c	Both T4a e T4b are present
T4d**	Inflammatory carcinoma

* Lobular carcinoma in situ (LCIS) is considered to be benign entity, which was removed from the AJCC guide of breast cancer stating in its 8th edition.
** Inflammatory carcinoma is a clinical-pathological entity characterized by erythema and edema (peau d'orange), presenting lymphatic embolism of neoplasms, involving more than a third of the breast skin (classically a clinical diagnostic), associated or not with subjacent tumoral or nontumoral masses.

Regional Lymph Nodes

The regional lymph nodes are anatomically characterized as axillary ipsilateral to the breast between the levels I (lower axillary region), II (middle axillary region), and III (apical axillary region), in addition to the supraclavicular ipsilateral lymph nodes.

Note: Every lymph node metastasis is considered to be a distance metastasis (M1), including cervical lymph nodes or contralateral internal breast lymph nodes.

Definition of Regional Lymph Nodes (N)

The criteria employed to the pathological measure of lymph node metastasis is well defined. Multiple tumor deposits do not compose the pN category, but rather the largest contiguous tumor deposit (adjacent satellite tumor deposits are not considered).

The cNX category is invalid according to specialists unless the lymph node was removed and may not be clinical or radiologically examined.

The cN0 category is employed when lymph node undergoes a complete analysis and clinical and image exams are negative.

Clinical Definition of Regional Lymph Nodes (cN)

Clinical and pathological staging are diverse. Clinical staging includes lymph nodes detected by image examination (except scintigraphy) or clinical examination, presenting highly suspected characteristics for malignancy, or probable histological metastasis proven by the Fine Needle Aspiration (FNA) or by the thick needle biopsy (core biopsy).

cN Categories	cN Criteria
cNX*	Regional lymph nodes may not be evaluated (e.g., previously removed)
cN0	Absence of metastasis in regional lymph nodes (radiologically or clinically)
cN1	Metastasis in movable, ipsilateral, axillary lymph node(s) in levels I and II
cN1mi**	Micrometastasis (approximately 200 cells; bigger than 0,2 mm, but smaller than 2,0 mm)
cN2	Ipsilateral axillary metastasis in levels I and II clinically fused or non-movable; or metastasis in internal ipsilateral lymph node(s), in the absence of axillary lymph node metastasis
cN2a	Ipsilateral axillary metastasis in levels I and II clinically non-movable or fused to one another or to other structures
cN2b	Metastasis solely in internal lymph nodes, in the absence of evidence to support axillary lymph node metastasis
cN3	Infraclavicular internal ipsilateral lymph node(s) metastasis in the III axillary level, associated or not with metastasis in lymph nodes from the I and II levels; or internal ipsilateral lymph node(s) metastasis in the I and II axillary levels; or supraclavicular ipsilateral lymph node(s) metastasis, associated or not with internal or axillary lymph node(s) metastasis
cN3a	Infraclavicular ipsilateral lymph node(s) metastasis
cN3b	Ipsilateral internal and axillary lymph node(s) metastasis
cN3c	Supraclavicular ipsilateral lymph node(s) metastasis

Notes: Suffixes (sn) and (f) must be conditioned to N-category to demonstrate the presence of metastasis as a result of sentinel lymph node biopsy or thin/coarse needle biopsy, respectively
*The cNX category is carefully employed whenever regional lymph nodes were previously surgically removed or when there is no documentation of the medical axillary examination
**The cN1mi category is rarely employed but may be appropriated in cases that the sentinel lymph node biopsy is performed before the tumor resection (mostly in cases that neoadjuvant therapy is employed)

Regional Lymph Nodes Pathological Definition (pN)

The lymph nodes' histopathological classification requires the surgical resection and further analysis of at least the lower axillary lymph nodes (level I), generally including six or more lymph nodes. Facing lymph nodes free of neoplasms commitment, even if the usual number to be examined has not been found, it is classified as pN0.

The examination of one or more sentinel lymph nodes may be employed for the pathological classification. If the classification is solely based on the sentinel lymph node biopsy without subsequent dissection of the axillary lymph nodes, it must be designated as (sn), representing the sentinel lymph node, e.g., pN1(sn).

pN Categories	pN Criteria
pNX	Regional lymph nodes may not be evaluated (e.g., whenever previously surgically removed to pathological or diverse reasons)
pN0	Absence of regional lymph nodes metastasis or solely isolated tumor cells (ITCs)
pN0(i+)	Solely ITCs (malignant agglutination of cells not superior to 0,2 mm) in regional lymph node(s)
pN0 (mol+)	Molecular findings through reverse transcriptase of polymerase chain reaction (RT-PCR); ITCs non-detected
pN1	Micrometastasis; or 1 to 3 lymph nodes metastasis; and/or internal mammary lymph nodes without clinical findings but associated with micro or macro metastasis through the sentinel lymph node biopsy
pN1mi	Micrometastasis (approximately 200 cells, greater than 0,2 mm and smaller than 2,0 mm
pN1a	A third of axillary lymph nodes committed by metastasis, measuring – at least one of them – more than 2,0 mm
pN1b	Ipsilateral internal mammary sentinel lymph nodes metastasis, excluding ITCs
pN1c	pN1a e pN1b combined
pN2	Four ninths of axillary lymph nodes committed by metastasis or ipsilateral internal mammary lymph nodes with image suspicion in the absence of axillary lymph nodes metastasis
pN2a	Four ninths of axillary lymph nodes committed by metastasis (at least one agglomerate greater than 2,0 mm)
pN2b	Internal mammary lymph nodes metastasis clinically detected with or without microscopic diagnoses confirmation associated with negative axillary lymph nodes in pathological analysis
pN3	10 or more axillary lymph nodes committed by metastasis; or infraclavicular (III axillary level); or ipsilateral internal mammary lymph nodes with radiological suspicion on levels I and II; or more than 3 axillary lymph nodes and micro or macro metastasis diagnosed by sentinel lymph node biopsy, whenever facing ipsilateral internal mammary lymph nodes without clinical suspicion; or supraclavicular ipsilateral lymph nodes

pN Categories	pN Criteria
pN3a	10 or more lymph nodes committed by metastasis (at least on agglomerate greater than 2,0 mm); or infraclavicular lymph nodes metastasis (axillary lymph nodes of level III)
pN3b	pN1a or pN2a simultaneously to cN2b (internal mammary lymph nodes with radiological suspicion); or pN2a simultaneously to pN1b
pN3c	Supraclavicular ipsilateral lymph nodes metastasis

Note: Suffixes (sn) and (f) must be conditioned to N-category to demonstrate the presence of metastases through sentinel lymph node biopsy or thin/coarse needle biopsy, respectively, without additional lymph node resection

Definition of Distant Metastasis (M)

The pM0 category, according to the present group of specialists, is invalid. There is no case that may not be classified as cM0 or cM1; although, if cM1 is posteriorly macroscopically confirmed, the pM1 is employed.

M (Categories)	M (Criteria)
M0	No clinical and radiological evidence to support distant metastasis
cM0(i+)	No clinical and radiological evidence to support distant metastasis, simultaneously to no neoplasm agglomerates greater than 0,2 mm, detected by molecular technique using circulant blood, bone marrow, or other non-regional lymphatic tissue samples; asymptomatic patients and without metastasis signs
M1	Distant metastasis detected by clinical and radiological (cM) and/or histologically confirmed metastasis greater than 0,2 mm (pM)

Note: radiological analysis is not required to ratify a cM0 classification.

Post Neoadjuvant Therapy Stating (ypTNM)

The present group of specialists clarifies that the post neoadjuvant pathological category (YpT) is based on the largest residual tumor, whenever present. Fibrosis, consequently, to the treatment and adjacent to the residual invasive carcinoma, is not included to dimension ypT's category. Whenever facing multiple sites of residual tumor, the modifier (m) is included. The pathology analysis must encompass the size of the residual tumor and explain, thus, the reason for the YpT categorization and also include documented clinical category pretreatment (CT), whenever possible.

Pathological Complete Response (pCR)

The largest site of residual tumor in lymph nodes, whenever present, is employed to categorize the YpN. Fibrosis related to the treatment adjacent to residual tumor deposits in lymph nodes is not included in the dimension and classification of the YpN. In addition, any pathological site of residual invasive breast carcinoma or lymph nodes prevents the classification of pathological complete response (pCR). Even regarding clinical or pathological classification of a carcinoma such as M1, previously to therapy, it will be equally categorized as (M1) after neoadjuvant therapy, regardless of the response observed to therapy.

Recurrences or Reintervention Classification (rTNM)

The T, N, and M classification for recurrences or reinterventions is expressed by the lowercase prefix *r*: rcT, rcN, rc/rpM and rpT, rpN, rc/rpM. rc/rpM may include rcM0, rcM1, and rpM1.

The classification of recurrences or reinterventions is determined accordingly to cancer recurrence after an year interval during which the patient was considered free from disease (disease-free interval), or if the disease's progression occurs in a patient never considered free of it (even if no reintervention was planned).

Anatomical Staging and Prognostic Groups

Anatomical stating is solely employed whenever bio-markers are routinely unavailable.

Stating	Tumor (T)	Lymph nodes (N)	Metastasis (M)
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0	N1mi	M0
	T1	N1mi	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0

Stating	Tumor (T)	Lymph nodes (N)	Metastasis (M)
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Notes:
T1 includes T1mi
T0 and T1 tumors solely associated with lymph nodes micrometastasis are not included in IIA staging and are classified as IB staging
M0 includes M0(i+)
The pM0 naming is invalid, any M0 must be clinical
If a patient presents to be an M1 before neoadjuvant systemic therapy, the classification is sustained to be a Stage IV whether or not associated with therapeutic success
The designation of the Staging if postsurgical imaging studies reveal the presence of distant metastases, considering that these studies were performed within 4 months of the diagnosis in the absence of disease progression and considering that this patient did not receive neoadjuvant therapy
Postadjuvant therapy is designated by the prefixes "yc" or "yp" on the T and N classification. No staging is feasible whenever facing pathological complete response (pCR) to the neoadjuvant therapy, e.g., ypT0 ypN0 cM0

Histological Grade (G)

Every breast-invasive tumors must be graduated. The Nottingham's modification of the Scarff-Bloom-Richardson graduation system is recommended, based on morphological patterns such as tubular formation, nuclear pleomorphism, and the number of mitosis, and designating a value of 1 to 3 (favorable and unfavorable, respectively) for each feature. Further analysis relies on the scores' sums of these three categories and provides combined scores (3–5 points, Grade 1; 6–7 points, Grade 2; 8–9 points, Grade 3).

- GX – Grade may not be evaluated.
- G1 – Low histological combined grade (favorable).
- G2 – Intermediate histological combined grade (intermediately favorable).
- G3 – High histological combined grade (unfavorable).

Histological Types

- Carcinomas in situ: ductal carcinoma in situ*;* Paget's disease.
- Invasive carcinomas: invasive carcinoma of no special type (NST); ductal; inflammatory; medullar, NST; medullar with lymphoid stroma; mucinous; papillary (micropapillary); tubular; lobular; invasive Paget's disease; undifferentiated; squamous cell; adenoid cyst; secretory; cribriform

Prognostic Factors in Breast Cancer

Great efforts have been currently directed to identify new and accurate prognostic and predictive factors in breast cancer. Prognostic factors contribute to evaluate the risk of recurrences in patients based on indicators such as intrinsic tumor biology and the stage of the disease at diagnoses' time, being traditionally used to improve the reliability of patients' decisions, sparing them from unrequired adjuvant therapy.

The presence or absence lymph nodes metastasis, the tumor dimension, the nuclear grade, and the histological type are widely celebrated as well-defined prognosis factors in breast cancer. In addition, the lymphatic vascular invasion is also an important prognosis factor, as whenever histologically confirmed, it is associated with an increased risk of metastatic disease, local recurrences, and the reduction of life expectancy.

Regarding multiple histological types of breast carcinomas, some of them aforementioned, it is important to emphasize the following prognostic groups:

- Carcinomas with excellent prognosis (above 80% survival rate in 10 years): tubular, invasive cribriform, mucinous, and tubular-lobular
- Carcinomas with good prognosis (60–80% survival rate in 10 years): mixed tubular, alveolar lobular, mixed (NST and specific types), and medullar atypia
- Carcinomas with limited prognosis (50–60% survival rate in 10 years): medullar, invasive papillary, and classical lobular
- Carcinomas with bad prognosis (less than 50% survival rate in 10 years): mixed lobular, solid lobular, ductal NST, mixed (ductal NST/lobular), and inflammatory

In the 8th edition of the Breast Cancer Staging Handbook experts discussed, in addition to the aforementioned prognosis factors, the importance of integrating biomarkers into the TNM staging, preserving the ability to apply TNM-staging whenever biomarkers are not available, reinforcing that all breast invasive carcinomas should undergo estrogen receptor (ER), progesterone receptor (PR), and growth factor receptors human epidermal receptor 2 (HER2, also called erbB2 and C-neu) analysis, whenever possible.

The process of integrating hormonal receptors and the HER2 status, accompanies the genetical expression analysis and the multigene classification or signature, which also incorporates prognosis/predictive biomarkers (e.g., the Oncotype Dx ® Relapse Score). Besides that, it may also lead to additional predictive information, enabling further pathological staging and the determination of ER/PR and HER2, assisting to determine which patients may benefit from chemotherapy treatment. Another advantage to employ multigene tests is the fact that they are more reproducible and reliable when compared to the analysis of the cellular proliferation index through the immunohistochemical study of the Ki67, due to the lack of reproducibility and uniformity of the Ki67 parameters among different laboratories. Thus, patients with tumors displaying positive hormonal receptors, HER2-negative, non-metastatic lymph nodes, and low scores according to genetic tests (Oncotype DX ®, Mammaprint ®, EndoPredict, PAM50, and Breast Cancer Index, among others), regardless of the tumor dimension (T), may have their neoplasms classified.

Attempting to employ the molecular classification of breast cancer in clinical practice and to promote a greater access to the general population, reducing costs when compared to the multigene tests, is the appliance of the combined evaluation of the previously known immunohistochemical markers (ER, PR, HER2, and Ki67), which are similar to the molecular classification of luminal A, luminal B, luminal hybrid, HER2, and basal-simile. However, it must be observed that the molecular and immunohistochemical classification do not overlap completely, for example, not all basal-simile carcinomas, according to the molecular classification, will be triple-negative for ER, PR, and HER2 according to the immunohistochemical classification and vice versa.

In conclusion, the use of the previously known prognosis factors (e.g., tumor dimension, nuclear grade, and histological type), associated with biomarkers (ER, PR, HER2, and Ki67), combined with signature methods, whether score or multigene classification, become progressively more fundamental to determinate the distinct biological characterization profile of each mammary neoplasia. Thus, all of these combined factors may help to predict the probabilities of recurrences, regardless of systemic therapy, acting as residual risk markers, taking into account if the patient will receive endocrine therapy, or, as factors to predict different types of chemotherapy and thus contributing to the increasingly individualized treatment of breast cancer.

Recommended Reading

1. AJCC. AJCC Cancer Staging Atlas. 8a ed. New York: Springer; 2017. *8th actualized edition of the staging pathology (TNM) according to the AJCC (American Joint Committee on Cancer) developed by international specialists and combining together a wide range of knowledge currently available regarding Cancer staging in different anatomical topographies.*
2. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, Watson M, Davies S, Bernard PS, Parker JS, Perou CM, Ellis MJ, Nielsen TO. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009;101(10):736–50. *This article developed an immunohistochemical analysis of the expression of ER, PR, HER2 and Ki67 in mammary neoplasms, supporting the conclusion that the present group of experts may help in the distinction among luminary tumors A and B, also aiding in the differentiation of these tumors from the specific life expectancy and life free of recurrences.*
3. Cotter MB, Dakin A, Maguire A, Walshe JM, Kennedy MJ, Dunne B, Riain CÓ, Quinn CM. Comparison of Oncotype DX® Recurrence Score® with other risk assessment tools including the Nottingham Prognostic Index in the identification of patients with low-risk invasive breast cancer. Virchows Arch. 2017; https://doi.org/10.1007/s00428-017-2184-1. [Epub ahead of print]. *The objective of this study was to correlate risk groups according to Oncotype DX ® with traditional histopathological parameters and the results of other risk assessment tools (Recurrence Score-Pathology-Clinical, Adjuvant risk Index, Nottingham Prognostic Index and Adjuvant! Online 10-year score), demonstrating that there is a good correlation between the scores obtained using alternative risk tools.*

4. Elston CW, Ellis IO, Pinder SE. Pathological prognostic factors in breast cancer. Crit Rev Oncol Hematol. 1999;31(3):209–23. *Article encompassing some of the pathological prognosis factors in breast cancer, among them the tumor size, the degree and histological type of neoplasms, the staging of axillary lymph nodes, the neoplastic vascular invasion, the hormonal receptors and molecular markers (among them C-ErbB-2 and p53).*
5. Kos Z, Dabbs DJ. Biomarker assessment and molecular testing for prognostication in breast cancer. Histopathology. 2016;68(1):70–85. *Review article focused on Biomarkers such as ER, PR, HER2 and the controversial, but clinically implemented biomarker Ki67, and the multigene tests currently marketed to predict the characterization result and clinical evolution of tumors with greater precision.*

Epidemiology of Breast Cancer

Ruffo de Freitas Jr, Leonardo Ribeiro Soares, and Danielle Cristina Netto Rodrigues

Introduction

The study of breast cancer epidemiology allows for the discussion of strategies and interventions potentially useful for prevention and management of the disease within the public healthcare. In Brazil, it is important to highlight the importance of the Population-Based Cancer Registry, which collects and validates various pieces of information regarding breast cancer. These can be used for the statistical calculation of the variables of interest. If necessary, complementary information from the Brazilian Institute of Geography and Statistics, the Department of Informatics of the Unified Health System (SUS), and other databases will be used.

Incidence of Breast Cancer Around the World

Breast cancer is the most common malignant neoplasm in the world's population, with about 2.4 million cases occurring in 2015. In relation to 2008, there was a 20% increase in the overall incidence of breast cancer. Thus, mammary neoplasia represents one out of four cases of cancer in the female population and is the most common type of cancer among women in 140 out of 184 countries analyzed.

Although incidence rates are increasing in most regions of the world, there is great disparity between developed and developing countries (Fig. 1). The highest incidence rates remain in the more developed regions; in Western Europe, the incidence of breast cancer has reached more than 90 new cases per 100,000 women per year, compared with 30/100,000 in East Africa. In the United States, 252,710 new cases of breast cancer were estimated in 2017, which constitute 15% of all new

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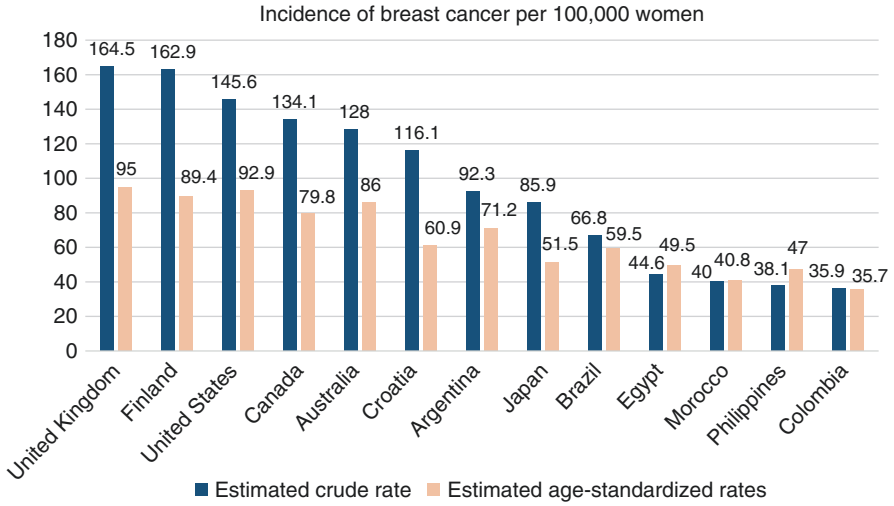

Fig. 1 Incidence of breast cancer in 2012 per 100,000 women in selected countries. (Source: International Agency for Research on Cancer (IARC). Available on: http://gco.iarc.fr/today/home)

cases of cancer in the country. This variation in incidence rates reflects differences in the distribution of disease risk factors and differences among the population's access to screening.

Incidence of Breast Cancer in Brazil

In Brazil, 57,960 new cases of breast cancer were expected in the 2016–2017 biennium, with an estimated 83,035 new cases in 2020. This type of cancer is the most frequent one in women in the South (74.30/100,000), Southeast (68.08/100,000), Midwest (55.87/100,000), and Northeast (38.74/100,000), excluding non-melanoma skin tumors.

In the North region, it is the second most incident neoplasm (22.26/100,000). In the Federal States (FS), rates vary from 14.93/100,000 in Amapá to 91.25/100,000 in Rio de Janeiro, with a tendency to increase incidence in most States.

Table 1 shows the staging of breast cancer at the time of diagnosis in five different Brazilian series published recently. Among the regional differences observed, the effectiveness of the mammographic screening performed in Barretos region and the incidence of the disease in the early stages are highlighted.

In the subgroups' evaluation, an increase in the incidence of breast cancer in young women in the last decades has been suggested. However, despite the overall increase in incidence rates with aging, population studies did not observe significant differences between the 20 and 39 age group, neither in the age group over 40 years.

Table 1 Staging of breast cancer in different Brazilian series published in the Brazilian Journal of Mastology (*Revista Brasileira de Mastologia*), between 2013 and 2016

Study/CS	In Situ	I	II	III	IV
Lavras 2008–2013 (n = 112)	8.9%	30.3%	37.5%	21.5%	1.8%
São Paulo 2012–2014 (n = 3566)	8.1%	17.2%	43.1%	28.6%	3.0%
Barretos 2003–2010 (n = 257)	24.4%	34.2%	24.0%	4.0%	1.6%
Ubá 2001–2014 (n = 647)	12%	34%	37%	11%	6%
Curitiba 1990–2009 (n = 5158)*	2.5%	11.7%	36.6%	21.0%	9.4%

CS clinical staging
∗18.8% not staged or with no information about

On the other hand, several studies have observed a positive association between the incidence of breast cancer and other clinical variables, such as black race, obesity, and the presence of certain genetic mutations, as in BRCA1, BRCA 2, and TP53 genes.

Death Rate for Breast Cancer Around the World

For the year 2015, it was estimated that 523,000 deaths of women and 10,000 deaths of men would occur due to breast cancer in the world. This would represent the fifth cause of deaths by cancer in the world. However, death rates present a large geographic variation, possibly due to socioeconomic factors and also related to the diagnosis and treatment of the disease (Fig. 2). Death rates, adjusted for age, range from 6.1/100,000 in East Asia to 20.1/100,000 in Africa. In the less developed regions, breast cancer is the most frequent cause of death by cancer among women, with a tendency of increase in death rates in recent years. In the more developed regions, this is the second cause of death due to cancer, reflecting a trend towards stabilization and/or drop in mortality since the 1990s. This stabilization is associated with changes in lifestyle and early diagnosis due to mammographic screening as well as advances in the treatment of the disease. Thus, by 2020, there is an estimation of 398,000 deaths by breast cancer in the less developed regions and about 217,600 deaths in the most developed regions of the world.

In population-based studies conducted in the United States, there was a linear association between increased tumor size and increased breast cancer-specific mortality. Likewise, higher death rates were observed in women with N1 and N2 staging compared to those with N0 staging. In other series, there was also a significant association between death rates and younger age at diagnosis, black race, histological grade III, and the expression of specific biomarkers, such as the HER2 oncoprotein. Thus, the understanding of tumor biology and the stage of the disease at diagnosis are fundamental for the critical evaluation of breast cancer mortality curves.

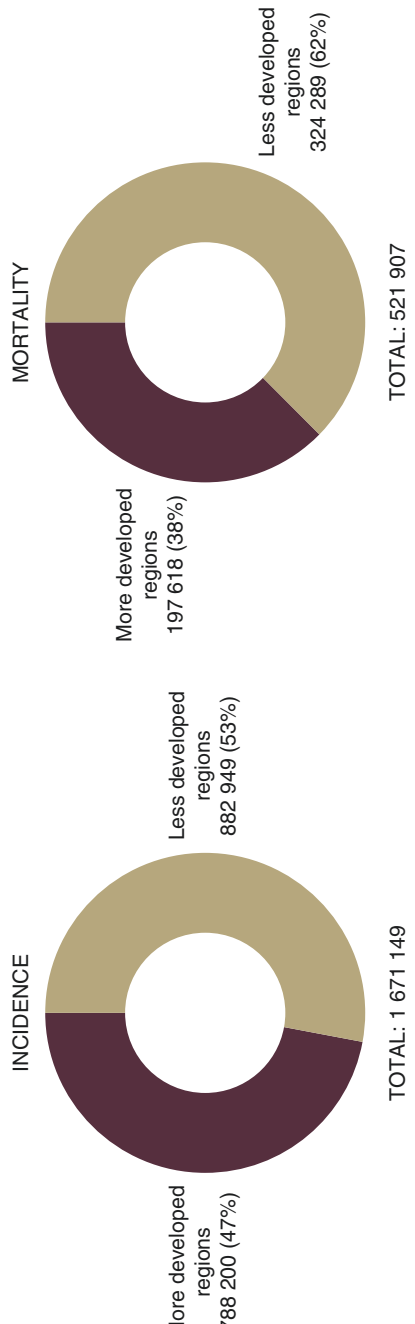

Fig. 2 Estimated incidence and death rates caused by breast cancer in 2012 around the world, based on regional socioeconomic development. (Source: International Agency for Research on Cancer (IARC). Available on: http://gco.iarc.fr/today/home)

Death Rate for Breast Cancer in Brazil

The gross death rate for female breast cancer in Brazil in 2014 was 14.7/100,000. However, the geographical variation of the death rate ranged from 6.9/100,000 in the North to 17.7/100,000 and 18.3/100,000, respectively, in the Southeast and South regions. This same heterogeneous pattern is observed in death rates in Brazilian FSs, and the highest rates were recorded in States with a higher socioeconomic level, such as Rio Grande do Sul, Rio de Janeiro, São Paulo, and the Federal District.

Regarding the temporal trend of mortality due to female breast cancer in Brazil, in the period from 1994 to 2009, the country presented stabilization of 0.4%. However, rates were uneven in the Brazilian regions and states, with a significant increase in the Northeast (5.3%), Central West (1.9%), and North (2.4%) regions, and a significant drop in the Southeast region (−0.9%). In the Brazilian states, the same profile was also observed: a trend of falling and stability in death rates in states with higher socioeconomic status and a marked increase among states with lower socioeconomic status. In other national studies, variations in death rates according to race or color of skin, human development index, and geospatial location (rural versus urban center) were also observed.

Mortality caused by breast cancer is also directly associated with factors related to tumor biology, such as the histological grade and molecular subtype of the disease. In this context, women with undifferentiated tumors and / or with a more aggressive tumor phenotype have higher lethality rates than those with more indolent tumors. In ecological studies, the impact of staging of the disease on prognosis and oncological clinical outcomes was also observed. In Brazil, a hospital-based study conducted in Vitória found a significant association between advanced disease at diagnosis (stages III and IV) and an increase in death rate. These data reinforce the importance of early diagnosis of breast cancer, which may contribute to the reduction of mortality in subgroups of poor prognosis.

Conclusion

In recent years, there has been an increase in the incidence rates of breast cancer in Brazil and in the world, especially in regions of lower socioeconomic development. Mortality curves, on the other hand, showed a tendency of reduction or stabilization in developed countries and rising trend in developing countries. In Brazil, death rates caused by the disease follow the same global profile, with a significant reduction in mortality in the Southeast alone.

Suggested Reading

1. da Saúde M, Saúde S d A à. Instituto Nacional de Câncer, Coordenação de Prevenção e Vigilância. Estimativa 2016: incidência de câncer no Brasil [internet]. Rio de Janeiro: INCA; 2016. Disponível em: http://www1.inca.gov.br/estimativa/2016/. This site puts together several estimations on epidemiology for breast cancer and other neoplasias in Brazil
2. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. CA Cancer J Clin. 2014;64(1):52–62. A study carried out by the *American Cancer Society* with a description of the incidence rates, death rates and survival to breast cancer in the United States.
3. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available on: http://globocan.iarc.fr. This site puts together several estimations on epidemiology for breast cancer and other neoplasias in Brazil and round the world.
4. Freitas-Junior R, Gonzaga CMR, Freitas NMA, Martins E, Dardes RCM. Disparities in female breast cancer mortality rates in Brazil between 1980 and 2009. Clinics. 2012;67(7):731–7. This is an ecological study that analyzed the time variation and geographic distribution of death rates caused by breast cancer in Brazil between 1980 and 2009. It observed mortality in Brazil since 1994, with different regional trends.
5. Wo JY, Chen K, Neville BA, Lin NU, Punglia RS. Effect of very small tumor size on cancer-specific mortality in node-positive breast cancer. J Clin Oncol. 2011;29(19):2619–27. A population-based study carried out with data from *Surveillance, Epidemiology and End Results* (SEER), in the United States. The meaning association between specific mortality by breast cancer, tumor size and axillary status was observed.

Prognostic Predictors: Genetic Signatures, Adjuvant!, and PREDICT

Marcelo Rocha Cruz and Antônio Carlos Buzaid

Definitions

Predictive factors are responsible in determining the recurrence risk and death related to cancer and therefore to stablish the natural history of the disease regardless the treatment performed. Predictive factors are those that determine the outcome to a treatment.

Methods and Interpretations

There are several commercially available laboratory tests capable of prognosticating, with reasonable accuracy, the risk of cancer recurrence. Some appear to present predictive capacity, enabling to determine, with an uncertain accuracy, whether chemotherapy combined with hormone therapy may or may not offer benefits to the patient.

The widest known tests, which are recommended by the international guidelines, are Oncotype DX, MammaPrint, Prosigna (PAM50), and Breast Cancer Index (BCI). Routinely, the most employed are Oncotype DX and Mammaprint. This is primarily due to the early development and release of these tests when compared to other genetic signatures, which accompany a greater volume of scientific data and clinical experience on these tests. Additionally, recent scientific evidence based on the only randomized study employing a genetic signature test on breast cancer, MINDACT, supports the recommendations of international guidelines on Mammaprint.

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Oncotype DX

The Oncotype DX is constituted by a 21-gene analysis by RT-PCR, among which 16 are tumor-related and 5 are comparison genes. The test is performed in paraffin block and the result is expressed by the recurrence score (RS) in 10 years, meanwhile tamoxifen adjuvant treatment. The RS is measured by a formula which emphasizes genes related to cell proliferation. Patients classified with an RS lower than 18 are considered to be low-risk; patients with an RS among 18 to 31 are considered to be intermediate risk; and patients with an RS greater than 31 are considered to be high risk. However, the application of this classification in retrospective studies that validated the test has not been incorporated into the methods of important randomized and prospective confirmatory studies, such as TAILORx, RxPONDER, and PlanB. The randomized TAILORx study, which is in progress, recently published data from a non-randomized group rectifying low-risk RS to be >11. It represents 16% of the total composed of over 10,000 women recruited so far. The group consists of ER+, N0, with RS < 11 patients that solely received adjuvant hormone therapy, being 99.3% distant metastatic disease-free and 98% were alive in 5 years. Approximately 70% of the patients in this study are classified as 11 < RS < 25, therefore understood as intermediate RS and consequently randomized among adjuvant chemotherapy followed by endocrine therapy versus solely endocrine adjuvant therapy. The final results of this study are yet to be published. The German PlanB study employed the classification of low risk as RS (recurrence score < 11), intermediate risk between 12 and 25 (intermediate > 12 and < 25), and high risk as greater than 25 (RS >25). In this study, all non-low-risk women received adjuvant chemotherapy (randomized among TC X 6 or ACT like therapeutic plans) followed by hormone therapy. Therefore, the main conclusion of this study lies solely in the group of low-risk patients: 15.3% of the total patients presented RS < 11 and obtained SVL in 3 years of 98%.

Mammaprint

The Mammaprint is a 70-gene test developed by the Netherlands Cancer Institute. Similar to Oncotype DX, the test is currently performed on a paraffin block of the tumor. Unlike other available tests, the result of Mammaprint is binary: good signature and poor genetic signature. It is the only genetic signature tool for breast cancer with early retrospective and prospective scientific-based evidence supported by a randomized study, recently published in the New England Journal of Medicine. The MINDACT study recruited over 6000 patients with initial breast cancer (committed by 0–3 positive axillary nodes). From this group, about 40% were classified (employing Adjuvantonline clinical criteria) as low risk by clinical and genomical standards and solely received adjuvant endocrine therapy; 27% of the patients were

classified as high risk by clinical and genomical standards and therefore received adjuvant chemotherapy followed by hormone therapy. The main objective of the study was to evaluate whether high-risk patients by clinical standards and low risk by genomic standards could be spared from the adjuvant chemotherapy (which encompassed 23% of the cases). This group was randomized whether to receive adjuvant chemotherapy or sole hormone therapy. The MINDACT study achieved scientific-based data to support that patients clinically considered high risk, but with low genomic risk by Mammaprint, are not benefited by adjuvant chemotherapy in order to be maintained free from distant metastasis (primary endpoint), and therefore this treatment should be avoided in this group of women. Regarding this result, the MINDACT study presents a 43% indication of chemotherapy reduction for patients clinically considered to match high-risk criteria but genomically classified as low risk. The data in this study led the American Society of Clinical Oncology (ASCO) to revise its guideline on the use of biomarkers in breast cancer (published in 2016, without MINDACT data) and, more recently, recommend the employment of this test on women with breast cancer ER+, N0, or 1–3 positive axillary lymph nodes.

Prosigna

The Prosigna test (known as PAM50) evaluates the expression of 50 genes and divides the risk of recurrence (ROR) for women in post-menopause with ER+, N0 tumor, in three categories: ROR 0–40, low risk; 40 < ROR < intermediate risk; ROR > 60, high risk. The prognostic value of this test was validated in prospective-retrospective studies. It presents great accuracy for patients with both negative and positive lymph nodes. Regarding a recent study that included several genomic signatures, the test performance on prognostications overcame Oncotype DX in patients with positive lymph node.

Breast Cancer Index

The Breast Cancer Index (BCI) test evaluates the expression of 11 genes (seven related to the tumor and five comparison genes). Most genes are cell proliferation and the signal pathway of the estrogen receptor related. Therefore, retrospective-prospective studies that validated the test mostly involved the risk of long-term recurrence and the employment of adjuvant hormone therapy (agent nature and endocrine therapy time). The major value of the test lies in predicting (predictive value) who may be spared from long-term hormone therapy. Patients with low BCI present a very low recurrence risk after 5 years on hormone therapy and may have their treatment suspended.

Adjuvant! and PREDICT Plus

Adjuvant! (www.adjuvantonline.com) is a clinical tool that generally enables to prognosticate a patient and determine the risk of recurrence reduction based on the adjuvant treatment. This tool has not yet incorporated the HER2 status and addresses the tumor size as a categorical variable (e.g., a 1.1 cm tumor has the same prognosis of 1.9 cm).

The British-developed PREDICT (www.predict.nhs.uk) is a tool similar to Adjuvant!. However, unlike Adjuvant!, it addresses tumor's size as a continuous variable, incorporates HER2 status, and presents a more accurate prognostic capacity than Adjuvant!. Both Adjuvant! and PREDICT calculate the magnitude of benefit from chemotherapy, hormone therapy, and the combination of both treatments in reducing the risk of recurrence and death by cancer.

Indications

Oncotype DX, MamaPrint, Prosigna, and BCI tests may be useful to determine whether a patient with initial breast cancer, ER+, N0, should or should not receive adjuvant chemotherapy.

The most common clinical features that trigger the necessity of these tests are the 2nd-degree, ER+, smaller than 5 cm, and N0 tumors. Mammaprint, since MINDACT's publication, also encompasses the evaluation of ER+ and 1–3 positive axillary nodes. This recommendation was recently reviewed by ASCO, after careful evaluation of the results of MINDACT. The present group of experts reinforces the recommendation against the employment of Oncotype DX, Prosigna, and BCI for N+ patients due to scarce scientific-based data that effectively support such indication.

Generally, these tests offer useful data to reduce the number of patients receiving adjuvant chemotherapy and due to the economic benefit are often paid by insurance companies in the United States and Europe. In Brazil, there is yet no coverage for these tests.

The Adjuvant! and PREDICT tools are useful to medically determine the prognosis, but its major advantage is to describe the benefit of chemotherapy and hormonotherapy adjuvants and to enable physicians to provide autonomy for patients whenever facing risks-versus-benefits decisions of chemotherapy. However, it is important to emphasize that Mammaprint's genetic signature was superior to Adjuvant!'s clinical-pathological classification in the proper selection of patients who are not compatible to receive adjuvant chemotherapy.

Limitations

The major criticism and limitation to Oncotype DX, Prosigna, and BCI is that these tests were incorporated into clinical practice supported by retrospective-prospective data without definitive scientific evidence from randomized studies. Therefore, its predictive value, especially in the group of intermediate-risk patients – which represents the majority of patients in these tests (around 60–75%), has not yet been validated. Aiming to enhance the role of Oncotype DX on selecting adjuvant therapy based on the RS, a major study is currently underway in the United States, called TAILORx, which has successfully recruited over 10,000 women diagnosed with tumors presenting positive estrogen receptor. Further results are yet to be published. The study's methods address women with an RS > 11 who solely received adjuvant hormonotherapy; those with an RS > 25 received adjuvant QT followed by adjuvant hormonotherapy; and those with RS among these values were randomized between QT followed by hormone therapy versus isolated hormonotherapy. The RxPONDER study is also underway and evaluates the role of Oncotype DX in patients with positive lymph nodes.

Regarding Mammaprint, the MINDACT study (discussed earlier) disposes this test as the first genomic 1A evidence level signature test.

Contraindicated or Unrequired Situations

Molecular tests are not primarily indicated whenever the physician is comfortable with an adjuvant treatment proposal. Thus, these tests are not indicated for patients with clinical and biological factors that denote low risk of recurrence, for instance, ER +, Grade I, T1, N0, or higher risk of recurrence, for instance, triple-negative (basal) tumors and positive HER2, and patients committed by positive lymph nodes, except in patients with N1mi disease.

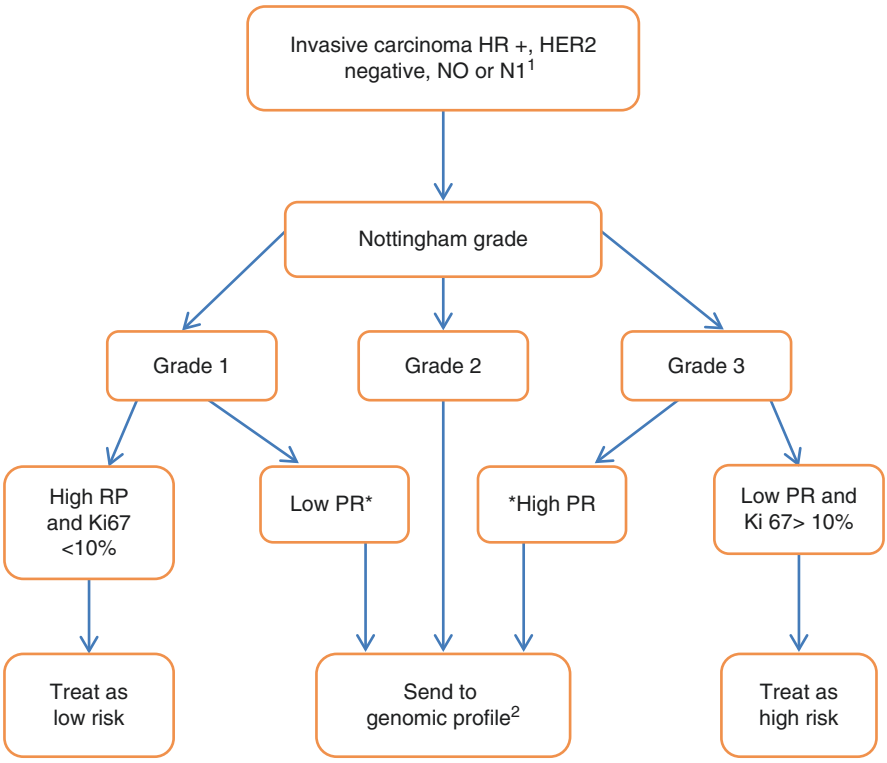
Perspectives

Oncology's future is based on the individualized treatment destined to all clinical situations (adjuvant therapy, neoadjuvant, and metastatic disease). Several studies are underway to improve the genetic profiling of the tumor not only to enhance prognosis predictions, but mainly to help the selection of cancer drugs. We believe that within 5 years, this strategy will already be incorporated into clinical practice.

Practical Recommendations

Regarding Oncotype DX's expenses and given that the test is focused on the gene expression of proliferation and hormonal receptors, several studies have compared their employment versus careful evaluation by IHC of the hormonal receptors and Ki67. Finally, studies support that it is possible to avoid the employment of Ocotype DX and consequently reduce costs by following anatomopathological criteria (Fig. 1).

Tables 1 and 2 encompass clinical-pathological criteria employed by MINDACT study to classify patients between low risk versus high risk. Therefore, in patients who present the high-risk characteristics described, the employment of the Mammaprint test must be considered. Additionally, in patients who do not meet high-risk characteristics described below, we consider appropriate to employ Oncotype DX or Prosigna tests. Regarding the greater volume of data obtained by Oncotype DX, we encourage the use of this test.



1 - High risk, except Grade 1 and < 2 cm; See Genomic signatures indications
2 - See Genomic signatures indications

Fig. 1 Gene signature decision

Table 1 Clinical risk definitions for patients free from positive lymph nodes

GRADE	T Size	Clinical Risk
1	<3 cm 3,1 a 5 cm	Low High
2	<2 cm 2,1 a 5 cm	Low High
3	<1 cm 1,1 a 5 cm	Low High

Table 2 Clinical risk definitions for patients with 1 to 3 positive lymph nodes

GRADE	T Size	Clinical Risk
1	<2 cm 2,1 a 5 cm	Low High
2	Any T	High
3	Any T	High

Addressing the employment of extended hormone therapy in women, the BCI and Prosigna test have offered superior results than the ones observed by Oncotype DX in prognostication accuracy. We favor BCI as it also presents a predictive value in whether to stablish extended hormone therapy. The Mammaprint has not been evaluated in this context and therefore must not be employed to define the hormonotherapy length.

Recommended Reading

1. Allison KH, Kandalaft PL, Sitlani CM, Dintzis SM, Gown AM. Routine pathologic parameters can predict Oncotype DX recurrence scores in subsets of ER positive patients: who does not always need testing? Breast Cancer Res Treat. 2012;131(2):413–24. *Algorithm based on pathological anatomy that suggests which patients do not need to undergo OncotypeDx analysis in the decision-making process.*
2. Cardoso F, van't Veer LJ, Bogaerts J, et al. J 70-gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med. 2016;375(8):717–29. *Results of the randomized study employing Mammaprint test.*
3. Duffy MJ, Harbeck N, Nap M, et al. Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM). Eur J Cancer. 2017;75:284–98. *European guideline encompassing the use of molecular signatures on initial breast cancer.*
4. Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016;34:1134–50. *ASCO's guideline on the recommendations of molecular signatures. This publication was updated in 2017 after the publication of the MINDACT study.*
5. Krop I, Ismaila N, Andre F, Bast RC, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. J Clin Oncol. 2017. *Atualização da diretriz da ASCO publicada em 2016, com foco nos resultados do estudo randomizado MINDACT, ampliando a recomendação do teste Mammaprint. ASCO's updated guideline published in*

2016, emphasizing the results of the randomized MINDACT study, extending the recommendation of the Mammaprint test.

6. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med. 2015;373(21):2005–14. *Prospective analysis of the low risk group RS (<11) from the TAILORx study employing the Oncotype DX test.*
7. Wishart GC, Bajdik CD, Dicks E, et al. PREDICT Plus: development and validation of a prognostic model for early breast cancer that includes HER2. Br J Cancer. 2012;107(5):800–7. *This study demonstrates the value of the PREDICT tool* versus *Adjuvant! and demonstrates that the PREDICT, incorporating the status of HER2, is more accurate.*

Mastectomy

BBSG – Brazilian Breast Study Group

Mastectomy is the surgical removal of the mammary gland: it is the first effective treatment described for breast cancer and is used up to the present day. Simple mastectomy refers only to breast removal, while radical mastectomies are associated with axillary lymph node dissection (ALND). Surgical procedures that preserve the skin or the areola-papillary complex (APC) are called sparing or preserving mastectomies, often described as skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) or adeno-mastectomies.

Background Historical

Radical mastectomy was first described by William Halsted in 1894: the technique consisted of the complete removal of the mammary gland with adjacent skin, pectoral muscles, and axillary lymph node dissection. Halsted believed in the centripetal spread of cancer, but despite better local control of the disease, the radical nature of the procedure did not prevent many women from having adverse systemic outcome. Until the advent of conservative surgery, there were few advances in the surgical technique, as shown in Table 1.

Halsted's concept persisted for decades until the mid-1970s when Bernard Fisher, Umberto Veronesi, and other surgeons put radical surgery on the test: the era of randomized studies was beginning. The NSABP-04 study opened the way and demonstrated that less radical mastectomies, even without axillary approach, had the same survival performance when compared to "broader" strategies. The conservative breast surgery trials came along, as did the trials of systemic therapy, and the radical concept was replaced by the "minimum treatment required."

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Table 1 Milestones in mastectomy

Surgery	Author	Size of surgery		
		Breast	Pectoral muscles	Lymph nodes
Radical M.	Halsted, 1894	Yes	Major and minor	Levels 1, 2 and 3
Modified radical M	Patey, 1948	Yes	Only minor	Levels 1, 2 and 3
	Auchincloss, 1963	Yes	No	Levels 1 and 2
	Madden, 1965	Yes	No	Levels 1, 2 and 3
Extended radical M.	Urban, 1956	Yes	Major and minor	Levels 1, 2 and 3 + IMC

M mastectomy, *IMC* internal mammary chain

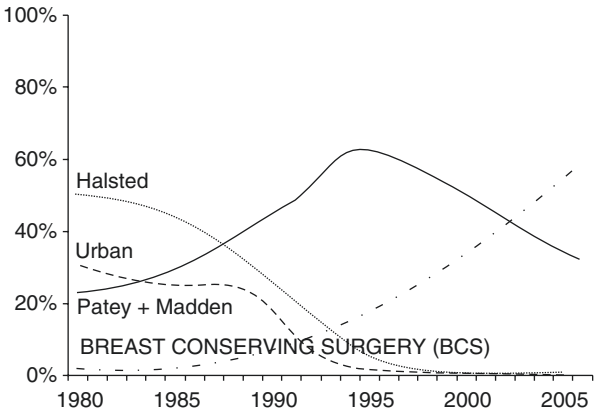


Fig. 1 Evolution of breast surgery (Adapted from Noguchi 2007)

This has had a major impact on mastectomy techniques. Radical and extended radical procedures, for instance, were reserved only for cases in which there was clinical involvement of these structures and the most used mastectomy became the modified radical mastectomy for presenting the same efficacy but with lower morbidity. Dogmas, such as the need for skin withdrawal on tumor, were torn down, resulting in the preservative mastectomy, which is currently the technique of choice in breast cancer surgery. The aesthetic outcome has evolved considerably, leading many women to paradoxically choose this technique even in situations that breast conservation is possible.

In general terms, the evolution of surgery can be seen in Fig. 1.

Conventional Surgical Technique

The conventional technique consists of horizontal fusiform incision ("Stewart" incision), followed by cutaneous flaps and axillary lymph node dissection (ALND) through the same incision (Fig. 2).

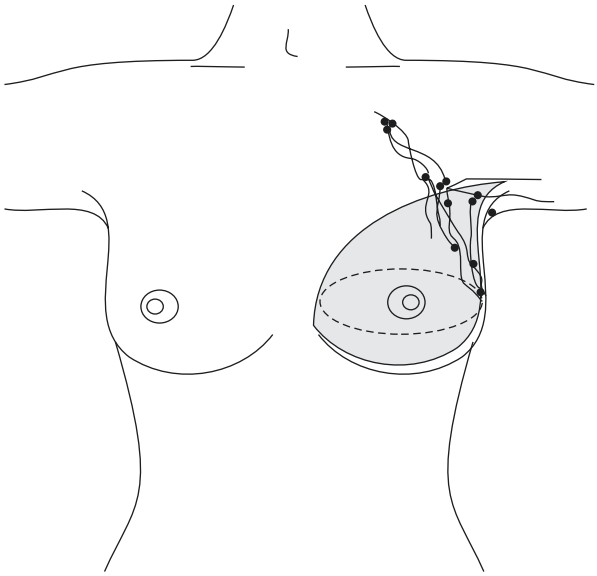


Fig. 2 Conventional mastectomy technique

Conservative Mastectomies

Conservative mastectomies are aimed at saving as much healthy tissue as possible to provide better aesthetic results in breast reconstruction. The main techniques include skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM). Despite the conceptual differences, both present oncological principles and similar risks. There are no randomized studies comparing the efficacy of these techniques; however, retrospective studies have shown an acceptable rate of local recurrence.

Surgical Technique of Conservative Mastectomies

The aim of the surgery is complete removal of glandular tissue with preservation of the entire skin flap and subcutaneous tissue (possibly the APC). The procedure is quite complex and handcrafted, as insufficient removal of the breast tissue may increase cancer risk and excessive removal impairs the reconstruction results.

Although some authors establish fixed thicknesses for the flap, no clinical studies are available. The remnant flap should generally respect the patient's constitution and the amount of subcutaneous tissue present, with dissection respecting the anatomic plane, the border between the subcutaneous tissue and the anterior mammary fascia (Fig. 3).

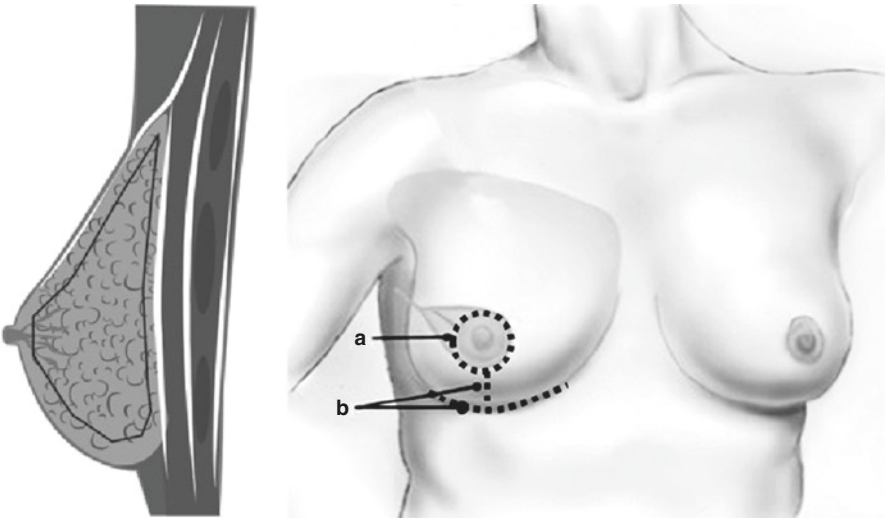


Fig. 3 Conservative mastectomy techniques: 1, skin graft and subcutaneous graft; 2, mostly chosen incisions – periareolar (**a**), radial and sulcus (**b**)

Cutaneous incisions should be discreet, but sufficient for the surgery to be performed. Several types of techniques have been described, and their choice should be individualized, with generally circular or elliptical incisions around the APC in the SSM (Fig. 3b), while in the NSM, the preferred incisions are those in the inframammary sulcus, radial or periareolar with radial extension (Fig. 3b). The radial incision, although providing good access to the breast, still brings some radical surgery stigma, while inframammary and periareolar incisions are technically more difficult, but with a cosmetic result usually superior when well-performed.

Results of Conservative Mastectomies

The rate of surgical complications is higher when compared to conventional mastectomies: necrosis of the skin flap and APC are the main ones, between 3% and 9% of the cases. Conservative mastectomies have become popular and the lack of randomized clinical trials has not prevented the use of these techniques in daily practice. Several case series and some cohorts demonstrate the clinical safety of the technique, as shown in Table 2 and in Fig. 4.

Table 2 Summary of NSM studies with over 100 patients

Author/Year	NSM	Stage	LR%	REC. APC%	Follow-up months
Benediktsson 2008	216	0-III	24	0	156
Petit 2009	579	0-I	0,9	0	19
Paepke 2009	109	0-III	0,9	–	34
de Alcantara 2011	156	0-III	0	0	10
Stanec 2012	241	0-III	4.1	1.2	63
Sakurai 2013	788	–	8.2	3.7	78
Coopey 2013	315	0-III	2.6	0	22
Eisenberg 2014	208	–	0.5	0.5	33
Poruk 2014	105	0-IV	0.9	0	26

NSM nipple-sparing mastectomy (adeno-mastectomies)
Adapted from Adam et al. EJSO 40 (2014) 1209–1215

Local recurrence rates in these studies are acceptable and comparable to radical mastectomies, but the study by Benediktsson et al. in 2008 presented high rates of recurrence. These results can be justified by the staging of the cancer, concomitant to the maintenance of a thicker subcutaneous flap than the recommended one and by absence of adjuvant radiotherapy. Recently, during the last St. Gallen International Breast Cancer Conference on initial breast cancer, the Milan group presented an update on the subject: 2011 patients undergoing NSM, with 17% after neoadjuvant systemic therapy. After 96 months of follow-up, recurrence rates were 5.1% and 4.3% for invasive carcinomas and carcinomas in situ, respectively, with a 93.5% overall survival. Participants in the St Gallen Consensus of 2017 also endorsed the technique after neoadjuvant treatment.

Adjuvant radiotherapy is also a matter of debate: its association may theoretically make these surgical procedures safer, but they worsen the final aesthetic result due to the higher rate of complication, especially in the reconstruction with implants. There are no clinical studies on the subject. Irradiation has generally followed the same recommendations for conventional mastectomies. Some authors choose to individualize each case, according to the surgeon's information on the amount of tissue remaining, suggesting mammography after surgery to aid in the evaluation of tissue (nonstandard procedure).

Local Recurrence

Study name	Risk difference	Standard error	Lower limit	Upper limit	p-Value	Relative weight
Adam	–0.034	0.017	–0.067	–0.002	0.040	20.31
Boneti	–0.004	0.025	–0.053	0.045	0.886	9.15
Burdge	–0.040	0.091	–0.218	0.137	0.656	0.70
Gerber	0.004	0.048	–0.089	0.098	0.928	2.50
Kim	0.011	0.011	–0.011	0.034	0.325	43.60
Poruk	–0.023	0.023	–0.067	0.022	0.317	11.17
Sakurai	0.006	0.024	–0.041	0.054	0.801	9.74
Shi	0.007	0.045	–0.081	0.095	0.874	2.83
	–0.004	0.008	–0.019	0.010	0.567	

Statistics for each study

Risk difference and 95% CI

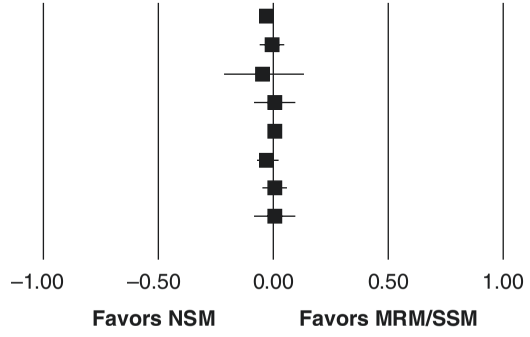
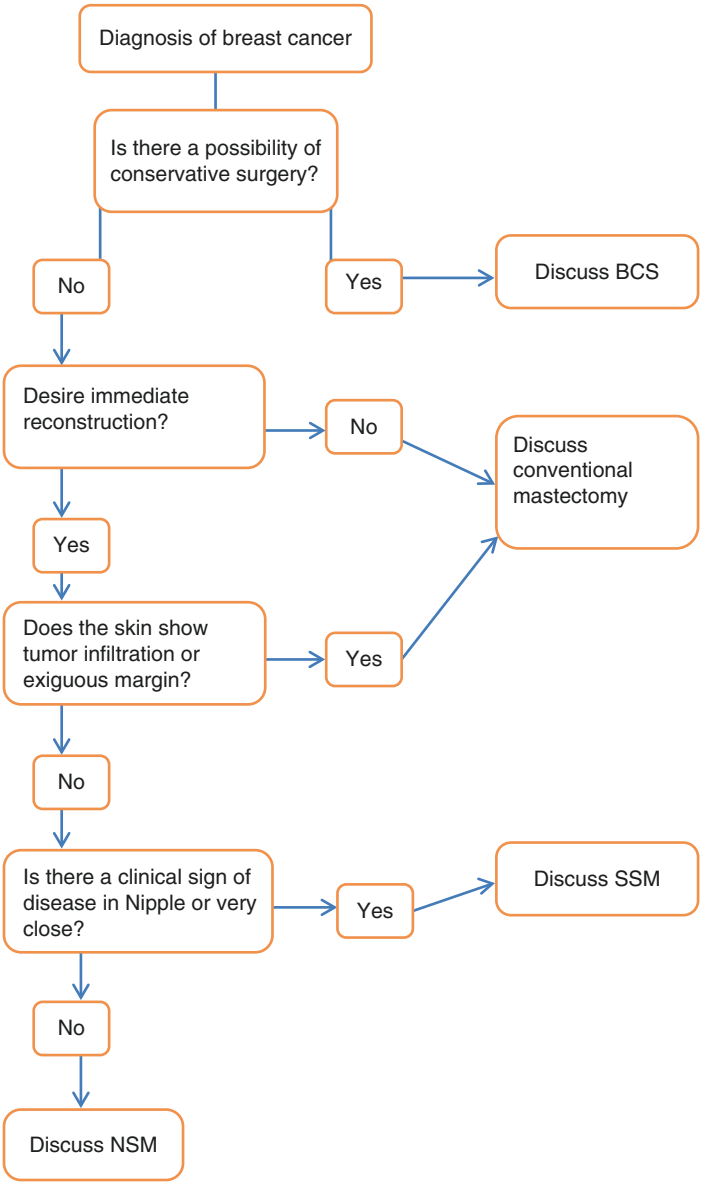


Fig. 4 Local recurrence *Forest plot* in NSM versus MRM/SSM (Adapted from De La Cruz et al [1])

Flowchart



Flowchart 1 Choice of the ideal mastectomy type

Recommended Reading

1. De La Cruz L, Moody A, Tappy E, Blankenship S, Hecht E. Overall survival, disease-free survival, local recurrence, and nipple-areolar recurrence in the setting of nipple-sparing mastectomy: a meta-analysis and systematic review. Ann Surg Oncol. 2015;22:3241–9. *Meta-analysis of NSM studies demonstrating the oncological safety of the procedure.*
2. Gerber B, Krause A, Dieterich M, Kundt G, Reimer T. The Oncological Safety of Skin Sparing Mastectomy with Conservation of the Nipple-Areola Complex and Autologous Reconstruction: An Extended Follow-Up Study. Ann Surg. 2009;249:461–8. *Cohort with 40 SSM, 60 NSM and 130 conventional mastectomies in patients with similar staging. The rates of local recurrence after 101 months were respectively 10.4%, 11.7% and 11.5%.*
3. Halsted WS. The results of radical operations for cure of cancer of the breast. Ann Surg. 1907;46:1–19. *First report on radical mastectomy. In a series of 50 cases followed up for 2 years, there were only 3 local recurrences. These results are far superior to the techniques described above*
4. Jy P, Veronesi U, Orecchia R, Curigliano G, Rey PC, Botteri E, et al. Risk factors associated with recurrence after nipple-sparing mastectomy for invasive and intraepithelial neoplasia. Ann Oncol. 2012;23:2053–8. *Cohort of 934 NSM cases with intraoperative radiotherapy on APC followed up for 50 months. There were 772 cases of ICD, with 3.6% of local recurrences and 0.8% of recurrences in APC. The cases of DCIS were 162, with 4.9% of local recurrence and 2.9% of recurrence in APC.*
5. Murthy V, Chamberlain RS. Defining a place for nipple sparing mastectomy in modern breast care: an evidence based review. Breast J. 2012:1–11. *Evidence-based review of NSM. The occurrence of occult disease in the mean APC is about 15% to 20%. However, the number of clinical recurrences observed is around 4%, with less than 2% recurrence in APC. The number of necrosis of APC varies between 0% and 7%.*

Breast Conserving Surgery

BBSG – Brazilian Breast Study Group

Introduction

Breast conserving surgery (BCS), also known as quadrantectomy, sectorectomy, or lumpectomy, consists of surgical removal of the primary tumor, with negative margins and whole breast radiotherapy (RT). The addition of RT to conservative surgery reduces the local recurrence rate by 50%, with an impact on mortality at 15 years, according to a meta-analysis by the Early Breast Cancer Trialists Collaborative Group (EBCTCG), showing that the omission of radiotherapy in BCS is not recommended.

Oncologic Safety

Survival of BCS was equivalent to mastectomy in six randomized clinical trials, but patients in these studies experienced greater local recurrence (LR) when compared to radical surgery. The NSABP-06 study, for example, started in the 1970s, showed ipsilateral LR around 14%. The addition of systemic therapy, aimed at reducing distant metastases, also reduced local recurrences. In the 1990s, the NSABP trials had LR ranging from 3.5 to 6.5% in 10 years. Improvement in breast radiology, as well as pathologic evaluation, also contributed to this decrease in LR. Currently, available data suggest that LR is more related to tumor biology than to the surgical technique. Patients with triple-negative tumors have the highest rate of recurrence, either in BCS or mastectomy.

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Surgical Technique

Besides adequate oncological control, the main objective of BCS is the maintenance of the corporal esthetics. Some dogmas have been incorporated into the surgical technique, although there is no scientific evidence to justify them. Systematic removal of the skin that is on the tumor, removal of the pectoral muscle fascia, resection of the percutaneous biopsy needle path, and the need to exit the drain near the cutaneous incision are examples of conducts that cause worse aesthetic outcome without improving local control and should therefore be avoided whenever possible.

There are several techniques outlined. In the simpler techniques, more cosmetic incisions are usually chosen, such as the periareolar or in the inframammary fold. Skin on the site can be mobilized, followed by tumor excision with macroscopic margins and appropriate guidance for histological analysis. The adjacent breast tissue can be approximated after resection, releasing any skin retractions and minimizing complications.

Occasionally, cutaneous incisions are necessary in other places. Arcuate incisions are preferably applied in the upper quadrant, while radial incisions are preferably applied in the inferior quadrants or on the lateral sulcus. Scars in the upper inner quadrant should generally be avoided, as shown in Fig. 1.

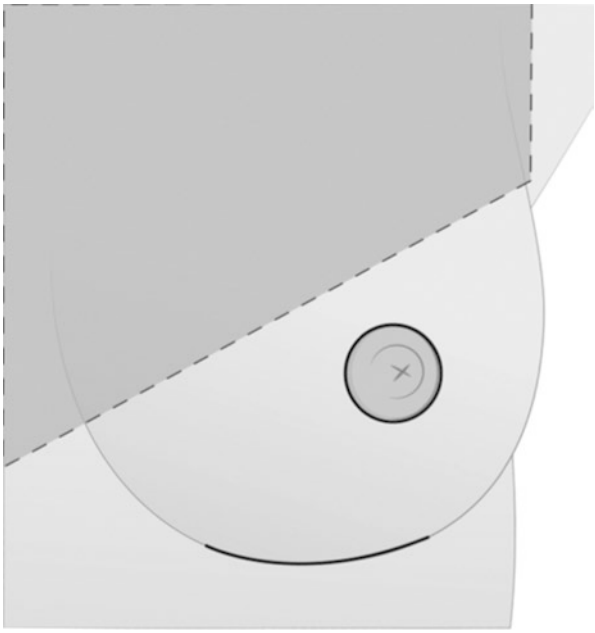


Fig. 1 Preferential incisions in conservative breast operations. The demarcated area in the dashed line should be avoided

There is no fixed limit of tumor size, but the ideal situation is that tumors undergoing conservative techniques occupy up to 20% of the total volume of the breast. Above this ratio, oncoplasty techniques are generally necessary to obtain satisfactory results: in this scenario, the marking of the resection site of the neoplasia with metal clips can be done to guide the radiotherapy (boost).

Tumor Staging

The correct evaluation of the tumor extension is fundamental for a good performance of the surgery. Physical examination and mammography are usually sufficient in most cases. Some patients may need to be supplemented with ultrasonography and magnetic resonance imaging (MRI). The use of MRI is controversial. Some studies have shown an increase in the detection of new tumor foci in 6 to 34% of cases, more frequently in high-risk women and in women with invasive lobular carcinoma, although the multicentric/multifocal nature has been known for decades (the aim of BCS has never been to eradicate completely the disease found in the breast), and old randomized studies of BCS did not experience a higher recurrence rate due to the omission of MRI. The indication of the exam should therefore be assessed on a case-by-case basis, especially when there is suspicion of additional disease or when the imaging tests are inconclusive.

Surgical Margins

A margin is assessed by means of measuring the distance between the ink applied on the surface of the specimen for any tumor cell. The ideal minimum margin in BCS was a matter of debate for many years. This concern began in clinical practice after the main randomized studies on BCS: the only study that established free margin as criterion was the NSABP 06, and not touching the ink was the recommended distance. The other five classic studies did not establish a minimum margin criterion, and macroscopic resection of the tumor was sufficient, that is, the status of the margin was unknown. The rates of local recurrence were still high after the advent of BCS, and minimizing local recurrence is very important. Studies to evaluate this matter were necessary, since reoperation rates were very high, reaching 25%.

The meta-analysis published in 2014 by Houssami et al. [3, 4] met such need: using 33 studies, with 28,162 patients, 1506 cases of LR (5.3%) were observed; after 79.2 months of follow-up, no difference in LR taking margin distances of 1, 2,

and 5 mm was found. This study concluded that positive margins affect local control, while the absence of ink on the tumor border (i.e., no cancer cells adjacent to any border) is considered adequate in the era of multidisciplinary therapy. Therefore, if the tumor does not "touch" the ink, the margin is negative. This is the current recommendation of the Society of Surgical Oncology (SSO), the American Society for Radiation Oncology (ASTRO), and the American Society of Clinical Oncology (ASCO) for invasive carcinoma, also recently endorsed during St. Gallen's consensus in 2017. These recommendations have already had a significant impact on mastology, as reoperation rates have decreased and so have mastectomy rates, according to a recent study.

The margin in ductal carcinoma in situ (DCIS) was also recently discussed and a consensus published in 2016 stipulated 2 mm as the appropriate minimum margin, although free margins below this measurement may not need to be expanded and can be evaluated case by case. The meta-analysis published by Luke Marinovich, with 20 studies (8651 patients), showed that margins wider than 2 mm are not related to lower LR rates.

There are several techniques for evaluating the margins, the main ones being macroscopy, cytology and frozen section. There are no studies that conclude on the ideal technique; however, intraoperative evaluation has declined over the years, especially after the consensus of margins.

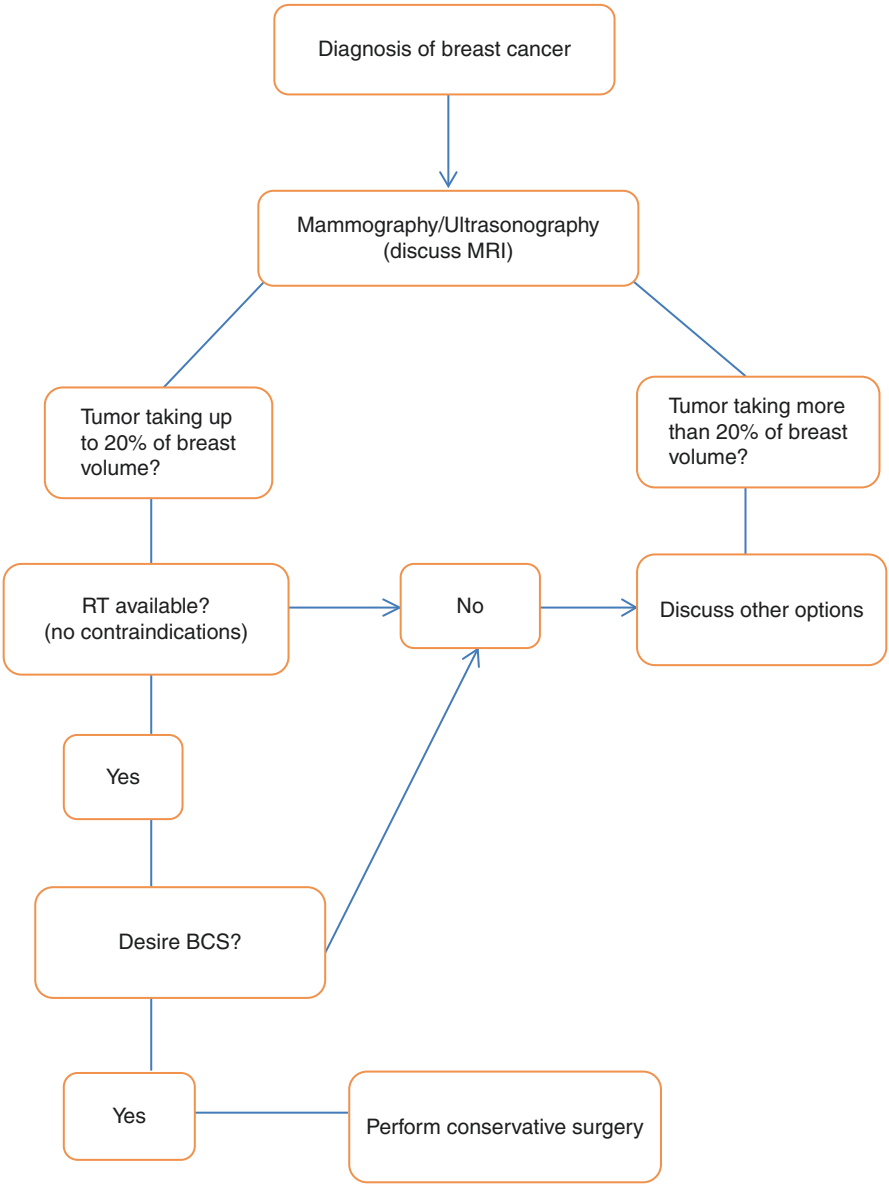
Adjuvant Treatment

The use of systemic therapy has a substantial impact on the reduction of LR. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found that the 10-year LR rate with tamoxifen was 8.7% compared to 18.6% without hormone therapy, a relative reduction of just over 50%. In addition, the use of anthracycline or cyclophosphamide chemotherapy, methotrexate, and fluorouracil (CMF) reduced the relative risk of RL by 30% to 40%. Improvement in systemic treatment was also important: the use of aromatase inhibitors or prolonged endocrine therapy with tamoxifen followed by an aromatase inhibitor showed a 20% to 50% reduction in the risk of RL compared to treatment with tamoxifen alone, as well as the addition of taxane to anthracycline results in an even greater drop in LR. The target therapy, through trastuzumab in women with HER2 expression, showed a significant reduction in LR regardless of the surgery chosen, use of radiation therapy or menopausal status, according to a study by the Memorial Sloan Kettering Cancer Center.

Conclusion

Breast conserving surgery is the ideal treatment for most cases of breast cancer. The conditions for performing it are the following: the patient's desire, possibility of oncological control, and preservation of breast aesthetics.

Flowchart



Flowchart 1 Steps for performing conservative breast surgery

Recommended Reading

1. Barrio AV, Morrow M. Appropriate margin for lumpectomy excision of invasive breast cancer. Chin Clin Oncol. 2016;5(3):35. *Review of the literature on available data regarding the relationship between margin status and local control for invasive breast cancer and the impact of molecular subtypes and systemic therapy on local control.*
2. Bodilsen A, Bjerre K, Offersen BV, Vahl P, Amby N, Dixon JM, Ejlertsen B, Overgaard J, Christiansen P. Importance of margin width in breast-conserving treatment of early breast cancer. J Surg Oncol. 2016;113(6):609–15. *A cohort study with 11,900 women, with a follow-up period of 4.9 years, with LR rates of 2.4% in 5 years and 5.9% in 9 years. It showed increased LR rates significantly associated with young age (<50 years), estrogen receptor negative, grade III, more than 4 positive lymph nodes and re-intervention.*
3. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol. 2014;21(3):717–30. *Meta-analysis on margins in invasive carcinomas. 33 studies, with 28,162 patients, found 1,506 cases of LR (5.3%), with a follow-up of 79.2 months. There was no difference in LR considering the distances of the margins of 1, 2 and 5 mm.*
4. Houssami N, Turner RM, Morrow M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. Breast Cancer Res Treat. 2017. *Revisions on mammary staging with MRI with 19 studies concluded that preoperative MRI is associated with an increased indication of ipsilateral mastectomy and contralateral prophylactic mastectomy.*
5. Marinovich ML, Azizi L, Macaskill P, Irwig L, Morrow M, Solin LJ, Houssami N. The association of surgical margins and local recurrence in women with ductal carcinoma in situ treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol. 2016;23(12):3811–21. *A meta-analysis of 20 studies evaluating patients with ductal carcinoma* in situ *and observing the LR according to the state of the margins. It has been shown that margins wider than 2 mm are not related to lower LR rates.*

Axillary Surgery and Other Regional Lymph Nodes

BBSG – Brazilian Breast Study Group

Surgery to remove axillary lymph nodes composes the classic treatment of breast cancer since the first description of radical mastectomy.

Initially it was believed that the retrieval of lymph nodes improved both global survival rate and local control. Subsequently, axillary staging also became essential to determine systemic treatment.

Meanwhile, recent studies support the entire axillary evaluation could be safely omitted in many patients with clinically negative lymph nodes, providing less morbidity.

Despite sentinel lymph node biopsy (SLNB) technique being spread, there are still controversies focusing the limitations of the indications.

Discussion on Lymph Node's Surgery

Classically, the surgical treatment of breast cancer has always encompassed the integral retrieval of axillary lymph nodes, aiming at either a therapeutic objective whenever facing greatly compromised lymphatic tissue or in order to prognosticate clinically negative patients. The following issues explore the possible benefits of this conduct, demonstrating that in the vast majority of patients the information obtained through the SLNB is sufficient to determine the proper treatment.

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Global Survival Rate

Randomized studies supported that lymph node removal does not impact the overall prognosis.

Fisher et al. [1] published a 25-year follow-up study named NSABP B-04 that randomized 1.079 patients to undergo mastectomy surgery with or without axillary clearence. Global survival was similar, even without any adjuvant therapy (Fig. 1).

Axillary Recurrence Screening

Following the NSABP B-04 study, patients who undergo simple mastectomy received no adjuvant treatment. The rate of axillary recurrences did not meet the expected percentage (18% against 40% in 25 years), and the vast majority were surgically treatable (98%).

Another study, conducted by the Curie Institute, compared the axillary clearence versus axillary radiotherapy. After a 15-year follow-up, the axillary recurrences were statistically equal.

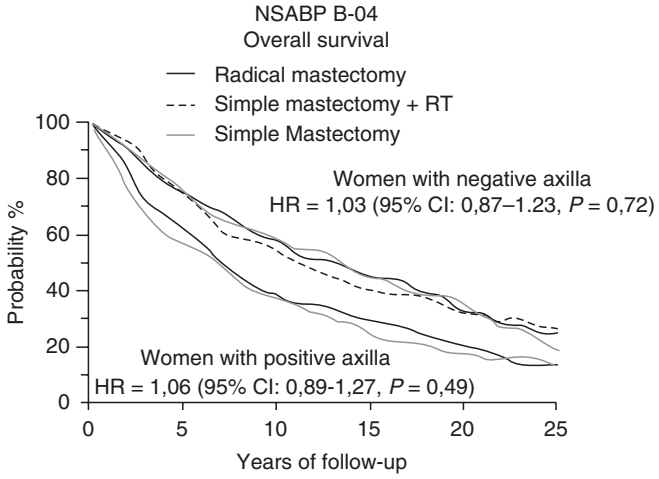


Fig. 1 Global survival results from the NSABP B-04 study. The analysis divided patients between clinically positive axillary lymph nodes ($N = 586$), which performed radical mastectomy or simple mastectomy with axillary radiotherapy, versus clinically negative ($N = 1.079$), which performed radical mastectomy, simple mastectomy, or simple mastectomy with axillary radiotherapy. The 25-year follow-up does not provide statistical data to support any difference in global survival (Adapted from Fisher [1])

Studies with sentinel lymph node biopsy have a fake-negative rate (FNR) of about 8%, but axillary recurrences in these studies, even with long follow-up, were almost irrelevant (< 0.5%).

Prognosis Calculation and Adjuvant Therapy Definition

In the early adjuvant chemotherapy, the axillary condition was mandatory to evaluate prognosis and also to define the therapeutics.

Currently, whether to indicate chemotherapy barely relies on the amount of lymph nodes removed. The most commonly employed parameters are related to tumor biology. Whenever required, the information obtained solely by the sentinel lymph node biopsy is sufficient.

The ACOSOG Z0011 and AMAROS studies randomized women with clinically negative lymph nodes and who presented positive SLNB, to either undergo radical axillary lymphadenectomy versus no axillary surgery, the rate of patients who received chemotherapy was statistically equal.

Whether adjuvant radiotherapy to post-mastectomy patients is required was defined by the amount of compromised lymph nodes (above 4). However, a meta-analysis published by the EBCTCG group in 2014 supported that radiotherapy after mastectomy is indicated even facing solely one compromised lymph node.

Indications for Axillary Clearence

Radical lymphadenectomy surgery (LS) presents limited indications, which encompass inflammatory carcinomas or clinically positive axillary lymph nodes during the surgical engagement.

Obviously, patients without any lymph nodes identified, due to procedure failures to define the correct site, also require radical surgery.

The minimum number of removed lymph nodes is yet to be consensus. Most clinical studies employed 10 lymph nodes as the minimum amount to be retrieved, followed by the vast majority of guidelines. However, AJCC standards enable axillary staging (pN) to be defined with at least 1 lymph node retrieved, and consider axillary clearence when levels 1 and 2 are removed.

Situations that May Not Require Axillary Surgery

We list below the clinical conditions that may spare axillary lymphadenectomy:

1. Ductal carcinoma in situ (DCIS): lymph nodes commitment by neoplasms in DCIS ranges from 2% to even smaller ratios, therefore axillary surgery should

not be performed. The solely formal indication encompasses mastectomies due to extensive lesions as they are associated to a greater risk of underestimated invasive injuries. Additionally, in the aforementioned situations the possibility to perform the sentinel node biopsy immediately after mastectomy is unfeasible. We also suggest the realization of SLNB in situations with considerable risk of underestimated invasive diseases, such as palpable lesions or extensive and high-grade injuries.

2. Neoplastic commitment of lymph nodes rate smaller than the false-negative rate of sentinel lymph node biopsy: sentinel lymph node studies in early stage tumors demonstrated FNR ranging from 7% to 9%. Therefore, the SLNB may not be required in tumors whose risk of axillary disease is smaller than this, such as non-special or lobular invasive carcinomas of up to 0.5 cm (pT1a) and special subtype carcinomas (tubular, mucinous, medullary, and cribriform) with up to 1.0 cm (pT1a-b).
3. Special situations in early-stage tumors: randomized studies evaluated not to perform axillary surgery in early-stage tumors.

Martelli et al. (2012) and IBCSG (2006), randomized elderly patients whether to undergo axillary analysis or not in early stage tumors and supported that no prognostic differences were observed.

Agresti et al. (2014) randomized 565 women ranging from 30 to 65 years diagnosed with early-stage tumors (T1 N0) whether to undergo conservative surgery followed by axillary lymph node radiotherapy or simple observation. A 10-year follow-up supported that global survival and disease-free time-lapse were statistically similar. The axillary recurrence rate was 9% in the group without axillary surgery versus none in the surgical group.

Obviously, the axillary analysis by SLNB is almost morbidity-free and its omission must be evaluated individually, preferably by the multidisciplinary group. Generally, invasive tumors should always have the axilla evaluated.

Regional Lymph Node Importance

Accurate enhancement of image methods enables a greater capacity to detect lesions in lymphoid tissue, such as in the internal breast site. Moreover, the staging system of breast cancer includes these chains. However, a surgical approach to the internal mammary lymph nodes chain or to other regional lymphoid sites must not be advised, as it has no prognosis impact and barely helps to define whether to undergo adjuvant treatment.

Facing local recurrences or locally advanced tumors, a higher frequency of anomaly lymphoid drainage may be observed, especially directed to other regional lymph node chains (internal mammary, subdiaphragmatic, or contralateral axilla).

However, the are no conclusions on whether to indicate surgery for these variations and, most of the times, the radiotherapeutic treatment is elected.

Sentinel Lymph Node Biopsy (SLNB)

SLNB is the ideal treatment for patients with clinically negative axilla at the surgical engagement time. In the early stages of mastology, patients with positive sentinel lymph node (SLN) were subjected to radical lymphadenectomy (RL). However, many patients with positive SLN may be safely spared from surgery.

Another controversial issue was the chemotherapy followed by SLNB, especially in cases of positive axilla before chemotherapy. Recent studies also authorized SLNB in these groups.

The idiosyncrasies are seen in the items below.

Negative SLN: Without Neoadjuvant Therapy

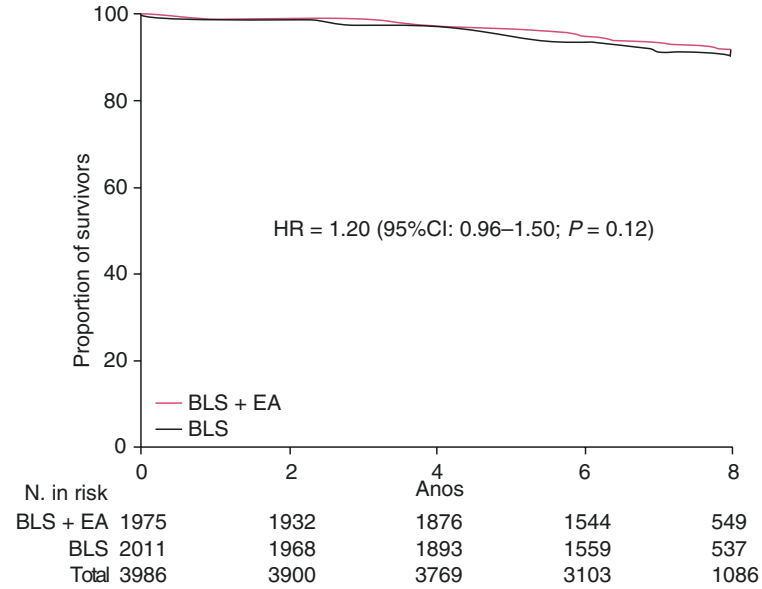
Patients with negative SLN do not require axillary lymphadenectomy. The first randomized clinical study directed to address these oncological outcomes was published by Veronesi et al. (2003). 532 women were randomized whether to undergo SLNB followed by lymphadenectomy versus solely SLNB, the second group of patients were indicated to axillary dissection only if the SLN were positive. The indication rate of SLN was 91.2%, the false-negative rate was 4.6% (8/174) and there was no statistical difference in mortality or oncological events, even after a 78-month follow-up.

The NSABP B-32 study, written by Krag et al. (2007), randomized 5611 women in similar method to the aforementioned study. The analysis supported a 97.2% rate of SLN and 9.8% of FNR. The main variable related to a false-negative augmentation was the quantity of removed lymph nodes (1 lymph node = 17.7%; 2 lymph nodes or more than 10%). The oncological results of the study may be seen in Fig. 2.

Micro-metastatic Committed Sentinel Lymph Node

The IBCSG 23–01 study randomized 465 patients committed by micro-metastasis in the SLN. The study compared radical lymphadenectomy versus no other surgery.

After 5-year follow-up, the disease-free survival was similar (HR: 0.78, 95%CI: 0.55–1.11, $p = 0.16$), as well as global survival (HR: 0.89; 90%CI: 0.52–1.54; $p = 0.73$). Axillary recurrences were rare and statistically similar in the two groups (1 vs. 4).



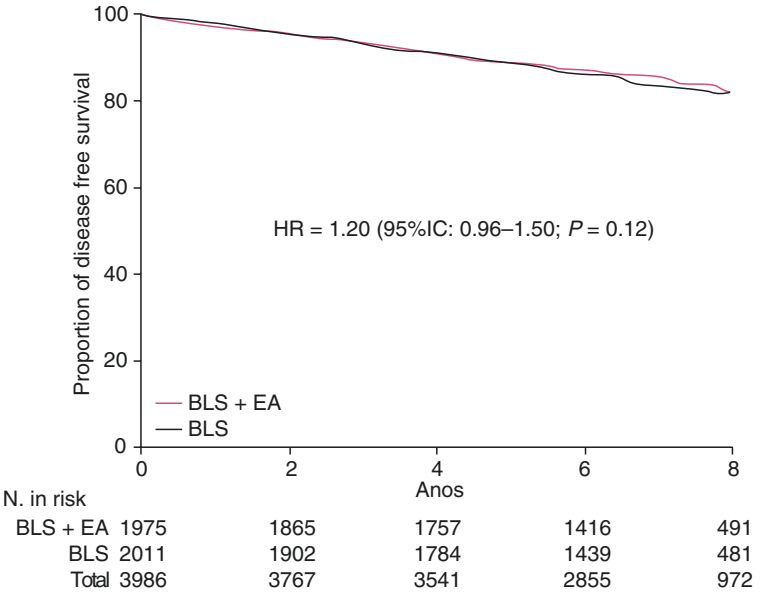


Fig. 2 Results of the NSABP B-32 study that compared sentinel lymph node biopsy (SLNB) followed by axillary lymphadenectomy (AL) versus solely sentinel lymph node biopsy. Global survival and disease-free time-lapse were similar (Krag et al. [5])

Table 1 Comparison of the three main studies addressing axilla preservation in patients committed by positive SLN

	ACOSOG Z0011	AMAROS	OTOASOR
Dimension of the tumor	< 5 cm	< 5 cm	< 3 cm
Mammary treatment	CC + RT	CC or mastectomy	CC or mastectomy
Axillary treatment	None	RT	RT
Number of patients	891	1.425	474
Follow-up time	111 months	73 months	97 months
Global survival	HR = 0,87 90%CI: 0,62-1,23	92,5% vs. 93,3% p = 0,34	77,9 vs. 84,8% p = 0,06
Axillary recurrences	HR = 0,75 90CI%: 0,40-1,40	1,2% vs. 0,4% p = 0,09	2,0 vs. 1,7% p = 1,00

Macro-metastatic Committed Sentinel Lymph Node

The ACOSOG Z0011, AMAROS, and OTOASOR studies randomized patients committed by macro-metastatic sentinel lymph node whether to undergo radical lymphadenectomy versus simple observation (Z0011) or axillary radiotherapy (AMAROS and OTOASOR). The characteristics and results of these studies may be seen in Table 1.

Patients Subjected to Neoadjuvant Chemotherapy

Negative Axilla Before Chemotherapy (cN0 → QT → cN0)

Patients with a clinically negative axilla before chemotherapy may be subjected to SLNB equally to those with early stages breast cancer. Several studies addressed the FNR and the prognosis impact, supporting that the technique is safe.

Class J et al. presented the results of the GANEA 2 study in 2016 (SABCS Oral Presentation). The study evaluated 432 women with negative axilla before chemotherapy who solely undergo SLNB. After a 3-year follow-up, the global survival rate was 98.7% and disease-free time-lapse was 94.8%, proportions comparable to patients treated with radical axillary lymphadenectomy.

Positive Axilla Before Chemotherapy (cN1–2 → QT → cN0)

There are three studies addressing FNR in patients with clinically positive axilla: ACOSG Z1071, SENTINA, and SN FNAC. In these analyses, patients undergo neoadjuvant chemotherapy followed by SLNB and radical axillary lymphadenectomy.

The characteristics of these studies may be seen in Table 2.

Table 2 Summary of the main studies regarding adjuvant chemotherapy followed by SLNB analyzing the false-negative rate

	ACOSOG Z1071	Sentina	SN FNAC
Axillar eligibility criteria	cN1–2∗	cN1–2	cN1–2
Is biopsy mandatory to confirm the diagnosis of metastasis?	Sim	Não	Sim
Number of patients	cN1 = 603 cN2 = 34	592	153
Identification rate of SLN	92,7%	87,8%	87,6%
False negative rate	12,6%	14,2%	13,4%

∗The ACOSG Z1071 study solely published results addressing cN1

Table 3 Impact due to surgical marking technique on FNR

	ACOSOG Z1071	Sentina	SN FNAC
General False Negative Rate	12,6%	14,2%	13,4%
FNR accordingly to marking technique			
One agent	20,3%	16%	16%
Double agent	10,8%	8,6%	5,2%
FNR accordingly the number of SLN			
1 SLN	31%	24,3%	18,2%
2 SLN	21,1%	18,5%	4,9%
3 SLN	9,1%	4,9%	

In order to obtain advanced analysis, the observation of dual marking of the SLN (blue patent and radiocolloid) and the removal of three or more lymph nodes provided false-negative rates of less than 10%. These numbers may be seen in Table 3.

Claude et al., 2016, demonstrated that marking suspicious lymph nodes during biopsy employing radioactive tools enabled even smaller results of FN (1.4%).

The controversial regarding the employment of SLNB is due to the lack of prospective studies supporting oncological security stablished by global survival rates and disease-free time-lapses.

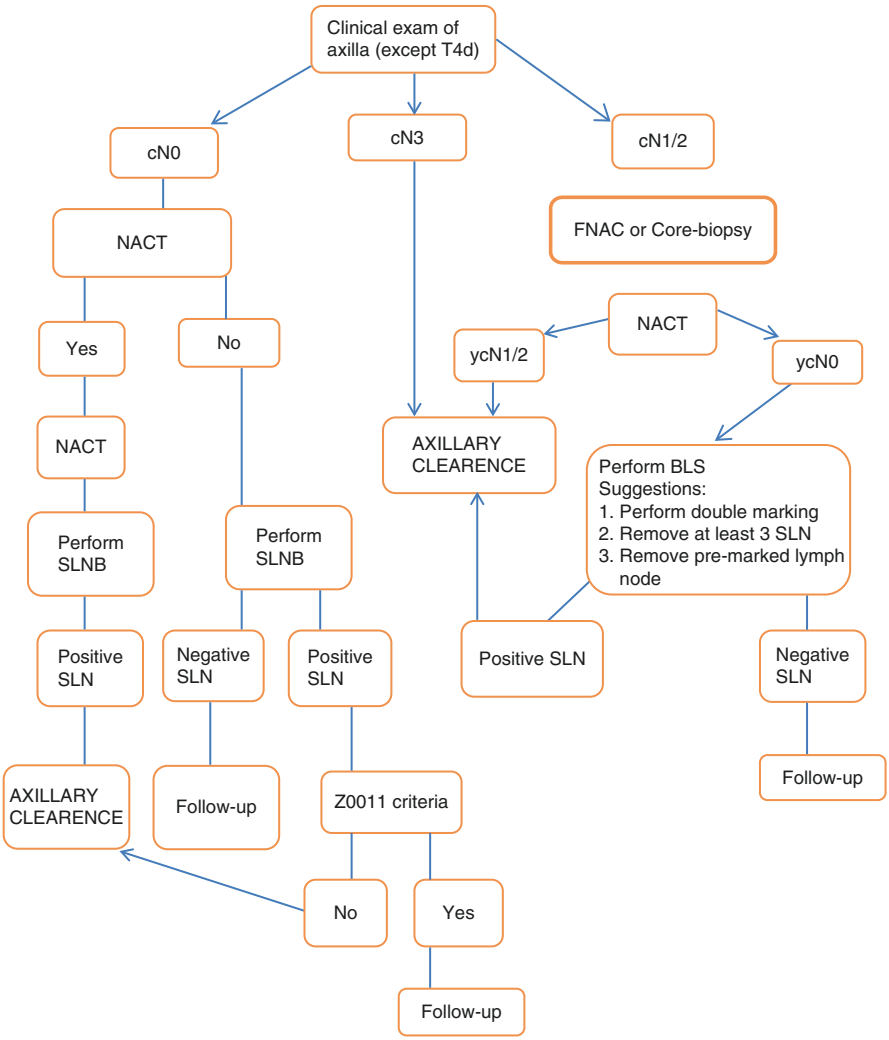
Facing the aforementioned panorama, Galimberti et al. [3], have published a retrospective analysis of 396 women with cT 1–4 cN0/1–2 tumors that underwent SLNB after neoadjuvant chemotherapy and were not subjected to axillary lymphadenectomy when facing a negative sentinel. After a 61-month follow-up, global survival was 90.7% (95% CI: 87.7%–93.7%) in the cohort.

There was no difference regarding the survival of cN0 women (93.3%; 95% CI: 90.0%–96.6%) compared to the cN1–2 women (86.3%; 95% CI: 80.6%–92.1%; $p = 0.12$).

Conclusion

Axillary surgery has proved to be progressively less important in patients with breast cancer and may cause important sequels. The conservation of axillary lymph nodes should be the target of all surgeries and solely excepted when facing situations that still require radical surgery.

Flowchart



Flowchart 1 Management of the axillary lymph nodes

Recommended Reading

1. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med. 2002;347(8):567–75. *Classic study that randomized 1079 women with clinically negative axilla to undergo simple mastectomy, radical mastectomy or simple mastectomy with axillary radiotherapy. After a 25 years follow-up the prognosis was equal in the 3 groups and the axillary recurrences were lower than expected (18%* versus *40%).*
2. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013;14(4):297–305. *Randomized study encompassing females diagnosed with micro-metastasis by the sentinel lymph node randomized to undergo radical axillary lymphadenectomy or simple observation. Axillar conservation did not impact the prognosis and axillary recurrences were not significant.*
3. Galimberti V, Ribeiro Fontana SK, Maisonneuve P, Steccanella F, et al. Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. Eur J Surg Oncol. 2016;42(3):361–8. *Retrospective analysis of 396 women diagnosed with cT 1–4 cN0/1–2 tumors that underwent SLNB after neoadjuvant chemotherapy and did not perform radical axillary lymphadenectomy in cases of negative sentinel. After a 61 months follow-up, global survival rate was 90.7% (95% CI: 87.7% - 93.7%) in the cohort. There was no difference in the survival of cN0 women (93.3%; 95% CI: 90.0% - 96.6%) compared with the cN1–2 women (86.3%; 95% CI: 80.6% - 92.1%; p = 0.12).*
4. Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. Ann Surg. 2016;264(3):413–20. *Randomized study encompassing 891 women diagnosed with early stage tumors (cT1–2 cn0) subjected to conservative surgery and radiotherapy that presented positive sentinel lymph node. The analysis compared the radical axillary lymphadenectomy* versus *simple observation. Global survival rate, disease-free time-lapse and axillary recurrences were similar in the 2 groups.*
5. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927–33. *Main study on SLNB in early stage tumors (cT1–2 cn0) that demonstrated that the preservation of the axilla whenever facing a negative SLN did not impact the prognosis and the axillary recurrences were not significant (0.5%). These results occurred despite a 9.8% FNR.*

Non-palpable Lesion Surgery

BBSG – Brazilian Breast Study Group

Introduction

In developed countries, with the increasing use of screening mammographic and improved imaging methods, 1/3 of the tumors detected are non-palpable lesions.

According to data from Surveillance Epidemiology End Results (SEER)/ National Cancer Institute (NCI), the 5-year survival of patients with non-palpable lesions is 96% and, in 20 years, for women with tumors less than 1 cm, is close to 90%.

The choice of radiological method of percutaneous localization or biopsy will be performed according to the type of lesion. Microcalcifications should preferably be marked by stereotactic (STX), while lesions seen under ultrasonography (US) should be marked by this method. The use of magnetic resonance imaging (MRI) is reserved for cases in which it is not possible to identify the lesion by other methods.

Surgery should ideally be performed after the histopathological diagnosis obtained by percutaneous biopsy, which reduces the need for intervention in benign cases and allows adequate planning in cases of cancer. This tactic reduces the need for reoperations by compromised margins and allows one-time resection of the breast lesion associated with sentinel lymph node biopsy (SLNB) when indicated.

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Surgical Techniques

Preoperative localization of non-palpable breast lesions is essential to ensure the removal of the suspected area with negative margins without removing large amounts of adjacent healthy tissues. Several techniques for precise surgical incision guidance have been developed, and their choice depends on the availability, cost, and familiarity of the surgeon with the available methods.

Among the techniques, the most important ones are metallic skin repair, methylene blue or gentian violet injection, activated charcoal, and metal needles. Kopans wire is the most used one, as well as radio-guided surgeries such as ROLL (radio-guided occult lesion localization), SNOLL (sentinel node and occult lesion localization), and more recently the use of radioactive seed (radioactive iodine seed: I125 – radio seed lesion localization).

Out of the methods described above, Kopans wire is the most widely used. Besides these, the use of radio-guided surgery, either by technetium or I125 seed marking has been widely used in developed countries. Some authors also describe the use of ultrasound-guided intraoperative localization.

Preoperative Localization with Metallic Wire

The most commonly used guides are metal wires with a distal end, which have hook-like tips that prevent their displacement, initially described by Kopans. These are introduced through guide needles, oriented by US, STX, or RM.

Although it is a relatively easy procedure, it presents some drawbacks: the need to perform the surgery after a short interval of thread insertion (to avoid its displacement), insertion of the needle in a location far from the desired lesion, with eventual removal of greater tissue than the necessary and aesthetic results that are not ideal, besides the possibility of rupture during the surgical procedure of the metallic thread. The part of the thread most likely to rupture is the hook. In case of rupture, the location of the fragmented part of the thread is very difficult. In case the patient remains with a fragment of the thread in her breast after the surgical procedure, the follow-up should be performed routinely and removal of the fragment is usually not indicated, as the thread is inert. Only if the lesion has not been resected, or the result is inconclusive can the withdrawal of the needle tip be performed by a new needling or other localization technique.

After marking the lesion by any of the available radiological methods, it is recommended that a mammogram be performed on the absolute medium-lateral and cranio-caudal incidences. This allows the surgeon to evaluate precisely the area of the lesion to be resected with clear margins, the position of the wire in coordinates and its correlation with the lesion. The aim is to program the best incision, the most directed resection possible, and better aesthetic results.

Among the complications, besides the yarn rupture, we can find the discomfort/pain of the patient, incorrect positioning of the thread, and rarely pneumothorax and migration of the wire to the lung or abdomen. Some studies have shown a slightly higher rate of wound infection in this method due to preoperative manipulation.

Still as an inconvenience, perfect synchronization between the radiologist and the surgeon is necessary, between the time of marking the lesion and the surgery, which makes it difficult to perform the procedure in places that do not have availability of a dedicated breast radiologist or surgeon with lesion marking ability.

Despite the described difficulties, this is still the most widely used method in most services.

ROLL: Radio-Guided Occult Lesion Localization

The technique described as ROLL was developed in the 1990s at the European Institute of Oncology (EIO), and it is based on the injection of a radioactive colloid (macroaggregated human albumin labeled with technetium 99 m) into the lesion, under the control of the most adequate radiological method (STX, US, or RM). In addition to the macroaggregated albumin, Dextran 70 or FITATO may also be used. To confirm that the injection was performed at the desired location, a small amount of radiopaque substance may be injected into the same syringe. Immediately after injection, as in the wire technique, two mammographic images (absolute medium-lateral and craniocaudal) should be performed to confirm the presence of the contrast in the desired area.

During the surgical procedure, a sodium iodide crystal probe, called gamma probe, captures the radiopharmaceutical signal, which is translated into pulse numbers, as evidenced in a digital display and an acoustic signal directly proportional to the detected level of radioactivity, in the same way as the sentinel lymph node biopsy is performed. In this way, through the emitted sound, the surgeon can locate the cutaneous projection of the lesion and carry out the planning regarding the surgical incision to be performed.

After removal of the surgical specimen, complete removal of the suspected area is confirmed by redirecting the gamma probe to the surgical bed. The absence of residual uptake of the radiopharmaceutical is expected, with uptake in the radiotracer at less than 10% of the maximum initial uptake.

ROLL presents some limitations, among them the location of extensive microcalcifications, multifocal lesions, or large multicentric lesions. Two concurrent ROLL procedures in the same breast should not be performed because the radioactivity emitted by one focus hinders the exact location of the other focus.

The most common complication of ROLL is the dissemination of the radiolabel by the ductal system. When this occurs, another marking technique must be performed. Mammary lymphoscintigraphy is performed after the injection to confirm

that the technetium remained in place and did not migrate through the ducts. The half-life of Tc 99m is approximately 24 h. In this way, it presents the same drawback of the metallic thread, in relation to the preoperative marking and surgical resection in a short interval of time.

In cases the SLNB is indicated, the ROLL technique may be performed in conjunction with the sentinel lymph node marking – SNOLL (sentinel node and occult lesion localization).

Radio Seed Lesion Localization *(RSL)*

This technique uses a titanium device which measures (4 ‘0.8 mm) 125 Iodine (I125)-labeled “seed,” originally used for treatment of prostate cancer. The “seed” of I125 is inserted into the lesion prior to surgery guided by US, STX, or RM, in the same manner as the previous methods. During surgery, the lesion is located through gamma probe with sensitivity to I125.

For the concomitant performance of SLNB, the wavelength for detection of Tc 99m (after the injection of this radiopharmaceutical prior to surgery) is changed in the gamma probe. It is necessary to have a gamma probe that allows evaluation of different wavelengths.

Once tissue resection is performed, the gamma probe is used to verify if the seed activity is present in the surgical specimen. After the evaluation of the margins, the Seed should be removed by the pathologist and sent to the sector in charge of the hospital’s radioactive waste.

It presents as main advantages: the half-life of Seed I125 of up to 60 days, which allows easy planning between the marking of the lesion and the surgery, easy identification of the seed in the mammography, and the surgeon’s opportunity to easily evaluate if the lesion was properly marked and if incision planning was appropriate.

As a disadvantage, the use of Seed I125 requires the regulation of the nuclear agency, which varies from country to country. In Brazil, there is no regulatory legislation of this method for breast surgery outside of research protocols, requiring approval for use within a research project.

Confirmation of Lesion Removal

After surgery, regardless of the method used, it is necessary to confirm the total removal of the lesion. In cases of microcalcifications, the mammography of the operative part must always be performed. This allows verifying if the lesion is present and centralized in the surgical piece, and it guides occasional extensions of operative margins.

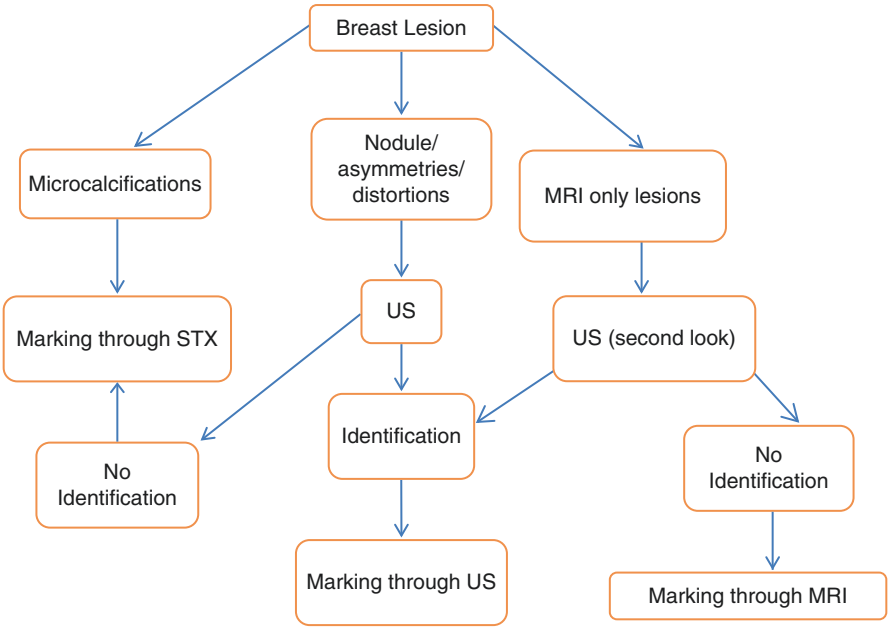
Comparisons Between Methods

In a recent systematic review conducted by Ahmed et al. [1], seven randomized studies comparing the use of radio-guided resections (including ROLL, SNOLL, and RSL) versus the use of Kopans wire marking were evaluated.

There were no significant differences regarding impaired margins, reoperations, and sentinel lymph node identification. It was observed that the radio-guided surgeries present shorter surgical time, but the Kopans wire technique presented lower excised volume according to the authors.

It was concluded that the methods present similar results and that radio-guided surgical procedures are safe alternatives to the Kopans wire marking, presenting the I125 seed technique – logistic advantages described above.

Flowchart



Flowchart 1 Non-palpable lesion (Note: The choice of location method depends on the availability of the same and the experience of the surgeon to deal with the technique.)

Recommended Reading

1. Ahmed M, Van Hemelrijck M, Douek M. Systematic review of radioguided versus wire-guided localization in the treatment of non-palpable breast cancers. Breast Cancer Res Treat. 2013;140:241–52. *Systematic review evaluating 7 randomized studies that compare radioguided surgery (Seed I125 or ROLL)* versus *Wire Guided Surgery as to margins, number of reoperations, sentinel lymph node identification, weight of surgical specimen, surgical time and excised volume, demonstrating similar effectiveness of the methods.*
2. Postma E, Witkamp AJ, den Bosch MAAJ V, Verkooijen HM, et al. Localization of non palpable breast lesions. Expert Rev Anticancer Ther. 2011;11(8):1295–302. *Reviewing the different methods of pre-surgical marking, which compares the advantages and disadvantages of each one.*

Handling of Surgical Specimen

Marcus Vinícius de Nigro Corpa and Felipe Correa Geyer

Introduction

Generally, laboratorial processes are subdivided into three sequential stages: pre-analysis (encompassing the collection, transport, and specimen storage), analytic (laboratory processing itself), and post-analysis (encompassing the interpretation of the results and the expert's opinion). Regarding the pathological anatomy, material's fixation in formalin is the main pre-analysis step, as the specimen disposed in formalin and paraffin included is the universal standard of tissue processing to undergo histopathological analysis. The proper fixation enables the architectural preservation of the cytological characteristics of tissues, crucial to the adequate morphological diagnosis, and consists in the standard preparation of the tissues for immunohistochemical (IHQ) analysis and other techniques such as in situ hybridization (ISH).

Therefore, breast cancer pursues an emblematic analysis, as the combined role of morphology and IHQ for estrogen receptors (ER), progesterone receptors (PR), and HER2 protein is greatly consolidated; ISH may eventually be employed to sample analysis, whether applying the fluorescent (FISH) or chromogen (CISH) methods, for the HER2 gene in therapeutic planning and to prognostic previsions. Morphologically, tumor size and histological grade categorization are mainly evaluated, the latter resulting from careful analysis of nuclear atypia degree and mitotic quantification and also by the index of tubular formation. IHQ and FISH provide information regarding tumor biology, guiding the decision of selective treatments

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such as hormone and anti-HER2 therapies. The cell proliferation index, established by the evaluation of the ki67 protein, although non-unanimous and lacking standardization, constitutes another important employment of IHQ, attempting to approximate the molecular classification of breast cancer, especially in positive ER/PR cases.

Due to the notorious variability during the process stages, recommendations were published by the American College of Pathologists (CAP) and the American Society of Clinical Oncology (ASCO), subsequently internationally endorsed by other entities, in order to standardize guidelines to proceed with the surgical specimen to ensure maximum quality of IHQ and ISH. As the publication of these recommendations follows, few studies have addressed their issues, supporting conflicting results. It is mandatory to emphasize molecular methods as a medical protagonist, almost all of them based on paraffin tissue, increasing the concern of care regarding surgical specimens. However, even considering the accuracy of these methods, the quantitative PCR and the large-scale sequencing (next-generation sequencing), for instance, when applied to tissues fixed in formalin, have been demonstrated to be dependent on adequate fixation, therefore reinforcing the adherence to CAP/ASCO recommendations.

Critical Aspects of Pre-analysis Stage

- Spatial directions of the specimen guided by the surgeon: The lack of directions performing this procedure directly impairs the accurate pathological report regarding margins that may eventually require to be expended.
- Surgical section of the specimen: Formalin is slowly diffused to the interior portion of the tissues. Therefore, surgical specimens directly disposed in the fixator, fully intact, may cause the inappropriate fixation of the target area in the center of the specimen. Therefore, it is recommended that the specimen be sectioned at least once in the lesion's site of interest by the surgeon (excluding the peroperatory pathological analysis). The section must always be performed following pathological criteria, in order not to impair the subsequent evaluation of the surgical margins.
- Cold ischemia time-lapse: This period of time, measured between the retrieval of patient's specimen to the moment it is placed in the fixation content, must not

extrapolate a maximum of an hour. Studies regarding specimens which undergo increasing cold ischemia periods support that the morphological derangements of IHQ and ISH generally occur from the first to the second hour of cold ischemia. Thus, CAP/ASCO's recommendation is evidence-based, and the maximum period of 1 hour is considered adequate.

- Fixation time: The minimum specimen time of permanence in fixation material is established to be no less than 6 hours. Maximum time is 48 hours to the HER2 analysis and 72 hours to hormonal receptors analysis. Therefore, it is recommended that mammary specimens' fixation time-lapse must range from 6 to 72 hours. Insufficient fixation issues are well-known by pathologists and include pattern known as "pseudo micro-papillary"(depending on retraction artifacts), cohesion of degradation cells (suggesting lobular morphology in cases of ductal carcinoma or even suggesting hematopoietic tissue), and autolysis of the material. Studies regarding prolonged fixation time-lapse support that derangements may solely be detected after 20 days, whenever actually impaired, an unacceptable period of time and inaccessible to the reality of the vast majority of laboratories. To maintain the proper control of the fixation time, it is mandatory to record the time since the placement of the material in the fixator, in order to enable, once in the laboratory, the technicians to set the appropriate time to start the processing. Studies dedicated to the evaluation of the CAP/ASCO parameters regarding the effect of cold ischemia time-lapse and the fixation time are scarce and limited, many of them with controversial results. New data is yet awaited to corroborate or alter those recommendations, but until then, we maintain their guidelines.

Critical Aspects of Analytic and Post-analysis Stages

The employment of adequate chemical compounds and calibrated equipment must be ensured, reinforced by proper internal and external controls, respecting the compliance with the established criteria to interpret immunochemical reactions. The quality of these procedures must be validated compared to external reference parameters.

Figure 1 is based on the available data.

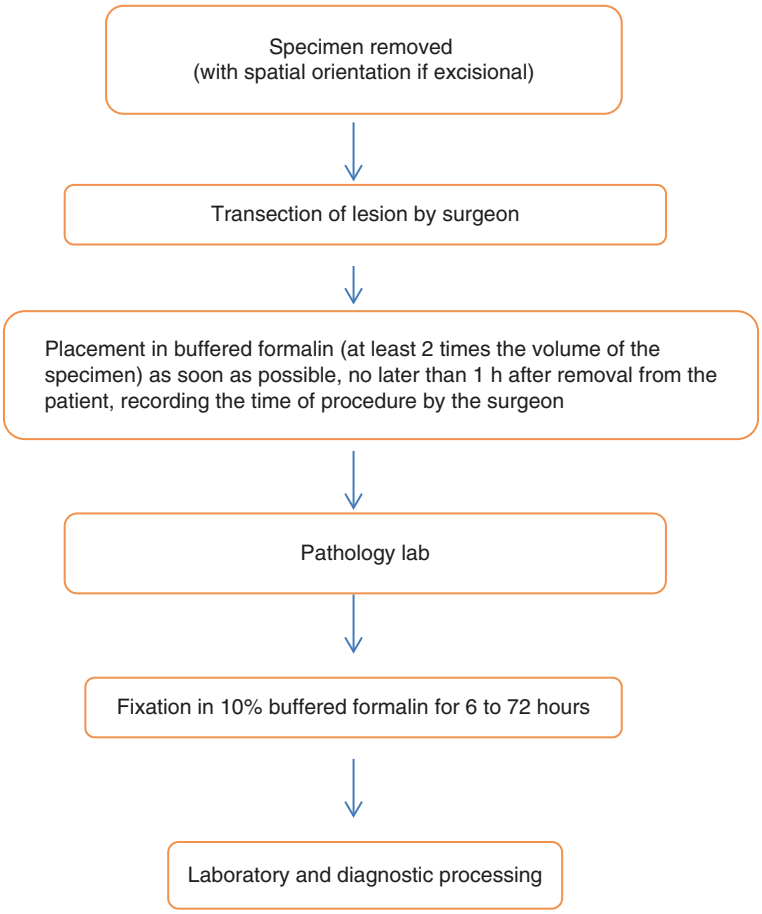

Fig. 1 Flowchart of conducts for surgical specimens

Recommended Reading

1. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med. 2010;134(7):e48–72. *Following published guideline regarding the HER2 article, this study discusses the aspects related to ER and PR immunohistochemistry. The ideal cold ischemia time-lapse (maximum of 1 hour) is described in this article, but is not mentioned in the HER2 article.*
2. Khoury T, Sait S, Hwang H, Chandrasekhar R, Wilding G, Tan D, et al. Delay to formalin fixation effect on breast biomarkers. Mod Pathol. 2009;22(11):1457–67. *Study of 10 cases that underwent careful sampling with different cold ischemia time-lapses. Held IHQ for ER, PR, HER2 and FISH for HER2. Alterations, when present, solely occurred after two hours of cold ischemia time-lapse. Significant variations were observed in IHQ for PR and FISH for HER2. This study was the main foundation for the CAP/ASCO guidelines.*

3. Poremba C, Uhlendorff J, Pfitzner BM, Hennig G, Bohmann K, Bojar H, et al. Preanalytical variables and performance of diagnostic RNA-based gene expression analysis in breast cancer. Virchows Arch. 2014;465(4):409–17. *Study demonstrating that the Endopredict®, gene-expression based on RT-PCR, was minimally affected in different cold ischemia time-lapses and fixation. Even samples kept to 20 °C with no preparation or fixed for up to 5 days presented results within the reference limits.*
4. Portier BP, Wang Z, Downs-Kelly E, Rowe JJ, Patil D, et al. Delay to formalin fixation 'cold ischemia time': effect on ERBB2 detection by in-situ hybridization and immunohistochemistry. Mod Pathol. 2013;26:1–9. *Study that defies the 1 h limit for cold ischemia time-lapse. Encompassing a greater number of cases than the Khoury* et al. *study, suggests that even periods exceeding 3 h have achieved satisfactory result. However, there were no sequential samples of the same specimen, employing as quality parameters the congruence among IHQ and HIS.*
5. Wolff AC, Hammond ME, Hicks DG, Dowsett M, LM MS, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31(31):3997–4013. *Encompasses the updated guidelines for the realization of the HER2 test in breast cancer. In addition to aspects related to pre-analysis variables, it addresses antibodies' aspects, antigenic recovery methods and interpretation criteria.*

Principles of Oncoplastic Surgery

BBSG – Brazilian Breast Study Group

Definition

Oncoplastic surgery (OP) is a major breakthrough in breast cancer surgery after sentinel lymph node consolidation. Approximately 30% of breast-conserving surgery (BCS) in the traditional model present late esthetic results considered unsatisfactory by patients and also have variable rates of reoperation due to compromised margins. The adoption of preventive measures with the integration of breast plastic surgery techniques into oncological surgery can modify this reality. Thus, OP is based on three fundamental principles: optimal cancer surgery, immediate contralateral homolateral reconstruction, and remodeling. This concept, initially limited to BCS, is also being applied in the immediate reconstruction after mastectomies with preservation of the skin and preservation of the nipple and areola complex (NAC).

General Principles

The basilar point of OP is to improve the quality of the life of patients with treatments that may be more effective from an aesthetic-functional point of view, without compromising oncological outcome. Figure 1 shows the main techniques described in breast surgery until the conception of OP, and in Fig. 2, the characteristics of the publications in the literature are shown. The most frequent residual deformities found after a BCS are:

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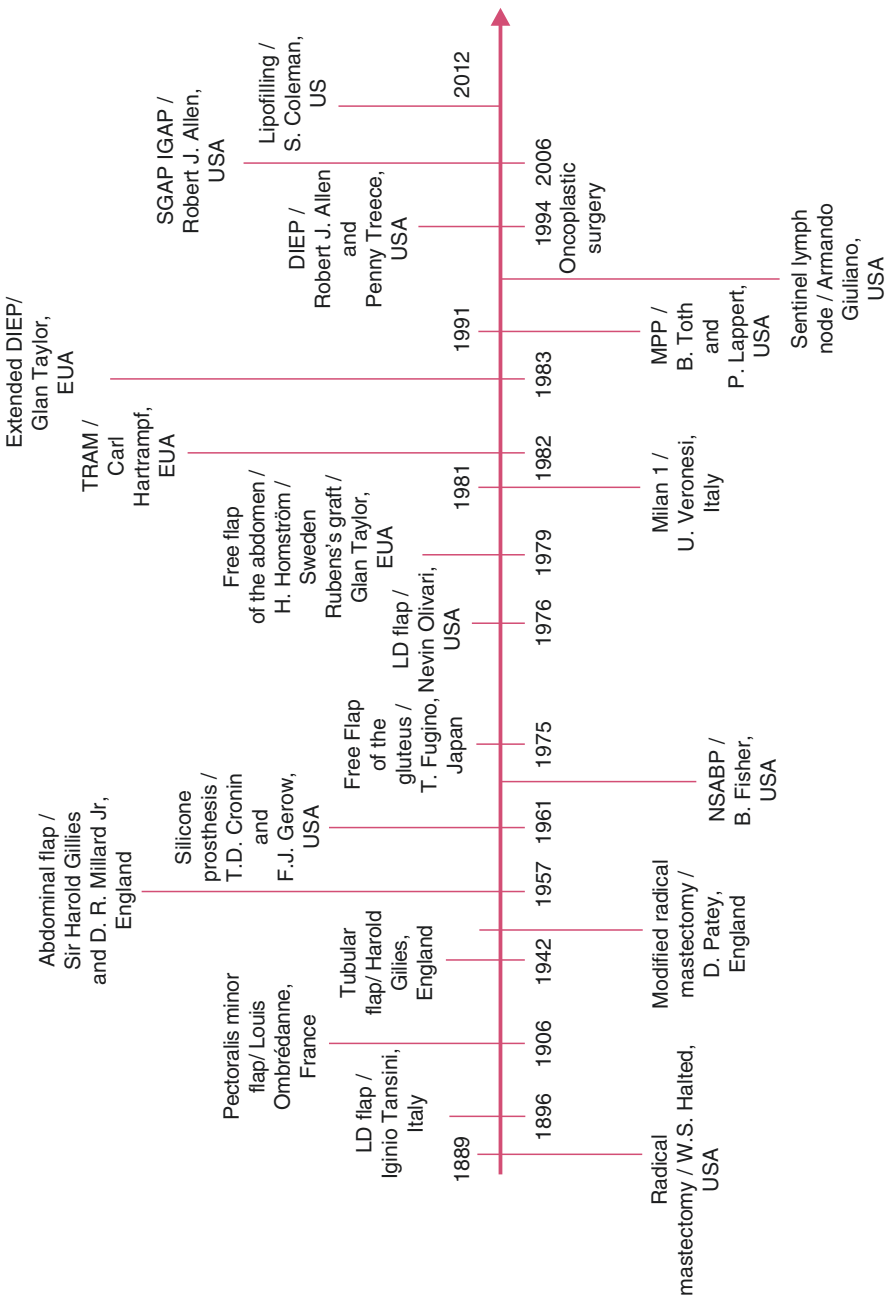
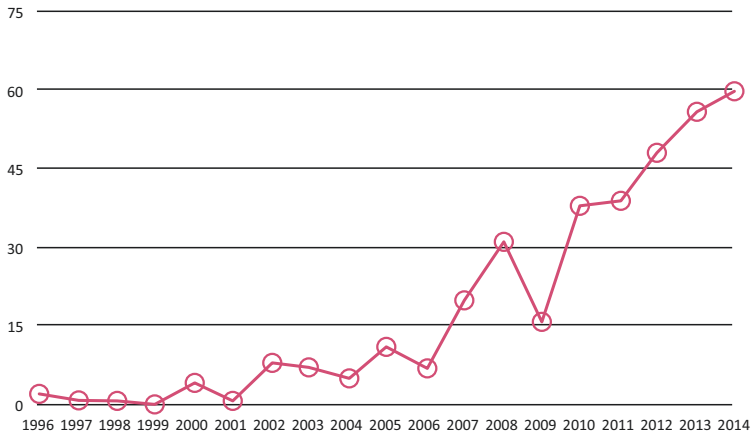


Fig. 1 Historical evolution of oncological and breast repair techniques



Characteristics	n(%)
Technical approaches	136 (38%)
Oncologic results	65 (18%)
Aesthetic results	15 (4%)
Satisfaction and quality of life	6 (2%)
Training	20 (6%)
Complications	7 (2%)
Review and others	107 (30%)

Fig. 2 Characteristics of publications in breast oncoplastic surgery. Source: PubMed 1996–2014. Access in 2014, Key-word (Title/Abstract): oncoplastic

- Deficiency of cutaneous-glandular tissue due to the resected breast volume and the late effects produced by radiotherapy
- Deformity of the NAC
- Reduction of ptosis and unilateral elevation of the inframammary fold as a consequence of fibrosis and retraction after radiotherapy

These changes are more evident in quadrantectomy than in tumorectomy and are related to the location of the tumor and its proximity to the NAC and the skin. The choice of the most appropriate technique for each patient should be made when anticipating the size and location of the defect, the proximity to the skin and to the NAC, and the clinical conditions of the patient (Fig. 3). Tables 1 and 2 show some practical recommendations that have been adopted to improve outcomes and to prevent complications. Patients should be guided by the existing limitations of a reconstructive surgery, which are greater than those existing in aesthetic procedures.

There are three possible situations for conducting OP in practice:

- Mastologist/breast surgeon with training in all breast repair techniques performs all reconstructions.
- Mastologist/breast surgeon performs most of the reconstructions but is associated with more complex cases with the plastic surgeon or mastologist with experience in reconstruction.
- Mastologist/breast surgeon and plastic surgeon work in all cases.

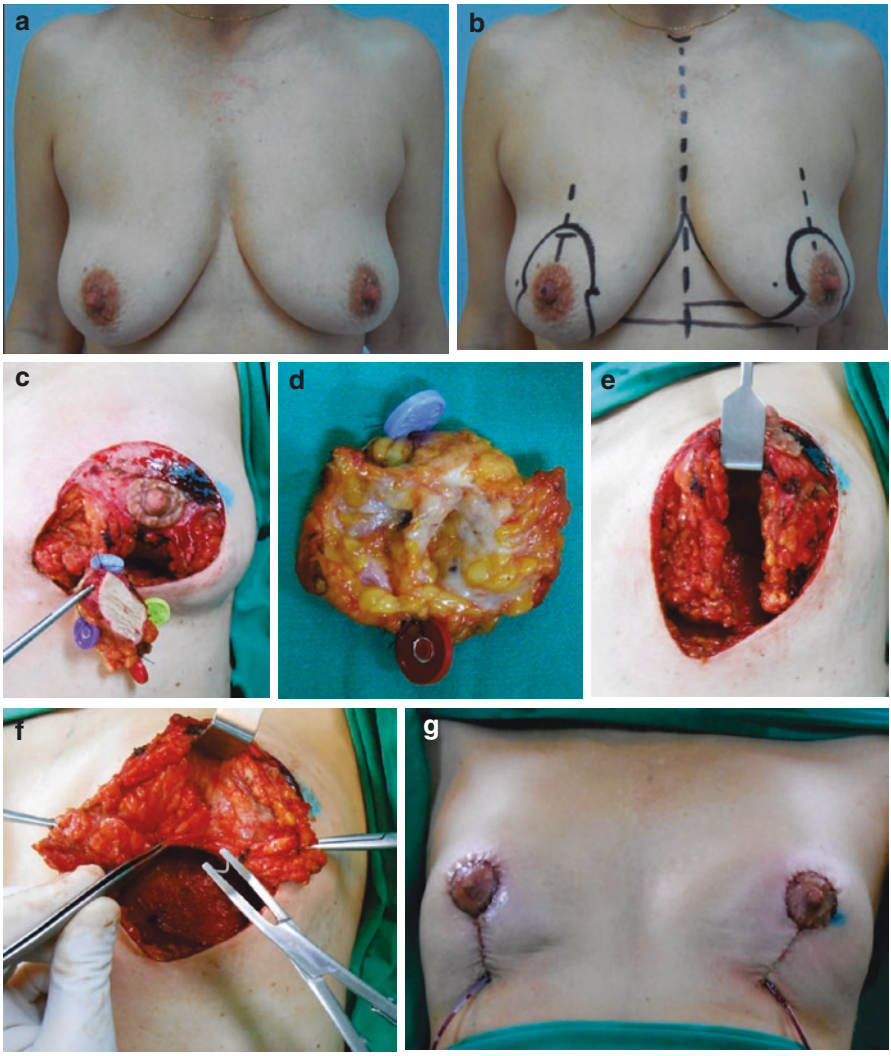


Fig. 3 Oncoplastic surgery of the breast step by step. (**a**): Preoperative patient's photo; (**b**) preoperative designs for upper pedicle; (**c**) tumor located at the junction of lower quadrants of the left breast; (**d**) demarcation of the margins; (**e**) pillars for breast reconstruction; (**f**) placement of radiotherapy clips; (**g**) immediate postoperative result after contralateral breast symmetrization

Main Techniques

The diversity of techniques that are used in breast aesthetic surgery can broaden the indications and even help to deal with the radical nature of BCS. The majority of them are reductive mammoplasty, based on the various pedicles that can be transported for oncologic surgery. The most important factors within the choice of technique to be employed include degree of ptosis; differences in volume and shape already in the

Table 1 How to improve aesthetic results in conservative surgery

Immediate repair of oncologic deformities
A detailed preoperative planning means half of the surgical success
Whenever possible, include the medial pillar for partial reconstruction
Symmetrization is needed in most cases

Table 2 Recommendations to prevent complications and medical claims in oncoplastic surgery

Beware on disproportionate expectations from patients
Antibiotic prophylaxis is needed, as surgical procedures are more extensive
Perform sentinel lymph node biopsy and axillary emptying by different incision to preserve vascularization of the lateral flap
Avoid the rotation of muscle-cutaneous flaps in partial corrections, as they may be the reparative options in case of future relapses
Whenever possible, avoid reconstruction with prosthesis due to radiotherapy
Consider the possibility of performing mastectomy in patients with small, non-ptotic breasts
Anticipate possible problems with hypertrophic scar and keloid
Patients who are smokers, have diabetes and collagen diseases, or have undergone previous radiotherapy present additional risks for unsatisfactory aesthetic results and healing problems
Avoid extensive combined surgery types because the oncology patient needs to be assisted by means of adjuvant treatment as well

preoperative period; height of the inframammary fold; degree of liposubstitution of the breast; height, shape, and size of the NAC; and, mainly, size and location of the tumor.

Tumors located in the upper quadrants in small- and medium-volume breasts with a small ptosis degree can be operated with the "round block" technique. Tumors located in the lower quadrants can be operated with *Lejour* or *Pitanguy* technique or similar reduction mammoplasty techniques depending on the volume and degree of breast ptosis. Large breasts with severe ptosis and/or with tumors located in the upper quadrants can be operated with breast reductions based on the lower pedicles. However, more advanced glandular remodeling or even the use of autologous tissues or prostheses to avoid major deformities is sometimes necessary. Basically, mastering three techniques—upper pedicle, lower pedicle, and round block—allows the remodeling of more than 90% of cases of BCS.

Concerning mastectomies with preservation of the skin or NAC, immediate reconstruction and contralateral remodeling at the same time also represent an important technical advance and follow the same OP principles. The breasts can be reconstructed with expanders and prostheses or with autologous tissue.

Influence on Oncologic Treatment

The basilar study that established OP draws attention not only to its cosmetic benefits, but mainly to the surgical margins in this procedure. At the *Institute Curie*, Paris,

Clough et al. [1] studied 101 patients operated by means of OP techniques between 1985 and 1999. The average tumor-resected breast tissue weight was 222 g (four times as much as in a classic quadrantectomy). In 90 patients, the margins were free, and in 11 patients they were positive. The mean follow-up was 3.8 years and the local recurrence rate was 9.4%. Overall survival in this group of patients was 95.7% and metastasis-free survival was 82.8%. Aesthetic results were considered favorable in most cases. The study was able to bring important elements for discussion in the scientific community and proved the capacity of this type of surgery to allow more extensive breast resections.

Two other studies at the European Institute of Oncology in Milan have demonstrated the oncological safety of OP. The first one, a prospective study, compared the quadrantectomy margins with the OP margins and found a higher negative margin index in OP, thus confirming previous data in non-comparative studies. The second one, a retrospective cohort, sought to assess late oncologic outcomes. In the period between 1994 and 1999, 148 patients with tumors T1 to T3 underwent this type of surgery. The mean follow-up of these patients was 74 months and showed a lower-than-expected local recurrence rate in conventional CS. There was no local recurrence in patients in the carcinoma in situ and the pT1 carcinoma groups. Recent meta-analysis also showed lower rates of reoperation with OP compared to BCS.

There are well-established indications for OP in BCS. The main one is for patients with gigantism, where the results of mastectomy with preservation of the skin or the NAC are usually unsatisfactory and the OP can also favor radiotherapeutic planning.

Therefore, besides allowing for aesthetic improvement, OP can also reduce reoperations with damaged margins in the BCS. Breast reduction also improves local conditions for radiotherapy planning in bulky breasts, or it even allows BCS in patients with small breasts or in cases of tumors located in regions at risk for obtaining a satisfactory aesthetic result and in multifocal and multicentric tumors. This advance definitively modified the view that the concern with aesthetics could impair the oncological result, or vice- versa. And with that, the aesthetic results in both BCS and mastectomy have improved significantly in recent years.

Recommended Reading

1. Clough KB, et al. Oncoplastic techniques allow extensive resections for breast-conserving therapy of breast carcinomas. Ann Surg. 2003;237:26–34. *A pioneering study that gave origin to the current stage of oncoplastic surgery.*
2. Losken A, Dugal CS, Styblo TM, Carlson GW. A meta-analysis comparing breast conservation therapy alone to the oncoplastic technique. Ann Plast Surg. 2014;72(2):145–9. *A unicentric study comparing the results of classical quadrantectomy with those of oncoplastic surgery in terms of surgical margins. The superiority of oncoplastic surgery was demonstrated in terms of oncological radicality.*

3. Rietjens M, Urban CA, Rey PC, et al. Long-term oncological results of breast conservative treatment with oncoplastic surgery. Breast. 2007;16:387–95. *A retrospective cohort study that demonstrated a rate of local recurrence with oncoplastic surgery in DCIS and t1 lower than those found in conservative surgery.*
4. Santos G, Urban C, Edelweiss MI, Zucca-Matthes G, Oliveira VM, Arana GH, et al. Long-term comparison of aesthetical outcomes after oncoplastic surgery and lumpectomy in breast cancer patients. Ann Surg Oncol. 2015;22:2500–8. *A study comparing the results of conservative surgery with oncoplastic surgery in terms of aesthetic results and quality of life.*
5. Urban CA. New classification for oncoplastic procedures in surgical practice. Breast. 2008;17(4):321–2. *Classification of oncoplastic procedures for the surgical practice based on abilities.*

Partial Breast Reconstruction

BBSG – Brazilian Breast Study Group

Definition

Partial reconstruction may be defined as the immediate regional repairing procedure, which follows the oncoplastic surgery (OP) model of mammary reconstruction and therefore encompasses the topographical symmetry and patient's quality of life. Extensive impairments after breast-conserving surgery (BCS) not immediately followed by reconstruction usually require further flaps or grafts to accomplish the complete correction, generally provided by the large dorsal muscle or from lipofilling. Moreover, due to radiotherapy, the most likely evolution of deformities is to be accentuated, providing extra difficulties and technical limitations and also increasing the complexity of further corrections. Therefore, esthetic results from late reconstructions are markedly limited, which elucidates the immediate breast reconstruction, even facing BCS. Generally, immediate partial correction may reduce these risks and offer better results encompassing less aggressive techniques.

Preoperative Planning

Basically, the decision of the proper technique to be performed is guided by tumor-related factors and patient-related factor, such as the morphology of the breast and the patient itself. The solely Cochrane referred element as a risk to an unsatisfactory result following CS is the resected breast volume above 20%. However, surgical experience reinforces to consider the following:

- Tumor size
- Tumor location and proximity to the skin

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- Tumor distance from the areola and the nipple
- Previous radiotherapy
- Previous mammary plastic surgery
- Breast size
- Ptosis degree and breast asymmetry
- Intensity of adipocytic substitution of the breast

Furthermore, associated comorbidities may impact the decision of the most appropriate technique to be performed. Diabetic patients, smokers, patients committed by collagen diseases, and over 70 years elderlies may present risks to unsatisfactory esthetic results and higher complications regarding the scar. Large resections and wide displacements of the nipple and areola complex (NAC) withhold a greater risk of steatonecrosis and partial or total loss of areola and/or nipple.

The ideal tumor location is within the mammoplasty resection site. When facing a tumor close to the skin, and outside mammoplasty resection site, it may be increase the OP procedure complexity and require combined techniques, enabling results that are not always satisfactory. In these patients, mastectomy should also be considered as a surgical possibility, as well as facing the requirement of wide resection of the skin. Flaps such as the one from the large dorsal muscle, which has different texture and coloration than the one presented in the breast, usually do not enable satisfactory results and should be exceptionally indicated.

Big and ptotic breasts enable surgeries with wider margins and generally more satisfactory results. Gigantomasty is a formal indication to OP procedures, due to the best radiotherapy planning, and reliev og this condition. Facing previous plastic surgery, it is mandatory to consider that the breast volume is artificial and may be impaired by important deformities. The major issue for OP are young patients, with conical breasts, without ptosis and with small or medium volume. In these cases, relying on the location and size of the tumor, local flaps offer limited results and mastectomy that encompasses the preservation of the skin or NAC with immediate reconstruction may be the most suitable decision. Large resections may impair esthetic results with local flaps. Simultaneously, a postoperative compromised margin may be difficult to be approached in a second-time surgery or compromise the esthetic outcome. Fortunately, this situation is uncommon in the OP. Moreover, associating the preoperative magnetic resonance in patients with considerable risk, which are those with dense breasts, prior plastic surgery, positive family history for breast cancer, carriers of BRCA1 or BRCA2 mutation, lobular carcinoma, or in boundaring indication for BCS.

Main Surgical Techniques

Local flaps employ previously existing tissues within the breast cone itself, being categorized as Class 1. Transposition, rotational, or interpolation flaps may be performed. The diversity of techniques employed in mammary esthetic surgery may not solely improve BCS results but also improve their indications. Most techniques

encompass a reducing mammoplasty, based on the various pedicles, which may be successfully transported to oncological surgery. Techniques involving the upper, lower, lateral, or medial pedicles and round-block may therapeutically improve the status of most cases. But there are also glandular and fascio-cutaneous flaps that may be adequately indicated in specific situations, such as the Holmstrom's flap, or even the association of techniques (Figs. 1–7). All these techniques may be employed according to the tumor location and characteristics of the breast.

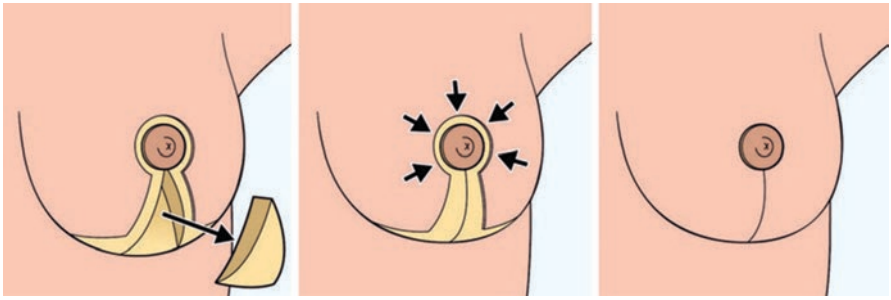


Fig. 1 Superior pedicle technique

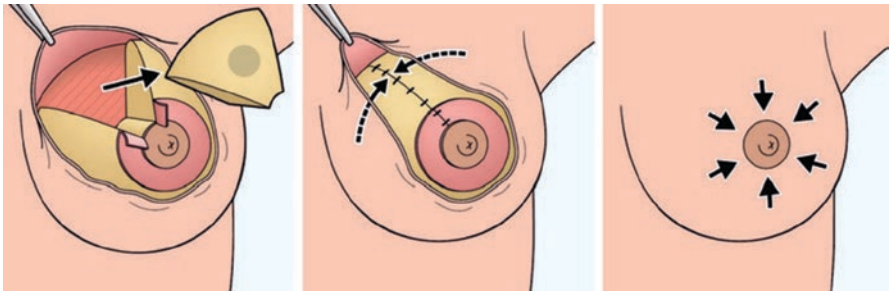
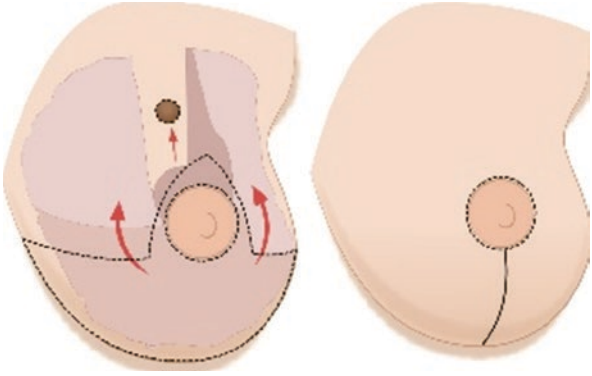


Fig. 2 Round-block technique

Fig. 3 Inferior pedicle technique



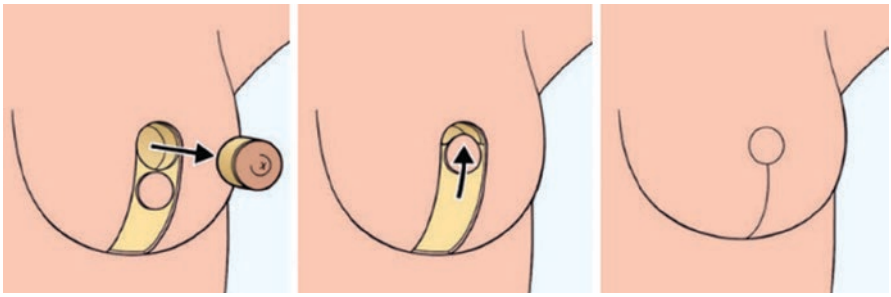


Fig. 4 Grisotti's technique

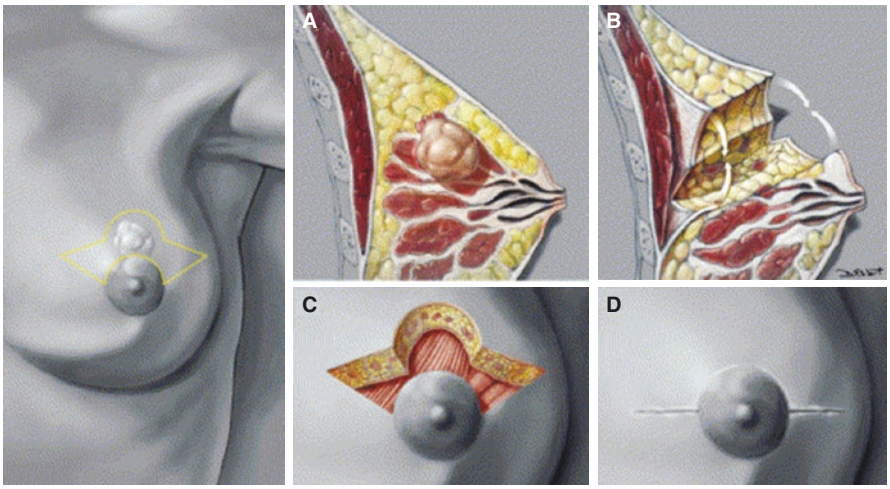


Fig. 5 Batwing technique

Indications and Limitations

The main indications and limitations of OP are presented in Table 1.

Oncological Safety

Despite being a conservative surgical technique followed by a partial breast reconstruction and, therefore, equal oncological results to setorectomy or classical quadrantectomy are to be expected, much is discussed about the lack of strong

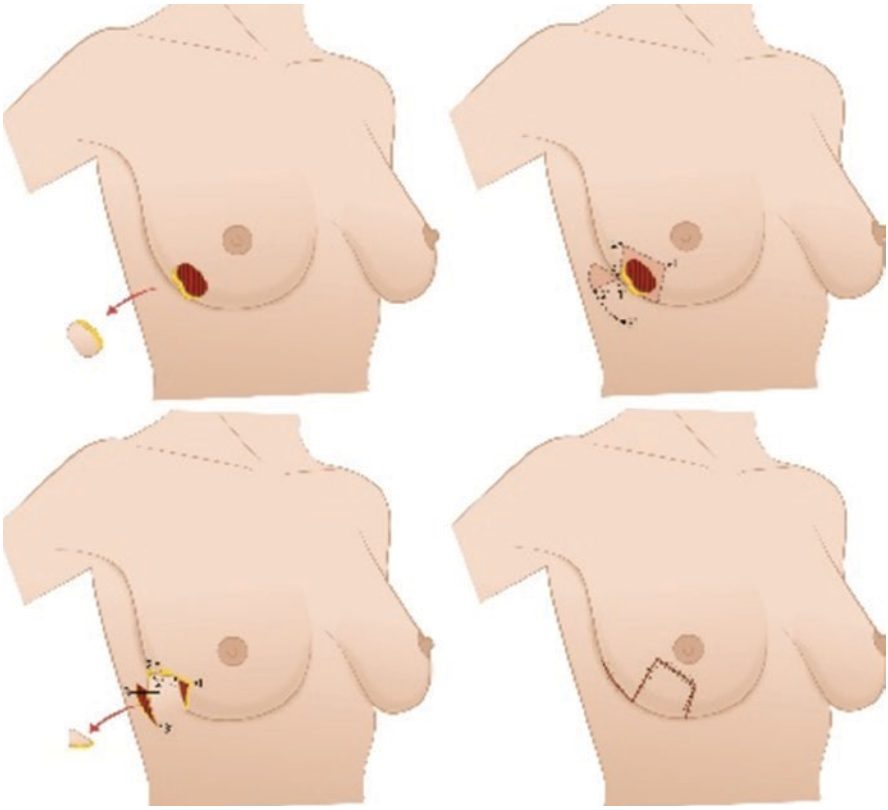


Fig. 6 Limberg's graft

evidence of these techniques. In late 2016, Losken et al., published a meta-analysis encompassing over than 8500 patients, supporting that oncoplastic techniques (mammoplasty or myo-cutaneous flaps) present oncological results similar to those of traditional conservative surgery. However, they presented a lower rate of compromised margins and reoperation, followed by a greater satisfaction with the final esthetic result.

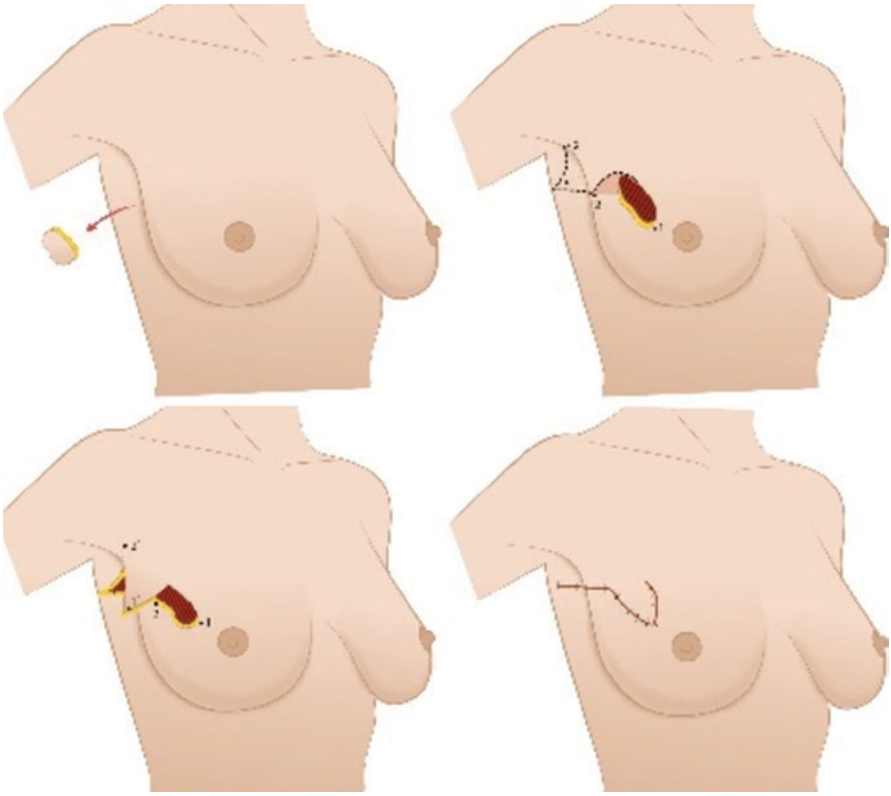
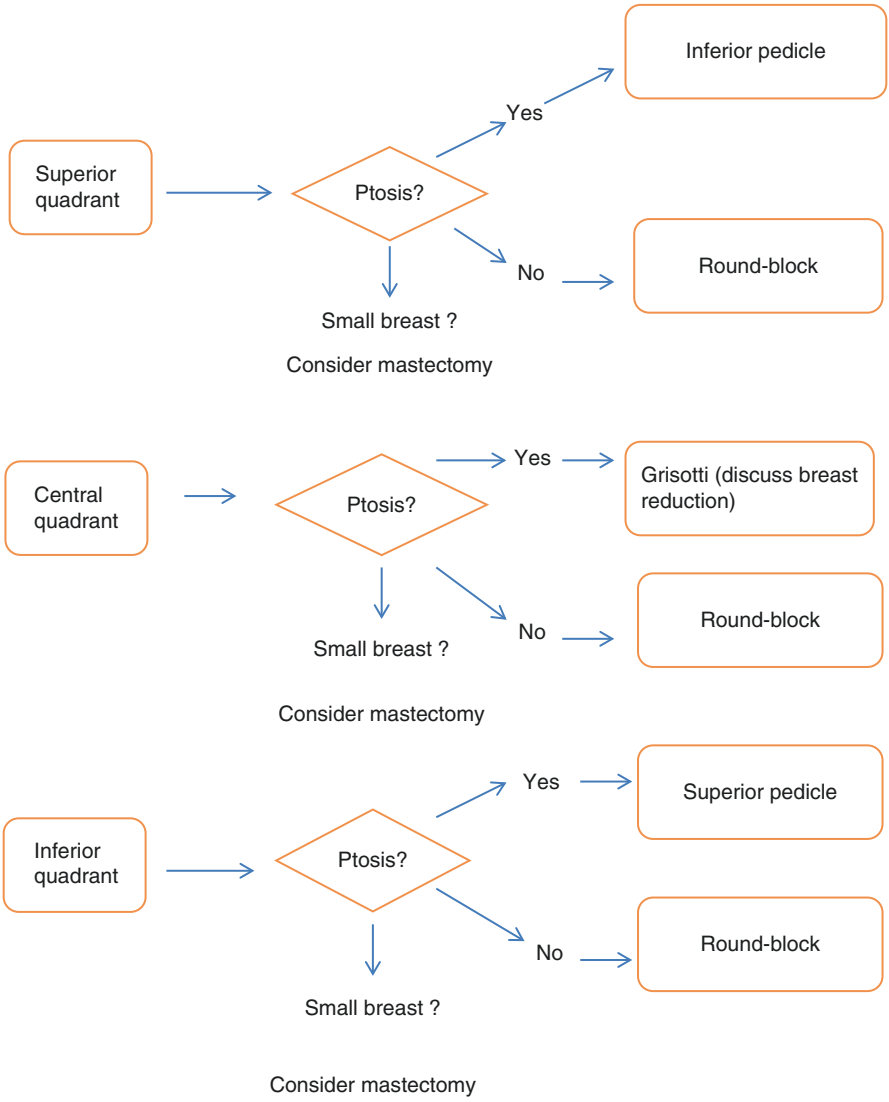


Fig. 7 Fascio-cutaneous flap

Table 1 Indications and relative contraindications of oncoplastic surgery

Indications
Big and ptotic breasts
Notorious mammary ptosis
Mandatory wide skin resection
Small breast committed by the possibility of defect due to mammoplasty
Tumors localized in classical areas of breast reduction
Central tumors, inferior and medial quadrantes tumors
Relative contraindications
Small breasts committed by extensive tumors localized in medial sites
Small breasts not committed by ptosis
Previously radiated breasts
Wide skin resection outside mammoplasty site
Nonstable diabetes and smokers
Disproportional expectations from the patient

Management Flowchart



Flowchart 1 Oncoplastic techniques

Recommended Reading

1. Clough KB, Kaufman GJ, Nos C, Buccimazza I, Sarfati IM. Improving breast cancer surgery: a classification quadrante per quadrant atlas for oncoplastic surgery. Ann Surg Oncol. 2010;17:1375–91. *Literature review on oncoplastic techniques and indication proposals encompassing the proportion of resected mammary tissue and tumor location.*
2. Rainsbury RM. Surgery insight: oncoplastic breast-conserving reconstruction--indications, benefits, choices and outcomes. Nat Clin Pract Oncol. 2007;4:657–64. *Wide literature review regarding oncological principles, repairing concepts and oncoplastic surgical capacitation.*
3. Rainsbury RM, Willet A (Editors). ABS and BAPRAS Oncoplastic breast reconstruction: Guideline for best practice, 2014. *European guideline of oncoplastic surgery.*
4. Urban C, Lima R, Schunemann E, Spautz C, Rabinovich I, Anselmi K. Oncoplastic principles in breast conserving surgery. Breast. 2011;(Suppl 3):S92–5. *Literature review on oncoplastic surgical principles and the main techniques and indications employed*
5. Waljee JF, Hu ES, Ubel PA, et al. Effect of esthetic outcome after breast-conserving surgery on psychosocial functioning and quality of life. J Clin Oncol. 2008;26:3331–7. *Study comparing the asymmetry degree after conservative surgery related to the quality of life in 714 patients from the University of Michigan. Patients with intense asymmetry presented depression symptoms and fear of dying, therefore compromising the quality of life more often than those with discrete or absent asymmetry.*

Breast Reconstruction with Implants

BBSG – Brazilian Breast Study Group

Introduction

The aim of breast reconstruction is to create a new breast that is symmetrical to the contralateral breast, allowing for a reduction of the psychological trauma and the psychosocial consequences related to the mastectomy. There is no ideal technique, but it is expected to be effective, fast-performing, with few complications and revisions, and reproducible in different sociocultural realities. It is within this context that breast reconstruction with prostheses and expanders (RP/E) fits.

If in the 1980s and 1990s most of the reconstructions were performed with myocutaneous flaps, the choice of treatment is different today. Prostheses and expanders are the most used techniques, comprising more than 80% of cases.

The increase in RP/E indications is mainly due to the early diagnosis and refinement of mastectomy techniques (preservation mastectomies), allowing the use of local structures for reconstruction. In addition, the evolution of prostheses and expanders, which present several forms, measures, and models, allow for the adaptation of an individualized model for each type of patient.

Indications

Most patients may be candidates for reconstruction with RP/E, provided that there is integrity of the cutaneous flap of the mastectomy and the pectoralis major muscle, with or without preservation of the nipple and areola complex (NAC). Patients with small breasts and with little ptosis present more favorable results since the skin flap

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completely accommodates the volume of the prosthesis. Women with big and ptotic breasts have less satisfactory results, and skin reduction is often necessary, leading to an increase in the risk of necrosis of the skin and the NAC.

Contraindications

There are some absolute contraindications for RP/E, as the low amount of skin to close the wound on the prosthesis or expander. This condition can occur after mastectomies for advanced tumors, in which a large amount of skin is removed or after previous radiotherapy that has damaged the skin and prevented its use. Another absolute contraindication is the presence of active infection at the time of reconstruction. In these cases, the best thing to do is a primary closure, placement of drains, antibiotic therapy and scheduling of a new reconstruction after at least 3 months.

Other contraindications are relative and will be discussed subsequently (Table 1):

Previous radiotherapy in chest wall: Considered by many authors absolute contraindication, previous radiotherapy increases the chances of prosthesis extrusion, infection, cutaneous necrosis and capsular contracture. Some series present complication rates above 50%, that is, high rates compared to the 10–20% complications after RP/E without radiotherapy. Therefore, it is recommended that the patient who has been previously irradiated (either by prior conservative surgery or neoadjuvant radiotherapy) be clarified about the risks of an RP/E, and about the advantages and risks, in these cases, of a reconstruction with autologous tissue. Disclaimer may be made to patients irradiated in the thoracic region during childhood or adolescence for treatment of Hodgkin's lymphoma. There are few publications that explore this issue, but if skin after mastectomy has good vascularization, an RP/E may be attempted.

Radiotherapy after mastectomy: This is a risk condition for poor outcome, capsular contracture and even loss of the prosthesis. It remains a controversial topic in the literature and it is not always possible to predict whether the patient will be a candidate for radiotherapy at the time of surgery. Some authors consider the need for postmastectomy radiotherapy to be an absolute contraindication for RP/E, as

Table 1 Indications and contraindications of RP/E

Indications	Contraindications
Virtually all patients	Absolute
Best indications	Unsatisfactory amount of skin to heal the scar on implant
Middle sized and small breasts	Relatives
Small ptosis or no ptosis	Previous radiotherapy
Area donating the graft	Need for locorregional radiotherapy
	Collagen disease (scleroderma)
	Smoking/diabetes and obesity
	Absence of pectoralis major muscle

well as for autologous tissue reconstruction. As previously mentioned, the rates of complications between RP/E and radiotherapy are high, regardless of whether pre or post mastectomy radiotherapy was performed. Complication rates range from 18% to over 60%. A 2011 meta-analysis has shown that post-radiotherapy complications are more frequent in the RP/E group (OR = 4.2, 95% CI); however, since there is a lack of level I evidence on this argument, the authors consider RP/E appropriate to be used, but the greater chance of postoperative complication should be clarified to the patient.

In a prospective study with 350 patients submitted to reconstruction with expander followed by replacement with prosthesis, Cordeiro P et al. demonstrated that in spite of a higher rate of capsular contracture (50% vs. 10%) in the final cosmetic evaluation, 80% of these patients were satisfied with the result. In addition, rates of prosthesis extrusion and implant loss were similar in both groups, and at 36 months follow-up only 4% of patients required new surgery. Kuroda F et al., in a series of Brazilian patients, found unfavorable results in immediate reconstruction with prostheses when radiotherapy was present. Therefore, indication of postoperative radiotherapy should not be considered an absolute contraindication for RP/E, provided that local conditions are adequate and there are no other risk factors (obesity, smoking, diabetes); in addition, patients should be risk-oriented as to poor aesthetic results, contracture, loss of prosthesis, and the need for revision.

- Smoking: Despite the difficulty to define the amount of cigarettes that can jeopardize reconstruction, active smokers have a greater chance of cutaneous necrosis of the mastectomy flaps and consequent exposure of the prosthesis. Some studies point out that dropping smoking a few weeks before the procedure can decrease the chances of complications.
- Collagen diseases: Among these, the most problematic one is scleroderma, which causes the skin to have little elasticity, thus preventing adequate expansion and favoring the occurrence of prosthesis extrusion and poor aesthetic result, being considered as a relative contraindication. If in active form, other diseases and syndromes such as SLE are contraindications to PR/E (Table 2).

Table 2 Advantages and disadvantages of RP/E

Advantages	Disadvantages
Fast execution	Mammary asymmetry during expansion
Few complications	Pain and thoracic discomfort
Simple and easy to reproduce technique	Less ptosis
Brief hospital stay	Rounder shape
Good results	Less natural feeling of breast when touched
Mammary skin similar to contralateral skin	Demands contralateral symmetrization procedure in most cases
Few scars	
No deformities in the donating areola (grafts)	

- Obesity: Despite little evidence, obesity can be considered a risk factor for cutaneous necrosis and prosthesis exposure, especially when associated with other previously exposed risk factors.
- Absence of pectoralis major muscle: Whether secondary to radical surgery or to congenital factors, such as Polland syndrome, the absence of the pectoralis major prevents the positioning of the prosthesis or expander in the retro-muscular space. Thus, there is no adequate protection for prosthesis, and the chance of extrusion may increase. Any minor cutaneous necrosis or scar dehiscence will cause exposure of the implant and the need for removal. Some recent series have shown safety in the positioning of the prosthesis in the subcutaneous space, provided that the dermo-cutaneous flap is viable, but this is still a subject that deserves additional studies to prove its safety and results in the long term.

Advantages and Disadvantages

Table 2 scheme shows advantages and disadvantages of RP/E.

Reconstruction Techniques

The surgery consists of dissection of the sub-pectoral space and de-insertion of the muscle of the medial portion (sternum) and also of every groove up to the point of finding the fascia of the rectus abdominis muscle. The pectoral muscle will then overlap the prosthesis. Laterally, the anterior serratus muscle can be dissected to complete the closure of the pocket along with the larger breastplate, forming the complete muscular pocket. For cases in which the mastectomy scar is non-lateral and the cutaneous flap is viable, a partial muscular pocket may be produced despite dislocation of the serratus muscle.

Reconstruction with prosthesis can be performed in one or two stages according to the prosthesis being used:

- One-stage reconstruction with definitive prosthesis: Reconstruction with definitive prosthesis can be performed in most cases, provided that local conditions allow it. The advantage is to accomplish everything in a single surgery. The contralateral breast symmetry can be performed together and is indicated in the majority of patients.
- One-stage reconstruction with definitive expander: Similar to what is described above, the difference of this prosthesis is that it has a predetermined volume of silicone gel and another compartment in which it is possible to inject saline solution to increase the volume gradually and to reach the best symmetry with the contralateral breast. The disadvantages are: the need to carry out a new procedure to remove the expander valve and the risk of deflation of the inflatable part, which leads to replacing the prosthesis.

- Two-stage reconstruction: This reconstruction is done through specific temporary tissue expanders. It is the most used technique and indicated mainly when there is a lack of tissue for the reconstruction with definitive prosthesis, when there is risk of a cutaneous necrosis, when there is desire of the patient to have a larger breast and, when the surgery should be fast. Cordeiro P et al. demonstrated the experience with 350 cases of reconstruction with temporary expander, rapid expansion during chemotherapy and capsulotomy surgery with definitive prosthesis insertion. The results were positive, including in the group that received radiotherapy, with satisfactory aesthetics in 90% of cases in the follow-up.

Complications

Complications of RP/E can be defined as immediate and late. Among the immediate complications, the most frequent ones are hematoma, infection (representing 1–3% of cases), persistent seroma, cutaneous necrosis, and extrusion (3–4%). In cases of extrusion and infection, the implant should be removed, and a new reconstruction is indicated after 3–6 months.

Late complications include deflation of the prosthesis/expander, "rippling" which means small folds of the implant that can be visualized and palpated by the patient, and the capsular contracture, which can occur in up to 50–68% of the cases followed by radiotherapy. The treatment of such complications is surgical, and it may be relapsing.

Table 3 schematically shows the immediate and late complications.

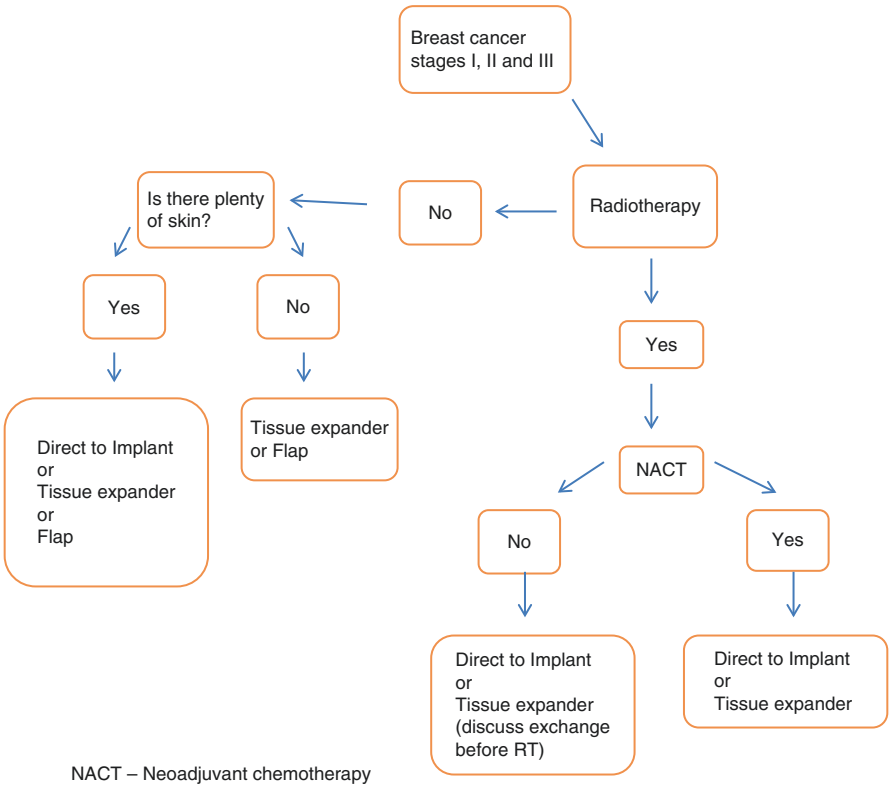
Reconstruction with Implant and Follow-Up

There is no consensus, besides clinical examination, for the follow-up of patients submitted to RP/E. Image exams should be indicated individually on a case-by-case basis, especially in cases of skin sparing and nipple-sparing mastectomies, in which residual glandular tissue should be assessed.

Table 3 Immediate and late complications after reconstruction with breast prosthesis

Complications	
Immediate	Late
Bleeding	Deflation of prosthesis
Infection	Rippling (palpation of implant fold)
Seroma	Capsular contracture
Cutaneous necrosis/ exposition of prosthesis	

Flowchart



Flowchart 1 Immediate reconstruction and implants

Recommended Reading

1. Barry M, Kell MR. Radiotherapy and breast reconstruction: a meta-analysis. Breast Cancer Res Treat. 2011;127(1):15–22. *A meta-analysis with 1,105 patients derived from 11 clinical studies evaluating the action of radiotherapy after breast reconstruction. Patients submitted to radiotherapy after reconstruction with prosthesis present 4 times more complications than non-irradiated patients. Reconstruction with autologous tissue better supports the action of radiotherapy.*
2. Cordeiro PG, McCarthy CM. A single surgeon's 12-year experience with tissue expander/implant breast reconstruction: part II. An analysis of long-term complications, aesthetic outcomes, and patient satisfaction. Plast Reconstr Surg. 2006;118(4):832–9. *Prospective cohort of 410 reconstructions with expander and prosthetic replacement within an evaluation of 1,522 immediate reconstructions from a single institution. The reconstruction with expander / prosthesis is safe and presents good cosmetic results. The indication of radiotherapy should not be considered a contraindication for its accomplishment.*

3. Kuroda F, Urban C, Zucca-Matthes G, de Oliveira VM, Arana GH, Iera M, Rietjens M, et al. Evaluation of aesthetic and quality of life results after immediate breast reconstruction with definitive form-stable anatomical implants. Plast Reconstr Surg. 2016;137(2):278e–86e.
4. Petit JY, Gentilini O, Rotmensz N, Rey P, Rietjens M, Garusi C, Botteri E, De Lorenzi F, Martella S, Bosco R, Khuthaila DK, Luini A. Oncological results of immediate breast reconstruction: long term follow-up of a large series at a single institution. Breast Cancer Res Treat. 2008;112(3):545–9.
5. Urban CA. Aesthetics or symmetry: what's the aim of breast reconstruction? Plastic Reconstr Surg. 2017;139:793e–4e. *Philosophical point of view on the real purpose of breast reconstruction and how it should be approached with patients to prevent exaggerated expectations regarding reconstruction from resulting in frustration.*

Breast Reconstruction with Myocutaneous Flaps

BBSG – Brazilian Breast Study Group

Introduction

Breast reconstruction with myocutaneous flaps constitutes one of the most employed methods in breast repair surgery. They encompass techniques that enable partial or total reconstruction of the breast, being the unique option to correct large defects of the thoracic wall. On the other hand, this type of reconstruction provides great morbidity in the donor area, antagonistically to reconstructions with implants.

The flaps may present pedicle or not; the modality free of vascular connection is solely performed by physicians with formal microsurgery training. The indication of the type of flap relies on the tissue abundance in the donor site, as well as the viability of the vascular pedicle.

It may be performed immediately after mastectomy or not and may often be an option if a first attempt of reconstruction with implants fails.

Regarding vascular pedicle-dependent flaps, the most commonly employed are myocutaneous flap of the transverse rectus abdomen muscle (TRAM) and latissimus dorsi muscles (LD). The most employed free flaps are the abdominals ones, based on the deep inferior epigastric artery and vein (DIEP) and superficial (SIEA), besides the free TRAM flap.

TRAM (*Transverse Rectus Abdominis Myocutaneous*) *Flap*

First described in 1982 by Hartrampf, the main objective of this type of reconstruction is to entirely reconstruct the breast combining skin and subcutaneous cellular tissue. The transverse rectus abdominal muscle is employed to preserve the vascular

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pedicle, which is composed by the upper epigastric artery and vein, maintaining the vascularization of the entire flap.

The flap may solely present one pedicle (mono-pedicle), whenever solely employing one transverse rectus abdominal muscle, or two pedicles (bipedicle), whenever employing both muscles. The criteria to decide whether one or two pedicles will be employed rely on the desired mammary volume (the larger the breast, the higher the flap necessity) and also the presence or absence of comorbidities (such as diabetes, smoking, and previous surgeries); the bipedicle flap is safer regarding the vascularization. On the other hand, the bipedicle flap promotes a greater defect in the donor site and increases the risk of hernias and abdominal wall distortions.

It follows bellow the illustration of the flap vascularization zones recently modified due to microsurgery studies (Fig. 1). Zone I is the most vascularized area and is located on the rectus (pedicle), zone II is lateral to the rectum (second best vascularized), zone III is immediately after the middle abdominal line (representing a poorly irrigated site by the vascular pedicle), and zone IV is the most distal region from the flap. Zone IV presents a decreased vascularization and must not be preserved during the surgical approach. Zone III may not be entirely or partially preserved, and the most vascularized areas are I and II zones.

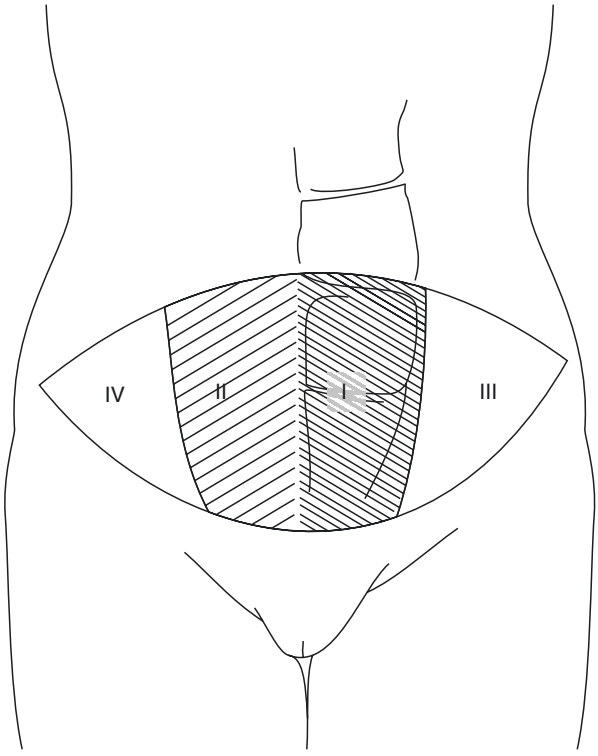

Fig. 1 Modified TRAM vascularization sites classification

Indications and Contraindications

It follows bellow the main TRAM indications and contraindications (Table 1).

Surgical Technique

The surgical drawing must be performed with the patient standing up, tracing a horizontal line just above the navel toward the bilateral iliac crest. Moving on, an additional line must be traced forward the suprapubic region, performing the entire drawing as demonstrated in Fig. 1. Surgery starts by degloving the upper abdominal rectus aponeurosis until the mastectomy-defected area, constructing a tunnel. Furthermore, one of the rectus is chosen to provide the pedicle, or two whenever facing a bipedicle. There is no significant difference between ipsilateral or contralateral mastectomy. The authors' preference favors the ipsilateral pedicle in order to avoid morphological deformations of muscle in the epigastric region. Prior radiotherapy is not a contraindication for ipsilateral flap. Although the caliber of the epigastric vessels is decreased, several studies support that it does not lead to a greater risk of necrosis.

Thus, the aponeurosis is accessed laterally and longitudinally to the muscle, from the substernal region to the Douglas arcade region and medially to the skin flap region (navel), not trespassing this site, and inferiorly to the Douglas arcade to the bottom of the skin flap (so the flap is disposed in the muscle and in the aponeurosis through the perforating vessel pathway). The aponeurosis is transversely accessed in its lower region, and the rectus is then sectioned, further to the ligature of the lower epigastric vessels. Finally, the navel is dispatched from the flap and is mobilized through the tunnel to the defected zone to be treated (Fig. 2). The wall must be primarily sutured whenever facing discrete tension. If tension is intense (most of the time it is present), the aponeurosis must be approximated as much as possible and a

Table 1 TRAM indications and contraindications

Indications	Contraindications
Extensive impairment due to mastectomy	Previous extensive abdominal surgery (angiotomography may be considered to analyze the presence or absence of epigastric vessels lesions)
Impossibility to perform prosthesis reconstruction	Insufficient donor area
Previous radiotherapy	Uncontrolled diabetes, smoking, and morbid obesity
Severe or recurrent prosthetic encapsulation	Previous abdominoplasty
In order to accomplish patient's desire not to use prosthesis and to obtain bulky breasts with natural ptosis	Young patients, who desire to become pregnant or to practice sports

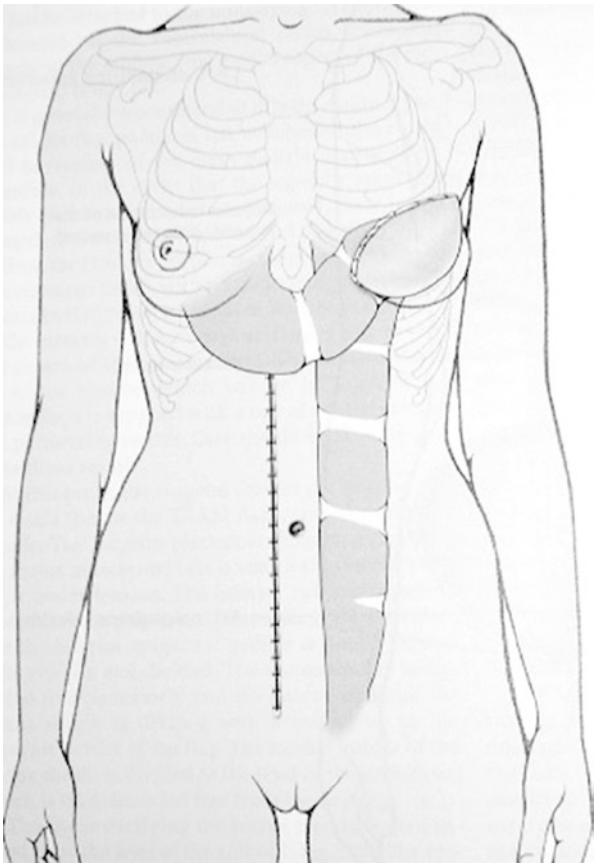

Fig. 2 Mono-pedicle TRAM flap rotation and suturing of the aponeurosis in the defected site

nonabsorbable or semi-absorbable screen must be employed. The skin is further sutured, promoting an incision through where the navel was trapped in the aponeurosis and also sutured. Vacuum draining is advised. Generally, while the abdomen is sutured, another surgical group may model the flap to correct the defect.

Complications

Complications may be related to the donor area or to the flap itself. The most feared flap-related complication is necrosis, in addition to dehiscence and hematoma, which are more frequent. Flap necrosis may be total (very rare in TRAM) or partial. There may be steatonecrosis, which causes partial flap loss over months after surgery, or dense neo-breast impairments. Alderman et al. published a prospective analysis of immediate and late mammary reconstruction of 12 American centers.

There was no significant difference between larger and smaller complications comparing different abdominal flap techniques. The most frequent complication in TRAM was steatonecrosis (14.9%), followed by infection (11.7%). The total loss of the flap solely occurred in 1.1% of the patients.

Regarding the donor site, immediate complications such as wound dehiscence, abdominal wall, and navel necrosis may occur, although rare. Late complications include hernias (ranging from 1% to 12%) and weakening of the abdominal wall with deformities (bulge), present in 7.8% of cases according to Alkerman et al., however ranging from 5% to 15% of cases.

In order to avoid the aforementioned complications, special attention must be provided to suture the abdominal wall. Primary aponeurosis suture may be performed; however, it is recommended to place a nonabsorbable screen, which decreases the incidence of abdominal hernia, which is supported by several studies. The abdominal surgery extent is directly proportional to the complications risk. For instance, complications are rarer in TRAM employing solely one pedicle than the bipedicle procedure, in which two portions of aponeurosis are resected. Reducing the amount of employed aponeurosis improves the primary suture closure. Experienced surgeons may dissect the muscle aponeurosis, solely employing this portion and a pedicle, excepting the area immediately below the flap where the perforates are located (muscle-sparing TRAM). In some cases, a portion of the muscle may be preserved by cutting and solely removing the vascular pedicle area (muscle-sparing TRAM). The aforementioned techniques are more complex to perform and may lead to serious complications to unexperienced surgeons.

The main complication-related factors encompass obesity (morbid or not), smoking, diabetes and arterial hypertension uncontrolled, surgeon's inexperience, advanced age, anemia, and prolonged hypotension in the perioperative.

Autonomization of the Flap

A technique directed to optimize flap perfusion and to decrease the risk of necrosis is to autonomize the procedure. TRAM's autonomization consists on the ligature of the lower epigastric arteries weeks prior to surgery. When the suture is performed, the blood flowing to the flap is reversed. Originally, the dominant vascular territory of the lower abdomen is provided by the inferior epigastric arteries. Sectioning the inferior portion of the muscle during the TRAM surgery promotes an immediate reversion to the upper epigastric arteries. Once established, there is an adaptation time lapse to the venous blood correctly flow back from the retail, which may promote stasis and consequent necrosis. By performing the autonomization a few weeks earlier, the reversal flow is induced as it provides time for the venous system to adapt to the new flow orientation (in addition to the stimulus of neo-angiogenesis caused by ischemia). Thus, the stasis and the necrosis risks are decreased as it is possible to maintain a bulky retail (III and eventually IV zones), employing solely one pedicle.

Several studies support that the autonomization of the retail improved its perfusion, although there is lack of randomized scientific-based data. Therefore, retail autonomization must be considered to high-risk patients indicated to mono-pedicle TRAM as smokers, obese, uncontrolled diabetics, and previous extensive abdominal surgery.

Reconstruction with Latissimus Dorsi Flap

First described in 1896 by Tansini and employed for breast reconstruction in 1912 by D'este, LD flap was long forgotten and began to be progressively employed in the late 1980, when prostheses became more accessible.

It consists on a versatile option and may be employed for almost all patients, excepting those committed by extensive skin defects in the mastectomy site. The disposal of breast prosthesis under the muscle is mandatory most of the times, as it is a thick muscle composed by a little adipose tissue coverture, unable to replace medium and large breast volumes. Features as one of the most secure flaps, with recued risk of major complications such as partial and total necrosis and also promotes a decreased morbidity in the donor area.

Facing breasts that must undergo reconstruction and are considered to be small, the technique may not employ any prosthesis in order to achieve reasonable volume, being classified as an autologous or extended flap, which consists on the complete removal, along with the myocutaneous flap, of the dorsal subcutaneous ipsilateral adipocytic tissue zones (composing of five adipocytic zones). Lipofilling also can be performed in order to increase the volume and not to add prosthesis. This technique is being developed in some Brazilian centers.

Indications and Contraindications

It follows the major indications and contraindications of the reconstruction by the latissimus dorsi flap (Table 2).

Table 2 Indications and contraindications of the reconstruction by the latissimus dorsi flap

Indications	Contraindications
Patients with small or medium breasts	Congenital absence of latissimus dorsi muscle
Other technique contraindications (prosthesis and TRAM)	Previous open chest surgery with muscle sectioning the muscle
Patient's desire	Vascular pedicle lesion
	Major axillary irradiation
	Patient's refusal
	Professional athletes with important superior members performance

Surgical Technique

Facing standing or sitting patients, the drawing of the flap to be removed is performed simultaneously to the definition of the muscle boundaries (superiorly to the inferior portion of the scapula, medially to the paravertebral muscle, inferiorly to the iliac crest and the oblique muscle, and laterally to the middle axillary and the serratus muscle). The flap may be drawn obliquely in order to correctly suture the dorsal skin avoiding any excess (dog ear). The isolated skin portion may be drawn horizontally to the line that the patient wears the bra or bathing suit, so that it does not appear obliquely whenever greater portions of the skin are required.

Surgery may be performed with the patient in lateral decubitus or ventral decubitus depending on the surgeon's experience and to specific requisitions. The skin is incised and the muscle is degloved to its limits. The muscle, as the presenting authors support, must be completely dissected, as it enables to completely cover the prosthesis to be placed in the neo-breast. If the flap is solely employed to close the thoracic wall, the dissection of the entire muscle is not mandatory. Following the posterior dissection, the origin of the vascular and nervous tissue of the large dorsal muscle is accessed and correctly identified, and the muscle tendon may be cut, enabling a greater mobility. It is possible for experienced surgeons to prevent postoperative fasciculations by cutting the muscle nerves (such procedure is optional and not essential).

Following the flap release, a passage tunnel is constructed to the anterior region, disposing the anterior serratus from the skin. The suture is performed in different layers, simultaneously; specific points (Baroudi's stetches) are sutured in the dorsal portion to reduce the risk of seroma. Vacuum draining is mandatory.

Finally, the patient is turned to dorsal decubitus, and the donor area is prepared, placing the prosthesis (mostly) or not and constructing the skin flap to create the neo-breast.

Complications

Complications of this technique are minimum, and the most frequent one is the presence of seroma in the donor site, which may be up to 75% of the cases according to Shin et al. Flap necrosis is very uncommon, and necrosis of the donor area may be more frequent in cases of extended latissimus dorsi, requiring the detachment of larger portions of subcutaneous adipocytic tissue. Late complications encompass most frequently enlargement of the dorsal scar (very common), late seroma, chronic pain, and limitations of arm movement that are easily prevented by performing postoperative physiotherapy.

Reconstruction Employing Free Flaps (Microsurgery)

Free flaps are an option to pedicle flaps; however, they require a well-trained surgical team, in addition to specific hospital structure for retail monitoring in the early

postoperative days. The main advantage of free flaps is minor morbidity of the donor area since the local muscular structures are preserved. On the other hand, the main complication is the necrosis and complete impairment of the flap due to thrombosis of the anastomosis. The main free flaps are listed below:

- Free TRAM: Similar to traditional TRAM, however solely sectioning a reduced portion of the rectus abdominal muscle in order to obtain the inferior profound epigastric artery. It is an obsolete technique, progressively replaced by DIEAP or SIEAP.
- DIEP (deep inferior epigastric perforator) or DIEAP (deep inferior epigastric artery perforator): Cutaneous transverse abdominal flap based on the inferior profound epigastric artery. Currently represents the most employed microsurgical flap in breast reconstruction. It consists on an evolution since free TRAM.
- SIEA (superficial inferior epigastric artery perforator): Cutaneous transverse flap based on the inferior superficial epigastric artery. Constitutes an alternative to DIEAP, however encompasses a greater surgical complexity. It may be considered as a natural evolution of DIEAP.
- SGAP (superior gluteal artery perforator): Cutaneous gluteus flap, based on the superior gluteus artery. Hardly employed due to local inexperience.
- TUG (transverse upper gracilis flap): Gracilis muscle free flap. Employed preferentially to small breasts reconstructions.

Recommended Readings

1. Clugston PA, Gingrass MK, Azurin D, Fisher J, Maxwell GP. Ipsilateral pedicled TRAM flaps: the safer alternative? Plas Reconstr Surg. 2000;105(1):77–82. *Retrospective cohort that evaluated the complications of ipsilateral and contralateral mono-pedicle TRAM, supporting that despite the commonly believed, the ipsilateral mono-pedicle is not related to a greater risk of complications.*
2. Granzow JW, Levine JL, Chiu ES, Allen RJ. Breast reconstruction using perforator flaps. J Surg Oncol. 2006;94(6):441–54. *Review encompassing all breast reconstruction techniques employing micro-surgical flaps, describing indications, contraindications and results.*
3. Hartrampf C, Scheflan M, Black PW. Breast reconstruction with a transverse abdominal island flap. Plast Reconstr Surg. 1982;69:216–25. *Traditional and classic study describing TRAM's technique.*
4. Nahabedian MY, Patel K. Autologous flap breast reconstruction: surgical algorithm and patient selection. J Surg Oncol. 2016;113(8):865–74. https://doi.org/10.1002/jso.24208. Epub 2016 Feb 26. *Review encompassing all breast reconstruction surgical techniques, employing myocutaneous flaps.*
5. Tregaskiss A. Perfusion zones of the DIEP flap revisited: a clinical study. Plast Reconstr Surg. 2006;118(3):816. *Describes the perfusion zones do define the inferior abdominal donor site to grant TRAM's best effectivity.*

Autologous Fat Grafting in the Breast: Lipofilling

BBSG – Brazilian Breast Study Group

Introduction

The use of autologous fat for correction of body contour defects is not new. The first descriptions date from the end of the nineteenth century, and in the twentieth century this procedure became widely used, mainly in surgical procedures of the hands and the face. The use of this technique in the breast began to be considered in the 1980s, stimulated by the advent of liposuction for aesthetic purposes.

As this procedure became popular, several surgeons began to use the aspirated fat as material for correction of body contour defects. However, the cosmetic results were considered unsatisfactory due to the high rate of reabsorption of the injected fat. In addition, mammographic screenings were initiated at that time, and changes in mammography examinations caused by lipofilling might hide neoplastic lesions or cause suspicious lesions, thus confusing the examiner. As a consequence, for more than a decade the mammary lipofilling was abandoned.

It was in the mid-1990s that breast lipofilling began to be used again, supported by clinical studies that proved the efficacy of the method. The main factor which contributed to this achievement was the American surgeon Sidney Coleman, who systematized the entire technique from obtaining the material, preparing fat grafting, and transforming this into a clinical study. In addition, in this context mammary radiology had already developed well enough to be able to safely differentiate breast lesions suspected of being benign. Therefore, since then, lipofilling has been used in the breast and is currently the subject of numerous studies and publications.

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Autologous Fat Grafting

Autologous fat grafting is nothing more than the transfer of mature adipocytes and adipocyte-derived stem cells (ADSCs) to the defective breast region. These ADSCs have the ability to stimulate local neoangiogenesis and stimulate fibroblasts locally, allowing these mature adipocytes to survive and integrate into the graft-receiving mammary environment.

The autologous graft is considered the ideal filling material for some reasons: it is autologous (it has no cross-reaction); it is easily obtained; it is abundant in most people; it is easily removed; and it has softened consistency, a pattern that is expected for the contour of the human body.

The main disadvantage of lipofilling is the impossibility of predicting how much fat will be reabsorbed, often requiring more than one procedure to obtain the expected result. In addition, data on the safety of the use of fat cells and fat stem cells in patients with a high risk or history of breast cancer are lacking.

Surgical Technique

The most widely used technique in the large published studies is the Coleman technique, with some variations from service to service. Here is a summary of the step-by-step technique:

Collection

Fat is collected by low-pressure liposuction (syringes of 10–60 ml are used) coupled to a blunt cannula of 3–5 mm. Before liposuction, a solution containing Ringer's lactate (500 ml) and 1 ampoule of adrenaline (Klein's solution) can be injected into the donor area to reduce bleeding and improve the material's recovery.

The basic principle of liposuction is that it is atraumatic, avoiding injury of the adipocytes and, therefore, improving the survival of the graft. The ideal cannula is one that combines an efficient collection of fat with minimal disruption of the neurovascular structures of the donor area. Also, it is important not to exaggerate pressure with the plunger of the syringe, so that this negative pressure does not break the adipocytes.

Fat Preparation

Fat should be separated from the blood, the infiltrated solution, and the cellular debris with minimal trauma. Centrifugation of liposuction is the method that offers the greatest benefits. This separates fat from blood and substances that promote cellular degradation like proteases and lipases. It has been shown in a recent study that

concentrated adipocytes, transferred from centrifugation, result in a greater number of adipocytes per milliliter of transferred fat than when it is not centrifuged. Thus, it is also possible to increase the ADSC concentration, which may reach 5% of the total aspirated cells. Centrifugation is performed for 3 minutes at a speed of 3000 RPM.

The result in the syringe after centrifugation can be divided into three distinct strata: a high layer, consisting of oil; an intermediate layer containing adipose tissue (to be grafted) and the remnants of connective tissue; and a bottom liquid layer with infiltration solution contents, along with blood debris. Figure 1 shows the material aspirated and Fig. 2 shows the material after centrifugation.

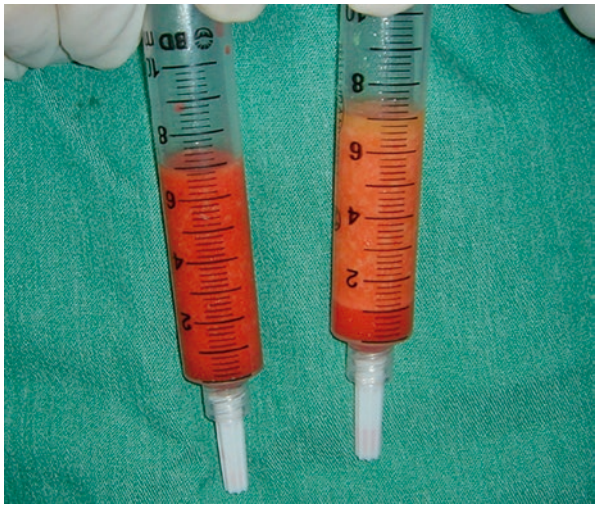

Fig. 1 Liposuction prior to centrifugation

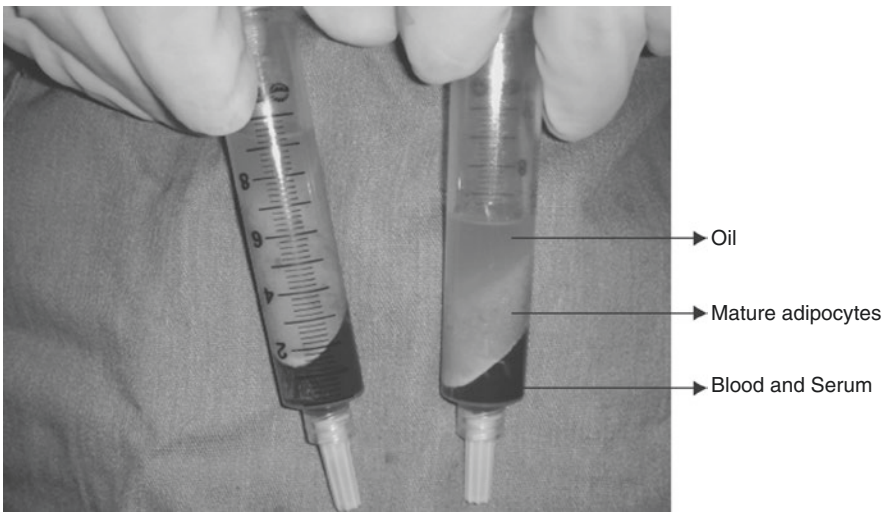

Fig. 2 Liposuction after centrifugation showing the three phases: oil, mature adipocytes and ADSC, and blood and serum

Grafting

Injection of the centrifuged material is performed with 17 and 18G cannulas during removal of the cannula after it has been inserted into the receiving area. This procedure should be done in several directions to achieve even fat distribution. Prerequisite for adequate integration of adipose tissue, implanted in the recipient area, is that the procedure be performed in small quantities and with a small gauge syringe. The syringe used must be able to avoid excessive pressure at the time of infiltration, thus avoiding the lysis of the adipocyte when passing through the syringe.

The infiltration is performed slowly and in small amounts, preventing formation of fat lakes, which can lead to asymmetries or poor local blood perfusion. The adipose tissue is injected until slight overcorrection of the defect occurs. After grafting, this area is massaged for a better distribution of the graft. The amount of fat injected varies among different publications. Most authors agree that graft diameter, unlike injected volume, has a greater impact on graft survival. This depends on the diffusion of nutrients coming from the neighboring capillaries, and therefore, little amount of graft can maximize its own survival.

Lipofilling and Breast Surgery

The main indications for lipofilling are the following:

- Correction of filling defects after breast reconstruction with implants or flaps.
- Correction of contour deformities after autologous flap reconstruction (TRAM/LD).
- Improvement of skin and subcutaneous quality after mastectomy and radiotherapy.
- Correction of filling defects after conservative breast surgery.
- Improvement of rippling feeling after reconstruction with implants or after augmentation mammoplasty.
- Treatment of capsular contracture after reconstruction with implants.
- Breast augmentation without the use of halogen implants.
- Improvement of the quality of the scar in the breast.
- It may be considered as an option in total breast reconstruction.

Complications

Fat grafting involves few perioperative and postoperative complications. The main complication is fatty necrosis and cellulitis, which can be easily treated on an outpatient basis with anti-inflammatories and antibiotics and in a few cases also through surgical drainage. Usually this condition is self-limited and is resolved in 2 weeks.

These complications amount to 3% (Rietjens et al. 2010). Theoretically there is a risk of fatty embolism, but no report of this event has been found in a lipofilling procedure. The most serious complication reported is a case of sepsis in a patient submitted to augmentation mammoplasty with autologous fat graft, but the case was resolved with drainage and surgical removal of the graft and antibiotic therapy.

Lipofilling, Mammography, and Breast Cancer

The interaction between mature adipocytes, ADSC and the normal mammary cell, as well as the carcinogen cell is still unclear. Thus, we can divide the oncology safety of the lipofilling in relation to the radiological alteration produced by it in relation to the association with new tumors or relapses of cancer.

Lipofilling and Breast Imaging

When the graft of fat does not survive, it suffers necrosis, causing pathognomonic mammary images such as oily cysts and gross calcifications. At the outset of this technique, it was thought that such changes could hide mammographic lesions and delay the diagnosis of an initial cancer or that such images could mimic an early cancer, thus generating unnecessary breast biopsies in addition to causing emotional damage to the patients.

Currently, we know that any procedure (thick needle biopsy, reduction mammoplasty and augmentation, oncologic surgery) can cause breast changes. The same happens with lipofilling. Recently, a meta-analysis published by Claro FJ et al. showed that radiological images are present in 13–82% of the cases of lipofilling. In another prospective, multicenter study comparing radiological findings from lipofilling with those of reduction mammoplasty, Rubin et al. found no significant difference between the two groups in relation to suspected findings or the number of biopsies performed. In this way, lipofilling causes radiological alterations in most patients, but these findings are not different from those caused by the other modalities of mammary surgery.

Lipofilling and Breast Cancer

ADSCs are stem cells capable of stimulating local neoangiogenesis, in addition to causing the migration of local fibroblasts, releasing growth factors such as VEGF, IGF, and others. In addition, mature cells promote the production of hormones such as leptin and enzymes such as aromatase that may be in some way related to carcinogenesis. Studies in animal and in vitro models demonstrate an association between

ADSC lipofilling and both local and distance tumor cell growth. In a recent systematic review of 28 experimental studies (in vitro and in vivo), Schweizer et al. demonstrated that there is a positive association between ADSC and cancer. The major criticism of these studies is that they use immunosuppressed animal models and very high tumor burden, which is not consistent with the reality of clinical cases.

Clearly, there is a gap between laboratory findings and those found in humans. To date, the overwhelming majority of studies have failed to demonstrate an association between this procedure and local recurrence or the onset of a new tumor. In 2012 Peti et al. presented a study comparing patients with a personal history of breast cancer submitted to lipofilling with patients with the same characteristics but without lipofilling treated at the European Institute of Oncology (Milan IT). In this analysis, recurrences were greater and significant in the lipofilling group, especially in patients with ductal carcinoma in situ, younger age, and more aggressive tumors.

However, despite being a level III evidence study (most of the lipofilling studies are level IV and V evidence), there are several biases for being a retrospective study. Subsequently, in 2015, these data were revisited, and such difference was disregarded.

Recently, a systematic review of Waked et al. [5], with more than 100 articles reviewed and 18 selected articles on oncology safety in clinical studies did not demonstrate an increase in local recurrence or new tumors associated with lipofilling, thus pointing to greater safety for the application of the method, although there is still the need for some more randomized and prospective studies.

Final Considerations

Autologous fat grafting is a great alternative in the correction of normal breast defects and especially in the sequelae of the multimodal treatment of breast cancer. The procedure standardized by Coleman is simple, easily reproducible, and generates few perioperative and postoperative complications. The results are good from the aesthetic point of view, and the mammographic changes caused by it are similar to those found in other procedures. However, it is still necessary to better understand the role of such procedure in patients with a history of breast cancer, to establish the real interaction between lipofilling and local recurrence. It is recommended that patients be evaluated preoperatively and followed up rigorously over the years with clinical and imaging examination.

Recommended Readings

1. Coleman SR. Structural fat grafting: more than a permanent filler. Plast Reconstr Surg. 2006;118(3 Suppl):108S–20S. *A classic Coleman article in which the technique is reviewed and long-term breast lipoxygenase data are presented, with emphasis on the efficacy of the method in healthy breasts.*

2. Gutowski KA. ASPS fat graft task force. Current applications and safety of autologous fat grafts: a report of the ASPS fat graft task force. Plast Reconstr Surg. 2009;124(1):272–80. *Review article of the American Society of Plastic Surgery regarding the applicability of lipofilling in the breast. It deals with different techniques, effectiveness and safety evidence. The ASPS authorizes the accomplishment of lipofilling provided that informed consent is made. In patients at high risk for breast cancer or with a history of breast cancer, although there is no negative evidence, it suggests that this type of patient be conducted within clinical studies.*
3. Lohsiriwat V, Curigliano G, Rietjens M, Goldhirsch A, Petit JY. Autologous fat transplantation in patients with breast cancer: "silencing" or "fueling" cancer recurrence? Breast. 2011;20(4):351–7. *Review article on basic research on the interaction between adipocytes, ADSC, normal cells and tumor mammary cells. There are factors that associate ADSC with the stimulation of tumor cells and others that would provoke inhibition effects. Interaction in humans should be investigated.*
4. Schweizer R, Tsuji W, Gorantla VS, Marra KG, Rubin JP, Plock JA. The role of adipose-derived stem cells in breast cancer progression and metastasis. Stem Cells Int. 2015. Epub 2015 Apr 27. S*ystematic review of 28 in vitro experimental studies and animal models evaluating the interaction between ADSC and cancer cells. All studies demonstrate accelerated growth of tumor cells, as well as faster growth of induced breast tumors in the models and metastasization.*
5. Waked K, Colle J, Doornaert M, Cocquyt V, Blondeel P. Systematic review: the oncological safety of adipose fat transfer after breast cancer surgery. Breast. 2017;31:128–36. *Systematic review of more than 100 articles, 18 prospective clinical studies and cohorts of patients with a history of breast cancer undergoing lipofilling were selected. There was no increase in recurrences in the lipofilling group. Despite the encouraging result, there are no prospective randomized studies. Avoid lipofilling in patients at high risk for local recurrence must be considered.*

Aesthetic Breast Surgery

Mónica Adriana Rodriguéz Martinéz, An Wan Ching, and Antônio Luiz Frasson

Introduction

The characteristics and appearance of the ideal breast are subjective in many aspects and vary between different societies and cultures. Size, position, contour, symmetry, and proportionality of both the breast shape and the nipple and areola complex (NAC) are important elements in the aesthetic evaluation. However, in addition to the visual impact, sensitivity, mobility, and texture must also be preserved. Breast aesthetic surgery seeks to improve the characteristics of the breast, trying to associate the ideal appearance with the satisfaction of the patient. Despite being considered by some as a surgery of the ends (in terms of satisfiyng the patients and medical-claims), reductive mammoplasty, mastopexy and augmentation mammoplasty present several limitations related to the different techniques, to the patient's individuality, patient's expectations and to the material used. Knowing how these elements interrelate can help improve the end result and also reduce the risk of complications. Thus, this chapter brings information on review of the main techniques of breast aesthetic surgery in relation to their indications, planning, surgical technique, complications, and limits.

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Ideal Breast Appearance

The ideal location of the breast is the anterolateral wall of the thorax, the largest volume being placed on the lower hemisphere. The contour lines should converge smoothly over the NAC, considered the maximum point of projection of the breast. The lower hemisphere should have a complete convexity, extending from the lower edge of the areola to the inframammary groove, at a distance of approximately 5–6 cm. The upper pole should have less volume and a single subtle convexity on the slope under the lateral view, with a distance of approximately 19–21 cm, measured from the sternal furcula to the nipple. A discrete ptosis is natural and desirable (Fig. 1).

Preoperative Aesthetic Evaluation

The patient should be standing. It is necessary to evaluate her biotype, height, weight and chest measurement. Examination should be made of the skin, considering color, texture, elasticity, presence of stretch marks, previous scars (mainly keloids or hypertrophic in the breasts or other parts of the body). Inspection of the degree of sagging is performed through the level of the papilla relative to the inframammary fold. It is also important to estimate breast volume, both visually and by palpation. Check the excess of parenchyma through the manual clamping maneuver, also evaluating the degree of elevation required of the NAC. Also, look for other breast deformities, such as the inverted papilla, the shape that may impact the final result. With the patient lying down, the breast parenchyma is palpated and the papillary discharge is evaluated.

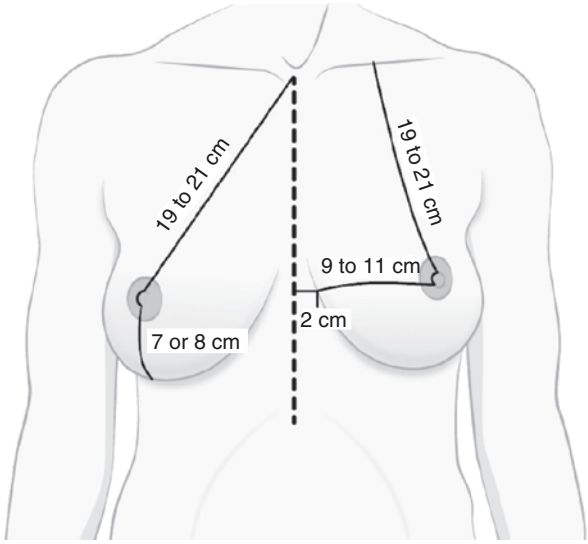

Fig. 1 Ideal breast appearance and anatomical relationships

When talking with the patient, it is important to determine her expectations regarding the volume of the breasts. A lucid, objective approach should be made and the patient needs to suggest what is best for her self-image. Risk factors for poor outcome and complications such as smoking, obesity, diabetes, collagen diseases, liver disease, as well as other comorbidities should be considered before surgery is indicated. As it is an elective procedure, it is ideal that underlying chronic diseases be controlled and that smoking should be stopped at least 4 weeks before surgery.

Reduction Mammoplasty and Mastopexy

Breast reduction and mastopexy are two different procedures, but they have many common points in relation to the techniques used. Both result in elevation of NAC and reduction of the cutaneous envelope of the breast. While recognizing some similarities between the two, the central focus of reductive mammoplasty is volume, and that of mastopexy is shape. In this sense then, the aesthetic requirement in mastopexy is in general higher than in the mammary reduction. Achieving a harmonious, symmetrical, stable, and minimal scarring is a challenge for every surgeon, as evidenced by the multiplicity of surgical techniques, with different accesses such as: inframammary and peri-areolar fold access; peri-areolar, vertical and horizontal (inverted T); peri-areolar and vertical; peri-areolar, vertical and lateral (L) horizontal; and isolated peri-areolar. Another factor that is also a technical challenge is to overcome the action of gravity on the weight of the mammary parenchyma, which causes a displacement of this cone to the lower pole, making it protrude and the upper pole, empty.

Following the skin-gland binomial, the vascular supply of the NAC, preservation of nipple sensitivity, preservation of the shape and function and the final quality of the scar, general indications for the techniques most used in practice are:

- Reduction mammoplasty using Pitanguy's classical technique: it is indicated for large hypertrophies, but it has a higher risk for loss of NAC when above 500 g and displacement of the same over 14 cm (Fig. 2);
- Reduction mammoplasty using Pitanguy's rhomboid technique: indicated for mild and moderate hypertrophies and for mammary ptosis;
- Reduction mammoplasty using Lyacir Ribeiro's pedicle flap: it can be used in large breast reductions and mastopexy, in inverted "T", vertical and periareolar techniques. It presents lower risk of loss of NAC than the inferior pedicle technique (Fig. 3);
- Reduction mammoplasty using Peixoto's technique: indicated for large, medium and small hypertrophies;
- Reduction mammoplasty using Jurado's technique: it uses an inferior pedicle, including the NAC. It is indicated for major ptosis;
- Free NAC transplant technique by Thorek: it has been used up to the present day, but unfavorable aesthetic results and changes in the sensitivity of the NAC cause it to be a rather infrequent indication;

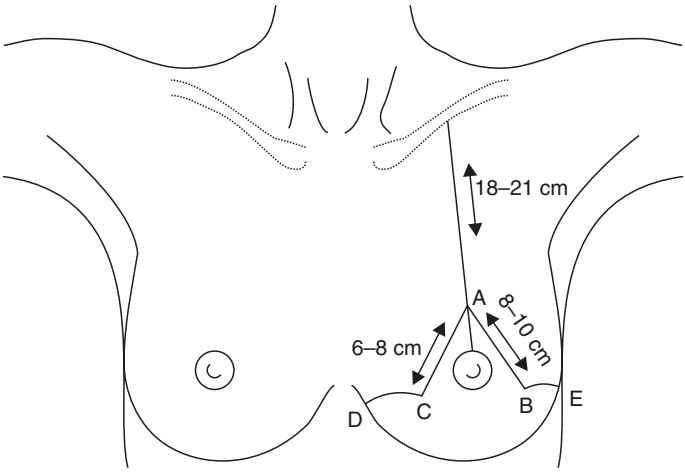

Fig. 2 Pitanguy's classical marking

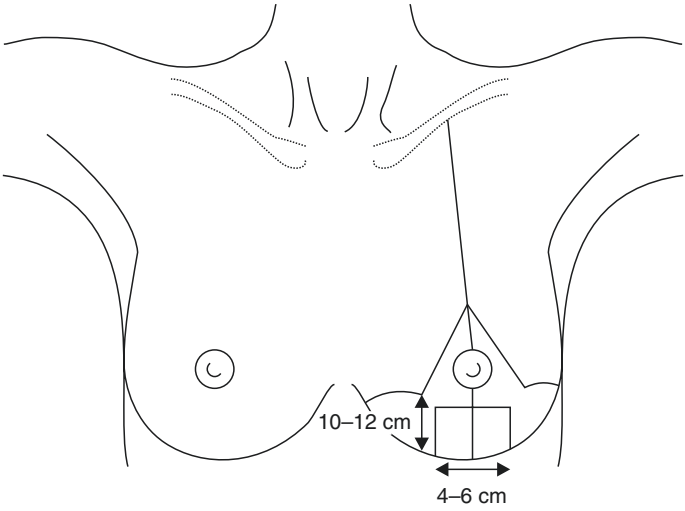

Fig. 3 Liacyr Ribeiro's marking of pedicle n. 1

- Reduction mammoplasty or round-block mastopexy as described by Benelli: this technique indicated in patients with hypertrophy and moderate ptosis or hypertrophy at young age, with firmer skin quality and breast tissue. It is contraindicated in cases of liposubstituted breasts or with a lot of extra skin. A periareolar mastopexy with dermal cerclage of the areola is performed by suturing a tobacco pouch in order to prevent the increase of volume of the areola and the scar in the postoperative period. This technique reduced the length of the horizontal scar, going from an inverted "T" technique to a vertical technique.

The main complications associated with mastopexy and reductive mammoplasty are the following: apparent scar, breast asymmetry, NAC necrosis (<2%), loss of NAC sensitivity and difficulties or even impossibility of breastfeeding.

Breast Augmentation Using Implants

Breast augmentation has become the most popular cosmetic surgery procedure, surpassing liposuction. Since the introduction of the first silicone implants in 1962, several modifications in the design, texturing, and gel cohesiveness have occurred over several generations. Thus, the implants may have a smooth or textured covering, whether coated or not with polyurethane; whether round or anatomical; filled with silicone gel, saline solution or both. The choice between the anatomical or the round prosthesis depends on the desire to project the lower pole of the breast and on the surgeon's experience. With the anatomical prosthesis, this projection occurs in a more accentuated way. The crisis involving prostheses by the French brand PIP in 2012 put on alert the professionals and the patients for a better quality control of the implants.

The main factor in choosing the ideal location is the adequate coverage of soft tissue tissues. Options can be as follows:

- Subglandular: it is more anatomical, less traumatic, faster, demanding shorter postoperative time, and with less pain and discomfort. There is interference in mammography;
- Subfascial: it presents retro-muscular advantages as to the upper pole;
- Submuscular: patients who are rather thin and with poor breast tissue, also with a higher but more natural pole and more prolonged postoperative may have more pain and discomfort, but with the advantage of this technique is less interference in imaging tests;
- Double plane: used in cases of ptosis or tuberous breast, using the pectoral muscle to the upper pole and mammary gland to the lower pole;

Possible surgical approach incisions:

- Inframmary fold: it allows direct access and greater visibility of the planes. It should be about 4 cm long, parallel to the groove;
- Infra-areolar: marginal to the areola between 9 and 3 hours, it is a better alternative when the areola is more than 3 cm in diameter and when there is doubt about the need for mastopexy;
- Axillary: it is performed on the second fold of the axilla. It is about 4 cm long, in an "S" shape. It is used when patients do not want to find traces of breast surgery;
- Transpapillae: it is seldom used for being more traumatic than the other techniques.

Single-use intraoperative sizers can be applied to define prosthesis size. Mammary pocket can be irrigated with an antibiotic solution (Cefazolin or Gentamicin). There is no need for prophylactic changes of the implants, but it is known that the risk of rupture after 10 years can be between 2% and 15%. Thus, it is recommended to evaluate the integrity of the implants every 3–5 years with magnetic resonance, which is the most sensitive examination. In the case of ruptures still detected in the intracapsular phase, the surgery is less traumatic and shorter. There is no systemic health impact with the use of silicone prostheses, even with rupture and extravasation to adjacent tissues.

Recommended Reading

1. Benelli L. A new periareolar mammaplasty: the "round block" technique. Aesthet Plast Surg. 1990;14(2):93–100. *A classical article in which Benelli's round-block technique is described.*
2. Lipworth L, Tarone RE, Ye W, Olsen JH, Nyren O, McLaughlin JK. Int J Cancer. 2009;124:490–3. *A review of the results of 2 important Scandinavian cohort studies with 3,486 and 2,736 patients respectively, who underwent breast augmentation between 1965 and 1963. There was no evidence of association between breast cancer and cancer risk of any type.*
3. Pitanguy I. Evaluation of contouring surgery today: a 30-year perspective. Plast Reconstruct Surg. 2000;105:1499. *A retrospective of 30 years' the main techniques of body contour developed by Pitanguy; among them, reduction mammoplasty.*
4. Puskas JE, Luebbers MT. Breast implants: the good, the bad and the ugly. Can nanotechnology improve implants? WIREs Nanobiotechnol. 2011; https://doi.org/10.1002/wnan.164. *A review article on the physical-chemical characteristics of mammary implants.*
5. Singh KA, Losken A. Additional benefits of reduction mammaplasty: a systematic review of the literature. Plast Reconstr Surg. 2012;129:562–70. *Systematic review of the literature showing other functional, psychological and quality-of-life benefits with reductive mammoplasty.*

Early Breast Cancer

BBSG – Brazilian Breast Study Group

Introduction and Definition

The increase in the number of women undergoing mammography translates in a rise in the diagnosis in the early stages. It is estimated that in 2020, 25% of the breast tumors diagnosed in Brazil will be smaller than 2 cm. Breast cancer is divided into three groups, which will guide behaviors and prognosis: early, locally advanced, and metastatic breast cancer. According to the American Joint Committee on Cancer (AJCC), locally advanced carcinoma comprises stages IIIA, IIIB, and IIIC, i.e., tumors with extensive lymph node involvement (N2 and N3) or chest wall invasion (T4a), skin (T4b), or both.

Based on this classification, the early breast carcinoma would cover stages IA (T1N0), IIA (T0N1, T1N1, T2N0), IIB (T2N1, T3N0), and T3N1. Metastatic tumors are classified as stage IV (M1).

However, in this chapter, initial carcinomas will refer to those cases that can be approached through conservative breast and axillary surgery.

Clinical Condition

When taking care of a patient who has experienced radiological alteration or who presents reports complaints about her breast, a directed anamnesis is mandatory, highlighting personal and family risk factors for breast cancer.

The lack of risk factors in the anamnesis does not invalidate the importance of the finding. Especially in the lesions detected by the patient, so the complaint should be further analyzed.

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The time of onset of the lesion, associated skin changes, changes in size and the relation to the menstrual cycle should be investigated.

In the physical examination, the suspected changes of neoplasia should be outlined, for instance, retractions, bulging, skin ulcerations, skin and chest wall invasion, skin edema, suspicious papillary effusion, and nodule or thickening with hardened, fixed consistency and irregular edges.

Propedeutics

The diagnosis is based on the clinical, radiological, and pathological examinations. The clinical examination has already been mentioned above.

The radiological examination consists of exclusive bilateral mammography in patients with liposubstituted breasts. In young patients, digital mammography is more sensitive, with breast ultrasonography being complementary in these cases, or when mammography is normal, even with clinical alteration. Breast tomosynthesis presents an evolution in relation to digital mammography. In young women with dense breasts, several studies have demonstrated superior accuracy to digital mammography, with better distinction of focal asymmetries and lower recall rates.

Magnetic Resonance Imaging (MRI) is not a routine procedure and should be reserved for exceptional situations. There is no specific group with indications of this examination and the indication must be observed individually.

The pathological examination should preferably be obtained by core needle biopsy (CNB), whenever possible directed by ultrasonography. Another alternative in solid nodules is fine-needle aspiration (FNAC), but this method requires a team specialized in cytology tests; besides not differentiating between invasive and intraductal lesions, FNAC allows for immunocytochemical evaluation.

Preoperative assessment of patients should include: complete blood count, platelet count and coagulation tests. Systemic screening exams are not indicated in asymptomatic patients and should be reserved for cases with abnormal blood tests. If the patient has any signs or symptoms, a systemic investigation may be required.

Pathology evaluation should include type and histologic grade, hormone receptor determination, HER2 status and Ki-67 status.

The predictive value of Ki-67 has not yet been definitively confirmed in women with early and hormone-responsive breast cancer, although the results of the BIG1-98 study suggest a positive predictive value for patients receiving Letrozole. In addition, the use of ki-67 in the prediction of adjuvant chemotherapy in patients with hormone-responsive disease is still controversial. According to the ASCO (American Society of Clinical Oncology) 2017 Guideline for decisions on adjuvant treatment, this should not be a parameter used in the indication of adjuvant chemotherapy.

Table 1 Stratification of risk recurrence according to ESMO

Risk	Axilla	Tumor characteristics	Recurrence on 10 years (%)
Low	Negative	Tumor smaller than 2.0 cm Grade 1 Absent vascular inv. ER and/or PgR positive HER2 negative 35-year-old or above (all present)	<10
Intermediate	Negative	Tumor larger than 2.0 cm Grade 2–3 Extensive vasc. inv. ER and PgR negative HER2 positive Below 35-year-old (at least one present)	10–50
	Positive	1 to 3 positive lymph. ER and PgR positive HER2 negative (all present)	10–50
High	Positive	1 to 3 positive lymph. associated with ER and PgR negative or HER2 positive	>50
	Positive	4 or more positive lymph.	>50

In practice, the guidelines of the ESMO (European Society of Clinical Oncology) can be used as indicators of chemotherapy treatment, in the unavailability of performing genomic signatures, and a stratification of the risk of relapse among patients with initial breast carcinoma based on age, tumor size, histopathological grade, vascular invasion, axillary lymph node involvement, hormone receptor, and HER2 status (Table 1).

Treatment

Surgical Treatment

Breast-conserving surgery (BCS) is preconized for patients that do not present contraindication (Table 2).

When mastectomy is performed, breast reconstruction should be offered. Oncoplastic techniques or neoadjuvant therapy can be performed in those patients with larger tumors that do not present another contraindication, which can allow increasing the chances of preservation.

Table 2 Contraindications of conservative breast surgery

Absolute contraindications	Relative contraindications
Extensive and diffuse microcalcifications	Pregnancy
No possibility of free margins	Multicentric tumors
Too large lesions in relation to breast volume	Tumors >5,0 cm
Previous thoracic radiotherapy	Vascular diseases of collagen in activity (except rheumatoid arthritis)
Patient's desire	

Sentinel lymph node biopsy (SLNB) is the surgery of choice in patients with negative axilla. In those with palpable axilla, but not decidedly positive, a biopsy of the lymph node can be performed. If the test is negative, the sentinel lymph node biopsy is suggested, along with resection of suspected lymph nodes on palpation. In cases of positive FNAC, consider neoadjuvant therapy, especially in patients with triple-negative or Her2 3+ tumors, where the greater possibility of complete pathological response favors the performance of SLB and decreases the need for axillary lymphadenectomy (see chapter on "Axillary Surgery and Other Regional Lymph Nodes").

In recent years, after the publication of the ACOSOG Z11, IBCSG 2301, and Amaros's studies, the maintenance of axillary lymph nodes (LN) in the axilla with minimal involvement (up to 2 positive LN in Z11 and <3 LN in Amaros) showed no benefit of routine axillary dissection in terms of overall and disease-free survival. However, there was a higher incidence of complications, especially lymphedema in the group treated with axillary dissection. Thus, the National Comprehensive Cancer Network (NCCN) recommends the application of these protocols for patients who are in the recommended profiles (see chapter on "Axillary Surgery and Other Regional Lymph Nodes").

In addition, other authors suggest that the axilla should not be approached in situations the risk of lymph node involvement is lower than 5% (invasive carcinoma: pT1a; special subtype: pT1a and pT1b).

Radiotherapy

Adjuvant radiotherapy is part of the Breast cancer conservative treatment and its performance is strongly recommended.

The NCCN guideline of 2017, based on a randomized study (category 1 indication), makes an exception for patients who are 70 years old or above, with pT1N0

and positive hormone receptors undergoing conservative surgery. In these cases, radiation therapy can be avoided when using tamoxifen.

When adjuvant chemotherapy is indicated, radiation therapy is usually performed after completion of chemotherapy. In the Lancet publication (2011), The Early Breast Cancer Trials' Collaborative Group (EBCTCG) published the result of a meta-analysis in which radiotherapy showed its effectiveness in reducing the risk of local recurrence in patients undergoing BCS and in mastectomized patients. Mortality from breast cancer also went down by 3.8% in 15 years.

Systemic Treatment

The main goal of adjuvant systemic treatment is to control any remaining disease, reducing the relapse rate and improving long-term survival.

In a publication in the Lancet in 2012, the EBCTCG analyzed the effects of polychemotherapy on local recurrence and 15-year survival in patients with baseline breast cancer.

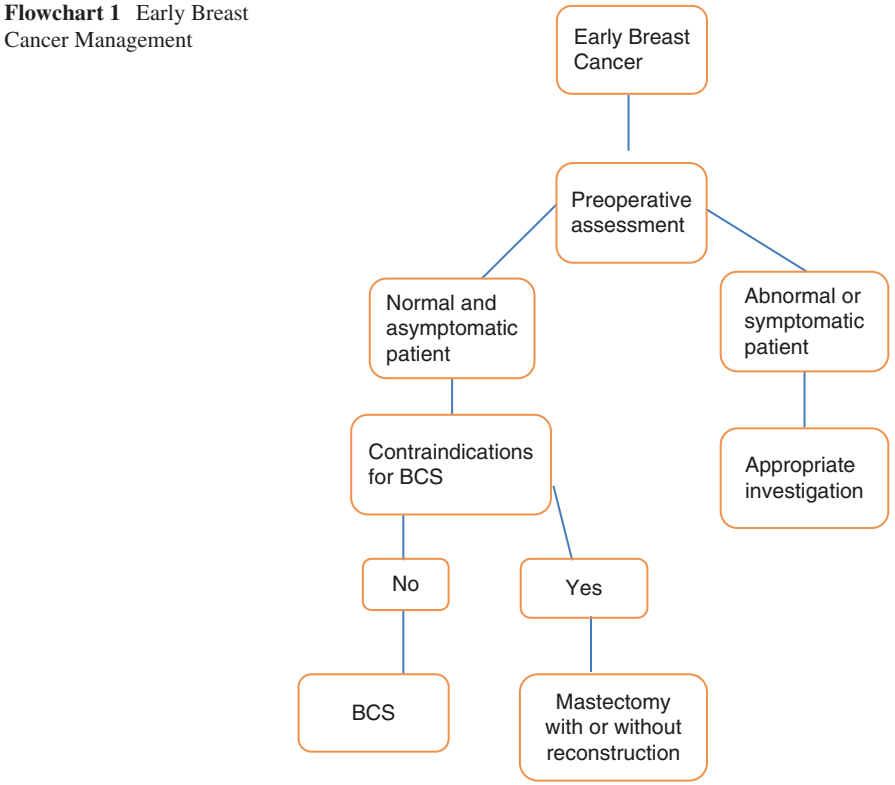
Between 1973 and 2003, analysis was made of 123 randomized studies, with more than 100,000 women with different chemotherapy regimens. The schemes evaluated were taxanes versus non-taxanes, anthracyclines versus CMF, high-dose versus low-dose anthracyclines, and multidrug chemotherapy versus no chemotherapy. A 10-year reduction in breast cancer mortality of 36% in chemotherapy regimens compared to no chemotherapy was shown. Patients considered low risk did not present gain of absolute benefit, when submitted to the chemotherapeutic treatment.

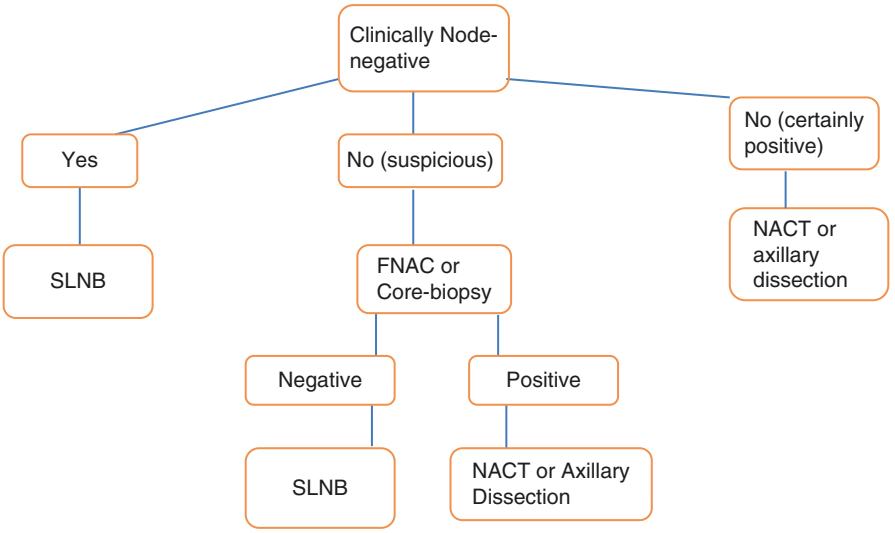
The NCCN recommends trastuzumab for all patients with overexpression of Her2, without hormone receptors, regardless of tumor size. In patients with positive hormone receptors and overexpression of Her2, trastuzumab may be indicated in tumors larger than 0.5 cm. Indications of aromatase inhibitors may be better studied in the specific chapter of hormone therapy.

The ASCO has provided a guideline for use of gene signatures capable of assessing prognosis and predicting response to chemotherapy in situations chemotherapy is controversial. Of the several signatures described, we have Oncotype Dx, Mammaprint, Prosigna and BCI (Breast Cancer Index). Although being very promising, the use of these tools is still incipient in Brazil. It is up to the mastologist to rationally evaluate the benefit of the indication to chemotherapy, and when necessary, the request of the gene signature that best suits.

Flowcharts

Flowchart 1 Early Breast Cancer Management





Flowchart 2 Axillary Management

Recommended Reading

1. Aebi S, Davidson T, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22(Supplement 6):vi12–24. *Breast cancer treatment protocols recommended by the European Oncology Society according to the level of evidence and degree of recommendation.*
2. De Felice C, Cipolla V, Stagnitti A, Marini A, Pasqualitto E, Meggiorini ML. The impact of presurgical magnetic resonance in early breast cancer: an observational study. Eur J Gynaecol Oncol. 2012;33(2):193–9. *123 patients with a diagnosis of invasive, unilateral and unifocal carcinoma, with indication of conservative surgery, were submitted to preoperative magnetic resonance imaging. In 34.2% of the cases, MRI findings led to surgery with a greater extension, and in 4.2% of the cases, the finding through MRI was not confirmed in the anatomopathological study (over-treatment). It concludes that in selected patients, MRI seems to be important in surgical planning.*
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10.801 women in 17 randomised trials. Lancet. 2011;378(9804):1707–16. *Analysis of these studies has shown that radiotherapy after conservative breast surgery not only reduces the risk of local recurrence but it also reduces the risk of death from breast cancer.*
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. Lancet. 2012;379(9814):432–44. *These studies showed a 1/3 survival gain in 10 years, regardless of the type of chemotherapy used. Patients with low risk of death had low benefit if they used chemotherapy. The authors suggest that the results of genetic marker exams and quantitative immunohistochemistry may aid in predicting risk and responding to chemotherapy.*
5. Garcia-Etienne CA, Tomatis M, et al. Mastectomy trends for early-stage breast cancer: a report from the EUSOMA multi-institutional European database. Eur J Cancer. 2012;48:1947–56. *13,569 patients 13 European centers for the treatment of breast cancer were evaluated between 2003 and 2010. Conservative surgery was performed in 73.3% of the cases. Annual statistical analyzes were performed, with a reduction of 4.24% per year in mastectomy indications.*

Locally Advanced Breast Cancer

BBSG – Brazilian Breast Study Group

Definition

The 7th edition of the American Joint Committee on Cancer (AJCC) classifies a locally advanced breast cancer (LABC) as those included in III stadium (IIIA, IIIB, and IIIC) represented by tumors >5 cm (T3) or those associated with chest wall (T4A), skin (T4B), or both (T4c) involvement or the presence of fixed or matted axillary lymph nodes (N2/N3) of one or more lymphatic drainage chains (axillary, supraclavicular, or internal mammary) or inflammatory carcinoma (T4d).

Epidemiology and Molecular Biology Features of Locally Advanced Carcinomas

The incidence of LABC varies geographically, encompassing remarkable distinctions even among developed countries. Regarding those nations, even adopting screening programs, from 4% to 8% of the tumors are in advanced stages when diagnosed. In the United States, according to the Surveillance Epidemiology and End results (SEER), locally advanced tumors encompass 4.6% of diagnosed neoplasms, while inflammatory carcinoma represents 1.3%.

The CONCORD study, published in 2013, evaluated the clinical staging of 18,962 women diagnosed with breast cancer; the data was obtained from population census performed in 12 European countries and 7 American states. The study supported an incidence of locally advanced carcinoma, solely considered as T4 N0-3, of 8% in Europe and 4% in the USA. Generally, the T3 tumors were particularly

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significant in Europe compared to the USA (14 × 10% respectively), following a greater lymphatic tissue impairment (33 × 26% respectively).

In Brazil, the incidence oscillates in different regions, ranging from 15 up to 46.5% in different studies.

The spectrum of locally advanced tumors includes indolent tumors, not being previously detected due to the limitations of screening programs, up to aggressive tumors regarding their molecular biology. Advanced tumors are especially frequent in Hispanic, young, black, and low-income women, particularly in underdeveloped countries, probably due to the limited national health systems.

The presenting tumors must be differentiated from inflammatory carcinoma (T4d), which encompasses aggressive molecular biology features, such as negative hormone receptors (ER/PR), significant histological impairment as high-degree neoplasms, higher cell proliferation rates, greater angiogenesis, and vascular and lymphatic tissue invasion. Therefore, inflammatory carcinoma withholds worse prognosis, confirmed by risk of death twice compared to locally advanced breast carcinomas.

Regarding the molecular biology of the LABC, those tumors are more frequently associated with basal-like or HER2 expression profiles ranging close to 45% and luminal A/B at 7%.

Clinical Features

The clinical diagnostic features encompass cutaneous impairment or large dimensions (>5 cm) associated or not with regional lymphatic involvement. Satellite cutaneous nodules, upper limb edema, and chest wall impairment may also be observed, justifying the inoperability proposed by Haagensen.

Propedeutics

The standardization of clinical mechanisms to diagnose and treat those tumors must be established.

The initial priority is to settle a histopathological and immunohistochemical diagnosis definition. Preferably through the percutaneous biopsy performed by core needle biopsy, which shall enable to decide a neoadjuvant chemotherapy (NACT).

Whenever facing clinically suspicious lesions that have not undergone any percutaneous biopsy, incisional biopsy must be performed. Regarding additional cutaneous involvement, skin biopsy (punch biopsy) may be an effective and low morbidity diagnostic alternative. The presence of lymphatic tissue involvement may also be a diagnostic alternative through the evaluation neoplastic embolisms of subcutaneous lymph nodes.

The clinical evaluation of the lymphatic chains enables the realization of an aspirational fine needle puncture of lymph node(s) in suspected areas, aiding the therapeutic planning.

Simultaneously to the histopathological diagnosis, the patient must undergo laboratorial exams and local and systemic radiological staging.

Mammography ought to be initially requested in order to evaluate neoplastic focuses, suspicious microcalcifications, multicenter impairments, and the contralateral breast. Ultrasonography may provide relevant complementary information to evaluate dense breasts, especially regarding lymphatic axillary tissues of internal, supraclavicular, infraclavicular drainage chains, also being helpful to guide biopsies. Magnetic resonance imaging (MRI) may improve the evaluation of the therapeutic response obtained from the systemic treatment and therapeutic strategy.

Metastasis may simultaneously be diagnosed with LABC in up to 30% cases, which justifies active imaging staging in these circumstances. Once the radiological evidence of metastases is established, these patients are classified as stage IV (metastatic disease) and the therapeutic planning should be re-adjusted.

Systemic staging must include classic laboratorial exams (hemogram, TGO, TGP, DHL, alkaline phosphatase, total bilirubin, and fractions) and radiological evaluation of the most probable metastases sites, employing skeletal scintigraphy and computed tomography (CT) of the abdomen and chest. Lesions in one of these images must be profoundly investigated. Positron emission tomography (PET) and PET/CT scans offer greater sensitivity detecting systemic metastases than usual imaging methods, may facilitate both diagnosis and response monitoring, and may additionally be very useful whether to indicate surgery in these situations.

Genetic counseling is recommended for patients considered to be at high risk for hereditary breast cancer and, according to the NCCN, must also be advised to triple-negative patients younger than 60 years.

Treatment

Principles

A multidisciplinary approach to LABC combined with NACT, surgery, and radiotherapy is capable to significantly improve the survival rates. Studies (previous to neoadjuvant treatments) supported that LABC was associated with a 25% overall survival (OS) in 5 years. Current NACT treatments improved the OS up to 80% and 45% to IIIA and IIIB patients, respectively. The EC IIIA encompasses T3N1M0, despite the preference to neoadjuvant treatment, surgery may eventually be firstly employed. Facing these cases, the adjuvant chemotherapy treatment plan must be the same, as it would have been regarding neoadjuvant scenarios.

Neoadjuvant Chemotherapy

The NACT mainly aims to reduce the tumor's volume (downstaging), to increase the possibility of performing non-radical surgeries, to treat subclinical micrometastasis, and to evaluate in vivo the tumor response to the systemic treatment. The importance of the obtained benefits regarding this treatment strategy to improve OS has not yet been proven, especially in patients with LABC, due to the limited number of validated clinical studies.

The NSABP B18 and B27 protocols consist of prospective, randomized, and double-blind studies to evaluate the efficacy of neoadjuvant systemic therapy compared to adjuvant therapy in tumors that may undergo surgery (T1-T3, N0-N1, M0). There were no OS differences between the groups. However, NSABP B18 supported a tendency for longer disease-free time-lapse and greater overall survival in women <50 years who underwent NACT. Both studies support that the groups treated with NACT had more breast conserving surgery. In study B27, the neoadjuvant implement of docetaxel increased the proportion of patients who had complete biological response compared to the group solely receiving CA (26% '13%, respectively, $p < 0.0001$). In both studies, the achievement of complete pathological response (PCR) was associated with longer disease-free time-lapse and greater overall survival.

Defining a chemotherapy protocol to be employed is based on clinical and biological variables. Approaches based on doxorubicin and cyclophosphamide, whether or not followed by taxanes, were more significantly studied, supporting a reduction of at least 50% of the tumor in more than 75% of the cases. There is a consensus that chemotherapy should be employed to its maximum in the neoadjuvant phase.

New agents and therapeutic regimens have been tested in clinical studies achieving promising results such as trastuzumab, pertuzumab, capecitabine, and gemcitabine.

Facing increased genetic transcription and translation of HER2, the double-block with trastuzumab and pertuzumab associated with docetaxel chemotherapy has presented surprising PCR when compared to the isolated trastuzumab employment (45.8% versus 29%), according to the NeoSphere study. An additional drug, capable to inhibit the tyrosine kinase pathway, the lapatinib, associated with trastuzumab and paclitaxel in a neoadjuvant basis was associated with greater PCR when compared to trastuzumab solely combined with paclitaxel – data supported by NeoALTTO study.

Most recent trials showed that triple-negative or Her-2 breast cancer which don't achieve pathologic complete response should be treated with adjuvant chemotherapy. Triple-negative patients with incomplete response benefit from adjuvant capecitabine and Her-2 patients with incomplete response benefit from adjuvant T-DM1.

Neoadjuvant hormone therapy in hormone-positive tumor patients may be an option, especially in elderly patients, with comorbidities that increase the risk of cytotoxic treatment.

For patients with inoperable LABC with disease progression even undergoing chemotherapy, palliative radiotherapy (RT) should be considered.

Surgical Treatment

Surgery is essential regarding therapeutic strategies to LABC. Despite the lack of evidence to support clinical and radiological complete responses, it is mandatory to perform surgical treatment. Few studies compared radiotherapy alone to surgery plus radiotherapy in this setting and demonstrated unacceptable recurrence rates when surgery was not performed. Mauriac et al., 1997, demonstrated local recurrence of 34% in patients with LABC that underwent RT alone of the breast and lymphatic drainage chains after obtaining complete clinical and pathological responses.

For selected patients, breast-conserving surgery (BCS) after NACT can be a local treatment option (Table 1). NSABP B18 supported a 27% mastectomy conversion to BCS after NACT. There was no significant increase in local recurrence in both groups when the initial indication was an BCS, but when conversing a mastectomy to a BCS, a greater local recurrence was observed. It must be emphasized that in this study, negative margins were solely considered as the absence of neoplastic tissue, regardless the distance between the tumor and the resection border; some authors consider that it may be beneficial to obtain larger margins to reduce local recurrence in this situation, but this data is not yet consensual. Overall survival was not impacted by the type of surgery, nor was the indication for neoadjuvant or adjuvant chemotherapy.

The indication of BCS follows the patient's desire, favorable relation between breast and tumor volume, the achievement of acceptable cosmetic result, and favorable clinical and radiological response. The presence of extensive microcalcifications, multicentricity, and lymphatic permeation of the skin are contraindications to conservative treatment.

Table 1 Summary of the main studies addressing neo-QT

		% non-radical surgery (BCS)		Local recurrence		Overall survival	
Study	Follow-up	Neo-QT	QT	Neo-QT	QT	Neo-QT	QT
Curie	66 mo	82%	77%	24%	18%	86%	78%
Royal Marsden	48 mo	89%	78%	3%[a]	4%[a]	80%	80%
NSABP B18	72 mo	68%	60%	7.9%	5.9%	80%	80%

[a]Local recurrence regarding the *Royal Marsden* study to BCS

In these circumstances, performing the mastectomy with or without reconstruction should be discussed with the patient. Nipple-sparing mastectomy may constitute an alternative to traditional mastectomies when the indication criterium for non-radical surgery is unfeasible, as long as the patients are previously free of cutaneous impairments (T4b, c, or d). In these situations, the intraoperative evaluation of the retro-areolar region by frozen section may be indicated.

MRI represents a useful tool in the radiological evaluation of these patients, constituting one of its indications. The ACRIN 6657 study evaluated the dimensions and contrast washout of tumors by MRI before, during, and after NACT, and the response patterns were associated with greater recurrence-free survival, both in cases of PCR and partial response, supporting the importance of this radiological examination in this scenario of neoadjuvant systemic therapy.

Immediate Reconstruction

Immediate breast reconstruction must be individualized, since these patients are usually sent for radiotherapy after surgical treatment. There is no contraindication to immediate reconstruction in RT candidates, but cosmetic results may be impaired and special RT techniques must be employed especially facing implants (tissue expander or direct implants). The patient must be informed about risks and benefits of the techniques for each case.

Axillary Surgery

Most LABC are associated axilla involvement and the role of sentinel lymph node biopsy (SLNB) in these cases has been the subject of debate.

Fine needle aspiration (FNAC) or core-biopsy enable adequate initial assessment of axillary status and adjuvant radiotherapy planning, whenever the lymph node is converted after neoadjuvant therapy.

SLNB may be performed following certain concepts obtained from performed studies.

In the randomized SENTINA study, a group with clinically negative axilla lymph nodes (cN0) at initial presentation and positive SLNB before neoadjuvant treatment underwent a new SLNB after the treatment followed by lymphadenectomy, with a 61% identification rate and false-negative (FN) rate of 52%, supporting disappointing results for this scenario (SLB before and after neoadjuvant treatment).

One of the earliest prospective studies on this subject, GANEA, prospectively evaluated the feasibility of SLNB after NACT in cN0 and clinically negative axilla lymph nodes (cN+) at initial presentation. In cN0 patients, the identification rate encompassed 95%, and FN rate was 9% versus, respectively, 82% and 15% in cN+ cases.

Table 2 Prospective SLNB studies in cN+ before NACT

Study	N (cN1-cN2)	cN0 prior to neo QT (%)	Identification (%)	FN (%)
Sentina	592	100	80	14
Acosog Z1071	689	83	93	13
Sn Fnac	153	–	88	13

Adapted from Pilewskie and Morrow [4]

Table 3 cN+ before NACT: Sentinel Lymph Node Biopsy modificators

	FN (%)			*p*-valor	FN (%)		*p*-valor
Study	1 SLN	2 SLN	≥ 3 SLN		Unique marking	Double marking	
SENTINA	24	19	7	0.008	16	9	0.15
ACOSOG Z1071		21	9	0.009	20	11	0.05
SN FNAC	18	5	5	–	16	5	–

Adapted from Pilewskie and Morrow [4]

Tables 2 and 3 summarize data from the 3 largest prospective studies that assessed the accuracy of SLNB after NACT in cN + cases at initial presentation.

The SENTINA and ACOSOG Z1071 were negative studies, as FN rates were higher than those established (10%). However, as given in Table 3, the results were acceptable when three or more SLN were identified. These were phase II studies; therefore, they did not evaluate the impact of these FN rates on disease-free survival (DFS) and overall survival (OS) of the patients. The most consistent actualized data were supported by a retrospective study of the European Institute of Oncology, where 396 patients cT1-T4, cN0-N2 underwent NACT and SLNB was performed in cases with ycN0 following the treatment and without axillary lymphadenectomy. The mean follow-up was 61 months, and the OS in 5 years was 86% in the patients who initially were cN1-2 and 93% in those with cN0 – non-significant difference. The complete pathological response was a positive predictive factor in the survival calculation. In the 147 patients previously cN+, 70 (47.6%) had no more clinical lesion in the axilla. All solely underwent SLNB, encompassing a 100% identification rate. Even without axillary lymphadenectomy in this group, there was no case of axillary recurrence in 5 years.

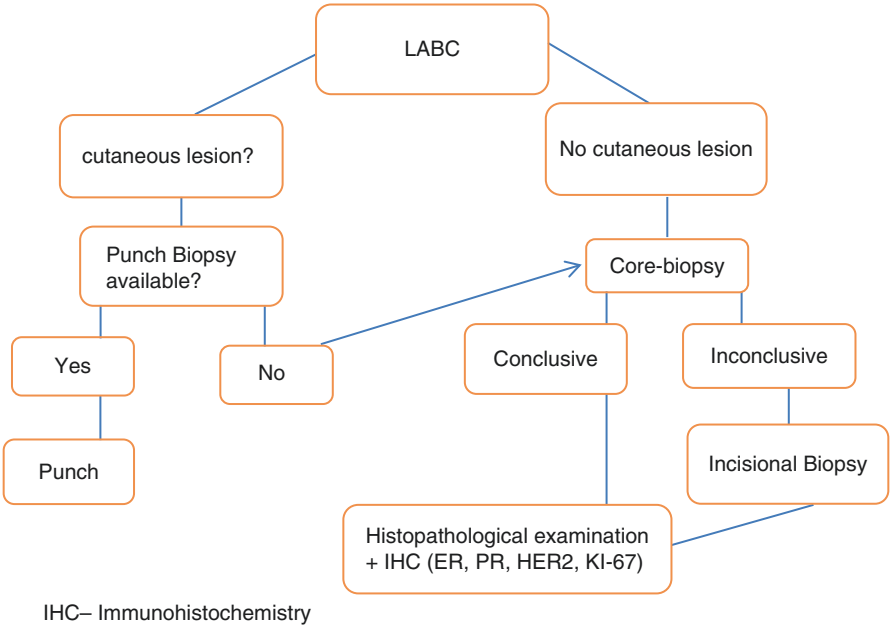
Radiotherapy

Adjuvant radiotherapy composes the treatment of LABC. Facing non-radical surgeries, its indication remains unrestricted and similar to the initial tumors. The need of the boost in these patients with PCR or largely reduce tumor's volume are uncertain and further randomized clinical trials must evaluate this situation in order to decide whether the initial staging indication remains.

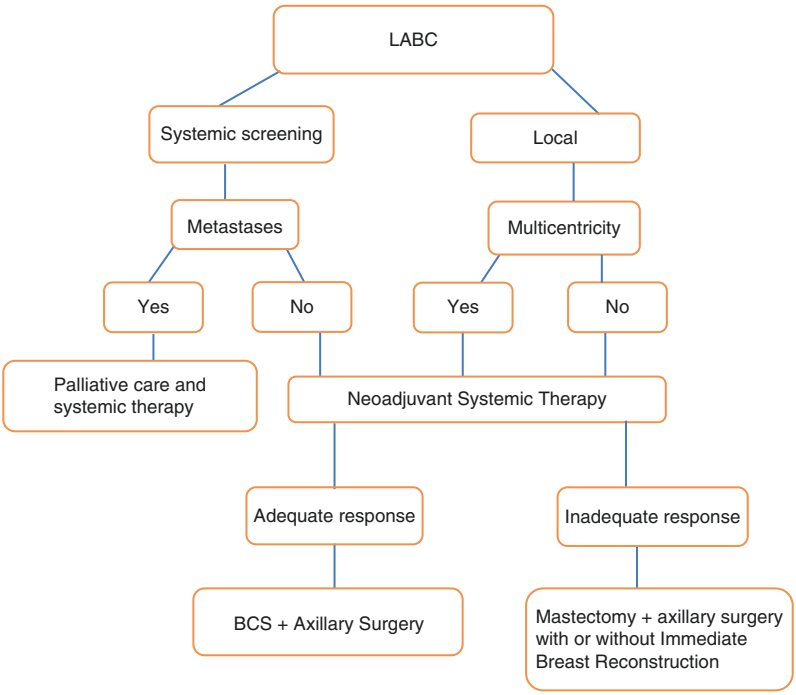
A study performed at the MD Anderson Cancer Center, patients diagnosed with LABC who underwent mastectomy with complete biological response, followed or not by RT had local recurrences in 15% and 33%, respectively.

Currently, a clinical trial in progress – NSABP B-51/RTOG – was designed precisely to address the necessity of RT after PCR. Patients with biopsy-confirmed lymph node metastases who had a complete post-mastectomy response were randomized into 2 groups: chest wall and drainage chains irradiation versus no additional treatment; in BCS: breast irradiation with or without drainage chains irradiation. ALLIANCE is an unfinished clinical trial that aims to assess the impact of RT in patients treated with NACT and who had residual lymph node disease confirmed by SLNB. One group was submitted to axillary lymphadenectomy and another to axillary radiotherapy. The results of these two aforementioned studies will complement the existing gaps to treat LABC following NACT.

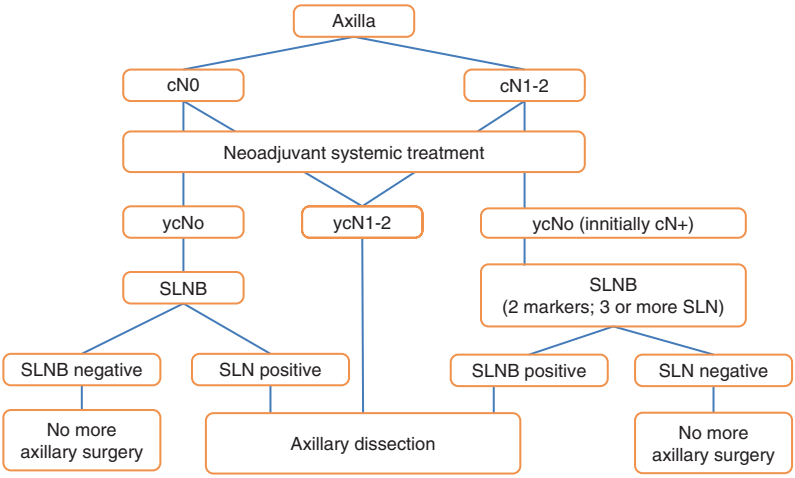
Flowcharts



Flowchart 1 LAC diagnostic guideline



Flowchart 2 Breast surgery in LABC



Flowchart 3 Axillary surgery in LABC

Recommended Reading

1. Allemani C, Sant M, Richardson LC, Baili P, Storn H, Torrella-Ramos A, et al. Breast cancer survival in the US and Europe: a Concord high-resolution study. Int J Cancer. 2013;132(5):1170–81. *A study supporting different incidences among the clinical stages of breast cancer in approximately 20,000 women in 7 American states and 12 European countries. It has been demonstrated that there is a higher incidence of locally advanced carcinomas in European countries when compared to the USA.*
2. Galimberti V, Ribeiro Fontana SK, Maisonneuve P, et al. Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. EJSO. 2016;42:361–8. *A retrospective study supporting that patients submitted to neo-adjuvant QT, that SLNB is feasible in the group with clinically positive axilla that presented complete clinical response. Overall 5-year survival was the same when compared to the group with previously negative axilla. Patients with positive axilla, who were negative on chemotherapy and submitted to sole SLNB, presented axillary recurrence smaller than 1% in 5 years.*
3. Lee MC, Joh JE, Chau A. Axillary staging prior to neoadjuvant chemotherapy: the roles of sentinel lymph node biopsy and axillary ultrasonography. Cancer Control. 2012;19(4):277–85. *Axillary ultrasonography (with or without biopsy) and SLNB represent the safe and feasible staging and may be useful to plan surgical, radiotherapy, and chemotherapeutic approaches. The specificity and ability to detect impairment ranged from 70-96% and 50-73%, respectively. The specificity increased considerably with percutaneous SLN biopsies.*
4. Pilewskie M, Morrow M. Axillary nodal management following neoadjuvant chemotherapy: a review. JAMA Oncol. 2017;3(4):549–55. *Review article encompassing the main studies on SLNB and neo-adjuvant chemotherapy. Explains the identification rates, false negative rates and limitations of prospective studies, emphasizing SENTINA trial, FNAC SF and ACOSOG 1071. In cases with previously positive axilla and complete biological response after neo-QT, supported acceptable rates of FN when excised 3 or more SLN and the marking is performed by radioisotope and patent blue dye*
5. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and b 27. J Clin Oncol. 2008;26(6):778–85. *NSABP protocols B18 and B27 supported that neo-adjuvant QT is equivalent to adjuvant. In Protocol B18, women <50 years of age, treated with neo-adjuvant QT presented higher SLD and SG, trending towards statistical significance. RH 0.85. p 0.09 w / SLD and 0.06 w / wG). At B 27, the addition of taxane to the AC plan considerably increased the achievement of complete biological response (RpC). (26.13%, p = 0.0001). In both studies, patients who achieved RpC continue to present better SLD and SG, compared to those who did not.*

Influence on Histologic, Immunohistochemical, and Molecular Subtypes on Therapeutics

BBSG – Brazilian Breast Study Group

Introduction and Definitions

Breast cancer is a heterogeneous disease that may be classified according to clinical, histopathological, immunohistochemical, and, more recently, molecular characteristics. The features of breast cancer gene expression led to the classification of tumors into distinct molecular subtypes. These subtypes present different clinical outcomes, including different responses to available therapies. The incorporation of gene signatures could better identify which patients may benefit from chemotherapy and the subtypes that have the best response to neoadjuvant chemotherapy. In this chapter, the main subgroups and their influence on therapy are described.

Histological Division

The non-specific invasive breast carcinoma, or invasive ductal carcinoma, and lobular invasive carcinoma are the most common histological subtypes, but there are other histological classifications of invasive carcinoma of the breast (secretory, tubular, mucinous, apocrine, or medullary), which must be differentiated.

The treatment of these special breast cancer subtypes, in general, is similar to that of invasive low-grade ductal carcinomas. The risk of axillary involvement in tumors up to 1 cm in these lesions is historically inferior to 5%. Some authors suggest that the axillary study may be dismissed in these situations due to the false-negative risk in sentinel lymph node biopsies (SLNB), described in several studies from 5% to 10%, which may outweigh the risk of metastasis in the spe-

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cial subtypes. The guideline of the National Comprehensive Cancer Network (NCCN) recommends not to perform adjuvant treatment in tumors of histology compatible with tubular or mucinous carcinoma <1 cm, hormone receptors (HR) positive, N0 or with micro-metastases, to carefully evaluate hormone therapy in tumors measuring >1 cm and <2.9 cm and to certainly indicate hormone therapy for tumors >3 cm. Facing macrometastases (>2 mm), it has to be considered the employment of chemotherapy and hormone therapy. In this scenario, the use of the MammaPrint genomic assay may be useful, according to ASCO 2017 guideline. Special histology subtypes negative hormonal receptors (HR) are recommended to undergo the same treatment as invasive ductal carcinomas. Surgical and radiotherapy treatment follows breast cancer, the same recommendations as invasive carcinomas.

Metaplastic carcinoma is a unique subtype of breast cancer presenting a more aggressive biological behavior, sometimes similar to sarcomas, and the recommended treatment is similar to cases of invasive carcinoma. Usually, it presents an unsatisfactory response to neoadjuvant chemotherapy (NACT).

Molecular Biology Classification of Breast Cancer

Perou and Sorlieet al. [4], classified breast cancer employing the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor-type 2 (HER2). Initially, the division described five molecular subgroups with significant prognostic differences, including luminal A (positive ER and PR, negative HER2), luminal B (positive ER and/or PR, with positive or negative HER2), enhanced HER2 (negative ER and PR, with positive HER2), and basal (triple-negative). The luminal breast cancer represented the majority of cases (luminal A, 40%; luminal B, 20%), followed by triple-negative tumors (15–20%) and solely HER2-positive tumors (10–15%). Recently, other types have been identified and described as claudin-low, enriched interferon and molecular apocrine. An important study identified several subtypes of triple-negative (TN) in addition to basal carcinoma.

The differentiation between luminal tumors may be challenging. Some cutoff standards have been previously suggested and applied to clinical practice employing Ki67. In the St. Gallen 2017 Consensus, there was no definition whether to adopt the Ki 67 cutoff standard in order to differentiate luminal subtypes (A and B), since this test may have varying results. It was also recommended that the employment of gene signatures might be useful to evaluate the risk in luminal carcinomas.

Basal subtype tumors are commonly diagnosed in young and black women, whereas luminal A tumors are commonly diagnosed in postmenopausal women. Breast cancer prognosis is directly related to the molecular subtype: luminal carcinomas are associated with better prognosis, whereas the basal one is associated with worse survival rates.

Impacts of Breast Cancer Subtypes on Local-Regional Treatment

The treatment peculiarities must encompass clinical, histopathological, and immunohistochemical features. These variables directly impact the systemic treatment, but also influence local control, since tumor biology is an important factor to measure the risk of local recurrence (RL).

Mamounas et al. [3] retrospectively assessed LR in T1-2, N0, HR-positive/HER2-negative patients in the NSABP B14 and B20 studies that retrospectively compared tamoxifen to placebo and endocrine therapy combined with chemotherapy versus isolated hormone therapy. In 895 patients treated with tamoxifen on B14, the recurrence score (RS) based on Oncotype Dx (RS ODX) was significantly associated with local recurrence risk: after 10 years follow-up, local recurrence was 4.3% for the low-risk group (RS ODX < 18), 7.2% for the intermediate group (18–30), and 15.8% in the high-risk group (RS ODX > 31). In the B20 study, 424 patients received CMF + TMX. RS ODX also associated with local recurrence: 1.6% at low risk, 2.7% at intermediate risk, and 7.8% at high risk. There was no association of local recurrence with tumor size or grade.

Molecular subtypes also influence whether to indicate NACT. Regarding a recent meta-analysis, Cotazar et al. demonstrated a complete pathologic response (PCR) of 7% in luminal A tumors and 15% in luminal B tumors. Additionally to the low percentage of PCR, a significant proportion of luminal tumors may not benefit from chemotherapy and therefore are candidates for gene signatures after surgery. Low-risk Oncotype or low-risk MammaPrint is less likely to have complete chemotherapy response when compared to the high-risk test. Gene signature tests should be performed to HR-positive and HER2- negative patients. Patients with more aggressive subtypes, on the other hand, often benefit from prior systemic therapy. The NEOSPHERE and TRYPHAENA studies have supported that in HER2-enriched tumors, the double-blocking of HER2 with trastuzumab and pertuzumab, associated with chemotherapy, considerably increases the possibility of PCR. Triple-negatives also have a greater probability of PCR compared to luminal ones. Breast and axillary surgeries are directly affected after downstaging: a recent presentation during the St. Gallen consensus supported that tumors with aggressive biology (HER2 and TN) present a lower percentage of axillary lymphadenectomy if the sentinel lymph node biopsy is performed after systemic therapy. Additionally, to delay systemic therapy in these subtypes may affect mortality, as observed by Gagliato et al.

Gene Signature Influence on Systemic Treatment

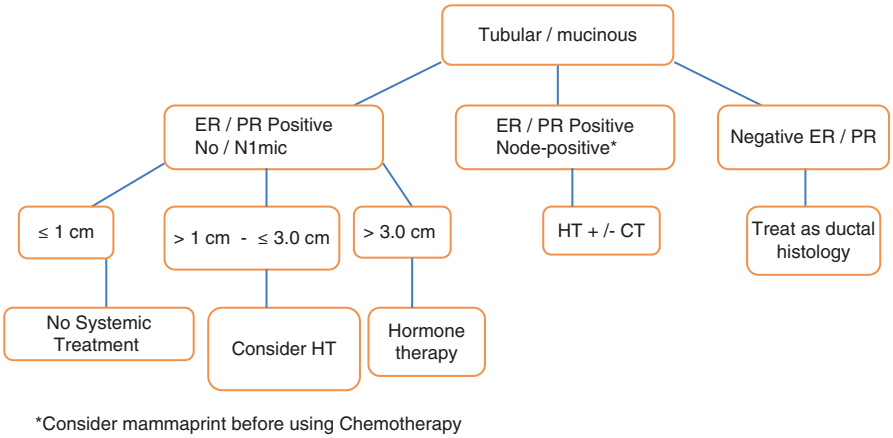
Systemic therapy, especially chemotherapy, decreased the rates of distant recurrences, ultimately reflected by a mortality reduction. However, the number of patients benefited by the treatment is limited compared to the volume of patients

submitted to the treatment, as demonstrated by the Oxford meta-analyses. The costs and adverse effects of cytotoxic therapy are important issues and better biomarkers are required to optimize the treatment. Genomic signatures are useful tools to aid deciding the peculiarities of adjuvant treatment, enabling to downstage the therapy, as demonstrated in some studies. The American Society of Clinical Oncology (ASCO) has recently published a genetic signature applicability guideline. In a simplified manner, the following recommendations were described:

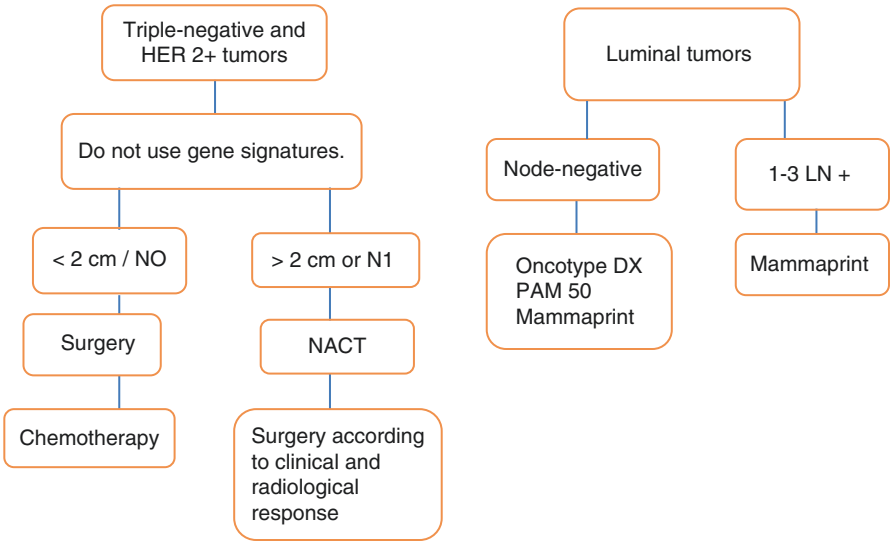
1. Genetic signatures should be avoided to enhanced HER2 and triple-negative tumors.
2. Oncotype Dx: may be fit for T1/T2, N0, positive HR, negative HER2 tumors. There is no current recommended employment regarding lymph nodes involvement.
3. MammaPrint: may be fit for T1/T2, N0-1(1-3 positive lymph nodes) positive HR, negative HER2 tumors, associated with high clinical risk. Following the MINDACT (Microarray in node negative disease may avoid Chemotherapy) study, no clinical benefit was observed by the addition of adjuvant chemotherapy to low clinical risk and high genomic risk. Thus, it is no formal recommendation to low clinical risk (following the criteria employed in the study). ASCO also advises caution regarding the decision to exclude chemotherapy facing positive lymph nodes.
4. PAM-50: may be fit for positive HR, negative HER2, N0 tumors associated with diverse histological and clinical features to evaluate whether patients would benefit from adjuvant chemotherapy. Must not be performed in patients with impaired axilla.
5. KI-67 must not be employed to decide whether to indicate adjuvant chemotherapy.
6. Positive HR, negative HER2, N0 patients that underwent 5 years of hormonal therapy, without any feature to suggest recurrences, are not fit to be analyzed by molecular biology standards of extended endocrine therapy (ODX, Endopredict, PAM 50, BCI, ou immunohistochemical (IHC) 4).

Therefore, the breast surgeon must previously evaluate clinical, histopathological, and immunohistochemical features in order to decide surgical treatment.

Flowcharts



Flowcharts 1 Special tumor guidelines



Flowcharts 2 Molecular biology test recommendations

Recommended Reading

1. Cardoso F, Vant Veer LJ, Bogaerts L, et al. 70 gene signatures as an aid to treatment decisions in early breast cancer. New Eng J Med. 2016;375(8):717–29. *A randomized study (Mindact - microarray in node negative disease may avoid chemotherapy in Breast Cancer) that evaluated the employment of mammaprint in 6,693 women and compared the genomic risk (employing mammaprint) combined to clinical risk (assessed by Adjuvant On line). There was no benefit to undergo chemotherapy treatment in low clinical risk and high genomic risk patients, as well as in those of high clinical risk and low genomic risk.*
2. Krop I, Ismaila N, Andre F, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early_stage invasive breast cancer: American Society of Clinical Oncology Practice Guideline Focused Update. J Clin Oncol on line. 2017;10. *Recommendations regarding biological markers, encompassing genetic signatures, in treatment decision.*
3. Mamounas E, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor–positive breast cancer: results from NSABP B-14 and NSABP B-20. J Clin Oncol. 2010;28:1677–83. *It evaluated the local recurrence in patients from B14 and B20 studies and demonstrated an association between RS and local recurrence.*
4. Perou C, Sorlie T, Eisen MB. Molecular portraits of human breast tumors. Nature. 2000;406:747–52. *Initial study that classifies the molecular subtypes of breast cancer according to gene expression (DNA Microarray) and correlation with different survival patterns.*
5. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-Gene expression assay in breast cancer. New Eng J Med. 2015;373(21):2005–14. *Study that evaluated the recurrence of breast cancer in T1-2, N0, N0, RH +, and Her-2 negative tumors, classified as low risk recurrence score (RS <10) according to ODX 21, included in the TaylorX study. Among the 1,626 women (15.9% of the 10,223 women included) with RS <10 and who solely received hormone therapy not followed by chemotherapy after local treatment, overall 5-year survival was 98%, demonstrating safety to dismiss the adjuvant chemotherapy in this population.*

Inflammatory Breast Cancer

BBSG – Brazilian Breast Study Group

Introduction

Inflammatory breast cancer (IBC) is defined as the rapid onset erythema and cutaneous edema, "orange peel" (or peau d'orange). It is a more aggressive disease when compared to locally advanced breast cancer (LABC), encompassing almost double mortality rates, even accordingly to adjusted risk factors.

Epidemiology and Physiopathology

The frequency of IBC ranges from 0.5% to 2% of cases of invasive carcinoma. Although recent series of cases supported a higher survival than the old ones (30% versus 5% in 5 years), these results are yet to be improved, compared to other types of breast malignant neoplasms. Additionally, 23% of patients present metastatic impairment at diagnosis time, and about 90% will be committed by metastases in less than 2 years. Figure 1 demonstrates the IBC survival compared to other locally advanced tumors.

When compared to LABC, IBC affects younger women (mean of 59 versus 66 years).

The main histopathological feature is massive tumor embolization of sub-dermal lymphatic vessels, which is probably the edema and cutaneous erythema cause. However, the histological absence of these emboli does not rule out the diagnosis.

Although most cases of IBC are featured as basal and ductal invasive carcinoma with positive HER2, it is not possible to establish a uniform histological or molecular entity.

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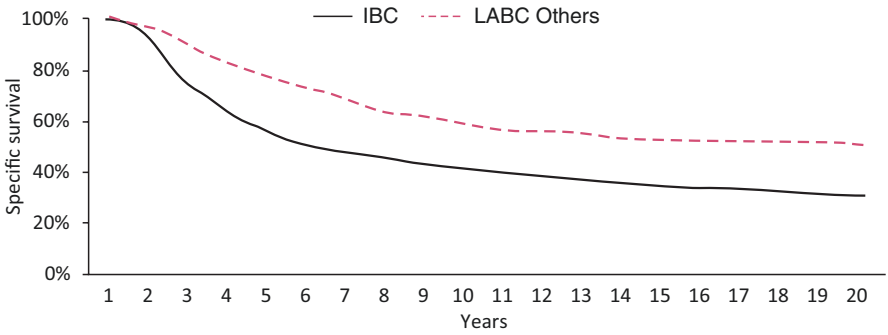


Fig. 1 SEER specific survival rate data regarding EC III tumors, comparing inflammatory breast cancer (IBC) to diverse LABC. (Adapted from Schlichting et al. 2012)

Diagnosis

Due to the clinical features of IBC being similar to an inflammatory impairment in breast tissue, confusion may delay the diagnosis. The IBC is characterized by a rapid appearance (usually within 3 months) of erythema and skin edema (peau d'orange type) involving at least one-third of the breast. It may be associated with a temperature increase and palpable mass, but those are not preponderant factors.

It is mandatory to differentiate typical IBC from LABC, whose natural clinical evolution may develop similar cutaneous impairments.

Regarding the diagnostic similarity to mastitis, detailed anamnesis and biopsies in suspected cases determine the diagnosis. Eventually, therapeutic tests with anti-inflammatory medications and antibiotics may be performed in dubious cases.

The presence of cutaneous biopsy containing tumor emboli in the sub-dermal lymphatic tissue is not mandatory to conclude the diagnosis. However, whenever possible, skin biopsy of the most suspected area must be performed, in addition to conventional biopsy.

Mammography and breast ultrasonography are routinely employed diagnostic exams, the most common findings are: skin thickening, cutaneous edema, papillary retraction, architectural distortion, axillary lymph node enlargement and breast enlargement. Ultrasonography findings correspond to areas of heterogeneous infiltration and architectural distortion, which are found in 90% of cases.

Magnetic resonance imaging (MRI) may be useful when the mammography and ultrasonography results are inconclusive. The typical outcome is the presence of multiple irregular masses, breast asymmetry and cutaneous edema.

IBC is associated with a greater risk of systemic disease. Therefore, thorax, abdominal and pelvis tomography (contrasted, whenever possible), as well as skeletal scintigraphy, are advised. Conventional examinations, such as radiography and ultrasonography, may be performed, but the employment of more sensitive methods is required whenever available.

PET / CT must be employed to patients with dubious conventional exams. Some authors advocate in favor an increase of disease-free time-lapse in patients submitted to this examination, with more effective metastatic disease treatment. However, this increase is actually due to a better evaluation of the metastatic group, which was excluded in assessed IBC cases.

Treatment

Following other invasive carcinomas, the treatment is based on clinical staging and also by the molecular biology classification of the tumor. The entire available therapeutic resources must be employed, encompassing surgery, chemotherapy, radiotherapy and, whenever required, anti-HER therapy and hormonal therapy.

The optimal therapeutic plan must be initiated with neoadjuvant chemotherapy (NACT). The most studied therapeutic strategy is based on anthracycline, providing survival reports ranging from 30% to 40% in 5 years, compared to only 5% in patients solely submitted to mastectomy.

The chemotherapy complementation in the current therapeutic plan ideally contains taxanes, since some studies supported an increase in clinical and pathological complete response employing these medicines.

The applicability of the dense-dosing strategies has not been proved superior to the aforementioned therapeutic plan.

In patients who underwent the ideal NACT, it is recommended not to employ adjuvant chemotherapy.

HER2 overexpression cases may benefit from the combination of double-block anti-HER2 therapy with trastuzumab and pertuzumab associated with primary chemotherapy. Due to cardiac toxicity, concomitant use of anthracyclics is not recommended. Treatment with trastuzumab must be complemented after surgery to a total of 12 months.

Other target therapies are associated with promising studies, such as lapatinib and angiogenesis inhibitors, such as bevacizumab. However, the routinely employment of these medications does not yet compose most international guidelines.

The surgical main aim must be to retrieve all neoplastic tissue with negative margins. Therefore, facing optimal response to primary treatment cases, the standardized surgical treatment is the modified radical mastectomy. The employment of conservative techniques to spare the breast or skin is not recommended, even in cases of excellent response.

Sentinel lymph node biopsy must not be performed due to the high rate of lymph node involvement (50–80%), followed by the reduced lymphatic drainage caused by tumor micro-emboli and high false-negative rates (>30%).

Breast reconstruction is not formally prohibited; however, the risks of surgical complications may delay the onset of adjuvant radiotherapy. Postoperative complications also discourage the employment of these techniques. However, patients with complete chemotherapy response might be candidates for reconstruction surgery.

Radiotherapy must include the surgical site and untreated lymphatic drainage, especially in radiological impaired areas prior to chemotherapy. Some studies suggest the employment of PET / CT to identify possible outbreaks of disease in lymphatic chains. In these cases, careful radiotherapy of these areas may be more efficient.

In patients who have not benefited to neoadjuvant chemotherapy or who have simultaneously disease progression, radiotherapy ought to be performed. Facing patients with satisfactory therapeutic response, surgery must be performed.

Facing hormone or HER2-positive receptors, standard therapy with hormonal or anti-HER2 blockers should be employed after surgery.

In metastatic patients, the treatment is similar to cases of invasive non-inflammatory carcinoma.

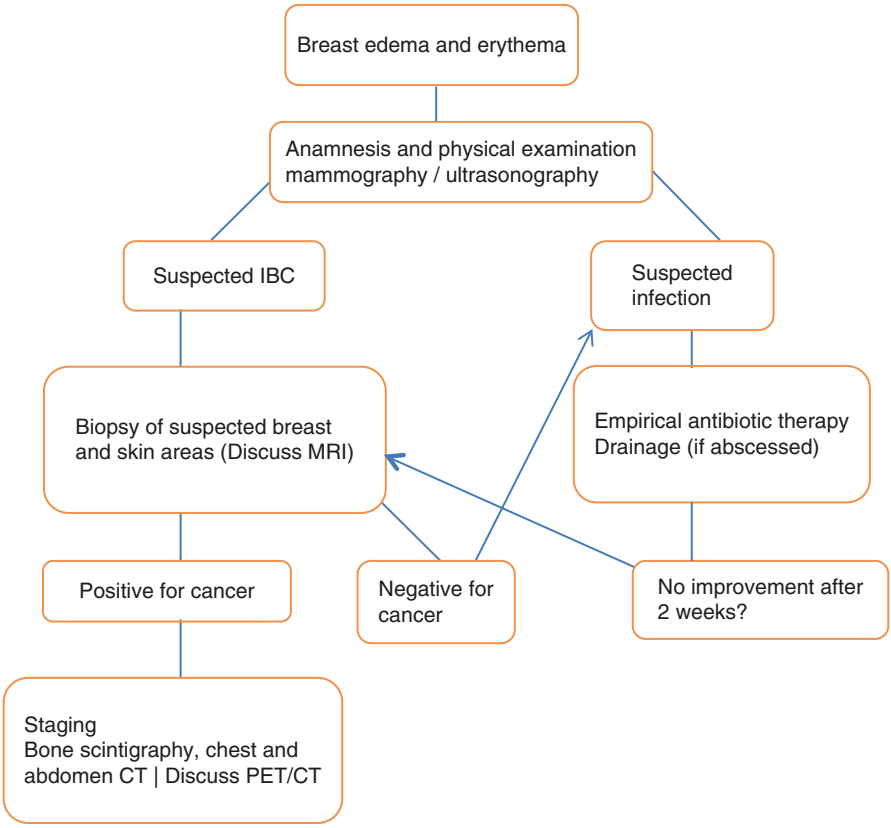
Prognosis

Despite treatment improvement, IBC is yet associated with low survival rates and high early recurrences. However, when compared to previous data, a significant improvement is observed.

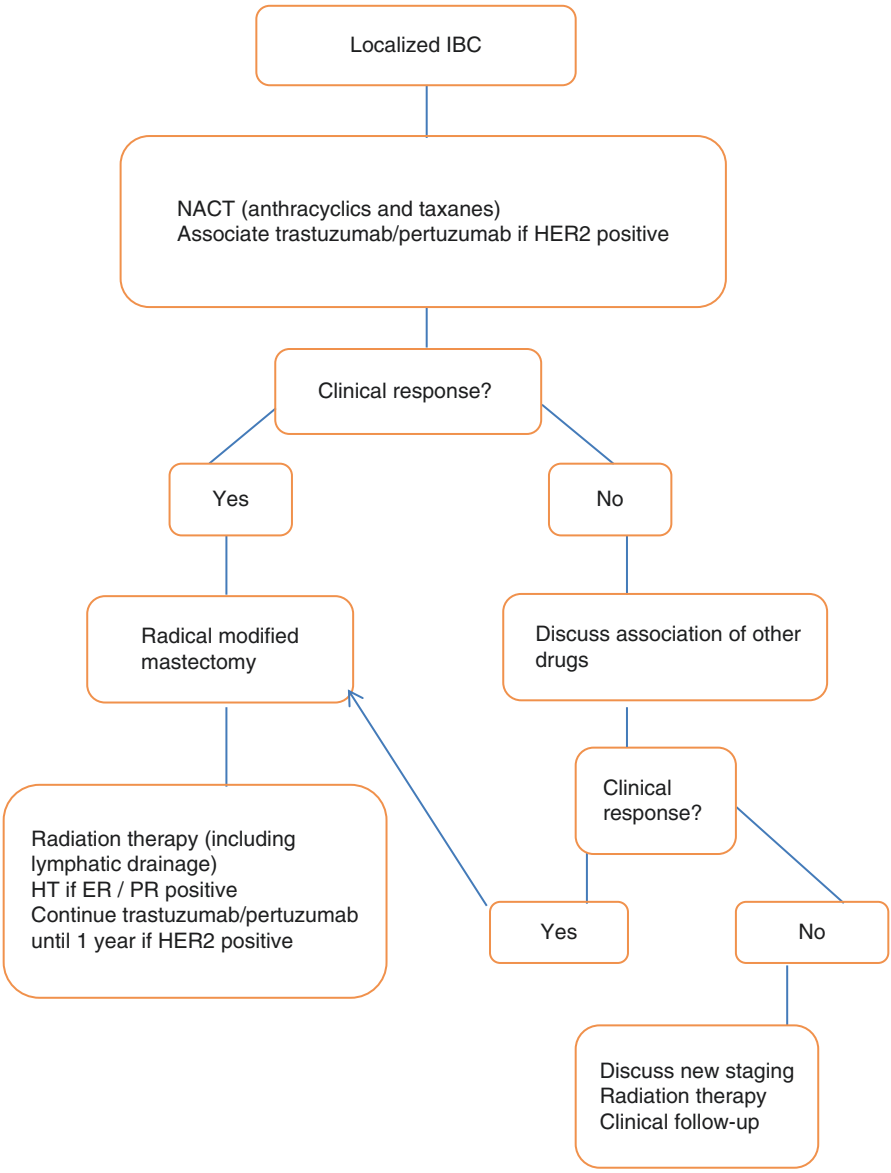
Conclusion

The peculiarities of molecular biology features of IBC are essential for the adequate treatment of the disease. The correct differentiation between diagnostic of inflammatory and locally advanced carcinoma associated to the response to neoadjuvant treatment is important to define prognostic of these tumors.

Flowcharts



Flowcharts 1 IBC propaedeutic



Flowchart 2 IBC treatment

Recommended Reading

1. Fouad TM, Barrera AMG, et al. Inflammatory breast cancer: a proposed conceptual shift in the UICC–AJCC TNM staging system. Lancet Oncol. 2017;18(4):e228–32. *It suggests a new classification for clinical stage IV by UICC-AJCC, dividing into non-inflammatory metastatic and inflammatory metastatic, due to the worse prognosis of inflammatory carcinoma.*
2. Haaggensen C. Inflammatory carcinoma. In: Disease of the breast. Philadelphia: W.B. Saunders; 1971. p. 576–84. *Classical definition of inflammatory carcinoma, stipulating the clinical conditions required to confirm the diagnosis.*
3. Liu J, et al. Chemotherapy response and survival of inflammatory breast cancer by hormone receptor- and HER2-defined molecular subtypes approximation: an analysis from the National Cancer Database. J Cancer Res Clin Oncol. 2017;143(1):161–8. *Differently than the non-inflammatory carcinoma, the presence of positive hormone receptors does not improve the prognosis when compared to other molecular biology subtypes.*
4. Nakhlis F, et al. The impact of residual disease after preoperative systemic therapy on clinical outcomes in patients with inflammatory breast cancer. Ann Surg Oncol. 2017; https://doi.org/10.1245/s10434-017-5903-6. *The clinical response to neo-adjuvant chemotherapy is the most important prognostic factor in Her2 positive and triple negative patients. The presence of carcinoma in situ after neo-adjuvant chemotherapy does not alter the prognosis of the disease.*
5. Simpson AB, et al. Immediate reconstruction in inflammatory breast cancer: challenging current care. Ann Surg Oncol. 2016;23(Suppl 5):642–8. *Immediate reconstruction is not related to prognosis limitations. The occurrence of operative complications may delay the adjuvant treatment. Patients with complete clinical response may be candidates for immediate reconstruction.*

Invasive Lobular Carcinoma

BBSG – Brazilian Breast Study Group

Introduction

Invasive lobular carcinoma (ILC) is the second most common histological type of breast cancer, accounting for approximately 5–15% of cases. It is characterized by an insidious tissue infiltration pattern, providing challenging clinical and radiological diagnosis. Additionally to its unique clinical, molecular biology, and pathological features, there are histological subclassifications that describe different proportions of neoplastic patterns, such as classic (less aggressive) and pleomorphic (more undifferentiated and aggressive). Such differences may imply different strategies of local-regional and systemic therapy.

Definition and Pathology

The ILC differs histologically and clinically from non-special invasive breast carcinoma (NSI), or invasive ductal carcinoma (IDC), as it is originated in the breast epithelial cells of secretory lobes and divided into subgroups according to the histological pattern of infiltration and cytology distortions. The cells are small and rounded with scarce cytoplasm and linearly invade the tissue without causing a significant inflammatory reaction.

The classic form encompasses approximately 60% of cases. Other variants have been described based on architectural characteristics (alveolar, solid, and trabecular) or cytological patterns (pleomorphic, apocrine, histiocytoid, and signet ring cells). Recently, they have been named mixed nonclassical and feature unfavorable clinical-pathological characteristics.

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ILC hardly induces adjacent desmoplastic tissue reaction, due to the insidious infiltration pattern caused by the non-expression of the e-cadherin adhesion molecule, unfavorable characteristic to create palpable masses, improving clinical diagnosis difficulty, aside from interfering on the lesion visualization and featuring a size-confounding factor to radiological examinations. The clinical-pathological aspects encompass positive hormonal receptors (estrogen and progesterone) in over 90% of cases, uncommon expression of HER2, lower nuclear grade (G1/2), low percentage of cellular proliferation (Ki-67 < 20%), and unlikely positivity for the P53 mutation when compared to NSI. Additionally, it presents larger tumors at diagnosis and a higher frequency of multifocality and multicentricity, which may be found in approximately 30% of the cases. A study on ILC genomic characterization, published in 2016 in the *Journal of Clinical Oncology*, demonstrated unique characteristics, such as increased number of Her2, Her3, and PI3K pathways compared to NSI. The relevance of these features is due to "target drugs" directed to those characteristics. Additionally, in this study, alterations in estrogen receptor (ESR1) require further investigation, especially considering endocrine therapy, especially relevant in these tumors.

The ILC metastatic dissemination pattern also differs from NSI. Pulmonary, cerebellar, and pleural metastases are not common; however, peritoneum, gastrointestinal tract, and pelvic organs, such as the ovaries, metastases are much more frequent. The incidence of ILC and NSI metastases to pelvic organs is estimated to be 16 and 1%, respectively.

Epidemiology

ILC accounts for 5–15% of breast cancer cases, particularly more frequent in postmenopausal women, especially after 60 years, however, in the last two decades, an incidence increase occurred in all age groups. A strong association is known between combined hormonal therapy (HT) and ILC incidence, according to six important studies: the estimated risk for ILC ranges from 2.6 to 3.7 times greater for women who underwent HT, while the NSI risk is discreet.

Clinical Features

The most common presentation is a palpable lesion to medical examination, with no significantly defined nodule. Cutaneous retraction is usually scarce due to the absence of local desmoplastic reaction. The clinical diagnosis of ILC may often be challenging and commonly axillary lymph node enlargement is the initial clinical feature.

Diagnosis

Nodular lesions and micro-calcifications are rare, improving the diagnostic difficulty. Mammography presents a sensitivity ranging from 57% to 89%; however radiology may underestimate the actual size of the lesion up to 48% of cases. Breast ultrasonography (USG) presents a sensitivity ranging from 25% to 97%, most of the times superior to mammography; however the method relies on the physician experience.

Magnetic resonance imaging (MRI) is the most sensitive method to diagnose occult lesions in the breast in ILC cases, offering a 93% sensitivity. MRI is also able to detect limited local tumors in up to 32% of cases, and the symmetric breast evaluation is associated with a 7% contralateral impairment, although it presents a considerable rate of false positives, ranging up to 15%. MRI may alter the surgical approach in approximately 28.3% of patients. MRI does not provide, despite the presented data, any cancer outcome improvement: a recent meta-analysis evaluated the employment of preoperative MRI in all breast cancer subtypes, supporting an increase in mastectomy rates, but with no reoperation rate reduction, neither local or distant recurrences.

The fine needle aspiration puncture (FNAC) cytological diagnosis sensitivity ranges from 60% to 75% as false negative ranges from 15% to 60% of cases, being additionally associated with a lower sensitivity in fragment biopsy when compared to NSI. The diagnosis of ILC nonclassical histological subtypes is associated with a greater sensitivity undergoing FNAC and fragments biopsy due to a greater cytological and histological undifferentiated characteristics.

Surgical Treatment

ILC surgical treatment aims the same as NSI, which is the entire neoplastic resection and axillary evaluation.

- Non-radical surgery: Breast-conserving surgery (BCS) is the preferable treatment. Biglia et al. review analyzed over 15 publications addressing local-regional recurrences after BCS to ILC and NSI, supporting a similar clinical outcome: recurrences rates, in 10 years, range from 8% to 18% to ILC and from 8% to 15% to NSI.
- Margins: Positive margins is more frequently in ILC rather than IDC, as demonstrated by Moore et al. review (Table 1). Despite that, BCS is not associated with greater recurrence rates.
- Axillary evaluation: The sentinel lymph node biopsy (SLNB) must be performed to clinically negative axilla. Facing positive SLNB, radical lymphadenectomy may be avoided in special situations, following the same management as NSI.

Table 1 Comparison of positive margins after BCS between ILC and NSI

Author	ILC	NSI	*p* value
Yeatman (1995)	17.5% (7/40)	6.9% (28/405)	018
White (1994)	63% (19/30)	60% (208/346)	NS
Silverstein (1994)	59% (96/161)	43% (489/1138)	< 003
Moore (1999)	51% (24/47)	15% (221/150)	< 05

Adapted from Moore et al. Annals of Surgery (2000)
NRS non-radical surgery, *ILC* invasive lobular carcinoma, *NSI* non-special invasive breast carcinoma

- Contralateral prophylactic mastectomy: Contralateral mastectomy is not routinely indicated, and the surgical procedure must be individualized, such as lesions in the contralateral breast. Pestalozzi B et al. published a study based on 9.000 patients, supporting no significant statistical difference between contralateral carcinoma in the breast facing ILC or NSI, 5.7% and 8.1% respectively.

Systemic Treatment

The ILC presents unique treatment features; however, it must follow the same routine treatment as ILC, despite studies supporting that neoadjuvant chemotherapy fails to provide equivalent therapeutic response as it does to NSI. The sole exception is when facing HER2 ILC.

Radiotherapy

Adjuvant treatment must be indicated following NSI guidelines.

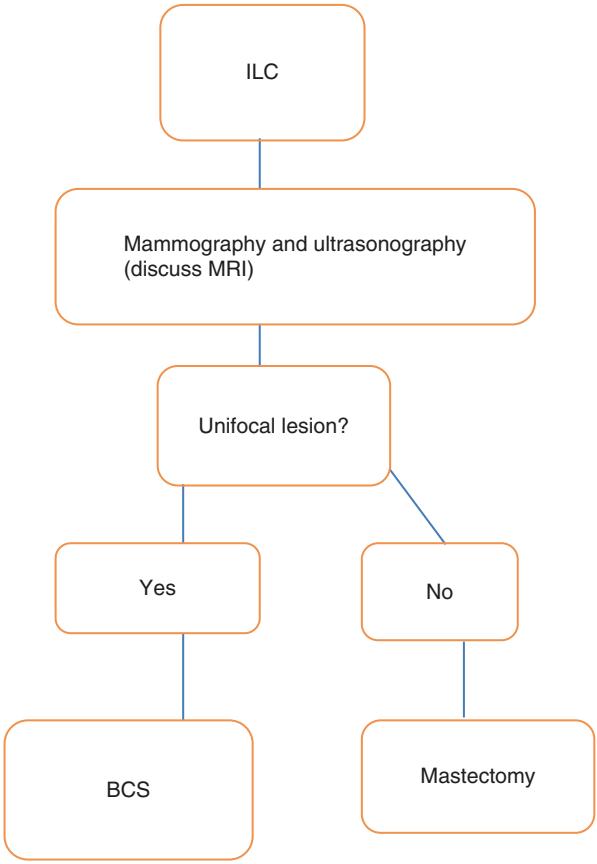
Prognosis

ILC prognosis has been widely debated. In the IBCSG publication, encompassing over 9000 cases of breast carcinoma, ILC presented better prognosis in the first 5 years of follow-up, after which it presented a worse prognosis when compared to NSI in the subsequent 5 years.

Orvieto et al. demonstrated, in 530 ILC cases, that prognosis parameters are the same once adopted to NSI, lymph nodes, tumor size, impairment degree, proliferation index, vascular invasion, and hormone receptors status; however the classic subtype showed better prognosis when compared to nonclassical variants.

Flowchart

Flowchart 1 Lobular Carcinoma Guideline



Recommended Reading

1. Al-Baimani K, Bazzarelli A, Clemons M, Robertson SJ, Addison C, Arnaout A. Invasive pleomorphic lobular carcinoma of the breast: pathologic, clinical and therapeutic considerations. Clin Breast Cancer. 2015;15(6):421–5. *Updated review of pleomorphic invasive lobular carcinoma. The authors support that although pleomorphic ILC is a rarer type of breast cancer, it is an important entity with distinct features. Interpretation: ILC is an aggressive variant and presents worse prognosis than classic ILC.*
2. Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res. 2004;6(3):R149–56. *Retrospective cohort, encompassing 50,339 cases of breast cancer database, comparing histopathological characteristics and long-term oncological results of CINE and ILC. The ILC presents pathological clinical features with better prognosis than CINE, but the oncological results are no different. Interpretation: The ILC prognosis is similar to CINE.*
3. Biglia N, Mariani L, Sgro L, Mininanni P, Moggio G. Increased incidence of lobular breast cancer in women treated with hormone replacement therapy: implications for diagnosis, surgical and medical treatment. Endocr Relat Cancer. 2007;14(3):549–67. *Systematic literature review on hormone therapy (HT) and breast cancer. ILC presents more favorable biological characteristics than CINE. It has a greater incidence in women who underwent HT. Prognosis is similar to CINE regardless the treatment type. Interpretation: ILC is more frequent in HT users. Conservative surgery is safe and is not related to greater local recurrences.*
4. Jacobs C, Clemons M, Addison C, Robertson S, Arnaout A. Issues affecting the loco-regional and systemic management of patients with invasive lobular carcinoma of the breast. Breast J. 2016;22:45–53. *Canadian literature revision supporting that invasive lobular carcinoma represents a unique variant of breast cancer with biological, pathological, and clinical specificities. Demonstrate that the treatment should be individualized. Interpretation: Despite the differences between them, the ILC prognosis is similar to CINE's.*
5. Katz A, Saad ED, Porter P, Pusztai L. Primary systemic chemotherapy of invasive lobular carcinoma of the breast. Lancet Oncol. 2007;8(1):55–62. Review. *Literature systematic review including all randomized trials of adjuvant and neo-adjuvant ILC therapy. Neo-adjuvant therapy presents reduced efficacy in ILC cases compared to CINE. On the other hand, there is no evidence to support that adjuvant therapy is ineffective in ILC cases. Hormone therapy plays a major role in ILC treatment. Interpretation: There is no evidence to support adjuvant therapy solely in histological type. Prospective studies are required to determine the role of chemotherapy in ILC.*
6. Pestalozzi BC, Zahrieh D, Mallon E, Gusterson BA, Price KN, et al. International Breast Cancer Study Group. Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: combined results of 15 International Breast Cancer Study Group clinical trials. J Clin Oncol. 2008;26(18):3006–14. *Retrospective cohort encompassing patients from 15 IBCSG clinical studies comparing the clinical-pathological characteristics and oncological results between ILC and CINE. ILC presents better prognosis in the first five years. However, in the five consecutive years it presents worsening of the prognosis in comparison to CINE. Interpretation: ILC encompass specific prognostic and therapeutic implications for each variant, according to the individual histopathological characteristics.*

Occult Breast Cancer

BBSG – Brazilian Breast Study Group

Introduction

Occult breast cancer (OBC) is uncommon, ranging from 0.1% to 0.8% of all diagnosed cases. The axillary adenopathy is due to breast carcinoma, not detected on clinical and radiological exams. Prognosis is usually similar to other tumors with the same clinical staging and immunohistochemical features, described as a T0 N1,2 or 3, M0.

Clinical Features

Most axillary lymph nodes enlargement is due to benign processes; therefore, the initial evaluation must adequately elect patients to undergo biopsy. The most suspicious characteristics of neoplastic commitment are hardened lymph nodes tissue, persistent for over 30 days in a single lymph node chain. Lymph node sizing is also important, as nodes smaller than a centimeter present reduced malignancy risk, while those larger than 1 or 2 cm may be malignant in up to 8 and 38%, respectively. Clinical examination must exclude the presence of infectious symptoms, such as fever and weight loss, in addition to exclude lymph node enlargement from other regions or hepatomegaly and splenomegaly.

Breast carcinoma in axillary lymph nodes, even in the supraclavicular fossa, is strongly associated with mammary neoplastic tissue: the untreated breast, for instance, will present ipsilateral lymphadenitis in up to 42% of cases; however, signs and symptoms of neoplastic systemic disorders must be investigated.

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Differential Diagnosis

Most axillary lymphadenopathy (around 70%) are due to nonspecific inflammatory processes and 7% by granulomas. Cat scratch disease, breast infections, or upper limb wounds stand out as the main benign causes.

Axillary lymph node diseases due to neoplastic tissue represent about 1% of the cases, among which we emphasize breast, thyroid, skin, and lung cancer and, less frequently, uterus, ovary, sweat gland, and gastric neoplastic impairments, besides lymphomas, melanomas, and sarcomas. The primary site is unidentified in 30% of the cases.

Propedeutics

Suspected neoplasia cases must undergo needle or excisional biopsy, followed by histopathological and immunohistochemical (IHC) appropriate analyses for invasive carcinoma. Magnetic resonance imaging (MRI) must be considered whenever mammography and ultrasonography are unfit to assess the entire disease extension: high resolution mammography solely identifies 7–29% of cases, while MRI ranges from 36% to 100% of neoplasms diagnosis. A systematic review regarding MRI employment to breast occult cancer has shown that 80% of the lesions could be localized by a second-look ultrasound.

There are no conclusive studies supporting mammary scintigraphy and PET / CT employment in OBC cases. The National Comprehensive Cancer Network (NCCN) recommends chest and abdominal tomography scans to assess distant metastasis.

Treatment

Breast surgery must include axillary dissection and breast lesion resection whenever identified, following the invasive carcinoma guidelines. Regarding T0N1M0 patients, treatment is yet controversial, and the available possibilities encompass: mastectomy associated with axillary dissection or axillary dissection alone followed by adjuvant radiotherapy in the breast and drainage chains. A meta-analysis with 7 studies representing 241 patients demonstrated that the mastectomy was not superior to axillary dissection associated with radiotherapy in patients committed by

Table 1 Case studies regarding the comparison of different treatments

Author	*N*	Follow-up Time-lapse	Therapy	Local Recurrences	Overall Survival
Foroudi (2000)	20	73 months	6 Observation	83.3%	50%
			2 Mastectomies	0%	50%
			12 AL + RT	25%	91%
Vlastos (2001)	45	7 years	13 Mastectomies	15%	75%
			32 AL + RT	13%	79%
Shannon (2002)	29	44 months	16 AL + RT	12%	88%
			11 Observation	69%	88%
Walker (2011)	750	10 years	94 Observation	NR	47.5%
			126 Solely AL	NR	58.5%
			268 Mastectomies	NR	63.5%
			202 AL + RT	NR	67.1%

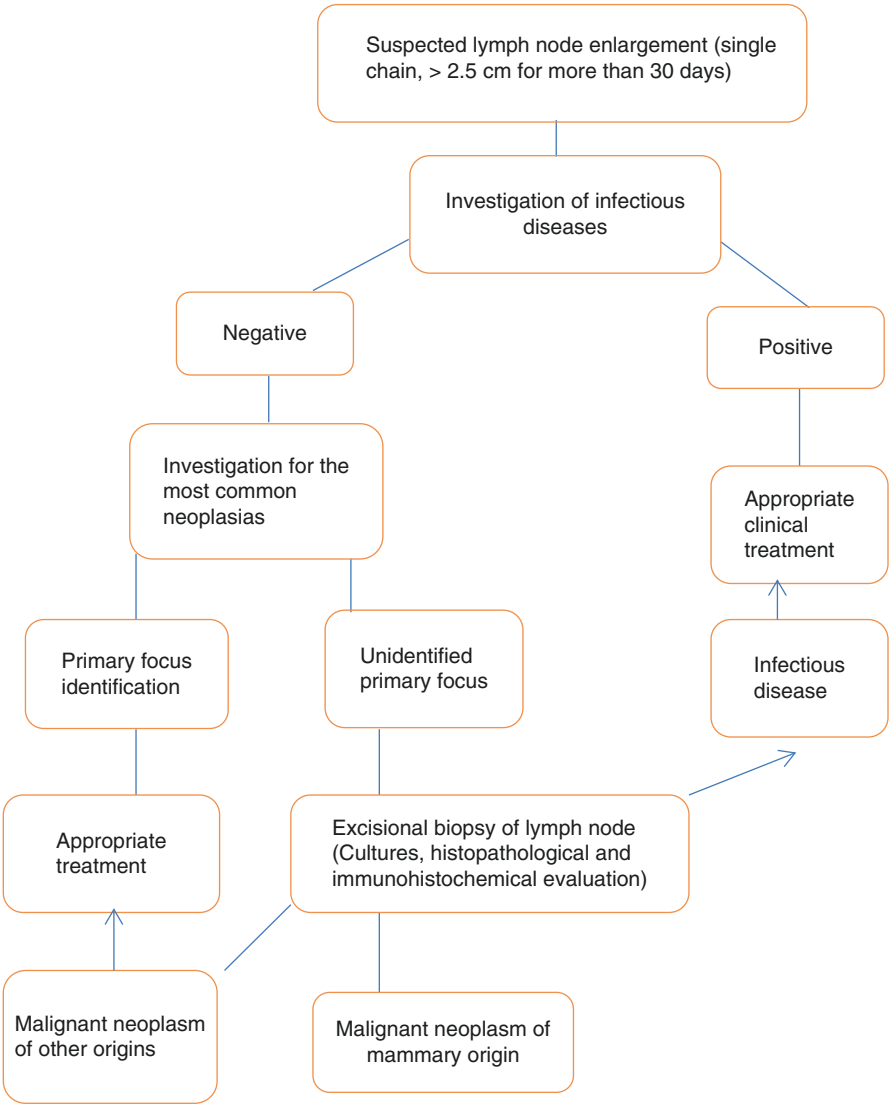
occult breast cancer. Clinical observation without local treatment is not recommended, as some studies supported worse local control and overall survival reduction (Table 1).

Systemic treatment (chemotherapy, target therapy, or endocrine therapy) must follow the stage II or III guidelines. Neoadjuvant treatment must be considered, specially to T0N2-3M0 women.

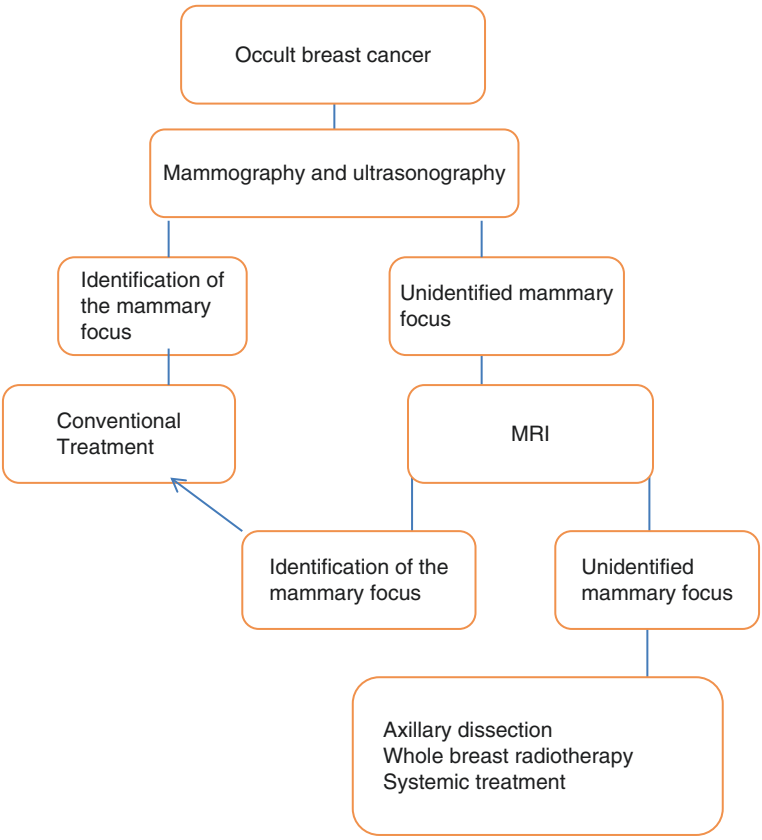
Conclusion

Despite consensus inexistence regarding the gold standard treatment, available studies support that mastectomy may be replaced by whole breast radiotherapy, as long as axillary dissection is performed. The overall survival rate relies on the systemic treatment and tumoral molecular biology features; therefore, mastectomy may generally be spared to special situations, such as further local recurrences.

Flowcharts



Flowchart 1 Suspicious lymph nodes enlargement propaedeutic



Flowchart 2 OBC guideline

Recommended Reading

1. De Bresser J, de Vos B, van der Ent F, Hulsewé K. Breast MRI in clinically and mammographically occult breast cancer presenting with an axillary metastasis: a systematic review. Eur J Surg Oncol. 2010;36:114–9. *Systematic literature review on the clinical MRI employment regarding breast cancer, which included eight retrospective studies, encompassing 250 patients.*
2. Francisco M, Joseph J, Flynn J, Michael J, Vljay K. Optimal surgical management for occult breast carcinoma: a meta analysis. Ann Surg Oncol. 2016. *A 8 studies meta-analysis encompassing 241 patients, of which 94 (39%) underwent axillary dissection with radiotherapy, 112 (46.5%) underwent mastectomy, and 35 (14.5%) underwent solely axillary dissection. Average follow-up was 61.8 months. Radiotherapy decreases loco-regional recurrence and, possibly, mortality rates of patients submitted to axillary dissection.*
3. Galimberti V, Bassani G, Monti S, Simsek S, Villa G, Renne G, Luini A. Clinical experience with axillary presentation breast cancer. Breast Cancer Res Treat. 2004;88(1):43–7. *Experience of the European Oncology Institute encompassing 50 patients committed by OBC. After careful evaluation of the breast by MRI, ultrasound and MMG, 23 subclinical lesions were identified, submitted to quadrantectomy + RT, followed by a tumoral focus identification in solely*

12 patients (24%). Twenty-seven patients without subclinical lesions were submitted to RT and axillary dissection. After a 41.3 months follow-up, 39 patients (84%) were free of distant metastasis, 2 patients had local recurrences and 5 deaths were accounted due to cancer.

4. Lu H, Xu YL, Zhang SP, Lang RG, Zee CS, Liu PF, Fu L. Breast magnetic resonance imaging in patients with occult breast carcinoma: evaluation on feasibility and correlation with histopathological findings. Chin Med J. 2011;124(12):1790–5. *Study encompassing 35 patients. 21 presented visible lesions in MRI. Sensitivity, specificity, and accuracy of MRI to detect primary malignancy were 95.2%, 71.4% and 85.7%, respectively. Invasive ductal carcinoma accounted for 81% (17/21). Estrogen receptor was positive in 46.9% (15/32), progesterone in 34.4% (11/32), Her-2 expressed in 43.8% (14/32) and 37.5% (12/32) were triple-negative.*
5. Walker G, Smith G, Perkins G, Oh J, Woodward W, Yu T, et al. Population-based analysis of occult primary breast Cancer with axillary lymph node metastasis. Cancer. 2010;116:4000–6. *SEER data review encompassing 750 cases of occult breast carcinoma. The study compared prognosis according to their classification and further treatment. The overall survival after 10 years was 64.9% regarding radical mastectomy or axillary lymphadenectomy with radiotherapy group and 47.5% for the non-treated patients ($p = 0.04$). It also concludes that mastectomy presents similar results to conservative breast therapy ($p = 0.79$).*

Paget's Disease

BBSG – Brazilian Breast Study Group

Introduction

Paget's disease (PD) is a rare breast impairment whose first cancer association was described by James Paget in 1874. PD is histologically characterized by large malignant cells presenting hyper-chromatic nucleus and pale cytoplasm inside of the epidermis that convers the nipple, exhibiting, in most cases, overexpression of HER2 in immunohistochemical tests (IHC).

Epidemiology

It accounts for 1–3% of all breast malignancies, affecting both sexes. Paget's disease incidence has been declining in recent years, which may be justified by mammography extended access and consequent earlier breast lesions detection before possible dissemination.

Physiopathology

Theories have been proposed to explain PD. We emphasize two: the epidermotropic theory, which describes a progressive mammary ducts cells impairment and subsequent dissemination along the basal membrane and nipple epidermis. This theory

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explains the similarity to nipple cells histology. On the other hand, the theory of in situ malignant transformation supports that the transformation is originated from preexisting cells in the nipple epidermis, unassociated with any other breast neoplastic processes, what may justify the absence of associated neoplasia in some cases.

Clinical Features

Clinical features are usually represented by nipple rash and eczema of the nipple, which may create hardened and ulcerated tissue, further impairing the areola. Skin thickening and vesicles may occur, promoting nipple flow. Nipple retraction is uncommon and occurs in more advanced stages, usually due to adjacent tumor. Invasive carcinoma (IC) or ductal carcinoma in situ (DCIS) are associated in up to 82–94% of cases. The majority of cases without palpable masses will present DCIS, whereas the finding of breast palpable masses (observed in more than 50% of all cases) is strongly related to IC. Isolated PD is more frequently observed in older women when compared to PD and IC. There is a greater probability to diagnose higher histological grades and negative hormone receptors (HR). Axilla is impaired in almost half of PD cases associated with IC, and HER2 is overexpressed in most invasive carcinomas.

Differential Diagnosis

The diagnosis may be delayed due to overlapping dermatological conditions, such as chronic eczema, and breast lesions associated with nipple flow, such as papilloma or ductal ectasia. Ulcer may be misdiagnosed as basal cell carcinoma. Melanoma must be included as a possible differential diagnosis, especially facing pigmented lesions.

Propedeutics

Diagnosis is usually based on clinical standards. Nipple histological analysis must be performed to suspicious lesions and encompasses incisional biopsy or cytology study. The sample must undergo IHC in order to determine the HR and HER2 status, preferably in infiltrating disease site. Due to the usual concomitant disease, radiological analysis must be carried out to improve therapeutic planning. Mammography (MMG) and breast ultrasound (US) must be performed. The most common findings encompass micro-calcifications, masses,

architectural distortion and asymmetries. Magnetic resonance imaging (MRI) plays a major role in PD since MMG and US have reduced sensitivity. On the other hand, negative imaging analyses do not ensure the exclusion of associated neoplasia.

Treatment

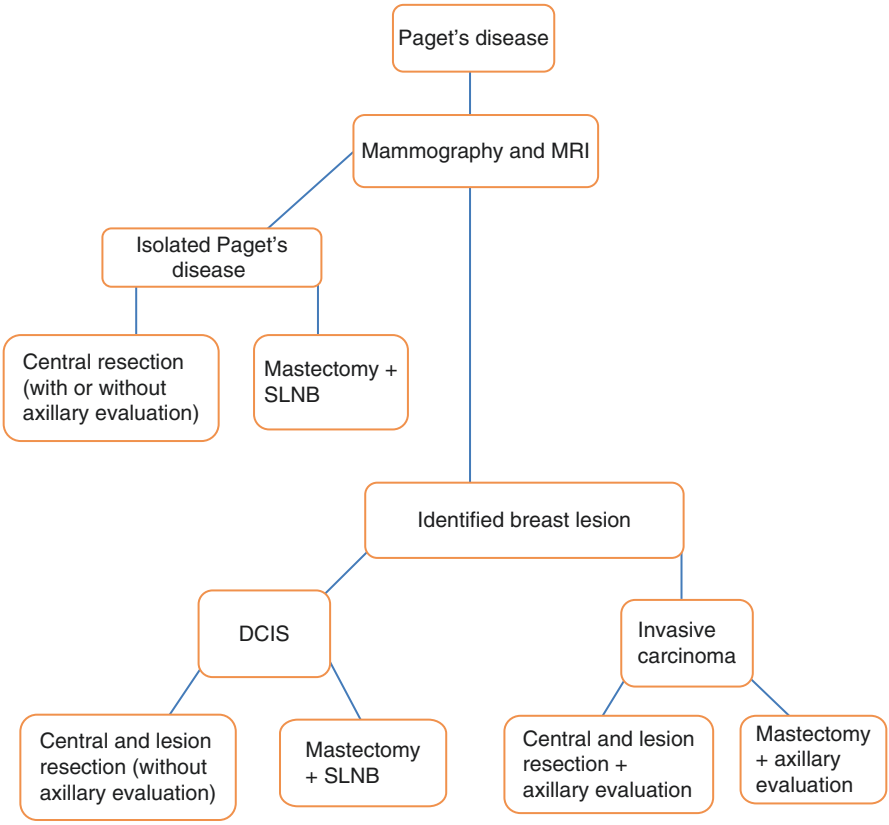
There are no available randomized trials on breast surgery regarding Paget's Disease. Several strategies have been described in the literature: mastectomy, isolated areola papillary complex resection and solely radiotherapy, for instance. Mastectomy remained the standard treatment for decades; however, the progressive knowledge regarding PD and breast surgical improvements have transformed the treatment. Breast conservative surgery (BCS) in early breast cancer stages may be applicable to PD. Studies support that even without palpable masses, acceptable rates of local recurrence after BCS were observed, not influencing disease-free survival. Conservative surgery without radiotherapy was also analyzed; however, the recurrence rates ranged from 20% to 60%. Sole radiotherapy, without surgery, has also been described as an option, especially in cases with no palpable mass or radiological abnormalities, but studies regarding the matter are limited and with a reduced number of patients.

Therefore, surgical extension relies on the presence and volume of associated diseases. The BCS consists on central resection, including complete removal of the areolar papillary complex and excision of the adjacent lesion whenever palpable or identified by image, including clear margins and obeying BCS criteria for IC or DCIS followed by whole breast radiotherapy. It includes equal criteria for conservative breast carcinoma treatment, adding the removal of the lesion and its boundaries. Facing the impossibility to preserve the breast, mastectomy, radical or not, must be performed. The decision of immediate breast reconstruction, as well as the chosen technique, must obey the same criteria employed for IC and DCIS, as well the radiotherapy indication.

Whether to analyze the sentinel lymph node in PD is not consensus, due to the lack of clinical trials. Generally, the procedure relies on associated lesions criteria; for instance, patients with IC must undergo sentinel lymph node biopsy when the axilla is clinically negative, whereas those with DCIS could undergo sentinel lymph node biopsy in selected cases, such as mastectomies indications or in suspected invasion cases. Axillary dissection following positive sentinel lymph node biopsy also must obey IC criteria and may even be spared in selected cases. Women with clinically positive axilla at the time of surgery must undergo axillary dissection.

The systemic treatment relies on clinical features and malignancy associated type, whereas the molecular biology and staging of the associated disease is crucial. Chemotherapy, adjuvant or neoadjuvant, must follow IC guideline, precisely as hormone and target therapy.

Flowchart



Flowchart 1 Paget's Disease Management

Recommended Reading

1. Bijker N, Rutgers EJ, Duchateau L, Peterse JL, Julien JP, Cataliotti L. Breast conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. Cancer. 2001;91:472–7. *A study conducted by the European Organization for Research and Treatment of Cancer (EORTC) encompassed 61 patients submitted to BCT, including women with palpable mass, supporting 7% local recurrence after a mean follow-up of 6.4 years.*
2. Lagios MD, Westdahl PR, Rose MR, Concannon S. Paget's disease of the nipple. Alternative management in cases without or with minimal extent of underlying breast carcinoma. Cancer. 1984;54:545–51. *Retrospectively evaluated a population of 200 women treated for PD over a 25-year period, with 20% of patients undergoing BCT while the rest underwent total mastectomy. The authors concluded that the surgery type performed did not influence disease-free survival.*
3. Marshall JK, Griffith KA, Haffty BG, Solin LJ, Vicini FA, McCormick B, et al. Conservative management of Paget disease of breast with radiotherapy: 10- and 15-year results. Cancer. 2003;97:2142–9. *This analysis, performed in patients with no palpable mass, supported local recurrence in 11% after BCT and a mean follow-up of 113 months.*
4. Morrogh M, Morris EA, Liberman L, Van Zee K, Cody HS 3rd, King TA. MRI identifies otherwise occult disease in select patients with Paget disease of the nipple. J Am Coll Surg. 2008;206:316–21. *58 patients evaluation comparing MRI to conventional examinations in PD, supporting that the sensitivity to detect IC in MMG and US were 79% and 74%, respectively. Regarding ISDC, the percentage was even lower (39% and 19%). MRI had, on the other hand, 100% sensitivity for IC and 44% for ISDC.*
5. Wong SM, Freedman RA, Stamell E, Sagara Y, Brock JE, Desantis SD, et al. Modern trends in the surgical management of Paget's disease. Ann Surg Oncol. 2015;22:3308–16. *Supported that PD associated to IC or ISDC incidence declined. Women were more likely to have higher histological grades, more commonly committed by negative hormone receptor (HR), and the axilla was impaired in up to 47.1% of IC cases.*

Non-epithelial Tumors

BBSG – Brazilian Breast Study Group and Márcia Cristina Santos Pedrosa

The most common non-epithelial breast tumors are phyllodes tumor, sarcomas, and lymphoma. Clinical features may be similar to carcinoma, but they significantly differ in prognosis and treatment.

Additionally to carcinoma, differential diagnoses encompass breast metastatic tumors, such as melanoma, neuroendocrine, and renal cell tumors.

Phyllodes Tumor (PT)

Originally described in 1838 by Johannes Muller, it was firstly named as cystosarcoma phyllodes, an obsolete terminology.

Its incidence ranges from 0.3% to 1% of all primary breast tumors and corresponds to approximately 2.5% of breast fibro-epithelial tumors. Bilateralism is infrequent and the highest incidence is between 40 and 50 years.

On average, 60–75% of PTs are benign. The heterogeneous nature of the tumor involves a benign epithelial component with anomalous and diverse stromal cellular component. Aggressive forms (malignant PT) exhibit histological characteristics similar to sarcoma features and may present distant metastases to almost all organs, especially to lungs and bones.

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Histopathological Classification

They are classified as benign, borderline or malignant, according to the World Health Organization (WHO) 2012 classification (Table 1). Literature data supports variable recurrence rates between benign (10–17%), borderline (14–25%), and malignant (23–30%) subtypes. It is established that metastases risk corresponds to the malignant variant (mean risk 16.71%).

Clinical Features

The initial clinical features are very similar to fibroadenoma, but present a faster growth to larger dimensions (>4 cm), which may produce bulging, distortion, or skin ulceration. Growth rate is not related to malignancy. About 20% of patients with bulky tumors have palpable lymph nodes in the axilla, which apparently inflammatory related. Axillary metastases are rare, since their dissemination is haematogenous.

Propedeutics

Preoperative clinical suspicion is important and differential diagnosis between benign PT and fibroadenoma is often difficult due to its morphological and radiological similarity.

The distinction between these neoplasms in fragments of percutaneous needle biopsy may also be difficult. Lee et al. (2007) reported characteristics to differentiate benign PT from fibroadenoma: stromal hypercellularity, fragmentation (stromal fragments with epithelium in one of the borders), and adipocyt stromal tissue.

Table 1 Histopathological PT classification, according to 2012 WHO guideline. HRA – High Resolution Area

Characteristics	Benign	*Borderline*	Malignant
Mitotic activity	<5/10 CGA	5–9/10 CGA	≥10/10 CGA
Stromal atypia	Absent or limited	Limited or moderated	Increased
Stromal cells	Slight non uniform nor diffuse cell hyper-proliferation	Moderate non uniform nor diffuse cell hyper-proliferation	Increased diffuse cell hyper-proliferation
Boundaries	Well defined	Well defined or locally invasive	Invasive

Treatment

The standard treatment for PT is surgical resection with negative margins: at least 1 cm are recommended, but lower margin does not require mandatory reoperation.

A 10-year retrospective cohort study, conducted at the Mayo Clinic and published in 2014 by Okendi et al., evaluated surgical resections (conservative surgery with negative margins shorter than 1 cm, greater than or equal to 1 cm or mastectomy) in malignant or borderline PT and supported that resections with wider margins did not impact on decreasing local recurrences. Predictive factors of higher recurrence rates were tumors greater than 5 cm, mitosis rates >10/10 HRA and stromal hyper-cellularity.

There is no indication for axillary surgery, even regarding malignant PT with palpable lymph node. Highly suspected lymph nodes must be retrieved, but radical axillary lymphadenectomy should be avoided.

Adjuvant radiotherapy role in the malignant variant is controversial. Limited data in non-clinical trials supported a greater control of local recurrences in large tumors cases, committed by notorious stromal growth. There is no indication of adjuvant pharmacological therapy.

In patients with metastatic disease, chemotherapy follows sarcoma treatment guidelines.

Factors related to local recurrence and metastasis may be seen in Table 2.

Prognostic

In SEER (Surveillance, Epidemiology, and End Results) published in 2006 encompassing 821 cases of malignant PT, overall patient survival was 84%, 77%, and 73% at 5, 10, and 15 years, respectively.

Sarcomas

Primary breast sarcomas are rare, accounting for less than 1% of breast malignant tumors. The most frequent type is angiosarcoma, followed by fibrosarcoma and pleomorphic sarcoma.

Table 2 Associated factors to local recurrences and metastasis in breast PT

Local recurrences (Benign, *borderline*, and malignant)	Metastases (*Borderline* and malignant)
Large tumors	Stromal excessive growth
Young ages	Increased cellularity or stromal atypia
Mitotic activity	Heterogeneous stromal features
Tumor necrosis	Increased mitotic index
Impaired margins or smaller than on centimeter	Impaired margins or smaller than on centimeter

Table 3 Soft tissue sarcoma staging (AJCC, 7th edition, 2010). T1 ≤ 5 cm; T2 > 5 cm; a: superficial; b: profound; N0: regional lymph nodes metastasis-free; N1: regional lymph nodes with metastasis; M1: distant metastasis

Stage IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

The clinical features encompass a painless fast growth breast mass with average size of 4.8 cm at diagnosis. Spread occurs through haematogenous tissue, usually associated with lungs, bones, and liver impairment. They rarely present lymph node involvement.

Suspected cases must undergo percutaneous thick needle biopsy, since thin needle punctures have unsatisfactory results.

The main prognostic factors are tumor degree and size. Some studies support other aspects that may also influence the evolution: number of mitoses, cellular pleomorphism, stromal atypia and infiltrative borders.

Staging of soft tissue sarcomas may be seen in Table 3.

Primary breast sarcoma treatment is mainly surgical, consisting of tumor excision with margins free of cancer cells (>1 cm), not requiring any axillary approach. In the initial stages, breast may be preserved. In larger tumors, mastectomy is usually required. There is no indication of systemic adjuvant therapy or adjuvant radiotherapy in tumors smaller than 5 cm. Larger tumors or positive margins, even after enlargement surgical, may benefit from adjuvant radiotherapy or chemotherapy, but the indication is yet controversial.

Five-year disease-free survival rates ranges from 44% to 66% and overall survival ranges from 49% to 67%.

Lymphoma

Primary breast lymphomas are rare, accounting for an incidence <0.5% among all malignant breast tumors and approximately 1–2% of extra-nodal lymphomas. They are usually non-Hodgkin type. Most are B-cell lymphomas and diffuse form is the most common histological. On the other hand, secondary breast lymphomas are common.

They mainly affect 50- to 60-year-old women and may occur in males. The main clinical feature of lymphomas regarding young women is the bilateralism, often with Burkitt's lymphoma characteristics.

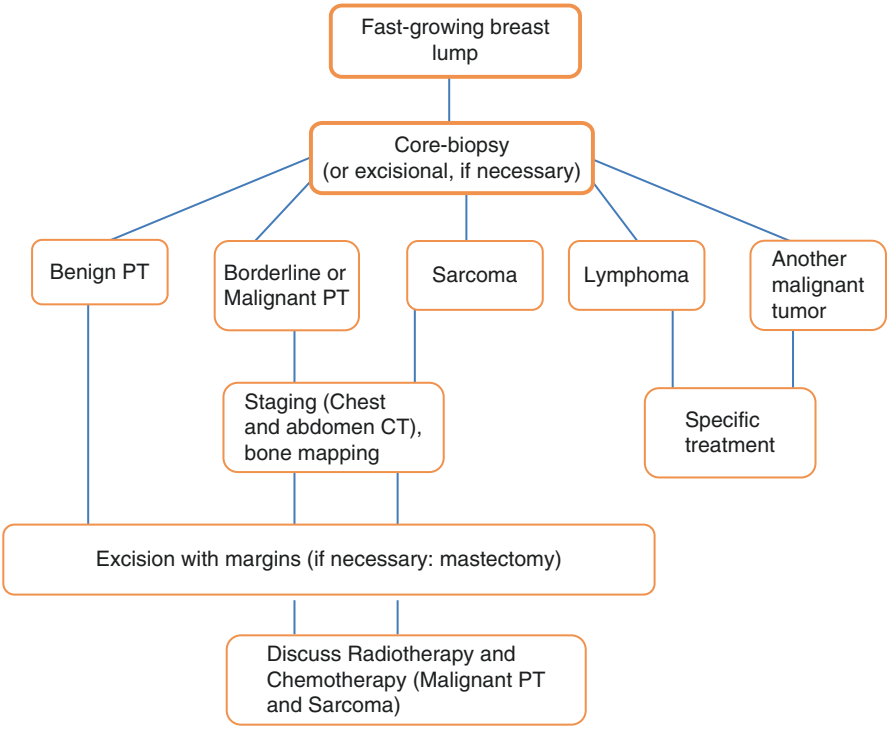
Breast primary lymphoma must encompass the following criteria: breast tissue infiltrated by lymphatic tissue, impairing ipsilateral axillary lymph nodes, absence of systemic manifestations of lymphoma, or extra-mammary lymphoma.

The clinical presentation is usually palpable, painful, and mobile mass. They are statistically associated with greater volumes than breast epithelial tumors, with an average size of 4 cm. Mammography may present a non-specific (or negative) lesion or dense circumscribed breast impairment without calcifications. Ultrasonography may reveal hypo-echogenic areas with defined borders and posterior acoustic shadow. PET-CT has an 89% sensitivity and 100% specificity diagnosing non-Hodgkin's lymphomas.

Staging is similar to other non-Hodgkin's lymphomas. Chest, abdomen, and pelvis tomography, bone marrow biopsy, complete blood testing encompassing differential count of cells, laboratorial screen, liver function, and LDH are part of the staging exams.

Treatment varies according to lymphoma subtype and stage. Surgery is generally not recommended.

Flowchart



Flowchart 1 Main non-epithelial tumors guidelines

Recommended Reading

1. Onkendi EO, Jimenez RE, Spears GM, Harmsen WS, Ballman KV, Hieken TJ. Surgical treatment of borderline and malignant phyllodes tumors: the effect of the extent of resection and tumor characteristics on patient outcome. Ann Surg Oncol. 2014;21(10):3304–9. *Retrospective analysis of 67 patients submitted to surgical treatment for phyllodes tumor (15 borderlines and 52 malignant) from 1971 to 2008 supported that the type of performed surgery and margin extension did not impact on disease-free survival. Predictive factors of higher recurrence rates were: tumors greater than 5 cm, mitosis rates> 10/10 HRA and stromal hyper-cellularity.*
2. Macdonald OK, Lee CM, Tward JD, et al. Malignant phyllodes tumor of the female breast: association of primary therapy with cause-specific survival from the Surveillance, Epidemiology, and End Results (SEER) program. Cancer. 2006;107(9):2127–33. *821 malignant phyllodes tumor patients were analysed from 1983 to 2002. Overall survival was 84% at 5 years, 77% at 10 years and 73% at 15 years.*
3. Guillot E, Couturaud B, Reyal F, et al. Management of phyllodes breast tumors. Breast J. 2011;17(2):129–37. *A Curie Institute retrospective study encompassing 165 cases of phyllodes tumors followed between 1994 and 2008, with an average follow-up of 12.65 months. Conclusion: Histological grade and tumor size were the risk factors with statistical significance for local recurrence; a pronounced risk was demonstrated in borderline PT patients and large volume tumors.*
4. Barrio AV, Clark BD, Goldberg JI, et al. Clinicopathologic features and long-term outcomes of 293 phyllodes tumors of the breast. Ann Surg Oncol. 2007;14(10):2961–70. *293 PT patients from the Memorial Sloan-Kettering Cancer Center, with a mean follow-up of 7.9 years. Pathological features: large tumor volume (> 7 cm), infiltrating borders, significant stromal proliferation with increased stromal cellularity, high mitotic index and necrosis were associated to worse prognosis. 5 patients (71%) developed metastases within 1.5 years.*
5. Al-Benna S, Poggemann K, Steinau H, Steinstraesser L. Diagnosis and management of primary breast sarcoma. Breast Cancer Res Treat. 2010;122:619–26. *Review of primary breast sarcoma. It highlights the prognosis importance of broad surgical margins. It should be emphasized that tumors larger than 5 cm or with positive margins may benefit from adjuvant QT or RT.*
6. Aviles A, Delgado S, Nambo MJ, et al. Primary breast lymphoma: results of a controlled clinical trial. Oncology. 2005;69:256–60. *Single prospective study encompassing patients with primary breast lymphoma, evaluating the impact of therapy on overall survival and disease-free survival. It supports that combined radiotherapy and poly-chemotherapy (cisplatin, doxorubicin, vincristine and prednisone) is effective in improving overall survival and disease-free survival.*

Pregnancy-Associated Breast Cancer

BBSG – Brazilian Breast Study Group

Introduction

Pregnancy-associated breast cancer is defined as breast cancer that is either diagnosed during pregnancy or within 1 year postpartum. However, solely, the first situation presents particularities that interfere in the selection of exams and treatment.

The association represents a major challenge, since the treatment of malignant neoplasms may disrupt fetal development. The ideal treatment must balance effective disease control with the preservation of the best possible maternal and fetal conditions.

Epidemiology

Breast cancer is the second most common malignant neoplasm diagnosed in pregnant women. Although this diagnosis is relatively uncommon, it accounts for 0.4% of all breast cancer diagnoses in women aged from 16 to 49 years old. As shown in Fig. 1, the incidence of disease during pregnancy increased. According to the authors, this is due to recent sociocultural changes, because women delay childbearing.

Pregnancy-associated breast cancer is similar to that in young patients: invasive ductal carcinomas (70–100%) of aggressive behavior (grade 3, angiolymphatic

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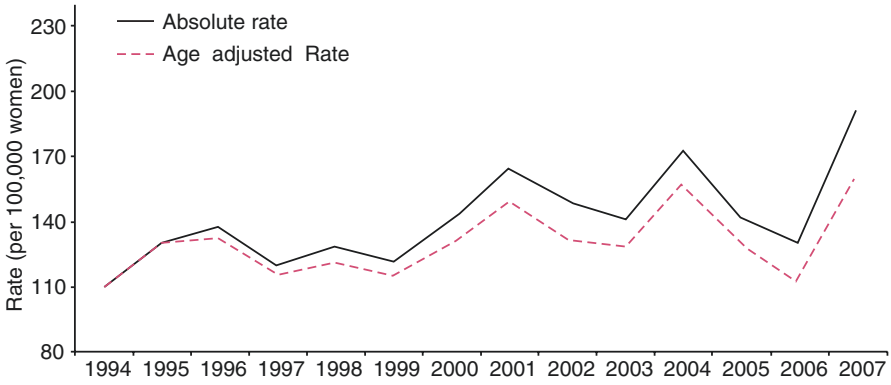


Fig. 1 Adjusted and absolute cancer rates related to patient's ages from 781.907 Australian parturient women. (Adapted from Lee et al. BJOG 2012)

invasion and negative hormone receptors). Her-2 levels are similar to the general population. Apparently, molecular biological characteristics are strongly associated with women's age, rather than the gestation itself.

Influence of Prognosis

There are conflicting reports regarding prognostic interference of gestational hormones. A meta-analysis of 30 studies, published by Azim et al. [1], compared data from 3628 pregnant women to 37,100 controls and observed that breast cancer associated with pregnancy presents worse overall survival, even after adjustments for age and tumor stage. In this study, the worst results were found in women with cancer after gestation (HR: 1.81, 95% CI: 1.34–2.46). For patients diagnosed within gestational period, the result was not significant (HR: 1.30, 95% CI: 0.95–1.79).

Pregnancy discontinuation does not improve the survival of breast cancer patients and must not be recommended. However, facing a first trimester of pregnancy diagnosis, the risks of delaying treatment must be considered and therapeutic abortion may be discussed.

It is apparently impossible to establish conclusive definitions regarding gestation influence on prognosis, since the available studies present important methodological limitations, with diverse confounding variables.

In a recent multi-centric case-control study, no statistically significant difference in disease-free survival or overall survival was observed when women previously diagnosed with positive estrogen receptors cancer who became pregnant versus the non-gestational group were compared. Gestation does not appear to influence the prognosis of previously treated patients with early breast cancer, even in the positive estrogen receptor group. However, the ideal time for pregnancy has not yet been

established, and an individualized conduct is required since, especially in this group of patients, pregnancy will involve questions regarding endocrine therapy duration and eventual pregnancy interruptions. In St. Gallen 2015 consensus, the issue was widely debated, and the most accepted recommendation is to wait at least 18 months after breast cancer treatment to recommend a possible gestation.

Diagnosis

Early diagnosis are not common during pregnancy; consequently more advanced stages are associated with breast cancer simultaneously to gestation. Therefore, even in pregnancy, any suspicion of breast lesion must undergo evaluation. Most patients are clinically diagnosed with a nodule on self-examination or by prenatal care. Generally, this group of patients is younger than 40 years and are not routinely screened. Any persistent breast or axillary mass for over 2 weeks must be radiological evaluated and, if indicated, a biopsy must be performed. Eighty percent of breast masses identified during pregnancy are benign, so the possibility of malignant neoplasia must not be neglected. The differential diagnosis includes fibroadenoma, fibrocystic impairments, galactocele, lactation adenoma, adipocytic tissue alterations, abscess, and, more rarely, sarcoma, leukemia, and lymphoma.

Ultrasound is the initial examination for any breast complaint during pregnancy. Radiation methods, such as mammography, must be cautiously indicated and require abdominal protection. Radiation toxicity is widely known to fetal doses greater than 0.1 Gy, regardless of gestational age. Although imaging tests present lower levels, their employment must be avoided or replaced whenever possible. Fetus exposure to ionizing radiation on the mammogram is less than 0.03 mGy and abdominal protection reduces the risk to an exceptionally lower level.

Magnetic resonance imaging (MRI) of the breasts may be indicated; however, there is no data about the usual contrast (gadolinium). In breastfeeding women, MRI contrast may be safely employed; however, the images may be difficult to interpret due to mammary changes during lactation. It is recommended that breastfeeding be discontinued for 12–24 hours after gadolinium administration and posteriorly resumed.

Percutaneous needle biopsy is the preferred method for diagnostic confirmation. Thin needle puncture must be avoided, since gestation is a factor responsible for false-positive cytology.

Usual staging may be performed, but bone scintigraphy must be replaced by magnetic resonance imaging without contrast. PET / CT do not compose traditional evaluation and there are few reports of its employment during pregnancy. Facing the requirement of nuclear medicine exams, palliative measures, such as bladder catheterization to prevent accumulation of radioactive contrast in the bladder, must be employed.

Surgery

Surgical and anesthetic procedures are relatively safe. The patient must be placed at 15° left lateral decubitus position to avoid cava compression and it is recommended to monitor fetal heart rate during surgical procedure since the end of the 2nd trimester. Currently, there is no consistent evidence favoring regional anesthesia or over general anesthesia employment for pregnant patients.

Surgical cancer treatment must follow the same standard oncological principles. As most patients require chemotherapy due to late diagnosis and / or young age, radiotherapy may usually be postponed to after birth. Therefore, conservative surgery is almost always authorized.

Sentinel lymph node biopsy employing radio-colloid (technetium 99 m) may be performed. However, dyes employment, such as patent blue (category C drug in pregnancy), must be avoided.

Breast reconstructions with implants may be employed. Due to gestational tissue impairments, techniques employing myocutaneous flaps are limited.

Radiotherapy

Fetal complications risk regarding doses beyond 0,1 Gy are described as following. The Table 1 demonstrates the main side effects divided by gestational age.

There are several reports regarding radiotherapy employment in pregnant women, mainly to treat central nervous system diseases.

Luis et al. (2009), evaluated 109 neonates submitted to radiation during intrauterine life and related adverse effects in 13 of them, regardless of the gestational age of treatment. However, the authors state that these adversities are not related to ionizing therapy employing.

Diverse authors support that women must undergo conventional radiotherapy technique during gestation, arguing that an effective treatment dose is insignificant, especially in the first trimester.

A conclusion regarding radiotherapy employment during gestation must be rational. Generally, treatment may be avoided or postponed after birth. However,

Table 1 Main potential fetus risks divided by gestational age regarding ionization exposure

Gestational Age	Potential Fetus Risks
Previous to implantation	0,1 Gy: 1,5% abortion rate (animal studies)
	1 Gy: 50% abortion rate (animal studies)
1–8 weeks	Mental impairment; Microcephaly; Multiple organs impairment
8–15 weeks	Mental impairment, microcephaly, bone, ocular and genitals malformations
15–25 weeks	Growth restriction, reduced risks regarding structural malformations, microcephaly and mental impairment risk
Above 30 weeks	Greater cancer risk due to ionization; intrauterine growth restriction

there are situations where the radiotherapy is indispensable, either due to risk of death or for appropriate cancer treatment. In these cases, patient must be advised regarding treatment risks and benefits.

Drug Therapy

Drug therapy in embryogenic stages (1st trimester) must be avoided. However, most studies authorize the medications employment from 14 to 35 weeks of pregnancy. Although most studies evaluating chemotherapy safety after the first trimester were retrospective, rates of fetal malformations were, on average, 3–5% lower compared to similar general population. However, there is a relatively higher risk of premature rupture of membranes, restriction of intrauterine growth, and preterm labor.

The use of anthracyclic-based chemotherapy regimens is the treatment of choice, supported by several reports indicating fetal safety. Chemotherapy must be discontinued 3–4 weeks before birth in order to avoid hematological disorders;

Schemes containing methotrexate are contraindicated due to elevated fetal trophoblastic tissue impairment risk.

The dose of chemotherapy in pregnant patients must be similar to non-pregnant women.

The European Society of Medical Oncology (ESMO) advises that taxanes may be employed in selected cases during pregnancy (triple-negative or HER2-positive) or when facing anthracyclines contraindications.

The employment of trastuzumab (category D drug) is not yet allowed during pregnancy. Exposure to trastuzumab during pregnancy has been associated with oligohydramnios manifestations, such as pulmonary hypoplasia, skeletal abnormalities, renal failure, and neonatal death. Anti-HER2 therapies must be reserved for situations of absolute necessity and after patient's consent.

Bisphosphonates are not allowed to pregnant women as it may cause bone impairment and hypocalcaemia. Despite reports supporting the this substance employment without side effects, the use is yet contraindicated.

The endocrine therapy must not be performed. The FDA has classified tamoxifen as D category drug due to its craniofacial impairment, ambiguous genitalia, and fetal death risks. Other therapies, such as aromatase inhibitors, oophorectomy, and GnRH analogue block are not encompassed as therapies of choice for premenopausal women.

Pediatric Development Specificities

Apparently, children exposed to breast cancer treatments during intrauterine life present the same development as the general population. Amant et al. (2012) analyzed 70 children exposed to the aforementioned situation with a mean follow-up of 18 months of life and reported that cognitive development, cardiac function, and

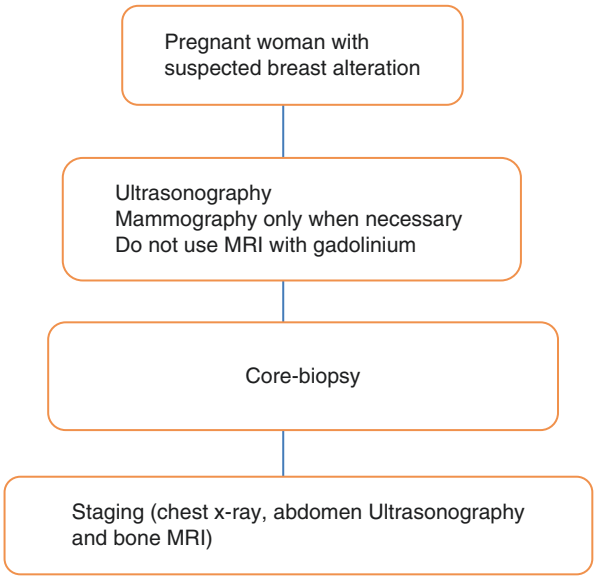
hearing were normal. Other studies also attest this fact and relate eventual issues reported with prematurity. Therefore, the iatrogenic abbreviation of gestation must always be avoided.

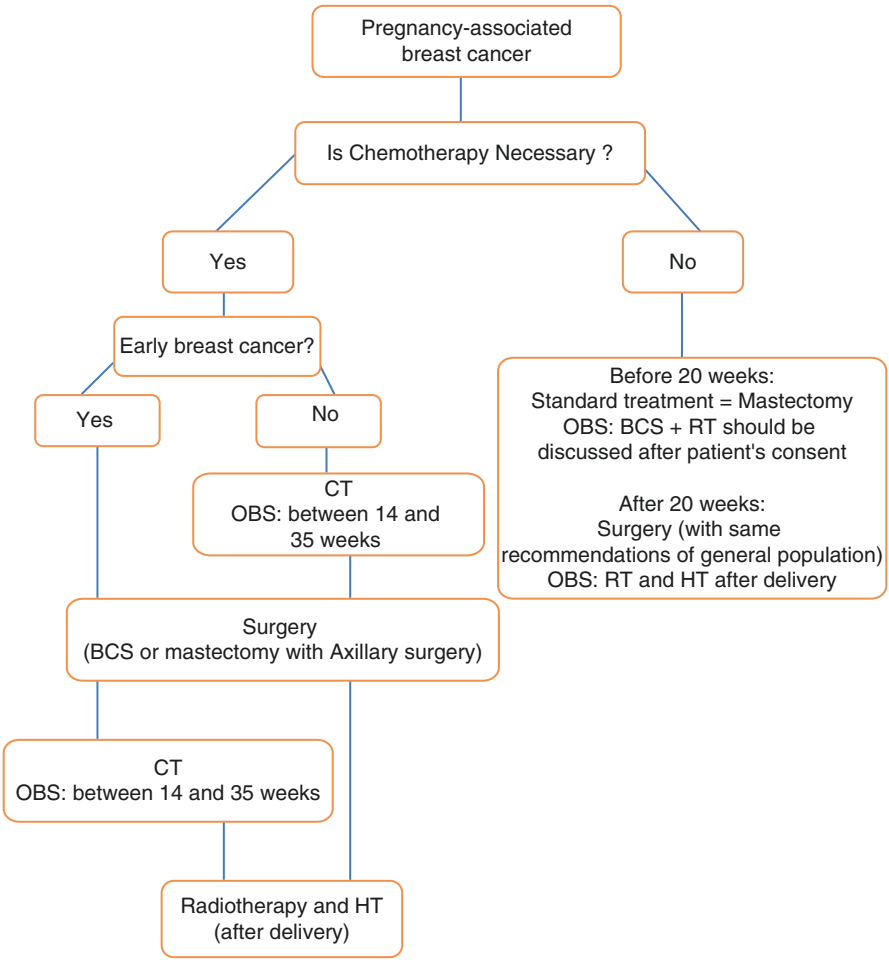
Conclusion

Pregnancy must not be considered as an aggravating factor for breast cancer. Breast cancer diagnosis, treatment, and prognosis are similar to the general population, with few variations. Regarding the management of gestational breast cancer, a multidisciplinary team is recommended to establish an individualized treatment plan, taking into account gestational age, tumor biology, and clinical staging. Obviously, the safest therapies for the fetus are preferred. Drugs supported by limited studies or known to be deleterious, must be avoided whenever possible and, if necessary, solely employed with patient's consent.

Flowchart

Flowchart 1 Pregnancy-associated breast cancer - diagnosis guidelines





Flowchart 2 Pregnancy-associated breast cancer - treatment guidelines

Recommended Reading

1. Azim HA Jr, Santoro L, Russell-Edu W, Pentheroudakis G, Pavlidis N, Peccatori FA. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. Cancer Treat Rev. 2012;38:834–42. *A meta-analysis of 30 retrospective cohorts that observed worse prognosis of breast cancer associated to pregnancy, even after adjusting age and stage groups. In this study, the worst prognosis was related to puerperal or breastfeeding patients.*
2. Cordeiro CN, MD GML. Breast cancer in pregnancy: avoiding fetal harm when maternal treatment is necessary. Breast J. 2017:1–6. *The review addresses breast cancer associated to pregnancy treatment and recent updates on surgical and chemotherapeutic treatment safety, regarding oncological and fetal outcomes.*
3. Krishna I, Lindsay M. Breast cancer in pregnancy. Obstet Gynecol Clin N Am. 2013;40:559–71. *Review article on breast cancer associated to pregnancy, focusing on all stages of treatment.*
4. Loibl S, Han SN, Von Minckwitz G, Bontenbal M, Ring A, Giermek J, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 2012;13:887–96. *A 447 patient's follow-up diagnosed with breast cancer associated to gestation, undergoing standard oncological treatment, which revealed the same disease prognosis as historical series and neonatal complications solely in cases of preterm birth.*
5. Shachar SS, Gallagher K, Mcguire K, Zagar TM, Faso A, Muss HB, et al. Multidisciplinary management of breast cancer during pregnancy. Oncologist. 2017;22:1–11. *Multidisciplinary guideline to treat breast cancer associated to pregnancy.*

Breast Cancer in Young Women

BBSG – Brazilian Breast Study Group and Márcia Cristina Santos Pedrosa

Introduction

Although there is no consensus in the literature, breast cancer in young women usually is defined when it occurs before 40 years old.

This is a rare event in such an age group, representing about 10% of cases of breast cancer diagnosed between the ages of 35 and 44, 2.0% between 20 and 34 year-olds, and only 0.1% of cases below 20 years of age.

In developing countries, there is a higher prevalence of cases in younger women when compared to developed countries. As these patients are outside the screening group and also because they present biologically more aggressive tumors (34% triple-negative and 22% Her2+, Azim and Pattridge [1]), they generally present a more advanced clinical stage when compared to the group of patients above 40 years old.

Figure 1 shows the staging of 9278 women with breast cancer under the age of 39, collected by FOSP (*Fundação Oncocentro São Paulo*) and INCA from 2000 to 2009. It is noted that most of the diagnosed cases were between the IIA and IIIB stages, with more than 60% in stage IIB or higher.

Characteristics of Breast Cancer in Young Women

There are several peculiarities in this age group that differ from the others and that impact on the therapeutic approach:

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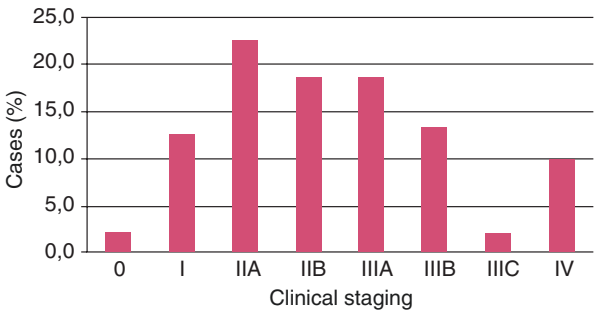


Fig. 1 Clinical staging in women below 40 years old. (Source: Pinheiro, Lauter, Medeiros et al. RBC 2013)

- More aggressive disease, with higher frequency of high-grade tumors, negative hormonal receptors and lymphovascular invasion (LVI), and lower rates of carcinoma in situ;
- Many studies relate earlier age with worse prognosis – which may be due to the factors mentioned above associated with the greater clinical staging at diagnosis;
- Higher deleterious mutations prevalence, mainly BRCA 1 and 2;
- Higher multicentricity and multifocality rates;
- Predominance of dense breasts and consequently greater use of MRI in the initial evaluation, which is associated with higher rates of mastectomies;
- Higher rates of risk reducing contralateral mastectomies;
- Desire of fertility preservation;
- Higher impact of hormone therapy on quality of life when compared to older women.

Clinical Condition and Propedeutics

The diagnosis often is made by a patient's palpable nodule or other clinical changes, since this group is outside the routine of the screening.

Multicentricity, multifocality, and dense breasts are common characteristics among women under 40 years old, and the use of magnetic resonance imaging becomes more frequent. This leads a change in the therapeutic planning up to 30% of cases and with a surgical conversion rate conservative treatment for mastectomy between 15% and 35%. However, some studies show that in up to 1/4 of the cases, mastectomy was considered unnecessary after definitive anatomopathological results. Up until now, no data have been found associating routine magnetic resonance imaging in this age group, with an increase in disease-free survival or overall survival.

Percutaneous biopsy is the best choice for histological diagnosis, and the immunohistochemical study is mandatory in this age group, where there is a greater predominance of triple-negative tumors and Her2+. This may be a decisive factor in the choice of initial therapy.

Although there are no differences in the recommendation for initial staging according to age, there are studies that show a higher prevalence of synchronic metastasis in cases of triple-negative tumors, despite the initial clinical stage, suggesting that in these cases imaging should be instituted, even when there is no symptomatology.

Treatment

Historically, it is known that rates of local recurrence after conservative treatment (CT) are higher in younger women. However, when evaluating overall survival rates, there are no differences between CT and mastectomy. On the other hand, in randomized clinical studies on CT versus mastectomies, subgroup analyzes in women younger than 40 years were generally hampered by small sampling.

In a large Danish premenopausal and breast cancer women series, Kroman et al. showed local recurrence rates after CT of 15% in women under 35 years and only 3% in those between 40 and 49 years. From the evaluation of the risk of metastasis and death versus type of treatment (CT or mastectomy) there were no significant differences between the groups studied (<35 years, 35–39 years, 40–44 years and 45–49 years).

In a retrospective analysis of Data collected from the Surveillance epidemiology and Results (SEER), showed in population of 14.764 women, aged between 20 and 39 years old with breast cancer, that conservative surgery was performed in 45 %, while mastectomy in 55% of cases. No significant differences were observed in relation to overall survival (OS) and specific mortality when compared both types of treatment. About one -third of patients had negative hormone receptor (HR) tumors. In the multivariate analysis, factors associated with poor prognosis were: Age at diagnosis, race, histologic grade, lymph node status, and progesterone receptor.

Few studies have evaluated molecular subtype and type of surgery in young women. In a series with 1930 women with triple-negative breast cancer, 289 (15%) are less than 40 years old, Rodosa et al. showed that the younger group presented more advanced stage in the initial diagnosis and higher rates of mastectomy, axillary lymph node dissection and chemotherapy.

However, no significant differences were observed regarding disease-free survival at 5 years and local recurrence during the mean follow-up right over 6 years. Age and type of surgery were not associated with a higher risk of metastases. Therefore, despite higher rates of local recurrences, CT is considered equivalent to mastectomy in young women.

Contralateral mastectomy indication is more frequently among young women with breast cancer, mainly because of a higher percentage of them can be allocated in the high family / genetic risk group. There are several recommendations for indication of genetic testing in this population, especially when the cancer presents basal-like phenotype. It is estimated that up to 30% of women with breast cancer before the age of 35 may be carriers of known deleterious mutations.

Some retrospective studies have shown benefit from the risk-reducing contralateral mastectomy in young women, but age alone should not be a determining factor for this surgery. Other factors should be taken into account, such as BRCA mutation and high family risk. There are no prospective studies evaluating the impact of contralateral mastectomy on disease-free survival and overall survival, and the strongest evidence to date is restricted to BRCA mutation group.

Systemic Treatment and Radiotherapy

Systemic treatment should not be different from the group of women over 40 years. The drug choice of chemotherapy and target therapy is based on staging and immunohistochemical profile. Differently, hormone therapy may be influenced by the age range among younger women. Data from the TEXT and SOFT studies showed that the benefit of ovarian suppression associated with the aromatase inhibitor was markedly higher in women younger than 35 years and at high risk for recurrence (GH3, N +, mainly 4 or more lymph nodes, T > 2 cm), reaching a 15% survival gain when compared to the group that only underwent tamoxifen hormone therapy.

Radiotherapy in the young patients follows the same principles and indications of that in patients over 40 years, whether for conservative surgery or mastectomy. However, age may be considered a risk factor for recurrence when associated with lymphovascular or positive axilla invasion after mastectomy, and it's an indication criterion.

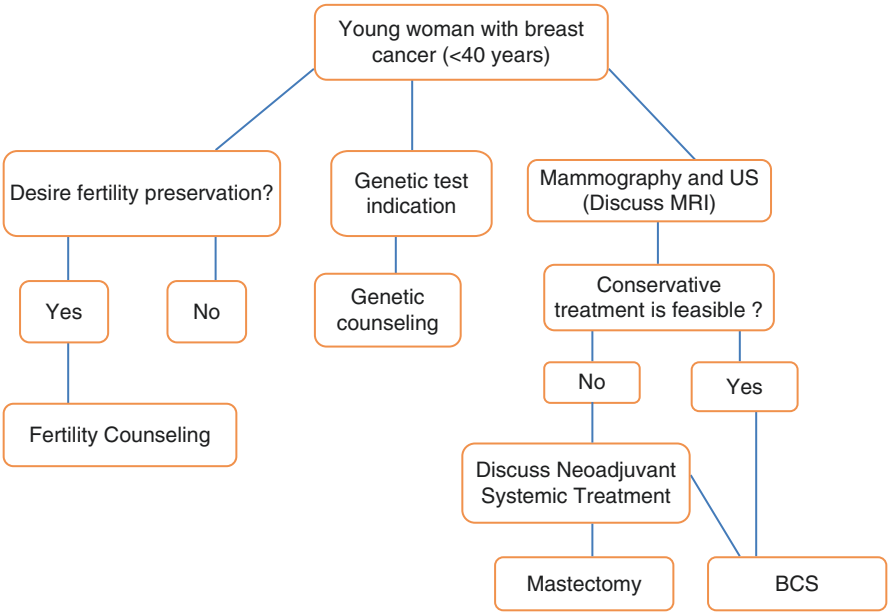
Boost should always be performed in patients under 40 years of age, as demonstrated in the EORTC randomized clinical trial published in 2007 by Bartelink H et al. The group that received the boost had a 50% reduction in local recurrence in 10 years.

Breast partial radiotherapy is contraindicated for this group of patients. Criteria of ASTRO and ESTRO place these patients in the high-risk group for local recurrence with this method of treatment, so it should be avoided.

Preservation of Fertility

About 15% of breast cancers occur in women in the reproductive range, and chemotherapy has a cytotoxic effect on ovaries, which can irreversibly impair fertility. Currently the strategies for preservation of fertility include the use of GnRh analog during chemotherapy (POEMS study), with cryopreservation of ovarian tissue and ovules being valid options. The best option would be the preservation of embryos, as long as the patient has a partner who agrees with the fertilization.

Flowchart



Flowchart 1 Management of Breast Cancer in young women

Recommended Reading

1. Azim HA Jr, Partridge AH. Biology of breast cancer in young women. Breast Cancer Res. 2014;16:427–36. *Review on the biological characteristics of breast cancer in young women and the impact on the treatment and outcome of the disease.*
2. Boughey J, Attai DJ, Chen SL, et al. Contralateral Prophylactic Mastectomy (CPM) Consensus statement from the American Society of Breast Surgeons: data on CPM outcomes and risks. Ann Surg Oncol. 2016;23(10):3100–5. Publication of a review compiling the results of the main studies on risk-reducing contralateral mastectomy.
3. Hwang ES, Lichtensztajn DY, Gomez SL. Survival after lumpectomy and mastectomy for early stage invasive breast cancer. Cancer. 2013;119:1402–11. *Analysis of the California-US database between 1999 and 2014 showing that conservative treatment was associated with better disease-free survival rate, regardless of age and hormonal status.*
4. Mahmood U, Morris C, Neuner G, et al. Similar survival with breast conservation therapy or mastectomy in the management of young women with early-stage breast cancer. Int Radiat Oncol Biol Phys. 2012;83(5):1387–93. *SSER analysis shows no benefit from mastectomy in young women below 39 years of age and with initial breast cancer*
5. Rodosa JC, Eaton A, Stempel M, et al. Evaluation of local and distant recurrence patterns in patients with triple-negative breast cancer according to age. Ann Surg Oncol. 2017;24(3):698–704. *A study that evaluated the impact of age on outcome (free survival and disease and metastasis) of patients with triple-negative tumors. Age and type of surgery were not associated with risk of metastasis, but with classic factors such as lymph node staging and lymphovascular invasion.*

Breast Cancer in Elderly Women

BBSG – Brazilian Breast Study Group

Introduction

Elderly patients are more likely to receive incomplete treatment for breast cancer because they generally present with physical comorbidities that may limit cancer treatment. In addition, cancer in this group tends to be less aggressive and life expectancy is consequently lower.

On the other hand, observational studies demonstrate negligence in the diagnosis and treatment of these women. Such approaches may result in worsening of the disease, with consequent worsening of quality of life and survival.

Definition of "Elderly"

The definition of "elderly" is controversial. While Brazilian law grants benefits for people over 60, the World Health Organization sets 65 years as the cutoff point. Some developed countries only allow people to retire after age 70. Most of the clinical studies on breast cancer considered this latter age as limiting for the selection of patients.

From a medical point of view, age matters less than clinical comorbidities, but age is usually directly proportional to comorbidities, as it can be seen in Fig. 1.

Age should therefore be used as a criteria to select patients for more detailed clinical evaluation. There are nomograms that allow predicting life expectancy, but whenever possible, it is suggested that the evaluation be joint with a specialized clinical professional.

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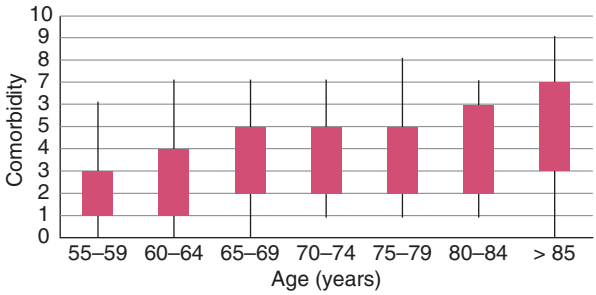


Fig. 1 Number of diseases according to age (confidence interval and median)

Number of Elders and Life Expectancy

Data from the Brazilian Institute of Geography and Statistics (IBGE, in Portuguese) have shown a higher aging rate of the Brazilian population in the last 50 years, similar to what happened in developed countries. Currently, about 15% of Brazilians are 60 y-o or older, and it is estimated that by 2035 this number will exceed 20% or 25% of the population.

Brazilian women's life expectancy is around 78 years; meanwhile, those who reached 70 years of age have an expectation of an additional 15 years, while those who reached 80 years may live 10 more years.

Epidemiology

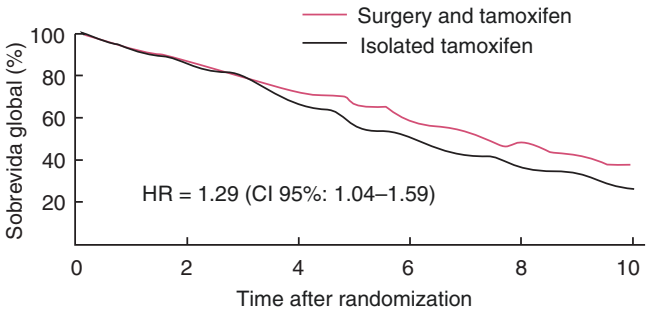
The risk of breast cancer increases with age, and the risk of neoplasia at age 75 is estimated to be twice as high as in women aged 50 years.

Many elderly women with breast cancer will die as a consequence of the disease and not from complications of any comorbidities. This is contrary to the general concept: about 20% of patients over 70 years with initial cancer die from the disease, and in those with locally advanced neoplasm specific mortality reaches 40%.

There is negligence in the screening of women over 70 years, causing a higher proportion of palpable tumors (larger than 2 cm) at diagnosis.

Although there is a higher proportion of luminal tumors in the elderly population, about 20% of the patients present more aggressive subtypes.

Analyses have shown that there is a greater proportion of elderly patients receiving incomplete therapy, with less indication of surgery, radiotherapy and systemic therapy. These numbers can be explained not only by the clinical limitations in these women, but also by the lower supply of adequate treatment performed by health professionals, which ultimately worsens the evolution of the disease.



Number in risk:

Surgery and tamoxifen	225	192	162	135	107	71
Isolated tamoxifen	230	199	152	120	87	57

Fig. 2 A study comparing surgery with hormone therapy against hormone therapy alone in women over 70 years of age with initial breast cancer. (Source: Adapted from Fennessy et al. [2])

Surgical Treatment

Clinical studies were made to evaluate the impact of surgery on tumors with hormone receptors. Comparison of surgery associated with hormone therapy with endocrine therapy alone demonstrated equivalence, despite better local control in the first group, but the longer follow-up also demonstrated an advantage in the survival among individuals in the operated group, as it can be observed in Fig. 2.

In general, surgery in the elderly should follow the usual guidelines for cancer treatment: retrospective analyses show little risk in breast surgery over 70 years, with mortality below 0.5% above 80 years.

Surgical time can be optimized by avoiding exaggerated procedures. Reconstructive surgery, for example, should be individualized and more complex techniques should be discouraged.

Axillary surgery can also be individualized in the elderly. Randomized studies demonstrated safety in not approaching the axilla in selected initial tumors.

In 2012, Martelli et al. randomized 238 women over 65 years of age with initial tumors (T1 N0) to perform axillary surgery or observation: after a 15-year follow-up, overall survival and axillary relapse rate were similar. The *International Breast Cancer Study Group* (IBCSG) also evaluated the surgery in this setting (women over 60 years with negative axilla) with similar clinical outcome.

Radiotherapy Treatment

Some studies have evaluated the benefit of radiotherapy in early tumors (cT1-2, cN0) with the presence of positive hormone receptors and undergoing conservative surgery and hormone therapy (tamoxifen). The characteristics of the main studies can be seen in Table 1.

The conclusion of these studies, individually or in joint analysis, demonstrated that radiotherapy does not alter the overall survival in these patients, but it significantly reduces the local recurrences. The meta-analysis of these studies can be seen in Fig. 3.

Systemic Treatment

Few data have been collected about patients over 70 years of age in randomized clinical trials; however, most guidelines suggest adopting the same therapies used in younger women as long as clinical conditions and performance status (PS) are favorable.

Table 1 Main studies that evaluated the benefit of radiotherapy in patients over 70 years and initial tumors with positive hormone receptors treated with conservative surgery and tamoxifen

Study	Year	*N*	Tumor size	Hormone Receptor
PRIME II	2015	1326	<3 cm	RE or RP +
CALGB 9343	2004	636	<2 cm	RE +
Fyles et al.	2004	325	<5 cm	Any (81% RE +)
Fisher et al.	2002	100	<1 cm	Any

Source: Adapted from Chesney et al. [1]

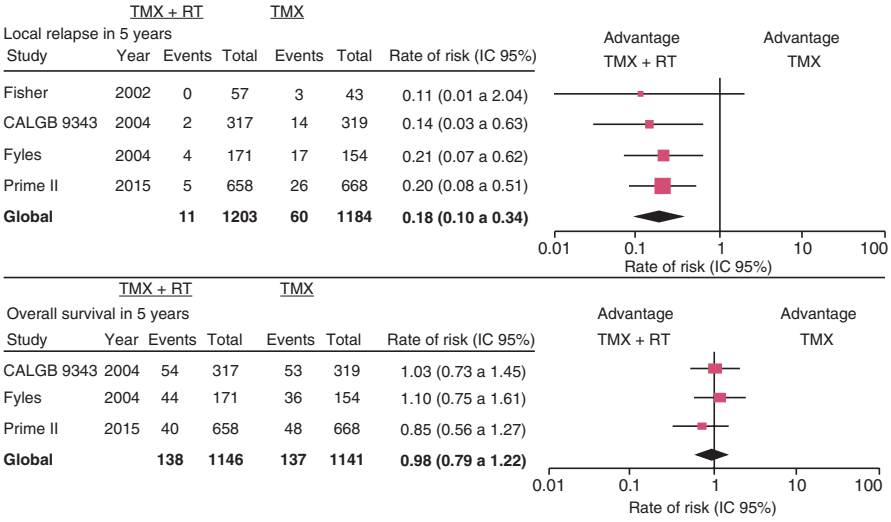


Fig. 3 Meta-analysis of randomized studies in women over 70 years of age with initial breast cancer and positive hormone receptor undergoing conservative surgery and tamoxifen (TMX). The studies evaluated the impact of radiotherapy (RT) on local recurrence and overall survival. (Source: Adapted from Chesney et al. [1])

Systemic therapy in the elderly can also be individualized. Studies on hormone therapy with tamoxifen or aromatase inhibitors have demonstrated oncological efficacy with few side effects, but the latter is generally preferred because of the lower risk of thromboembolic events.

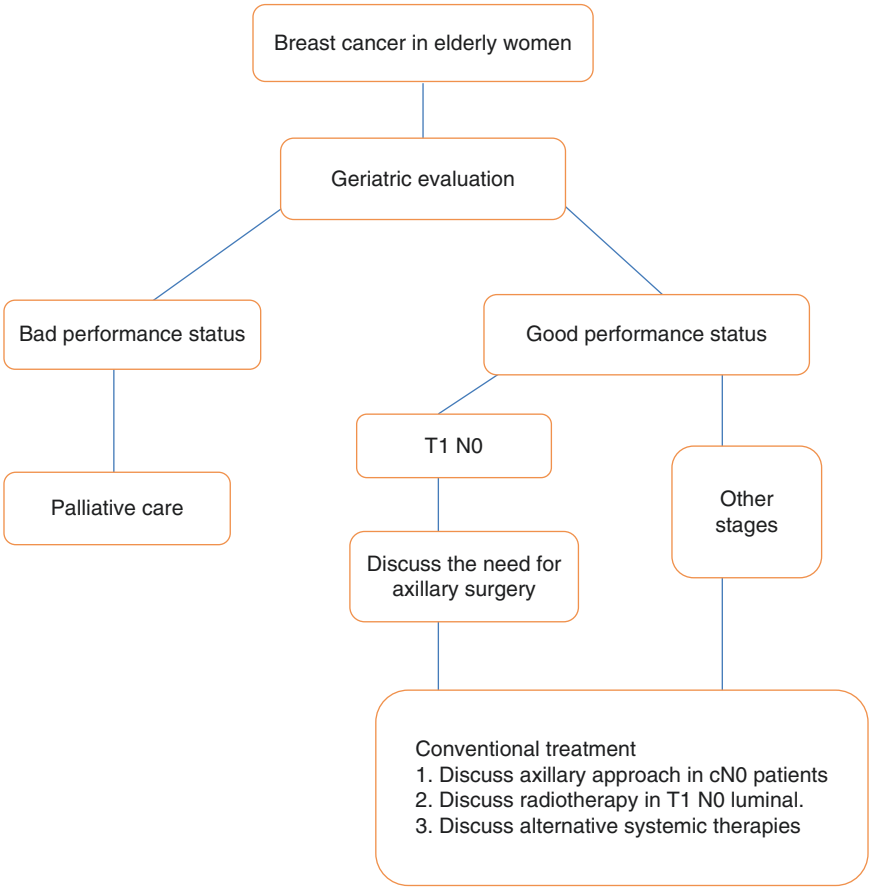
Chemotherapy is more controversial because efficacy tends to be lower and the side effects more frequent, but women with favorable PS may take gold standard treatment. Some authors advocate that patients with limitations to conventional chemotherapy use less effective (but less toxic) therapies such as Capecitabine or non-antracyclic or taxane therapies (for example: CMF).

Targeting with trastuzumab is generally indicated, and its association with four-cycle taxane may be a reasonable option with fewer side effects. There is no conclusive data yet on the use of anti-HER2 therapy alone or associated with hormone therapy.

Conclusion

The treatment of breast cancer in elderly women should be individualized, respecting the clinical limitations and the aggressiveness of the tumor. The treatment, in principle, should follow the guidelines valid for the general population, but some particularities can be discussed, such as the omission of axillary surgery and radiotherapy, in addition to the use of alternative systemic therapies.

Flowchart



Flowchart 1 Suggestion of breast cancer approach in elderly women

Recommended Reading

1. Chesney TR, Yin JX, Rajaee N, Tricco AC, Fyles AW, Acuna SA, et al. Tamoxifen with radiotherapy compared with Tamoxifen alone in elderly women with early-stage breast cancer treated with breast conserving surgery: a systematic review and meta-analysis. Radiother Oncol. 2017;123(1):1–9. *Meta-analysis of the main studies that evaluated the benefit of radiotherapy in patients over 70 years and initial tumors with positive hormone receptors treated with conservative surgery and tamoxifen. Radiotherapy reduced local recurrences (RR = 0.18 [95% CI: 0.10-0.34]), but did not change overall survival (RR = 0.98 [95% CI: 0.79-1.22]).*
2. Fennessy M, Bates T, MacRae K, Riley D, Houghton J, Baum M. Late follow-up of a randomized trial of surgery plus tamoxifen versus tamoxifen alone in women aged over 70 years with operable breast cancer. Br J Surg. 2004;91(6):699–704. *A randomized clinical study in patients*

over 70 years of age with initial breast cancer and positive hormone receptors. The study compared surgery and tamoxifen with tamoxifen alone. After 10 years of follow-up, women who had surgery had a longer relapse-free survival time (HR = 4.41 [95% CI: 3.31-5.58]), overall survival (HR = 1.29 [95% CI: : 1.04-1.59]) and specific survival (HR = 1.68 [95% CI: 1.15-2.47]).

3. Freedman RA, Keating NL, Partridge AH, Muss HB, Hurria A, Winer EP. Surveillance mammography in older patients with breast cancer-can we ever stop?: a review. JAMA Oncol. 2017;3(3):402–9. *Review on breast cancer screening in women over 70 who have had the disease. The authors suggest biennial mammography for all women with life expectancy above 5 years, similar to that recommended for those without prior disease.*
4. Martelli G, Boracchi P, Orenti A, Lozza L, Maugeri I, Vetrella G, et al. Axillary dissection versus no axillary dissection in older T1N0 breast cancer patients: 15-year results of trial and out-trial patients. Eur J Surg Oncol. 2014;40(7):805–12. *A randomized clinical study with 238 patients with T1 N0 tumors comparing the performance of axillary surgery or not. After 15 years of follow-up, overall survival was similar (37% vs. 33%) and axillary recurrences were acceptable (0% vs. 5%).*
5. Smith IE, Fribbens C. Management of breast cancer in older and frail patients. Breast. 2015;(Suppl 2):S159–62. *Review on the treatment of breast cancer in women over 65 years, with emphasis on the possibilities of systemic therapy.*

Multifocal, Multicentric, and Bilateral Carcinoma

BBSG – Brazilian Breast Study Group

Multifocal/Multicentric Carcinoma

Introduction

Multicentricity is defined by some authors as two of more foci located in different quadrants or 5 cm away from each other, but inside the same quadrant. Other authors also define tumors of different genetic clones or separated by normal mammary tissue.

Multifocality, in its turn, is defined by two or more tumor foci located in or near the same quadrant.

A meta-analysis containing 22 studies, published in 2015 with 67,577 patients, found 9.5% of multifocal/multicentric tumors.

With mammographic screening and improved accuracy of imaging methods, multicentric tumors have become important issues in the management of breast cancer.

Results of randomized clinical trials comparing total mastectomy and quadrantectomy, with or without complementary radiotherapy, showed no difference in disease-free survival or overall survival in multiple carcinoma patients compared to single uniforms.

The presence of multiple breast tumors has traditionally been considered contraindication to conservative surgery. In fact, many surgeons continue to propose mastectomy in this situation because initial studies have demonstrated a high rate of relapse after conservative surgery. However, advances in the techniques of oncoplastic surgery allowed a greater number of conservative treatments in this scenario, due to the possibility of resection of a greater amount of tissue, providing oncological safety with good aesthetic result.

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Staging and Prognosis

The clinical importance of multiple breast tumors occurs as a consequence of the increase in the rate of conservative surgical procedures and the improvement in the accuracy of the diagnostic imaging tests. Multifocal tumors have been reported in 30% of surgical pieces of mastectomy.

The American Joint Committee on Cancer (AJCC) classifies the multicenter tumor in the "T" category (size) by the largest diameter of the tumor, and not the sum of the multiple tumor foci, using the suffix (m) to indicate the multicentricity.

Some authors have correlated lymph node involvement with the sum of tumor diameters. However, in most cases, multivariate analyses consider similar lymph node positivity in single and multiple tumors, considering the corresponding tumor diameter.

According to the AJCC, multicentricity is not related to the prognostic parameter.

Diagnosis

Despite the successful selection of patients for conservative surgery (CS) with conventional and low-cost routine examinations (clinical examination, mammography, and ultrasonography), the increase in magnetic resonance imaging (MRI) in selected cases increased the detection of multifocal/multicentric tumors.

The Role of Mammary Ultrasonography (US)

Ultrasonography has been widely used in the Brazilian population due to low cost, accessibility, and good tolerance of the patients, but its impact on the selection of patients for conservative breast surgery is conflicting. Berg and Gilbreath reported 15% of multifocality identified after mammary US in their series, and Moon et al. demonstrated 14% of 201 patients with multifocal or multicentric tumors identified by mammary US. In contrast, Golshan et al. found only 18% of abnormalities on ultrasonographic examination in 426 patients. Out of these, only 12 patients (2.8%) had neoplasms.

The Role of Magnetic Resonance Imaging (MRI)

The high sensitivity of the MRI causes many radiologists to advocate the idea of the need for this exam in the indication of CS. This is not justified. Despite the identification of additional tumor between 25% and 30% of the patients by MRI, it is difficult to correlate their importance in the clinical impact of MRI, as data in the literature show that 90–95% of the patients selected for CS based on clinical

evaluation only and mammography did not present recurrence in 10 years of follow-up. A meta-analysis published by Houssami in 2017, including 19 studies on the preoperative MRI evaluation, showed no decrease in local recurrence rates in patients submitted to this test.

The increase in the indications for mastectomy after preoperative MRI occurred at the beginning of the use of this exam, when it was not possible to perform biopsies, and the radical conduct was defined by the radiological finding.

With MRI, we have the ability to detect tumor foci previously identified only in the evaluation of surgical specimens. However, the clinical implications of identifying these additional lesions are still uncertain. To date, there are no data from studies that justify the routine use of MRI in the surgical planning of breast cancer.

Treatment

Conservative Surgery *Versus* Mastectomy

There are few studies in the literature regarding conservative surgery (CS) in multiple breast tumors. Initial studies, with a limited sample of patients and short follow-up periods reported a high rate of local recurrence after CS. Currently new studies have demonstrated the feasibility of the method with oncological safety similar to CS in unifocal tumors. However, most of these studies have evaluated a small number of patients; thus CS is still a relative contraindication in multifocal/multicentric tumors of the breast (Table 1). The inconvenience with conservative surgery in these cases is found in the aesthetic result. In motivated and well-selected patients it may be an option, using oncoplastic surgery techniques, with good aesthetic results and oncological safety.

Lymph Node Biopsy and Multifocal/Multicentric Tumors

The presence of multifocal/multicentric tumor is not contraindication for sentinel lymph node biopsy. Studies of lymphatic drainage of the breasts indicate that all quadrants of the breasts drain into the same lymph node. Both the

Table 1 Conservative surgery for multiple breast tumors

	Carpenter (2008)	Gentilini (2009)	Lim (2009)	Okumura (2004)	Bauman (2010)	Eriylmaz (2011)
No. of patients	56	476	147	34	22	59
Follow-up (months)	44	73	59	45	42	20
Recurrence	1.7%	4.9% MF/8% MC	2%	3%	4.5%	–

MF multifocality, *MC* multicentricity

radiopharmaceutical radio-guided technique and the use of dye have high accuracy for lymph node detection.

In 2011, Gentilini et al. published the experiment of the European Institute of Oncology with sentinel lymph node biopsy in 337 patients with multicentric tumors, with an average follow-up of 5 years. Axillary relapse after negative sentinel was only 2.2%, confirming the safety of the method.

Bilateral Breast Cancer

Tumors diagnosed bilaterally at the same time, or 3–6 months apart (divergent data in the literature), are called synchronic; when the temporal difference between the diagnoses exceeds 3–6 months, they are called metachronous.

The incidence in the literature is rather variable, with rates ranging from 0.5% to 9%. These rates are from studies that used less effective methods of diagnosis compared to the present time.

Risk Factors for Bilateral Breast Cancer

Some risk factors for bilateral breast cancer are now known: young patients, lobular carcinoma, large tumors, high family risk, and specific genetic mutation.

In these situations, an accurate propaedeutics approach is recommended, and in selected patients magnetic resonance imaging is indicated.

Special attention should be paid to patients with lobular carcinoma in situ (LCIS). They are at increased risk for bilateral disease regardless of the primary location of the LCIS. These patients, when choosing follow-up or chemoprophylaxis with tamoxifen, should undergo any propaedeutics indicated for patients at risk.

Treatment

The surgical planning of bilateral carcinoma is based on the staging of each breast. The efficacy of bilateral conservative surgery has been proven in several studies. The association with oncoplastic techniques allows for satisfactory static results.

Considering patients who are candidates for bilateral mastectomy, reconstruction can be safely planned in most cases.

The indications for adjuvant therapy are based on the characteristics of the tumor of worse prognosis.

Hormone therapy is indicated in the presence of positive hormone receptors, despite its unilateral or bilateral positivity.

Prognosis

Modern series suggest a worse prognosis for bilateral tumor patients when compared to unilateral ones. This difference is small in synchronous tumors, but increases significantly in metachronous tumors diagnosed within a shorter interval of 3–5 years from the initial tumor.

Metachronous tumors diagnosed later have a more favorable prognosis than the earlier ones, demonstrating perhaps a greater aggressiveness and lack of response to the adjuvant treatments of diagnosed tumors in a short period of time.

Recommended Reading

1. Houssami N, et al. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. Breast Cancer Res Treat. 2017. *Meta-analysis including 19 studies on the evaluation of preoperative magnetic resonance imaging and surgical results. By increasing this preoperative evaluation the chances of ipsilateral and contralateral mastectomy also go up.*
2. Iacconi C, Galman L, Zheng J, et al. Multicentric cancer detected at breast MR imaging and not at mammography: important or not? Radiology. 2016;279(2):378–84. *Retrospective study of 73 patients with multicentricity diagnosed only through resonance. In 75% of cases, they were invasive carcinomas and in 25% of cases they were larger than 1.0 cm.*
3. Lyman GH, Temin S, Edge SB, et al. American Society of Clinical Oncology Clinical Practice. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2014;32(13):1365. *Guideline of the American Society of Clinical Oncology, guiding the accomplishment of sentinel lymph node resection in multicentric tumors.*
4. Nijenhuis MV, Rutgers EJ. Conservative surgery for multifocal/multicentric breast cancer. Breast. 2015;24(Suppl 2):S96–9. *Treatment of multicentric tumor with conservative surgery (CS), chemo-neoadjuvant and radiotherapy results in low rates of local recurrence. CS may be indicated in patients who are eligible for CS criteria and with satisfactory aesthetic results.*
5. Vera-Badillo FE, et al. Effect of multifocality and multicentricity on outcome in early stage breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014;146(2):235–44. https://doi.org/10.1007/s10549-014-3018-3. Epub 2014 Jun 14. *Meta-analysis including 22 studies, with 67,577 women; 9.5% of multicentric tumors were found. In univariate analysis, multicentricity presents worse overall survival, disease-free interval, and local recurrence in 5 years*

Breast Cancer in Men

BBSG – Brazilian Breast Study Group

Introduction

Breast cancer in men is rare, with about 2600 cases/year in the United States, accounting for approximately 1% of all cases. About 11% of the cases involve in situ disease. The mean age at diagnosis is 67 years, and that is higher when compared to women. Few specific prospective studies are available to better characterize biology and treatment, despite the increasing numbers of survivors.

Pathophysiology

Most cases express hormone receptors, whereas the triple-negative subtypes and HER2 represent about 1 and 5% of the cases, respectively. Lobular carcinoma is very uncommon due to lack of lobular development in men. Major risk factors include Klinefelter's syndrome (XXY), environmental risk, age, radiation exposure, family history, and other genetic abnormalities. Some drugs that alter the "hormonal environment" used to be linked to the risk of breast cancer, for example, finasteride. However, this drug does not appear to increase the risk of breast cancer in men despite increasing the risk for gynecomastia.

The presence of mutation is another important risk factor. Change in BRCA2 is found in 4–14% of the non-selected cases. The lifetime risk for breast cancer in men with this mutation is approximately 5–10%. Pathogenic mutation of BRCA1 is also reported in some families, but it is less frequent and with a lower lifetime risk (1–5%). The National Comprehensive Cancer Network (NCCN) guideline includes

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breast cancer in men as a factor for investigation of hereditary breast/ovarian cancer syndrome.

Despite some similarities, it is possible that the evolutionary behavior of breast cancer in men is different from the one in women, but this is not well understood and we do not know how to deal with these differences. The rate of cases with positive hormone receptors is higher in men, and it does not increase with age; also, histological grade does not present a direct correlation with clinical outcome, as it occurs with breast cancer in women. The prognosis of breast cancer in men is similar to that in women, though, when matched by stage. The Afro-American race has worse evolution, as it happens in women.

Clinical Condition

The palpable nodule is the most common finding, usually in a retro-areolar situation, and it may occur in another position within the breast in 20% of cases. Skin ablation and retraction can also be observed, especially in more advanced lesions, such as papillary flow and pain. Lymph node involvement is more common in men, possibly related to the more advanced staging at the time of diagnosis.

Differential Diagnosis

The main differential diagnosis is gynecomastia. In fact, most of the times that a man is investigated due to breast complaint, the conclusion is benign in more than 90% of the cases, with gynecomastia accounting for about 80% of these changes.

Propedeutics

Investigation of cases is similar to the procedure for cancer in women. When malignancy is suspected, a diagnostic mammogram can be performed for planning, and a histological sample should be obtained through needle biopsy. Occasionally, ultrasonography may aid in the diagnosis and collection of tissue. There is no definite

role for the use of magnetic resonance imaging in men. Immunohistochemistry follows the same principle for female neoplasia, as well as staging exams, which should be requested when there is presence of symptoms or in a more advanced stage.

Treatment

The approach should be multidisciplinary, in order to maximize the effectiveness of therapeutic resources.

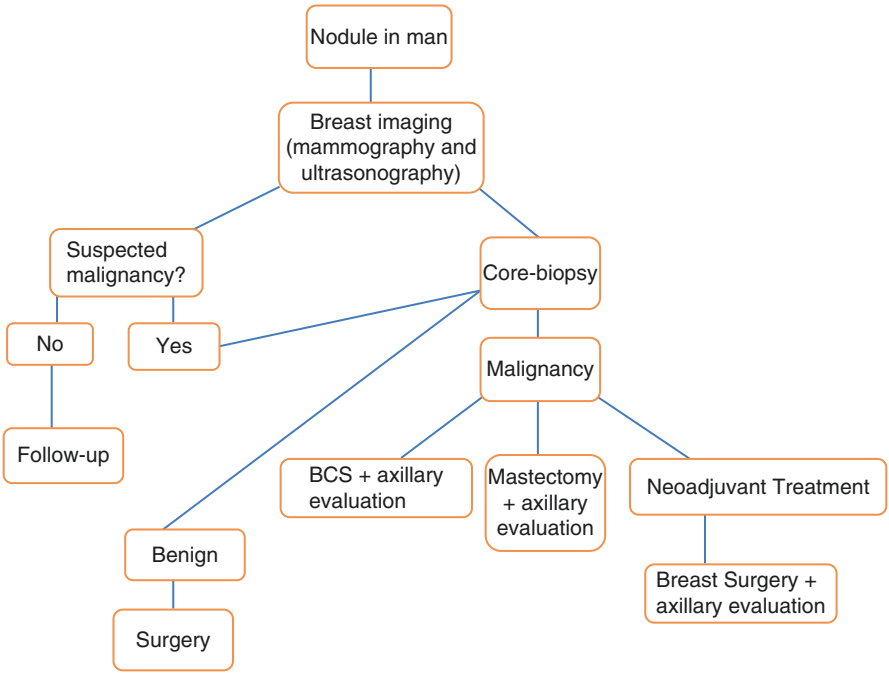
Most men undergo mastectomy because tumors often involve the central region of the breast, and breast reconstruction is rarely used, even considering lipofilling. The indications for adjuvant radiotherapy (RT) after mastectomy have been increasing over the years, and approximately one third of cases with lymph node involvement will receive treatment.

Data obtained from *Surveillance, Epidemiology, and End Results (SEER)* showed survival benefit in the addition of radiotherapy after mastectomy in male patients with positive axilla.

Conservative breast therapy is feasible, as long as the lesion is unicentric, and resection is done with free margins. Adjuvant radiotherapy is recommended. A recent study has shown comparable survival to mastectomy in early breast cancer. Sentinel lymph node (SL) can be performed if the axilla is clinically negative, following the same recommendations as invasive carcinoma in women. Some studies showed identification rates higher than 90%, with acceptable false-negative results. There are no important studies on preservation of the axilla after positive sentinel lymph node (men were not included in axillary preservation studies after metastatic SL), as well as the use of SL after neoadjuvant chemotherapy: in the latter two situations, case-by-case evaluation and common sense will determine the best approach.

In general, systemic therapy should follow the guidelines used for women. Chemotherapy, with or without biological therapy, is usually recommended for locally advanced tumors, young age, high grade, and lymph node involvement. The hormone therapy follows the same principles, tamoxifen being the usual choice. There is little data on the use of aromatase inhibitors in men, mainly because there is controversy whether it should be performed associated with gonadal suppression or not.

Flowchart



Flowchart 1 Nodule management in men

Recommended Reading

1. Dietz JR, Partridge AH, Gemignani ML, Javid SH, Kuerer HM. Breast cancer management updates: young and older, pregnant, or male. Ann Surg Oncol. 2015;22(10):3219–24. *Review study on breast cancer in men: mastectomy is the most used surgical approach, although conservative surgery associated with radiotherapy is acceptable in selected cases.*
2. Flynn LW, Park J, Patil SM, Cody HS, Port ER. Sentinel lymph node biopsy is successful and accurate in male breast carcinoma. J Am Coll Surg. 2008;206:616–21. The sentinel lymph node in breast cancer in men had a 97% and identification rate and false-negative rate at 8%, similar to that found in women.
3. Freedman RA, Partridge AH. Emerging data and current challenges for young, old, obese, or male patients with breast cancer. Clin Cancer Res. 2017;23(11):2647–54. *Review that highlights risks for breast cancer in men, as well as the differences between male and female cancer. At the moment, there is an effort of the scientific community to conduct studies that can improve the understanding of cancer in men.*
4. Shak S, Palmer G, Baehner FL, Millward C, Watson D, Sledge GW. Molecular characterization of male breast cancer by standardized quantitative RTPCR analysis: first large genomic study of 347 male breast cancers compared to 82,434 female breast cancers. J Clin Oncol. 2009;27:15s. *The use of Oncotype Dx in men, although showing some similarities, evidenced*

a greater expression of estrogen receptor and progesterone, compared to women, as well as greater expression of Ki67.

5. Zaenger D, Rabatic BM, Dasher B, Mourad WF. Is breast conserving therapy a safe modality for early-stage male breast cancer? Clin Breast Cancer. 2016;16:101–4. A study that demonstrated survival after conservative breast cancer therapy in men comparable to mastectomy in cases of initial breast cancer (T1-T2, N0).

Local Recurrence After Surgery

BBSG – Brazilian Breast Study Group

Introduction

Local recurrence (LR) is the return of ipsilateral breast disease, while locorregional relapse is the resurgence of neoplasia in the breast and/or drainage chains after conservative surgery or mastectomy for the treatment of cancer. The psychological impact may be significant for women, since it means a new surgical approach, new alternatives of systemic treatment, causing a feeling of intractability of the disease and decrease of the possibility of cure. LR rates have been decreasing over time: earlier diagnosis, evolution of imaging and pathological analysis, and the addition of adjuvant treatment (especially systemic) are factors related to better locorregional control.

Epidemiology

LR after conservative breast therapy (conservative surgery (CS)) tends to be generally later (3–4 years) when compared to mastectomies (2–3 years); in the latter it is usually related to true recurrence, while in the CS it is more often associated to a new primary tumor. Metastasis at the concomitant distance to LR after mastectomy is more common than when compared to CS. Most LRs after invasive carcinoma through CS (80%) will be infiltrating and 5–15% associated with distant metastasis, whereas carcinoma in situ in the primary presentation will have 50% invasive recurrence. The prognosis after LR is variable. In NSABP studies, for instance, distance-free survival rates were 67% for women with negative axilla and 51% for those with positive axilla; and overall survival was between 60% and 70%.

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Risk Factors for Recurrence

Adjuvant radiotherapy (RT) and margins are determinant for LR. The irradiation of the breast in the CS, for instance, reduces in 70% the risk of LR in 10 years in the invasive disease, decreasing the mortality after 15 years. Thus, in general, one death is avoided every four recurrences, according to meta-analysis. The margins should also be free of neoplasia, because when they are positive/compromised, the risk of local recurrence more than doubles. Clinical-pathological factors may influence LR: intraductal component, young age, tumor size, positive lymph node, grade, angiolymphatic invasion, negative or low expression of hormone receptors (HR) are example. Tumor biology is also very important in local control, and triple-negative tumors are those whose risk of relapse is greater, both after conservative surgery and after mastectomy. Better biomarkers can also assess risk, such as genomic signatures, especially Mammaprint and Oncotype.

True Recurrence Versus New Primary Tumor

The differentiation between new neoplasia and true recurrence is important after CS: 50–90% of recurrences occur in the same quadrant of the primary tumor, determining true recurrence in most cases. Most studies evaluating the outcomes of a true recurrence compared to a new tumor showed that the second primary tumor had more favorable biological characteristics, with better overall survival rates and disease-free time.

Some parameters can be used to differentiate them. The interval between initial surgery and local recurrence can be decisive: the longer the time between events, the greater the chance of being a new tumor. The imaging and biology features may also help, such as histological type, HR and HER2 expression, as well as breast location and radiological appearance.

Clinical Aspects

In CS, LR is usually diagnosed by radiological exams, mammography, and ultrasonography most of the time, but the alterations caused by RT, such as fibrosis and local thickening, make diagnosis difficult. Skin involvement after LR in CS is uncommon and usually with unfavorable prognosis. Magnetic resonance imaging (MRI) in the follow-up of these patients may be added to this scenario; however, its use is still controversial because despite being more sensitive than conventional examinations, MRI is not specific and may result in unnecessary biopsies. LR after mastectomy is usually detected by physical examination.

Tissue sample, aspiration puncture, and fragment biopsy means a fundamental step, the latter being preferred because it allows for immunohistochemistry.

Systemic staging is recommended because of the increased risk of concomitant disease in distant organs.

Local Treatment After Local Recurrence

Once distant metastasis impairment is disregarded, LR should be treated initially. The therapy will depend on what has been done previously (conservative surgery or mastectomy, axillary dissection or sentinel lymph node biopsy, previous radiotherapy or absence). The age, interval between the primary tumor and LR, biological characteristics of the new disease, and patient preference should also be considered.

LR After Mastectomy

About 85% of cases present single lesions, with local resection possible, but extensive relapse may make surgical resection difficult. Radiation therapy should be associated, if not previously performed or if feasible, regardless of the surgery.

LR After Conservative Surgery

The established standard treatment is mastectomy. A new CS, also called "reintervention," may be indicated in selected patients, such as the absence of previous RT, in small tumors with long intervals, or in those cases the clinical condition prevents radical surgery. The main limitation of this approach is the possibility of RT, being a new irradiation evaluated case by case.

Axillary Evaluation After LR

Axillary disease is classically found in 15–25% of LR cases. The discussion is about the local modifications related to the first procedure, which may hinder the lymphatic drainage of the breast tissue, making it anomalous, especially after mastectomy. A meta-analysis of 26 studies observed anomalous drainage in 47% of the cases, the main sites being contralateral axilla and internal mammary chain.

In the sentinel lymph node (SL) era, however, a new axillary approach is feasible, since in 2/3 of the cases there will be identification of the SL, especially if the previous surgery was conservative or with minimal anterior axillary approach. In general, after CS and SL prior, axillary evaluation is recommended, while in mastectomy or cases of previous axillary dissection in CS, the recommendation is only for resection of the lesion in the chest wall or in the breast, respectively.

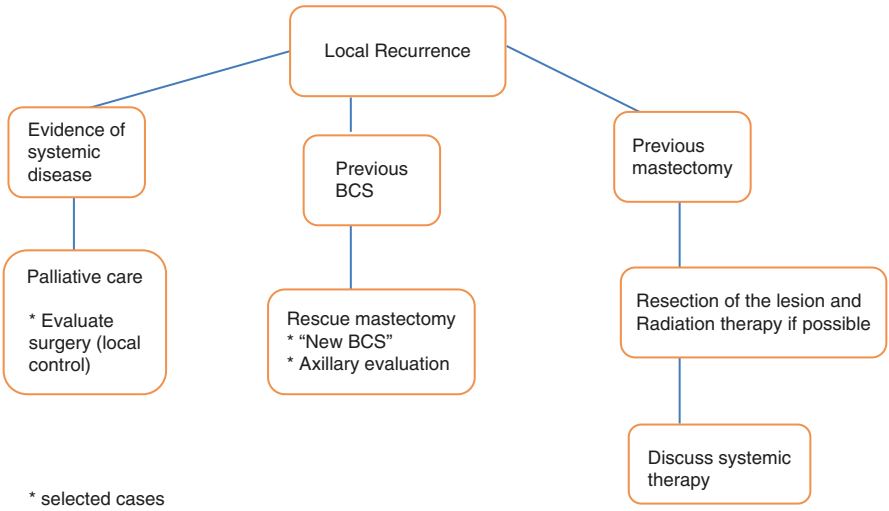
Locorregional Relapse

In axillary relapse, lymph node salvage surgery is recommended in spite of previous surgery, if possible. In the presence of injury in other drainage chains, isolated RT is the treatment of choice.

Systemic Treatment After Local Recurrence

Systemic therapy with adjuvant chemotherapy (CT) after LR alone is a reason for discussion, because although it has an impact on the initial treatment of cancer, there are few data in the LR scenario and they should be evaluated in a personalized way, since these patients have a significant risk of metastasis at the subsequent distance, ranging from 45% to 80%. Recently, the CALOR (Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer) study selected women with LR for CT or observation after resection with LR margin and demonstrated that therapy should be recommended, especially in tumors with negative HR. The limitation of this study is sample size.

Flowchart



Flowchart 1 Local recurrence management

Recommended Readings

1. Braunstein LZ, Taghian AG, Niemierko A, et al. Breast-cancer subtype, age, and lymph node status as predictors of local recurrence following breast-conserving therapy. Breast Cancer Res Treat. 2017;161(1):173. *The risk of recurrence after conservative surgery is greater in non-luminal subtypes, young patients and number of compromised lymph nodes, which are similar to post-mastectomy risks.*
2. Hattangadi-Gluth JA, Wo JY, Nguyen PL, et al. Basal subtype of invasive breast cancer is associated with a higher risk of true recurrence after conventional breast-conserving therapy. Int J Radiat Oncol Biol Phys. 2012;82(3):1185–91. *Patients with baseline histological subtype and HER2 presented higher rates of local recurrence after surgical treatment. Chemotherapy and target therapy act concurrently to decrease local recurrence.*
3. Huang E, Buchholz TA, Meric F, et al. Classifying local disease recurrences after breast conservation therapy based on location and histology: new primary tumors have more favorable outcomes than true local disease recurrences. Cancer. 2002;95(10):2059. *Patients with a new tumor have better survival rates when compared to patients with true recurrence; however, they present a higher chance of contralateral carcinoma. Patients with true recurrence have a greater chance of distant metastasis.*
4. Maaskant-Braat AJ, Voogd AC, Roumen RM, et al. Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. Breast Cancer Res Treat. 2013;138(1):13–20. *A meta-analysis with 692 patients showed an identification rate of 84.5% in the present study. Among these, 47% of the lymph nodes were found in extra-axillary homolateral chains, mainly the contralateral axilla and the internal mammary chain.*
5. Yi M, Buchholz TA, Meric-Bernstam F, Bedrosian I, et al. Classification of ipsilateral breast tumor recurrences after breast conservation therapy can predict patient prognosis and facilitate treatment planning. Ann Surg. 2011;253(3):572. *Evaluation of 397 patients, differentiating true recurrence and second primary tumor, which present different clinical evolution.*

Breast Cancer After Aesthetic Surgery

BBSG – Brazilian Breast Study Group

Introduction

Breast aesthetic surgery is one of the most performed and widely accepted procedures throughout the Western world. According to data from the International Society of Aesthetic and Plastic Surgery (ISAPS), in 2015 approximately 1,490,000 augmentation mammoplasties were performed in the world. In Brazil, approximately 166,000 breast augmentation mammoplasties were performed and about 80,000 lifting and reduction breast surgeries in the same year. This is important because, according to the Brazilian National Cancer Institute (INCA), 57,960 new cases of breast cancer were expected in 2016, occurred in 2016 and about 10% of these women had undergone breast aesthetic surgery. Therefore, this is a special situation, since few relevant data is available regarding this increasingly frequent condition in the population.

It is interesting that, for each aspect that we will discuss, a distinction should be made between breast augmentation with implant and reduction mamoplastie. Although both are aesthetic surgeries, they constitute completely different surgical techniques, presenting diverse peculiarities in the diagnosis and treatment of an eventual associated breast cancer and reduction mammoplasty are separately issued, due to different techniques involved, presenting specific diagnosis and treatment characteristics facing associated breast cancer.

Breast Implant and Breast Cancer

There was a great controversy in the 1980s, But nowadays prosthesis and breast cancer association are ruled out. Numerous studies, including meta-analyses, have supported safe data of silicone implants in relation to breast cancer risk.

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However, the Food and Drug Administration (FDA) recently published data associating silicone prostheses to anaplastic large cell lymphoma (ALCL), a rare type of T-cell lymphoma. The estimated incidence ranges from 1:500,000 to 1:3,000,000 cases in women with implants. The cure rates, however, are greater than 90% and the treatment consists on the complete removal of the implants and the overlaying capsule, in order to obtain free margins. No chemotherapy or radiotherapy are required whenever the tumor is restricted to the capsule (in situ). In case of invasion, treatment may involve chemotherapy, radiotherapy, and lymphadenectomy. The diagnosis is still notoriously challenging, and it is believed that the disease is underreported. It must be suspected in cases of late or recurrent seroma, as well as when solid images appear on the capsule or when the patient presents a palpable nodule close to the implant. The diagnosis must be performed by seroma needle aspiration and specific lymphoma screening, as many laboratories do not routinely perform such evaluation. Pathophysiology seems to be associated to implants textured rather than smooth ones, although there is no clear explanation. Due to its extreme rarity, it is difficult to make definitive conclusions about its etiology.

Breast Cancer Screening

Previously we never had consensus, But an increasing amount of data supports no negative effect to early diagnosis associated to mammoplasties (augmentation or reduction).

- Reduction mammoplasty: It was believed that parenchymal fibrosis and calcifications due to the procedure, and the consequent healing process, could mask breast cancer diagnosis or mimic suspicious lesions, increasing the number of unnecessary biopsies. Literature demonstrates that despite the aforementioned changes related to surgery, most of the time, they present as benign changes easily interpreted by the radiologist.

Muir evaluated over 4000 women with reduction mammoplasty in a screening program and found that there was no significant difference in the number of recalls for complementary imaging and biopsy when compared to a similar group without mammoplasty. The only difference observed was a lower percentage of carcinoma in the group submitted to mammoplasty, demonstrating that the procedure is associated to breast cancer risk reduction.

- Augmentation mammoplasty with implants: Silicone implants does not increase breast cancer risk; But it is still debatable if breast implant interfere with breast cancer diagnosis. The implant is radiopaque and may obscure some portions of the mammary gland, distorting the parenchyma or simply preventing adequate compression. Thus, in these cases, it is necessary to perform maneuvers that detach the implant from the mammary gland (Eklund maneuver) and to employ complementary methods such as ultrasound and MRI. To assess implants integ-

rity, MRI is recommended every three years, according to FDA recommendations, although this indication is also not consensual.

Several publications supported that breast cancer patients with and without prosthesis have similar rates of overall and disease-free survival. Tumor size as well as lymph node status are not different between the two groups in most studies. Additionally, patients with implants are most likely to clinically diagnose lesions than those without implants, due to the easier assessment of palpable lesions (implant compression against the breast parenchyma), and more frequent perform self-examination and medical consultations. Therefore, it should not be stated that implants impairs early diagnosis of breast cancer, nor that they have worse prognosis, as previously supported, despite presenting with more palpable tumors.

However, implant breast positioning is particularly important. Regarding higher risk patients, it is observed that implant placement in the sub-muscular pocket if preferable, since radio-opacity of this area due to the implant is separated from the glandular parenchyma by the pectoral muscle, thus facilitating the mammographic evaluation. However, there are no scientific-based data available on this suposed benefit, and the approach of placing the implant in retro-muscular or retro-glandular space must not be based on this hypothesis.

Breast Surgical Treatment

Following breast cancer diagnosis, it is possible that the surgical therapy is influenced by the type of previously performed aesthetic surgery. However, indications of conservative surgery or mastectomy must follow the same criteria adopted for patients without prior breast surgery.

- Reduction mammoplasty: This may be associated to a higher risk of skin or nipple and areola necrosis when performing a skin sparing mastectomy or nipple sparing mastectomy due to the presence of extensive scars, which may impair flaps vascularization. Several studies supported that prior mammoplasty is a risk factor for postoperative complications
- Augmentation mammoplasty with prosthesis: there is no consensus regarding gold-standard therapy for these patients. From the surgical point of view, conservative surgery is feasible as long as free margins are obtained. Most of the times, however, women seeking breast augmentation already have low glandular volume. In addition, after placing the implant, a significant atrophy of the mammary parenchyma follows up to 50% over the years. Thus, there is often limited available glandular parenchyma to remodel the breast after tumor resection with free margins, and it is only feasible with small tumors or after tumor reduction with neo-adjuvant therapy.

Some authors consider keeping the implant after conservative surgery, provided that it is positioned in the sub-muscular pocket or that the implant capsule must not

be removed. In the case of sub-glandular implant pocket, it is strongly recommended to replace the implant by a new one, placing it in the sub-muscular area, in order to reduce radiotherapy impact, such as implant extrusion or capsular contracture, as the contracture is the main complication after treatment. Therefore, publications are very conflicting. Guenther demonstrated in 1994 that 85% of patients with breast implants undergoing conservative surgery (associated with radiotherapy) had satisfactory aesthetic results. One of the factors associated to better outcomes was placing the prosthesis in the retro-muscular area, providing less visible capsular contracture. On the other hand, the Handel publications demonstrated capsular contracture greater than 50% in patients undergoing conservative surgery. Half of which were once again submitted to surgery in order to correct the sequel.

Alternative radiotherapy techniques may be employed to decrease capsular contracture and asymmetry. A study conducted by De Lorenzi at the European Institute of Oncology (Milan, IT) demonstrated that the IORT (intraoperative radiotherapy) employment in patients with implants prevents the occurrence of capsular contracture in cases that this technique is indicated. Other alternatives are the use of conformational radiotherapy and Intensity Modulated Radiation Therapy (IMRT) technique to reduce the capsule injury, consequently reducing capsular contracture intensity.

Additionally, there is a caveat to the interference of an implant to radiotherapy planning. Significant large prosthesis or "symmastia" may impair radiotherapy planning. Despite this concern, several published studies have supported that radiotherapy may be successfully performed in these patients. Mastectomy followed by immediate reconstruction is the most adopted strategy in these cases according to several publications. In these studies, 85–97% of the patients are submitted to mastectomy, either due to technical impossibility to perform conservative surgery, or motivated by surgeon's or patient's preference.

Preferably, the surgical technic should preserve the skin and may also spare the nipple. It is frequently possible to reconstruct the breast with implants or expanders. Usually, patients with previous prosthesis have higher esthetic expectations and demand larger breasts with reduced ptosis, and implant reconstruction is best suited for this desire. In some cases, if the implant is positioned in the sub-muscular pocket, it is possible to maintain it, as long as the aesthetic result is adequate.

Facing large skin resections, late reconstruction or reconstruction with myocutaneous flaps may be performed.

Axillary Surgical Treatment

Sentinel lymph node identification relies on the integrity of the breast lymphatic system. Thus, it was hypothesized that mammary scars could block and prevent adequate lymphatic drainage from the breast to the axilla and thus becoming a contraindication to Sentinel Node Biopsy (SLNB). Although there is no prospective randomized study, in 2005 Luini demonstrated the feasibility of SLNB after previous breast surgery in more than 500 patients. The SLN detection rate was

99% and the positive results were similar to the randomized studies. Thus, SLNB in patients with previous breast surgery has been widely employed and is no longer considered a contraindication.

Based on this same assumption, the presence of previous breast aesthetic surgery must not be a contraindication for SLNB. Rodriguez, in 2009, in a series of 70 patients with prior aesthetic surgery (reduction mammoplasty and augumentation mammoplasty through the nipple or infra-mammary fold) submitted to SLNB had an 100% identifcation rate and the positivity rate was similar to the randomized studies.

Thus, the performance of SLNB in this group of patients appears to be safe and must be encouraged.

Prognosis

All studies with more than five years follow-up, the prognosis of patients submitted to breast aesthetic surgery was exactly the same as those without aesthetic surgery. The study published by Silverstein in 1988, in which patients submitted to augmentation mammoplasty presented worse prognosis, was unable to support its results after an recent update. Therefore, the prognosis is equal for patients with or without breast aesthetic surgery and relies exclusively on tumor staging and molecular biology features.

Conclusion

Breast aesthetic surgery is one of the most successful surgical techniques in the history of medicine. It is also an achievement of the modern woman, interfering positively in their self-esteem and life quality. A progressive amount of performed procedures are associated to increasing data regarding how to properly treat breast cancer in this group of women. Breast prosthesis is not a risk factor for breast cancer nor does it make diagnosis difficult, and do not interfere with the disease prognosis. Breast reduction surgery does not increase the number of unnecessary biopsies, but rather, it decreases the risk of breast cancer. Although there is yet a lack of scientific-based data, it is not necessary to wait for randomized studies, which are difficult to be performed, to indicate SLNB and conservative surgery in selected cases. These patients must be treated following the same protocols indicated for patients without breast aesthetic surgery. New prospective studies on the incidence, pathophysiology, and treatment of Anaplastic Cell Lymphoma associated to breast prosthesis are required in order to improve the understanding of this disease. Information regarding the rarity and good prognosis of the aforementioned pathology must be provided to the patients, avoiding panic to those who want to undergo aesthetic breast implant surgery.

Recommended Readings

1. Geunther JM, Tokita KM, Giuliano AE. Breast-conserving surgery and radiation after augmentation mammoplasty. Cancer. 1994;73:2613. *Prospective cohort of 20 patients with breast implants submitted to quadrantectomy and adjuvant radiotherapy. There was no technical difficulty in performing radiotherapy and in 85% of the patients, the final aesthetical result was considered satisfactory or excellent. After 4 years, no local recurrences were detected.*
2. Handel N, Silverstein MJ. Breast cancer diagnosis and prognosis in augmented women. Plast Reconstr Surg. 2006;118(3):587–93. *A prospective cohort study in which 4082 cases of breast cancer were analyzed in women between 1981 and 2004. Among which 129 presented breast cancer after breast implant. In the first publication, the implant group demonstrated worse oncologic prognosis at diagnosis. In this update, the prognosis was not significant different between the two groups, and there was no difference at baseline stages. In the implant group, more diagnoses were performed with the self-examination technique than in the control group, suggesting that the implant would facilitate the diagnosis of breast cancer.*
3. Kaartinen I, Sunela K, Alanko J, et al. Breast implant-associated anaplastic large cell lymphoma – from diagnosis to treatment. Eur J Surg Oncol. 2017. ejso.2017.05.021 [Epub ahead of print]. *Literature review regarding Anaplastic Lymphoma and mammary prosthesis. Rare disease, most often related to an excellent prognosis, but with increasing incidence.*
4. Muir TM, Tresham J, Fritschi L, Wylie E. Screening for breast cancer post reduction mammoplasty. Clin Radiol. 2010;65(3):198–205. *A cross-sectional cohort study encompassing over 244,000 women undergoing mammographic screening in Australia, of which 4734 had previous mammoplasty. It was significant lower the incidence of breast cancer in the group with previous mammoplasty (RR: 0.71). There was no difference in the number of recalls for further mammographic examination between the two groups. Conclusion: Changes in the mammary parenchyma after augmentation mammoplasty do not interfere with mammographic screening.*
5. Rodriguez Fernandez J, Martella S, Trifirò G, Caliskan M, Chifu C, Brenelli F, Botteri E, Rossetto F, Rotmensz N, Rietjens M, Veronesi P. Sentinel node biopsy in patients with previous breast aesthetic surgery. Ann Surg Oncol. 2009;16(4):989–92. *A prospective cohort study encompassing 70 patients with prior aesthetic breast surgery (breast reduction and breast implants), diagnosed with breast cancer and submitted to sentinel lymph node biopsy. The SLNB identification index was 100%. SLN was positive in 32% of the cases and in an average follow-up of 19 months, no axillary recurrence was observed.*
6. Veronesi P, De Lorenzi F, Loschi P, Rietjens M, Veronesi U. Current trends in the oncologic and surgical managements of breast cancer in women with implants: incidence, diagnosis, and treatment. Aesthet Plast Surg. 2016;40(2):256–65. *Breast cancer review encompassing patients with implants, discussing diagnostic, treatment and prognosis aspects. Results of the IORT study in a patient with prosthesis and conservative surgery, demonstrating that this technique decreases capsular contracture and asymmetry.*

Locorregional Treatment in Patients with Metastatic Breast Cancer

BBSG – Brazilian Breast Study Group

Introduction

Local treatment using surgery with or without radiotherapy in patients with metastatic breast cancer has always been reserved for extreme situations of locally advanced lesions, with the objective of symptom palliative measures ("hygienic" surgery).

However, retrospective studies published in the last decade demonstrated a possible benefit of surgery in the overall prognosis of patients with metastatic disease at the time of diagnosis (de novo). In parallel, studies on carcinomas of other organs, such as the kidney and ovary, also observed better survival in patients who had the primary tumor removed even with metastatic disease.

Such facts have renewed interest in the local approach of women with metastatic breast cancer at diagnosis. This increase in the number of patients under these conditions is due either to the improvement in survival or to an increase in the sensitivity of diagnostic methods.

Epidemiology

It is estimated that about 5% of new cases of breast cancer in developed countries are metastatic. In other less developed parts of the world, these numbers can reach much higher levels.

Brazilian data estimate that about 5–10% of new cases of breast cancer already have disseminated disease.

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Disagreeing Biological Theories

Animal studies suggest that the removal of the primary tumor leads to increased circulation of cell growth factors that stimulate the growth of metastases.

However, other similar studies demonstrate increased tumor permeability to medications, improved nutritional status, and increased effectiveness of therapy after cytoreduction.

Retrospective Studies

North American population data found that slightly more than half of the patients with stage IV (EC IV) breast cancer underwent primary tumor surgery. In the 1990s, most surgical procedures occurred to improve local symptoms, but in the following decade, about 2/3 of the procedures had a therapeutic goal.

Numerous retrospective studies evaluated the prognosis of operated women compared to the group without removal of the primary tumor. The joint analysis of these studies demonstrated the benefit of the surgery (Fig. 1).

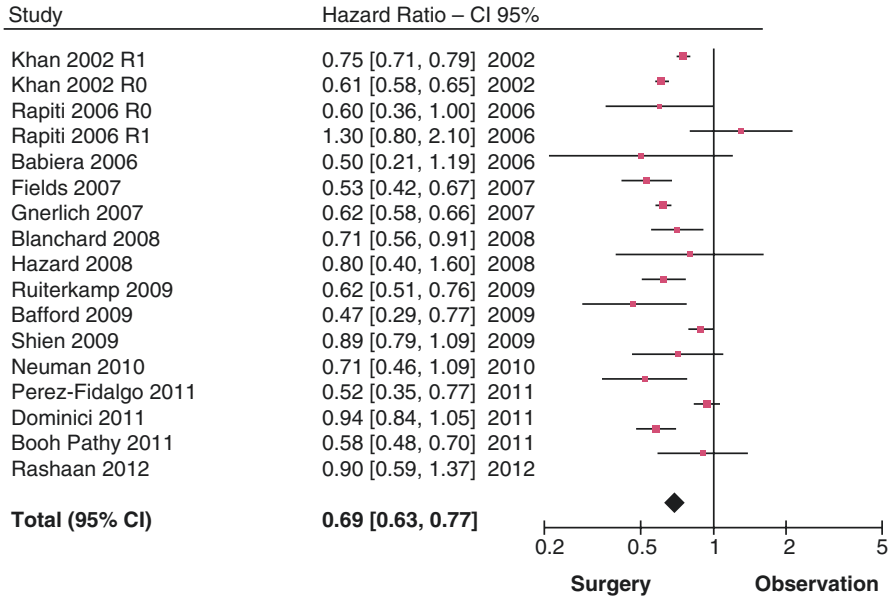


Fig. 1 Meta-analysis of retrospective studies on the impact of breast surgery in patients with metastatic breast cancer on overall survival. (Source: Adapted from: Petrelli and Barni [4])

Although these studies suggest that surgery is advantageous, a more careful analysis demonstrates that this is due to the selection of the best patients. In the majority of reports, operated patients were younger, with better socioeconomic status, with less visceral metastases, and with lower disease volume.

However, even with these limitations, some impressions about surgery can be obtained. The first is that apparently women who had free surgical margins had a better evolution than those with affected margins, suggesting that the surgical technique should be similar to the initial tumors.

Another consideration is that the surgery appears to be relevant for women with stable or controlled disease between 3 and 9 months after diagnosis and not on newly diagnosed tumors (unpredictable evolution) nor on those stable for more than 9 months (not very aggressive).

Finally, retrospective studies also suggest that luminal tumors would have the greatest impact on surgery.

It is not possible to assess the optimal axillary surgery or radiotherapy in these studies, since the data are rather scarce.

Randomized Clinical Trials

Three prospective randomized trials have been published or presented on this subject in the following countries: Turkey, India, and Austria. In addition, there are two other studies still in progress (the USA/Canada and Japan).

The main randomized trials basically follow these designs:

- Primary randomization of study patients between surgery or observation
- Initiation of initial chemotherapy and randomization only of patients with clinical response

Surgery and radiotherapy followed the same patterns of initial tumor operations. Chemotherapy also followed the usual protocol of the respective institutions, with their limitations. The Indian and Turkish studies used chemotherapy based only on anthracycline in most patients, with little use of taxane or anti-HER-2 therapy. Nevertheless, the Austrian and American studies used every therapeutic arsenal available in current medicine.

The first studies presented were the Turkish and the Indian at the end of 2013. Initially both were negative, demonstrating that the surgery did not alter the prognosis of the patients. However, further follow-up of the Turkish study suggests that there is benefit of surgery in younger patients with luminal tumors and bone metastases or unique visceral metastases.

The Indian study, written by Badwe et al., was published in 2015. In this study systemic therapy was initially done and unresponsive patients were excluded.

Randomization included 350 women with metastatic disease. Surgical therapy was the same as that for initial tumors, and systemic therapy was almost exclusively done with anthracycline (virtually no taxane or anti-HER-2 therapy was used).

The evaluation after 2 years showed an average survival of about 25% in both groups. Subgroup analysis also showed no benefit from the surgery. The Turkish study, performed by Soran et al., was presented at ASCO 2016. In this study the patients were randomized directly to surgery or observation.

Unlike the Indian study, randomization was not adequate, selecting cases with better prognosis (lower volume of disease, less visceral metastasis, and more luminal tumors) for the surgery group.

A total number of 274 patients were evaluated, with an average follow-up of 5 years. The final analysis showed a better prognosis in the group submitted to removal of the primary tumor. This benefit was observed in young women with luminal tumors, with only bone disease or single metastasis.

Finally, the Austrian study was presented by Fitzal et al. at ASCO 2017. The design of the study was similar to the Turkish one, randomizing patients before any initial therapy. Randomization was also inadequate, however, this time selecting the best patients (less volume of disease and more taxane use) for the group without surgery.

Follow-up of 37.5 months showed no advantage in performing surgery. Preliminary data from the US study, led by King et al., suggest no advantage in the operated group. However, research is still ongoing. Characteristics of the main known studies can be seen in Table 1.

In progress, a randomized phase III study from the *Eastern Cooperative Oncology Group* (ECOG) called E2108 will evaluate overall survival, quality of life, and incidence of intractable thoracic wall disease in patients undergoing surgery versus palliative control without surgery.

Conclusion

Surgery of the primary tumor in patients with metastatic disease should be restricted to cases of ulcerated disease, aiming at local control and improvement of the quality of life.

The few available randomized trials about the role of surgery in improving prognosis are inconclusive. It appears that surgery does not alter the chances of cure, but there may be some benefit in a specific group of young women with luminal tumors and few bone metastases.

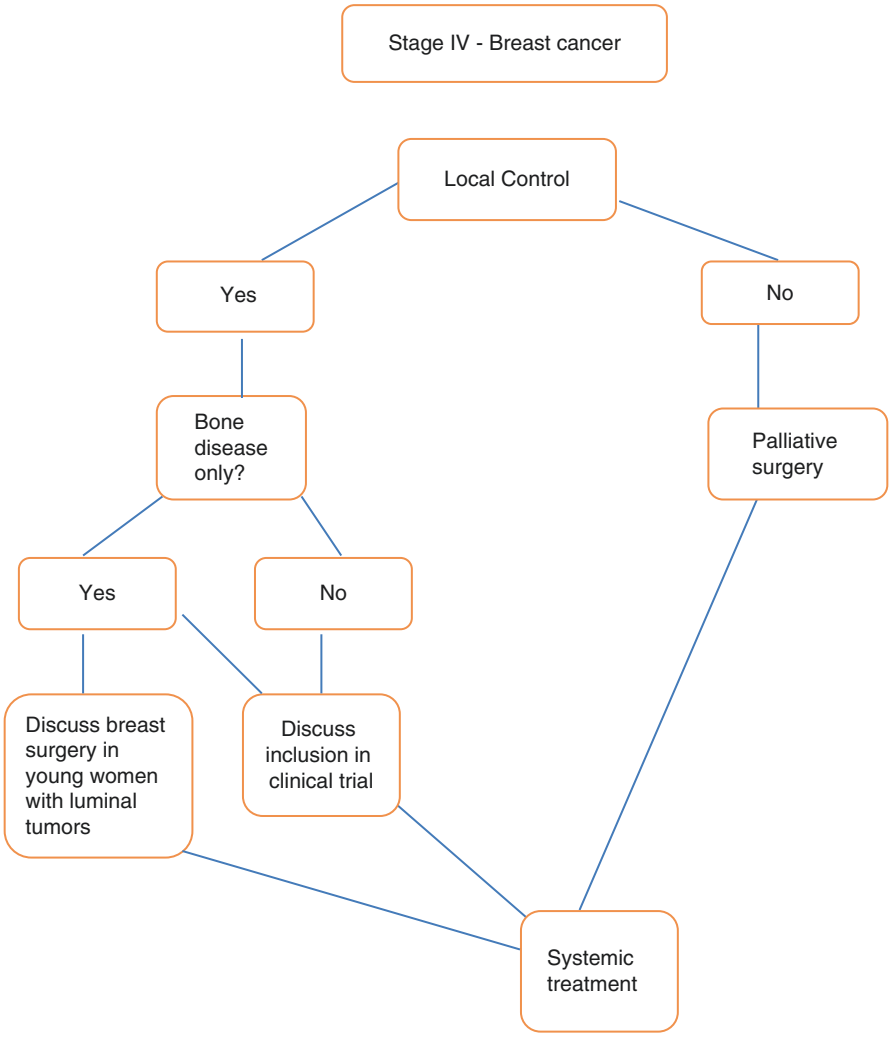
Table 1 Comparison between prospective studies on primary tumor surgery in EC IV patients

Study	Initial ChT	*N*	Adequate randomization	Follow-up	Average survival		*P*
					Surgery	Control	
Badwe et al.	Yes	350	Yes	24 months	25%	25%	0.79
Soran et al.	No	274	No	60 months	41.6%	24.4%	0.005
Fitzal et al.	No	90	No	37.5 months	34.6 months	54.8 months	0.267

ChT Chemotherapy

Note: results in the study by Fitzal et al. are presented in median survival months

Flowchart



Flowchart 1 Approach of patients with metastatic disease by the time of diagnosis (de novo)

Recommended Reading

1. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol. 2015;16(13):1380–8. *Publication of the Indian study.*
2. Fitzal F, Balic M, Bjelic-Radisic V, Hubalek M, Singer CF, et al. Primary operation in synchroneous metastasized invasive breast cancer patients: first oncologic outcomes of the prospective

randomized phase III ABCSG 28 POSYTIVE trial. ASCO 2017 – oral presentation. http://abstracts.asco.org/199/AbstView_199_185733.html. *Oral presentation of the Austrian study at ASCO 2017.*

3. Khan SA. Surgical management of de novo Stage IV breast cancer. Seminars Radiat Oncol. 2016;26:79–86. *Review on the role of surgery in metastatic breast cancer.*
4. Petrelli F, Barni S. Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression. Med Oncol. 2012;29(5):3282–90. *Metanalysis of the main retrospective studies about the impact of surgery on prognosis. The assessed studies clearly showed the choice for the best cases for indication of surgery.*
5. Soran A, Ozmen A, Ozbas S, Karanlik H, Muslumanoglu M, Igci A et al. A randomized controlled trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer: Turkish Study (Protocol MF07–01). ASCO 2016 – oral presentation. http://meetinglibrary.asco.org/record/122669/abstract. *Oral presentation of the Turkish study at ASCO 2016.*

Radiotherapy for Breast Cancer

Ernane Bronzatti and Ludmila Oliveira Siqueira

Introduction

Radiotherapy plays a prominent role in the therapeutic management of patients with breast cancer, both in the early stage and in the locally advanced cases, being a determining factor in local control and survival. It is also presented with an important palliative action in the relief of symptoms of metastatic disease.

In this chapter, we will discuss indications of radiotherapy in the conservative treatment of "in situ" and invasive lesions, as well as their indication after mastectomy.

Brief Background Facts

The history of modern radiotherapy started in 1951 in Ottawa, Canada, where the first commercially available mega-voltage photon-emitting equipment was produced. Known as telecobalt therapy, it was the first to be used on a large scale in the clinical practice. Today, it has almost entirely been replaced by linear accelerators (Fig. 1), driven by powerful pieces of software, which are able to emit the radiation more safely and accurately, greatly minimizing side effects and complications.

Throughout this period, we have observed its consolidation in the scenario of multidisciplinary treatment of breast cancer. In this context, walking along with the

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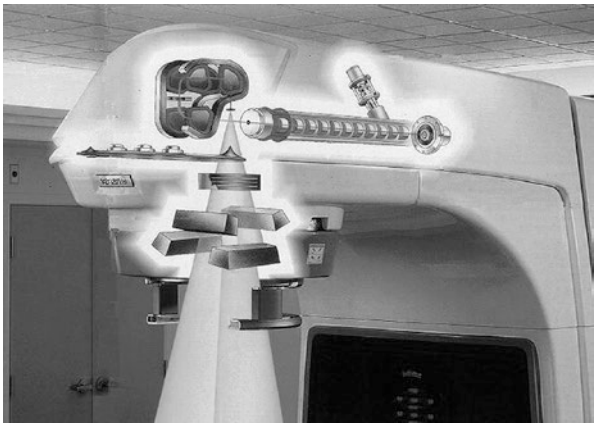


Fig. 1 Linear accelerator

technological evolution, there is a permanent evolution in the concepts related to the treatment offered.

From the classic and well-established indications of postmastectomy radiotherapy in the case of locally advanced tumors or adjuvant radiotherapy for the whole mammary gland after conservative surgery for initial tumors, we began to consider and implement concepts such as partial breast irradiation (e.g. intraoperative radiotherapy) and decrease in total treatment time (hypo-fractionation).

The technological evolution of imaging, its capture, and use in innovative planning systems allowed the implementation of more sophisticated irradiation delivery techniques such as 3D planning, where absolute dose prediction and control in each organ close to the target.

Main Types of Schemes

The type of radiation in clinical use for the treatment of cancer patients is ionizing radiation, capable of promoting changes in the structure of cellular organelles or even in the DNA strand.

It can be generated by sources far from the target (teletherapy) or sources that are in direct contact with the target (brachytherapy): the most frequently used in breast cancer is teletherapy, external radiation with energy with high penetration power known as megavoltage and produced by linear accelerators or telecobalt therapy.

The standard treatment uses irradiation of the whole mammary gland, with daily fractions, in five fractions per week and with an average duration of 5–6 weeks. The indicated dose enhancement after completion of irradiation of the entire breast is known as boost and is performed on the surgical bed of the resected tumor.

Indications

Below we describe treatments with consolidated literature, level I of evidence and grade A of recommendation. Consensus, new treatment modalities or even trends were not included as standard treatment.

Carcinoma "In Situ" (Stage 0)

It comprises approximately 20% of the diagnosed breast cancer cases, being divided between ductal and lobular. Lobular carcinoma in situ is considered a precursor lesion, indicating a high risk of breast cancer. There is no role for radiotherapy in its management.

Ductal Carcinoma In Situ (DCIS)

Radiotherapy should be considered for patients who have undergone conservative surgery. There is no role for radiotherapy in patients undergoing mastectomy with or without immediate breast reconstruction.

There are three randomized trials and one systematic review evaluating the role of radiotherapy after conservative surgery. They show that adjuvant radiotherapy significantly decreases the chance of relapse (Table 1).

A 15-year review of the NSABP-17 study confirmed that the association of radiotherapy and tamoxifen post-conservative surgery provides excellent long-term prognosis.

In some cases, the benefit of adding radiotherapy is lower, but based on prospective studies it was not possible to determine a subgroup of patients who would not benefit from adjuvant radiotherapy. However, observation after conservative surgery is an option in selected cases. In this sense, a retrospective study [15] with approximately 32,000 patients from the SEER (*Surveillance, Epidemiology, and End Results*) database demonstrated survival benefit only in patients below 60 years,

Table 1 Surgery with or without radiotherapy or surgery + Rt

	Local rec.		
Study	CIR	CIR + RT	
NSABP B171	31.7%	15.7%	$P < 0{,}000005$
eortc 108532	25%	15%	$p < 0{,}0001$
ukcccr3[a]	14%	6%	$p < 0{,}0001$

[a]The use of tamoxifen was evaluated

with tumors larger than 1.6 cm and with a high nuclear grade. It may be considered acceptable not to perform radiotherapy in situations that do not include these factors and present with wide free margins.

The recommended dose ranges from 45 to 50 Gy (unit measure of absorbed radiation dose, in joules/kg) in conventional fractionation (1.8–2 Gy/day), and it should include all mammary gland. Boost may be indicated, although questioned by some authors in the case of DCIS operated with free resection margins.

Invasive Carcinoma: Clinical Stage I to IIB

Conservative surgery associated with radiotherapy is considered the standard treatment for most patients with early stage tumors. A number of prospective studies such as NSABP B-06 [6] and EORTC-10801 [14], in addition to the meta-analyses, confirm the equivalence between Conservative Surgery (CS) associated with adjuvant radiotherapy and Radical Mastectomy (RM). In these assays, both local control and overall survival are similar for the two therapeutic modalities. In addition, a meta-analysis of 17 studies involving more than 10,000 patients comparing CS alone versus CS associated with adjuvant radiotherapy demonstrated a benefit to the latter, including survival, especially in patients with poor prognosis.

Some studies [13] designed to evaluate the need for radiotherapy in conservative treatment indicate that the use of radiotherapy can be individualized in elderly (>70 years) with positive hormone receptors. In this context, the omission of radiotherapy would imply a greater local recurrence (1% × 4%), with no impact on overall survival.

When adjuvant chemotherapy is indicated, radiation therapy is usually performed after chemotherapy. Except for cases in which there are small or positive margins, delaying radiotherapy does not appear to increase local recurrence rates significantly. When a chemotherapy regimen with CMF (cyclophosphamide, methotrexate, and fluorouracil) is recommended, we can perform radiotherapy and chemotherapy concomitantly.

The recommended dose ranges from 45 to 50 Gy in conventional fractionation (1.8–2 Gy/day), and it should include the entire mammary gland. In conservative surgery, boosting the dose in the tumor bed (boost) should be performed since up to 80% of the recurrences occur around the original site of the neoplasia.

Phase III studies showed a 6% decrease in local recurrence in ten and even 20 years for patients who received a boost in the surgical bed. The recommended doses range from 10 Gy in five fractions to 16 Gy, the latter in cases of positive or close margins in which reexcision is not performed. Irradiation of drainage sites will be discussed below.

Modified Fractionings (Hypofractioning)

The total time of treatment is an aspect to be considered, not only due to the quality of life of the patients but also due to the financial and social cost resulting from the absence of these women from their home and work routine. In this context, randomized trials were developed to evaluate the non-inferiority of hypo-fractionated regimens (fewer fractions and higher dose per fraction) than conventional treatment.

The efficacy of these regimens was reviewed, both from the point of view of cancer control and cosmetic outcome, in a 2010 meta-analysis involving 7095 women in four randomized trials at a 5-year evaluation. There was no difference in relation to the usual fractionation scheme in the following parameters: risk of local recurrence, overall survival, and irradiated breast appearance.

Concerning toxicity, the hypo-fractionated schemes presented minor reactions both acute and late. Two of the studies included in this meta-analysis (START-A and START-B) have already been evaluated in 10 years of follow-up confirming the safety and effectiveness of a hypo-fractionated regimen. The use of this regimen, however, is still not well defined in the case of more advanced tumors, T > 5 cm with positive lymph nodes, and in the possible association with systemic therapies, whether chemotherapy or monoclonal antibody.

Partial Breast Radiotherapy

It refers to the use of radiotherapy at higher doses per day and involving a smaller volume of breast tissue, only the surgical bed with margin. Among the available modalities, the following are included: brachytherapy, which may be with multiple catheters implanted in the breast, or through implantation of a single catheter that has a balloon at its end; MammoSite, which is positioned in the tumor bed; intraoperative radiotherapy; and radiotherapy conformed strictly to the surgical bed.

The rationale for the treatment of the tumor bed alone comes from extensive series that show that local recurrence is located, in most cases, in the surgical bed.

Although preliminary results show feasibility and low toxicity, the selection of patients eligible for partial breast radiotherapy needs to be judicious [3]. Therefore, it is recommended that eligible patients be carriers of single tumors with less than 3 cm, with favorable histological characteristics, free resection margins, absence of lymph node involvement and postmenopausal.

Table 2 describes recommendations by ASTRO (*American Society of Therapeutic Radiology and Oncology*, Smith et al. 2009) and ESTRO (*European Society for Therapeutic Radiology and Oncology*, Polgar et al. 2010) for patients eligible for partial radiotherapy. Patients who do not meet these criteria should perform the procedure within a controlled clinical trial.

Table 2 ASTRO (American society of radiation oncology) and estro (European society for radiotherapy and oncology) guidelines for partial breast irradiation

Variable	Acceptable ASTRO	Low-risk ESTRO
Age	60 years old	50 years old
BRCA gene mutation	No	Indifferent
Tumor size	Smaller than 2 cm	Smaller than 3 cm
T staging	T 1	T1 and T2
Margins	Negative £ 2 mm	Negative
Grade	Indifferent	Indifferent
Lymph vascular invasion	No	No
Hormone receptors	Positive	Any
Multicentricity	Unicentric	Unicentric
Multifocality	Unifocal	Unifocal
Histology	DCI, mucinous, tubular, or colloid	Any
DCIS	No	No
Extensive in situ component LCIS associate	No	No
LCIS associate	Allowed	Allowed
Nodal stage	pN0 by SLNB or lymphadenectomy	pNo by SLNB or lymphadenectomy
Neoadjuvant treatment	No	No

Randomized studies are being performed to establish equivalence with the irradiation of all the breast area, especially NSABP B39/RTOG 0413 already with closed recruitment. ELIOT study [18] conducted by the European Institute of Oncology, Milan, has a 5-year local recurrence rate higher than that of the whole breast (4.4% × 0.4%) but in the low-risk group with 1.5% versus 0.4%. Anyway, longer follow-up are needed.

Invasive Carcinoma: Clinical Stage IIB and III

Patients with locally advanced breast cancer usually undergo mastectomy with axillary clearance, but in some cases it is possible to perform conservative treatment. Patients submitted to neoadjuvant chemotherapy should be managed according to prechemotherapy clinical staging. Radiotherapy after mastectomy is related to benefit, including survival.

In a meta-analysis [10] with 22 randomized trials, a 17–19% gain in local control was observed in 5 years, with an absolute survival benefit of around 5% with a

15-year follow-up. It is formally indicated in patients with T3 or T4 stage tumors, in the presence of more than three axillary lymph nodes involved or when there is capsular extravasation and when there are affected margins. Some centers indicate adjuvant radiotherapy when there is involvement of 1–3 lymph nodes in axillary clearance, despite unclear evidence regarding the benefit.

In mastectomized patients with tumors with a higher risk of recurrence, radiotherapy on the chest wall or on the reconstructed breast should be considered. Among the risk factors considered in this scenario, the following should be noted: age, presence of vascular-lymphatic invasion, immunohistochemical profile (IHC), and histological tumor grade.

Lymphatic drainage sites: The anatomical areas that are associated with lymph node dissemination are supraclavicular fossa (FSC), internal mammary (IM), and axilla. The recommended dose for treatment is 45–50.4 Gy in conventional fractioning. In the presence of axillary involvement, with four or more positive lymph nodes, we indicate FSC irradiation. In cases in which there are 1–3 lymph nodes involved, other risk factors, such as the extent of axillary clearance, should be considered to evaluate the indication for complementary radiotherapy. In cases of positive axilla in which less than ten axillary lymph nodes were removed, or the proportion of lymph nodes compromised in relation to those removed is high, FSC irradiation should be indicated, and axillary field irradiation should also be considered. In addition, other factors should be taken into account when less than four lymph nodes are involved: tumor size, presence of vascular-lymphatic invasion, capsular extravasation, IHC profile, menopausal status, and tumor size. Radiation of the internal mammary chain is controversial and should be used when there is clinical, radiological, or pathological evidence or characteristics that strongly suggest the involvement.

Basic Technical Notions

Radiation therapy known as conventional therapy is the most widely used irradiation technique for the treatment of breast cancer in Brazil. The area to be irradiated is based on external anatomical references and two-dimensional (2D) images. Patients are treated in the supine position. The arm on the affected side must be abducted at least 90 degrees.

In the case of conservative surgery, all breast tissue should be included in the tangent irradiation fields (Fig. 2).

Conformational planning (based on computed tomography) or IMRT (intensity-modulated radiation treatment) is recommended, which allows limiting dose to organs of risk such as the heart and lung and generating a better coverage of the target volume (Fig. 3).

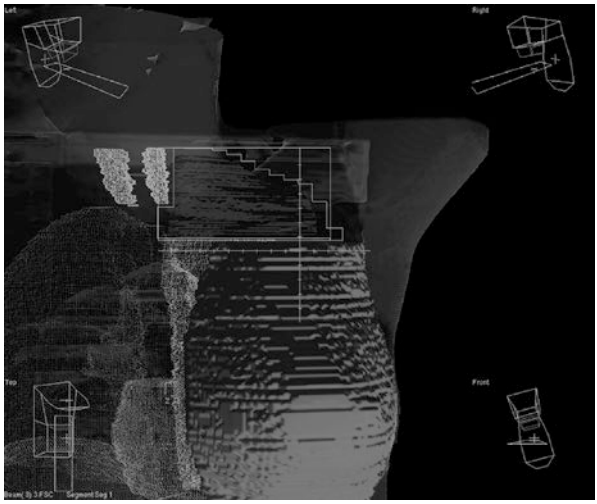


Fig. 2 Tangent fields

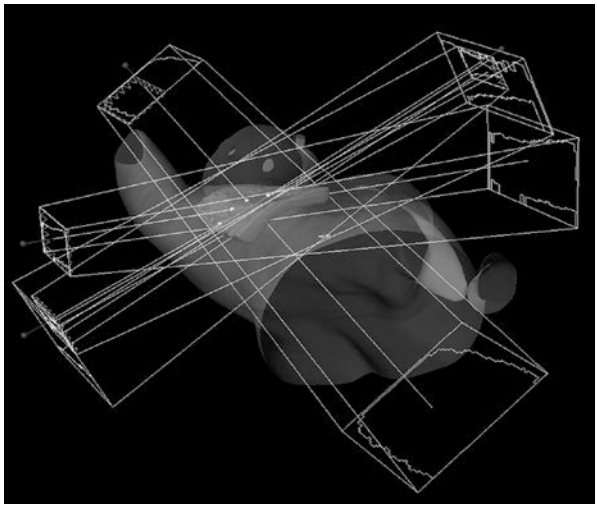


Fig. 3 Therapeutic planning

Side Effects

Complications are classified as acute (<90 days) or chronic (>90 days). The most commonly observed acute toxicity is cutaneous (radiodermatitis), and redness of the skin is the main symptom observed. Other symptoms described, though less commonly, include fatigue, discomfort associated with local pain, and edema.

A late complication that can be observed is upper limb edema, which is more frequent when axillary clearance and FSC with axilla radiotherapy are associated. Very rarely other symptoms are telangiectasia, cutaneous and pulmonary fibrosis, rib fracture, and cardiotoxicity. This can be potentiated by the use of anthracycline and trastuzumab. Brachial plexopathy and carotid stenosis are described when FSC and axilla are irradiated.

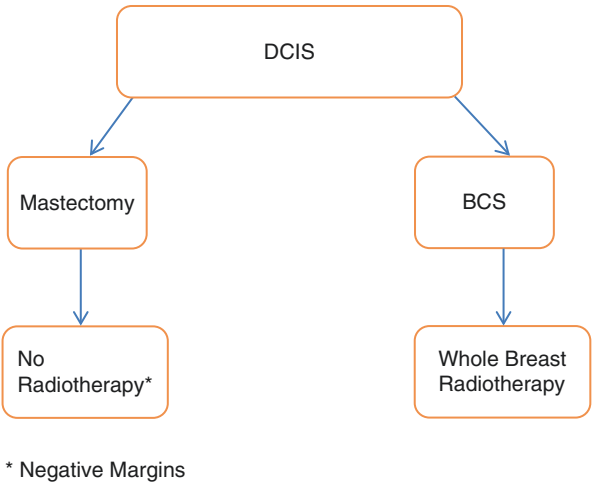
According to the EBCTCG (*Early Breast Cancer Trialists' Collaborative Group*), there was an increased risk for second neoplasm (leukemia, sarcoma, esophagus, and lung), excluding breast cancer, of 0.1% in 10 years.

Contraindications

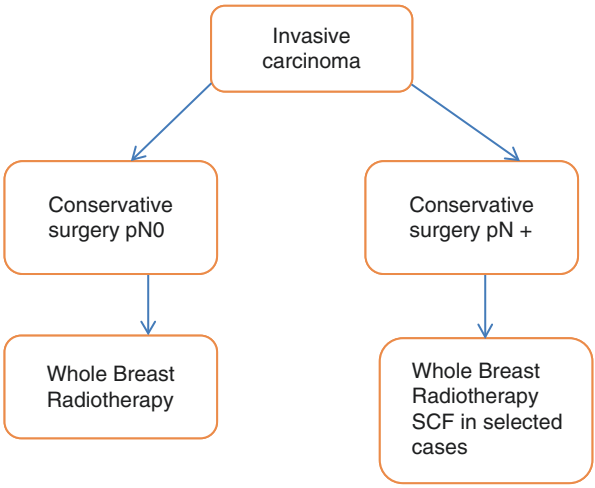
Radiotherapy is contraindicated in cases of pregnancy. It is considered to be relative contraindicated in this conditions: collagen diseases such as systemic lupus erythematosus (SLE) and scleroderma, in addition to previous irradiation of the thoracic wall.

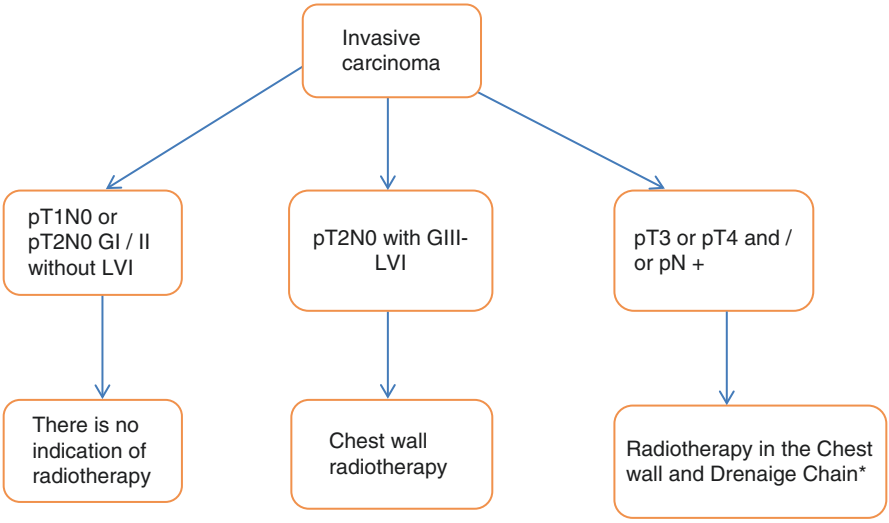
Flowcharts

Flowchart 1
Radiotherapy for DCIS



Flowchart 2
Radiotherapy for invasive carcinoma and bcs (breast conserving surgery)





LVI: linfovascular Invasion
* Selected cases

Flowchart 3 Radiotherapy for Invasive Carcinoma and Mastectomy

Recommended Readings

1. Bartelink H, Maigon P, Poortmans P, et al. Whole breast irradiation with anda without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up a randomized phase III trial. Lancet. 2015;16:47–56. *This study compared the performance or not of dose boost after 50 Gy (Boost) in 5318 patients after a 20-year follow-up. Interpretation: Even in the long term, there was a clear benefit in local control, especially for young patients.*
2. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366:2087–106. *Meta-analysis of studies comparing CS x CS + RT; total 7300 women. Interpretation: gain in local control and survival.*
3. Correa C, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. Pract Radiat Oncol. 2017;7(2):73–9.
4. Cuzick J, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol. 2010;12(1):21–9.
5. Early Breast Cancer Trialists' Collaborative Group (EBCTGG), Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patients data for 10.801 women in 17 randomized trials. Lancet. 2011;378:1707–16. *Meta-analysis has shown that radiotherapy performed after conservative surgery halves the rate of relapse in 10 years and the risk of death from breast cancer by about 1/6 in 15 years.*
6. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347:1233–41. *NSABP B-06 - Randomized study comparing: radical mastectomy x CS x CS + RT (50 Gy). 1851 patients, EC: I and II (<4 cm with negative margins) followed by 20 years. No difference in SG or SLD. Interpretation: Reduction of local recurrence (39% x 14%), when added RT in the CS group.*
7. Fisher B, et al. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med. 2002;347(8):567–75, 4 ago.
8. Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database Syst Rev. 2009;(1). Art.No.: CD000563. *Both techniques have short follow-up, but promising results for low-risk patients. At present, they are recommended only within institutional protocols.*
9. Group E, et al. Breast-conserving treatment with or without radiotherapy in Ductal Carcinoma-In-Situ: ten-year results of European Organisation for Research and Treatment of Cancer Randomized Phase III Trial 10853—A Study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol. 2006;24(21):3381–7.
10. Group EBCTCG, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383(9935).
11. Havilland JS, Owen JR, Dewar JA, et al. The UK Standardization of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. Lancet Oncol. 2013;14:1086–94.
12. James ML, Lehman M, Hider PN, et al. Fraction size in radiation treatment for breast conservation in early breast cancer. Cochrane Database Syst Rev. 2010.
13. Kunkler I, et al. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015;16(3):266273.

14. Litière S, et al. Breast conserving therapy versus mastectomy for stage I–II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. Lancet Oncol. 2012;13(4):412–9.
15. Sagara Y, Freedman RA, Vaz-Luis I, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. J Clin Oncol. 2016;34:1190. *Both meta-analyses have shown that the radiotherapy hypo-fractionation in the postoperative period of conservative surgery of initial tumors of breast cancer have the same results in terms of local control as the usual fractions in evaluation up to 10 years.*
16. Sagara Y, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. J Clin Oncol, 2016.
17. Silverstein MJ, Fastner G, Maluta S, et al. Intraoperative radiation therapy: a critical analysis of the ELIOT and TARGIT trials. Ann Surg Oncol. 2014;21:3787–92.
18. Veronesi U, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013;14(13):1269–77.
19. Wapnir IL, Dignam JJ, Fisher B, et al. Long term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized trials for DCIS. J Natl Cancer Inst. 2011;103:478. *Systematic review of four randomized studies on RT in DCIS: NSABP B17, EORTC 10353, UKCCCR and SweDCIS. Reduction in total relapses: 51% (95% CI: 0.41-0.59). Interpretation: benefit in all subgroups of patients and negligible side effects.*
20. Wapnir I, et al. Long-term outcomes of invasive Ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst. 2011;103(6):478–88.

Adjuvant Hormone Therapy for Breast Cancer

Andrea K. Shimada, João Victor Machado Alessi, Bruna Zucchetti, and Artur Katz

Introduction

Estrogen plays a key role in the development of breast cancer, and its blockage is the basis of hormone therapy.

Hormone treatment is the cornerstone of adjuvant systemic treatment based on its benefits and the number of patients who are candidates for it.

A Few Background Facts

More than a century ago, Beatson first showed the dependence of estrogen on the genesis of breast cancer.

Several studies and meta-analyses have demonstrated the overall survival benefit of endocrine therapy in the adjuvant setting in patients with hormone receptor positive tumours (HR+) associated with a mild and manageable toxicity profile.

In this context, the agents employed are selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AI).

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https://doi.org/10.1007/978-3-030-13636-9_58

Main Types

Selective Estrogen Receptor Modulators (SERMs)

These are drugs that can function as agonists, antagonists, or agonist antagonists, depending on the target tissue in which they will act. They are tamoxifen, raloxifene, and fulvestrant.

Among such drugs, tamoxifen was the most studied and used in adjuvant setting. It inhibits the growth of tumor cells by competitive antagonism at the estrogen receptors (ER) of the breast tissue.

However, its action is complex, as it also acts as a partial agonist. This agonist effect can be both beneficial (prevention of bone demineralization) and malefic (increase in the incidence of endometrial cancer and thromboembolic events). The activity of tamoxifen is dependent on the status of ER and, to a lesser extent, on the status of the progesterone receptor (PR). As adjuvant, the benefit of its use does not depend on age, axillary involvement, and previous use of chemotherapy.

Tamoxifen has become the standard treatment for women with RH + breast cancer. Its use for 5 years led to relative reductions in relapse rates (41%) and death from breast cancer (34%), as well as a reduction in the incidence of contralateral breast cancer (39%). The standard dose is 20 mg daily for 5 years until recent studies have shown benefit in long-term treatment.

The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) study evaluated the impact of extending treatment with tamoxifen for 10 years. It included nearly 13,000 pre- and postmenopausal women who were on completion of tamoxifen treatment for 5 years or who had completed their use in the last year. Patients were randomized, without the use of placebo, to terminate treatment at the end of 5 years or to prolong it for more 5 years.

Among women with RH + tumors, the continuity of tamoxifen for 10 years provided a reduction in tumor recurrence when compared to recurrences among patients who discontinued their use after 5 years. Thus, the risk of relapse and mortality was significantly reduced in terms of statistics.

The cumulative risk of relapse between years 4 and 14 of follow-up was 21.4% among women who underwent treatment for 10 years versus 25.1% who discontinued tamoxifen after 5 years.

Likewise, within the same evaluation period, mortality was reduced from 15% to 12.2%, with an absolute reduction of 2.8%, favoring the treated group for 10 years.

Prolonged treatment was well tolerated, not associated with an increase in mortality from other causes (relative risk of 0.99; $p = 0.84$) when we exclude breast cancer as the cause of death.

An increased risk of pulmonary embolism (relative risk of 1.87; $p = 0.01$), stroke (relative risk of 1.06), ischemic heart disease (relative risk of 0.76; $p = 0.02$), and endometrial cancer (relative risk of 1.74; $p = 0.0002$) has also been observed. The absolute risk of developing endometrial neoplasia between the 5 and 14 years of

follow-up was 3.1% (mortality 0.4%) versus 1.6% (mortality 0.2%), favoring patients treated for 5 years.

For premenopausal patients without contraindication and good tolerance and for those with contraindications or intolerance to AIs, the duration of tamoxifen treatment for 10 years should be considered.

In addition to ATLAS data, we are still awaiting the publication of the UK study aTTom (*Adjuvant Tamoxifen Treatment offer more?*), which ratifies the benefit of adjuvant tamoxifen for 10 years. In this study, presented at the ASCO Annual Meeting in 2013, approximately 7000 women were randomly assigned to discontinue tamoxifen after 5 years or extend treatment up to 10 years. The study showed benefit in decreasing recurrence, breast cancer mortality and overall survival after the seventh year of treatment.

Some drugs may interfere with the metabolism of tamoxifen, reducing the conversion of the drug into endoxifen, its most active metabolite, potentially reducing its efficacy and consequently increasing the risk of recurrence of breast cancer. Among them are those that inhibit cytochrome P450 2D6 (CYP2D6) such as fluoxetine, paroxetine, sertraline, cimetidine, amiodarone, ticlopidine, haloperidol, and others.

Although clinical studies, especially retrospective studies, have produced conflicting results regarding the potential interference of these drugs in the activity of tamoxifen, it is considered opportune, if possible, to avoid the concomitant use of tamoxifen and the aforementioned agents.

Aromatase Inhibitors (AIs)

These are drugs that inhibit the conversion of androgen into estrogen in peripheral tissues (especially adipose tissue and liver) and in the tumor through enzymatic inhibition. They are exclusively used in postmenopausal women, to whom the aromatization of androgen represents the main source of estrogen. In these patients, AIs produce an additional benefit in relation to tamoxifen, especially in terms of reduction of relapse and incidence of second primary tumor.

Until recently, the standard treatment was the use of AIs for 5 years or the switch scheme using 2–3 years of AIs followed by tamoxifen or 2–3 years of tamoxifen followed by AIs completing 5 years of endocrine therapy. Current studies, however, show a possible benefit in increasing the duration of hormone treatment in selected cases.

The MA.17R study sought to assess the impact of extending AI use for another 5 years, adding up to 10 years of hormone therapy in women who were on completion of 5 years of treatment with tamoxifen or AIs and that had completed treatment in the past year. About 2000 women were randomized to receive letrozole or placebo for another 5 years with the primary goal of assessing progression-free survival with the extent of hormone therapy.

The 5-year progression-free survival was 95% with letrozole and 91% with placebo, but there was no overall survival benefit at 5 years (93% with letrozole and 94% with placebo).

The extent of AI use was related to decreased relapse and the incidence of new contralateral lesion; however, a greater number of bone fractures were observed, and they should be analyzed with caution and individually to establish which candidates may have additional benefit with prolonged treatment.

In low-risk patients, with severe osteoporosis, or that do not tolerate AIs, can be treated exclusively with tamoxifen. Extended treatment should be seen as an option, especially for patients considered to be at high risk, such as those with lymph node involvement.

AIs are contraindicated for premenopausal women and should be used with extreme caution in those patients who present chemotherapy-induced amenorrhea, since recurrence of ovarian function may occur despite the persistence of clinical amenorrhea.

Women that are over 40 years old should have their ovarian function monitored, and they should be instructed to inform the physician if the menopausal symptoms are no longer present. In these cases, the levels of FSH and estradiol should be investigated continuously, in order to certify the absence of ovarian function.

Women that are younger than 40 years should not receive AIs alone, and, if there is an interest in using it (e.g., contraindication to tamoxifen), the ovarian function should be suppressed.

In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study, it was observed that patients with normal bone mass did not develop osteoporosis with the use of AIs, although osteopenia occurred in some cases. Patients with baseline osteopenia had a small risk of developing osteoporosis.

The highest rate of bone mass loss occurred within the first 2 years of AI use, and the recommendation for early use of bisphosphonates is based on data from the Z-FAST and ZO-FAST studies, showing increased bone mass with early treatment.

The use of bisphosphonates, such as zoledronic acid, may reduce bone loss associated with treatment and confer benefit in terms of disease-free survival (relative reduction of 40% in risk of recurrence).

Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis demonstrate benefit in decreasing bone recurrence, fracture risk, and improved survival of postmenopausal patients on AIs. Zoledronic acid 4 mg intravenously is recommended every 6 months for 3 years, in addition to calcium and vitamin D supplementation. Denosumab is a monoclonal antibody that inhibits osteoclast activity by binding to RANK-L.

It was recently incorporated into oncology because of its benefits for preventing bone loss and decreased bone events in metastatic disease. In the adjuvant setting, the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-18 study evalu-

ated the use of denosumab in postmenopausal women using adjuvant hormone therapy.

The results demonstrated clear benefit in reducing fractures and possible gain in progression-free survival. These data are promising, though unpublished yet; and until the definitive results of the ABCSG-18 and D-CARE studies, we lack definitive recommendations for their use in the adjuvant setting. Current evidence still favors the use of bisphosphonates in terms of survival.

Indications

Endocrine therapy should be offered to all women with RH + breast cancer. The choice should be based on the hormonal status (pre- or postmenopausal) of each patient and administered only after the end of the chemotherapy period.

For premenopausal patients the standard treatment is tamoxifen 20 mg daily for 10 years based on data from the ATLAS study.

Ovarian suppression, ablative or hormonal, should be considered in selected cases and individually discussed in very young women (younger than 35 years), at high risk of recurrence and who continue to menstruate regularly at the end of chemotherapy treatment based on the results of the studies SOFT (Suppression of Ovarian function Trial) and TEXT (Tamoxifen and Exemestane Trial), which demonstrate benefit of AI-associated ovarian suppression (exemestane) in these patients.

In the SOFT study, ovarian suppression was performed by bilateral oophorectomy, ablative ovarian radiotherapy, or chemical castration with gonadotropin-releasing hormone (GnRH) agonist.

Of the total number of patients randomized to these studies, 240 patients under 35 years of age in the SOFT study were assessed, while assessment was made of 145 patients in the TEXT study who underwent ovarian suppression shortly after chemotherapy or concomitant chemotherapy (in the case of TEXT) for 5 years.

The update of these studies, published in June 2017, on treatment efficacy and quality of life, showed that the 5-year breast cancer-free interval in women younger than 35 years was 67% with tamoxifen, 75.9% with ovarian suppression + tamoxifen, and 83.2% with ovarian suppression + exemestane.

Very similar data were found in the TEXT study, in which the 5-year breast cancer-free interval was 79.2% with tamoxifen + ovarian ablation and 81.6% with exemestane + ovarian ablation.

Vasomotor symptoms, such as hot flashes and sweat, were the ones that caused the most discomfort and loss of quality of life, followed by vaginal dryness and loss of libido, but were not more intense than those observed in patients over 35 years of age. It should also be noted that there was loss of early bone mass observed in these

Table 1 Recent study on hormone adjuvance

	ATLAS	SOFT	TEXT	MA17-R
Proposed treatment	Tamoxifen 20 mg/day for 10 years *versus* Tamoxifen 20 mg/day for 5 years	Premenopausal women: tamoxifen *versus* Tamoxifen + ovarian supression (OS) *versus* Exemestane + OS (OS for 5 years)	Premenopausal women: tamoxifen + ovarian suppression (OS) *versus* Exemestane + OS (OS for 5 years)	Hormone therapy extension after 5 years: Letrozole 2.5 mg/day for over 5 years *versus* Placebo
Results	Absolut reduction of mortality by 2.8%	Disease-free survival in 5 years: 90.7% tamoxifen *versus* 91.3% tamoxifen + OS *versus* 93% exemestane + OS	Disease-free survival: HR 0.72 (95% CI, 0.60–0.85) in favor OS + exemestane	Disease-free survival in 5 years: 95% with letrozole *versus* 91% with placebo (HR: 0.66)
		No significant difference on overall survival was observed	No significant difference on overall survival was observed	No significant difference on overall survival was observed

patients. Despite the adverse effects related to ovarian blockade, they can often be manageable without interruption of treatment.

For women at high risk and less than 35 years of age, there was a clear increase in the 5-year progression-free interval with the use of ovarian suppression associated with exemestane.

For postmenopausal patients, the standard treatment is 5–10 years of AIs (anastrozole 1 mg/day or exemestane 25 mg/day or letrozole 2.5 mg/day).

Women who started hormone therapy during premenopausal years and who experienced ovarian failure may replace tamoxifen for AIs, provided that there are no contraindications or limiting side effects, and complete 10 years of endocrine therapy.

Women who received 5 years of tamoxifen benefit from the additional use of 5 years of AIs, especially those at high risk, represented mainly by those with lymph node involvement.

For low-risk women with contraindications to AIs or poor tolerance, tamoxifen may be considered. Table 1 summarizes the findings of the ATLAS, SOFT, TEXT, and MA17-R studies.

Side Effects

Tamoxifen

- Cardiovascular: flushing, hypertension, peripheral edema, venous thromboembolic events, deep venous thrombosis, angina, cardiac ischemia
- Neurological: mood changes, depression, insomnia, dizziness, headache, anxiety, fatigue
- Skin: skin changes, rash, alopecia
- Endocrine: hot flashes, water retention, menstrual changes, amenorrhea, hypercholesterolemia
- Gastrointestinal: nausea, lower weight gain, diarrhea, or constipation
- Genitourinary: vaginal alterations, vaginal bleeding, endometrial hyperplasia, polyps, endometrial cancer
- Skeletal muscles: weakness, arthritis, arthralgia
- Vision decreased visual acuity, retinal vein thrombosis, retinopathy, altered color perception, cataract

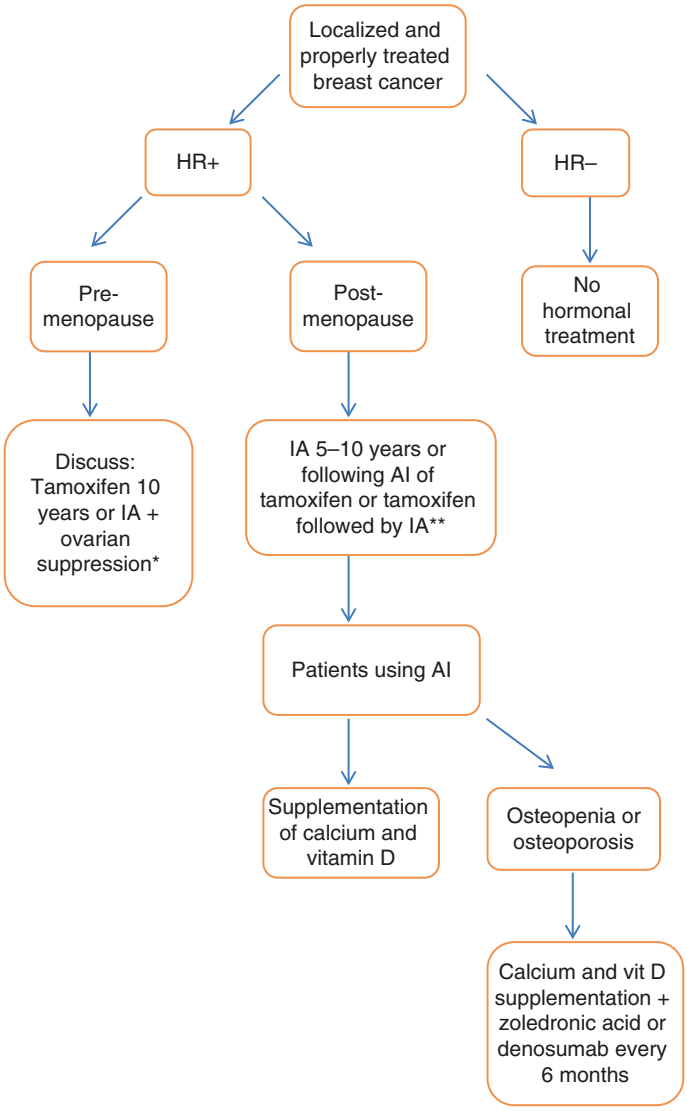
Aromatase Inhibitors

- Cardiovascular: vasodilatation, hypertension, peripheral edema, ischemic disease
- Neurological: mood changes, depression, insomnia, dizziness, headache, anxiety, fatigue, drowsiness, lethargy
- Skin: rash, alopecia, pruritus
- Endocrine: hot flashes, water retention, menstrual changes, amenorrhea, hypercholesterolemia
- Gastrointestinal: nausea, vomiting, diarrhea or constipation, abdominal pain, weight change, anorexia, xerostomia, dyspepsia
- Genitourinary: urinary infections, vulvovaginitis, vaginal alterations such as dryness, bleeding, leucorrhea
- Skeletal muscles: weakness, paresthesia, arthritis, arthralgia, myalgia, fractures, low back pain, bone pain, osteoporosis

The toxicity profile varies among medications, and while tamoxifen is associated with thromboembolic events and endometrial cancer, AIs are more linked to osteoporosis and fractures.

Flowchart

∗Patients that got in the menopause condition during the hormone period of hormone therapy.



Flowchart 1 Hormone therapy. (*HT* hormonal treatment; ∗Duration of HT: discuss case by case; ∗∗Patients who entered menopause during the period of hormone therapy)

Recommended Reading

1. Brufsky A, Bosseman LD, Coradonna R, Haley BB, Jones CM, Moore HC, et al. Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozol: Z-FAST Study 36-month follow-up results. Clin Breast Cancer. 2009;9(2):77–85. *Patients receiving adjuvant letrozole were randomized (301 in each group) to receive zoledronic acid early or late. After 12 months, bone densitometry showed a 4.4% higher lumbar spine density and, in the hip, 3.3% higher in the early treatment group. Early use of zoledronic acid prevents loss of bone mass in postmenopausal women using adjuvant letrozole.*
2. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of estrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381(9869):805–16. Available from: https://doi.org/10.1016/S0140-6736(12)61963-1. *Patients receiving adjuvant tamoxifen were randomized to discontinue treatment after 5 years or completing 10 years regardless of their age or menopausal status. Treatment for 10 years was associated with a significant reduction in the risk of tumor recurrence and death, and was associated with a small increase in the risk of pulmonary embolism, cardiac ischemia and endometrial neoplasia.*
3. Goss PE, Ingle JN, Printchard KI, Robert NJ, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med. 2016;375:209–19. *The MA.17R study evaluated the impact of extending the use of letrozole for an additional 5 years* versus *placebo. 1918 patients were included and those who received extended adjuvant showed increased disease-free survival with a 34% reduction in recurrence (HR 0.66 and p 0.01). The extent use of letrozole was related to a decrease in the incidence of new contralateral lesion and modest impact on distant relapse.*
4. Jonat W, Gnant M, Boccardo F, Kaufmann M, Rubagotti A, Zuna I, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol. 2006;7(12):991–6. *A meta-analysis of three clinical studies: ABCSG8, ARNO 95 and ITA with the aim of evaluating whether sequential treatment with anastrozole after 2–3 years of tamoxifen would be more effective than the continuation of tamoxifen for 5 years. Sequential treatment showed an increase in progression-free survival (HR 0.59, CI 0.48–0.74), distance free survival (HR 0.61, IC: 0.45–0.83) and overall survival (HR 0.71, CI 0.52–0.98).*
5. Prudence A, Francis MD, Meredith M, et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015;372:436–46. *A combined analysis of 4690 women treated with ovarian suppression plus exemestane or tamoxifen showed an advantage for combination with AI with disease-free survival at 5 years of 91.1% versus 87.3% ($p < 0.01$). The results were more robust when observed the population of women under 35 years (83.4% versus 78%).*

Adjuvant Chemotherapy of Breast Cancer

Sérgio Daniel Simon, Pedro H. Z. de Moraes, and Vladimir Galvão de Aguiar

Definition

Adjuvant chemotherapy treatment refers to the systemic administration of cytotoxic agents after surgical treatment. It aims at treating micrometastatic disease and consequently eliminating or lowering the chances of recurrence.

Background Facts

In the late nineteenth century, Halsted revolutionized cancer surgery by proposing an expansion of the surgical limits of the breast. According to him, breast cancer spread from the mammary gland, concentrically, to the surrounding tissues and, from these, to distant organs. This theory was universally accepted for about 80 years, until the 1960s, when Bernard Fisher and his colleagues at the University of Pittsburgh suggested that the failure of mastectomy to cure some patients would result from the presence of distant micrometastases already present at the time of surgery. In 1975, this pioneering group, NSABP (National Surgical Adjuvant Breast and Bowel Project), reported better outcome for patients treated with adjuvant oral mustard l-phenylalanine. In this way, Fisher's theoretical concept that any invasive disease is systemic was introduced, and, therefore, early treatment of micrometastases has brought benefits to patients, especially for those at high risk of relapse.

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There are several schedules available for adjuvant chemotherapeutic treatment. Anthracycline, taxanes, alkylators, and antimetabolites represent the classes of most active agents. Doxorubicin and epirubicin, paclitaxel and docetaxel, cyclophosphamide, methotrexate, and 5-fluorouracil are, respectively, the most effective and validated drugs through phase III studies in the adjuvant setting. In the specific case of HER2-positive disease, anti-HER2 antibodies, together with chemotherapy, have shown to be extremely effective in improving the adjuvant treatment of these patients.

Bonadonna et al. (1976) tested the combination of cyclophosphamide, methotrexate, and fluorouracil (CMF) and confirmed the benefits of adjuvant therapy. Many years later, doxorubicin (or "Adriamycin") was added to cyclophosphamide (AC) in an attempt to shorten treatment time. He demonstrated that four cycles of AC were equivalent to standard treatment of six cycles of CMF. In order to guarantee the benefit of the drugs used in the CMF scheme, methotrexate was replaced by anthracyclines in subsequent protocols, such as FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) and FEC (5-fluorouracil, epirubicin, and cyclophosphamide), with 21% reduction of mortality and 16% reduction of risk of relapse, according to the Danish Breast Cancer Cooperative Group (DBCG 89D) study. The NSABP-36 did not confirm these data, and there was worsening of the quality of life, with more amenorrhea in the FEC scheme, which is no longer indicated.

Taxanes were introduced in the early 1990s. Several randomized phase III studies (CALGB 9344, NSABP B-28, PACS 01, GEICAM 9906) evaluated the efficacy of their sequential use associated with anthracycline. All of them showed a significantly reduced risk of recurrence with an increase in progression-free survival from 17% (anthracycline only) to 36% (anthracycline and taxane combination), with an absolute benefit of 4–6%, respectively. To complement the benefit of these two classes, the BCIRG 001 study compared the TAC scheme (docetaxel, doxorubicin, and cyclophosphamide) against the FAC scheme (5-fluorouracil, doxorubicin, and cyclophosphamide), confirming an increase in progression-free survival and overall survival favoring the TAC scheme.

The most effective way to administer taxanes was studied by the Eastern Cooperative Oncology Group (ECOG) in the ECOG1199 study. In that study, 4950 patients with lymph node involvement and consequent high risk were randomized to receive four cycles of AC every 21 days, followed by one of these combinations: four cycles of *paclitaxel* 175 mg/m^2 every 21 days, 12 weekly cycles of the same drug at 80 mg/m^2, four cycles of *docetaxel* 100 mg/m^2 every 21 days, or 12 weekly cycles of the same drug at 35 mg/m^2. There was an increase in disease-free survival for the groups receiving either weekly paclitaxel or docetaxel every 3 weeks.

In order to minimize residual tumor burden, based on mathematical models of growth through the administration of more frequent doses than through dose escalation (without benefit in previous studies), INT/CALGB 9741 proposed the use of conventional AC doses followed by T at shorter intervals (every 14 days) associated with the administration of filgrastim 5 μg/kg of D3–D10 to prevent hematological toxicity. There was a 26% recurrence risk reduction and a 31% death reduction in the "dose-intense" group, with a 4-year progression-free survival of 82% (an abso-

lute gain of 7%), not accompanied by increased toxicity. The meta-analysis published by Bonilla et al. in 2010 [1] confirmed these results with benefit in hormone receptor-negative and high-risk tumors.

Recently, after the publication of the Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) study, another antimetabolite from the fluoropyrimidine group was added to the adjuvant treatment in a specific setting: HER2-negative patients with residual disease after neoadjuvant treatment containing anthracycline, taxane, or both. Capecitabine was given at a dose of 1250 mg/m^2 body surface area, twice daily from D1 to D14 every 21 days for six to eight cycles. There was significant disease-free survival benefit in the capecitabine-treated group, especially for patients with hormone receptor-negative patients.

In some situations, a reduction in treatment intensity may be advantageous. The ABC study suggests a lack of benefit of the addition of doxorubicin to the combination of taxane and cyclophosphamide for patients with hormone receptor positive and absence of lymph node involvement.

Main Chemotherapy Drugs

Overall, CMF is better than placebo, anthracycline-based regimens are better than CMF, and women at high risk and/or lymph node involvement benefit from the addition of taxanes in adjuvant therapy. The results are better when you can offer a larger variety of drugs and complete cycles, but this should be reserved for patients at higher risk of recurrence. Regimens containing anthracycline are more effective in HER2-positive patients in the same way as taxanes are favored in triple-negative patients. 5-Fluorouracil is contraindicated in localized breast cancer by increasing the risk of adverse events (neutropenia, fever, nausea, and vomiting) without increased progression-free survival and overall survival (Fig. 1).

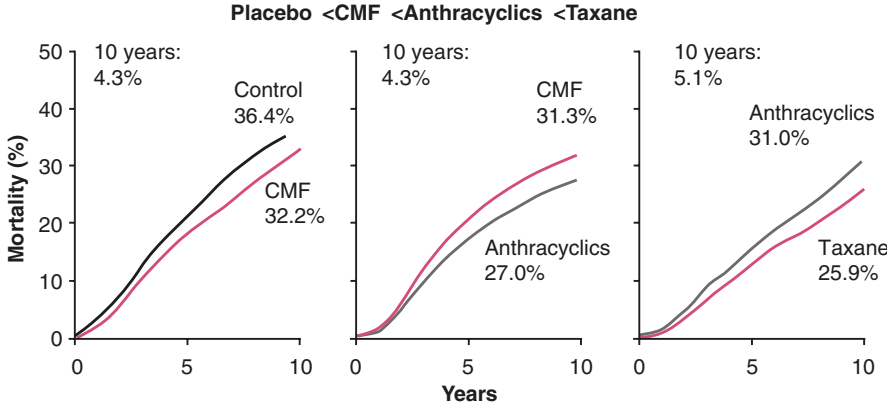


Fig. 1 Adjuvant treatment: San Antonio Breast Cancer Symposium 2007

Main Studies

Schemes	Doses and frequency
AC × 4 (NSABP B-15)	Cyclophosphamide: 600 mg/m^2 IV on D1 Doxorubicin: 60 mg/m^2 IV on D1 Every 21 days for four cycles
AC → T (E1199)	Cyclophosphamide: 600 mg/m^2 IV on D1 Doxorubicin: 60 mg/m^2 IV on D1 Every 21 days for four cycles followed by: Paclitaxel: 80 mg/m^2 IV weekly for 12 weeks or Docetaxel: 100 mg/m^2 IV on D1 every 21 days for four cycles
AC → T *Dose dense* (CALGB 9741)	Cyclophosphamide: 600 mg/m^2 IV on D1 Doxorubicin: 60 mg/m^2 IV on D1 Every 14 days for four cycles with support of G-CSF from D3 to D10 followed by: Paclitaxel: 175 mg/m^2 IV on D1 every 14 days for four cycles. Support of G-CSF from D3 to D10
TC × 4 *(US Oncology Research Trial 9735)*	Docetaxel: 75 mg/m^2 IV on D1 Cyclophosphamide: 600 mg/m^2 IV on D1 Every 21 days for four cycles
TAC × 6 *(BCIRG 001 Trial)*	Docetaxel: 75 mg/m^2 IV on D1 Cyclophosphamide: 500 mg/m^2 IV on D1 Doxorubicin: 50 mg/m^2 IV on D1 Every 21 days with support of G-CSF from D2 to D14 and prophylaxis with ciprofloxacin from D5 to D14
CMF (scheme IV) *(EBCTCG meta-analysis)*	Cyclophosphamide: 600 mg/m^2 IV on D1 Methotrexate: 60 mg/m^2 IV on D1 5-Fluorouracil: 600 mg/m^2 IV on D1 Every 21 days for six cycles
CMF (oral scheme) (Bonadonna regimen)	Cyclophosphamide: 100 mg/m^2 VO D1–D14 Methotrexate: 40 mg/m^2 IV on D1 and D8 5-Fluorouracil: 600 mg/m^2 IV on D1 and D8 Every 28 days for six cycles

Indications

The decision to offer adjuvant treatment should include the medical staff and the patient. Individual risk, magnitude of expected benefit with treatment, related side effects, and comorbidities already present should be considered.

The most important criteria to be evaluated for the definition of the individual risk of recurrence are tumor size and grade, angiolymphatic invasion, presence or not of affected lymph nodes, and HER2 positivity or not.

For this, mathematical tools are available that estimate local and distant recurrence as well as survival, such as AdjuvantOnLine! and Predict. In addition, gene expression tests are used to define the prognosis, as well as the benefit of adjuvant chemotherapy. Oncotype DX, which evaluates 21 genes by reverse transcription of DNA by polymerase chain reaction (RT-PCR), is the most used one in the USA. It presents validated data for estimating both the risk of recurrence (prognostic) and

the benefit of addition of chemotherapy to hormonal therapy in postmenopausal women with hormone receptor-positive tumors and negative for HER2 expression or amplification, regardless of lymph node involvement. The other available tests are MammaPrint (70 genes) and EndoPredict (8 genes), more popular in Europe, and PAM50 – Prosigna (50 genes).

Taking the above factors into account, the Saint Gallen Council sets the following criteria for risk assessment:

- High risk: low expression of hormone receptors; histological grade 3; high rate of cell proliferation; four or more lymph nodes involved; extensive peri-tumor vascular invasion; tumors greater than 5 cm
- Intermediate risk: tumors between 2 and 5 cm; low number of lymph nodes (1–3); histological grade 2
- Low risk: high expression of hormone receptors; grade 1 tumors; low proliferation rate; absence of axillary involvement; absence of vascular invasion; tumors smaller than 2 cm

The criterion of greatest severity for classification always prevails. High-risk patients benefit from adjuvant chemotherapeutic treatment, unlike low-risk patients. In patients at intermediate risk, therapy should be individualized. *Oncotype Dx* can be used in the latter two situations for better therapeutic definition (St Gallen 2017). For clinically high-risk patients as assessed by AdjuvantOnline! *MammaPrint* can be useful, as only patients with "biologic high risk" will benefit from adjuvant chemotherapy.

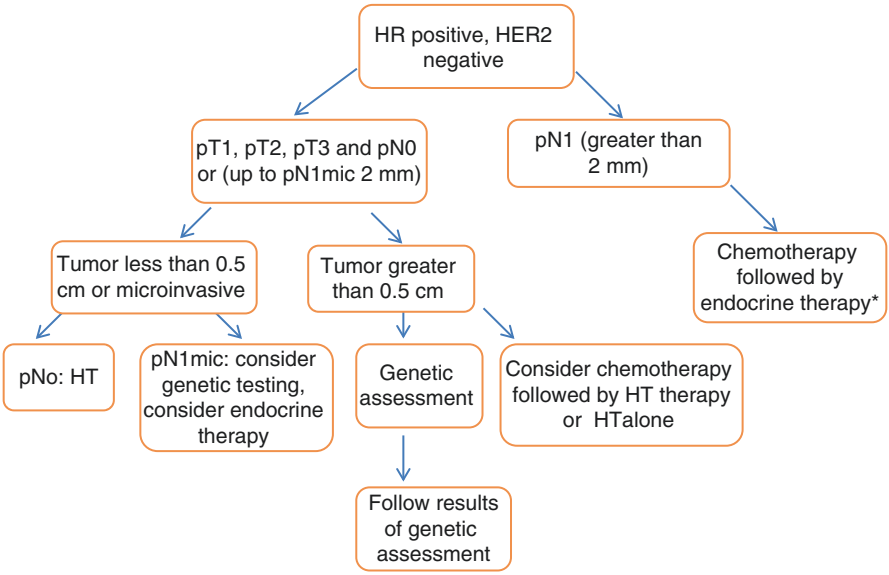
Side Effects and Medication Interactions

Chemotherapy treatments have common and specific side effects. Alopecia, which can be minimized with a cold cap, is the most frequent, especially when using AC or docetaxel. Marrow toxicity with neutropenia and subsequent nausea may also occur. As specific adverse events for taxanes, we emphasize neuropathy and anaphylaxis (paclitaxel). For anthracyclines, cardiotoxicity may occur, leading to reduced ejection fraction and congestive heart failure, in addition to the development of myelodysplasia and leukemia in the long term. Echocardiographic control of these patients is advised.

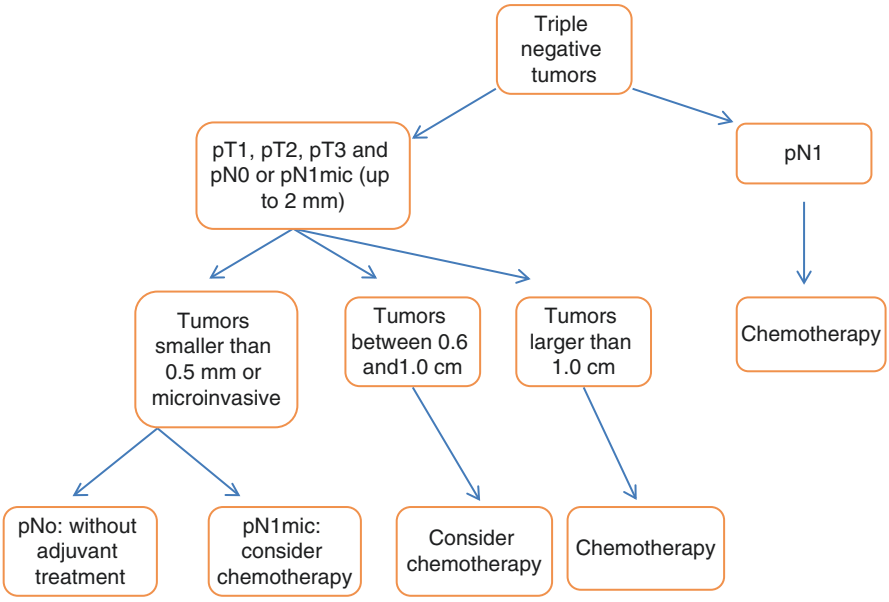
Contraindications

The use of high toxicity regimens in fragile patients (elderly patients, multiple comorbidities) should be avoided. The postoperative period should be respected for full healing. Radiotherapy should not be associated with it, since it potentiates the toxic effects of medications. In addition, it is important to consider previous cardiovascular disease and neuropathy (e.g., diabetics) in order to lower the use of anthracyclines and taxanes, respectively.

Flowcharts



Flowchart 1 Algorithm for adjuvant treatment of positive hormone receptor and HER2-negative tumors. (*HT* hormonal treatment; ∗Discuss genetic assessment)



Flowchart 2 Algorithm for adjuvant treatment of triple-negative tumors

Recommended Reading

1. Bonilla L, et al. Dose-dense chemotherapy in nonmetastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials. J Natl Cancer Inst. 2010;102:1845–54. *Systematic analysis and meta-analysis with 10 studies and more than 11,000 patients who evaluated a dense dose chemotherapy regimen in high-risk patients. Interpretation: dense-dose chemotherapy showed a gain in overall survival with HR 0.85 (95% CI 0.77–0.93) and progression-free survival gain at HR 0.81 (95% CI 0.75–0.88).*
2. Gnanta M, Harbeckb N, Thomssen C, Panel Members. St. Gallen/Vienna 2017: a brief summary of the consensus discussion about escalation and de-escalation of primary breast cancer treatment. Breast Care. 2017;12:102–7. *Review of the St Gallen conference in 2017. Updates in the areas of genetics and molecular biology, creating a panel to guide the adjuvant treatment of breast cancer. Interpretation: the therapeutic decision must be individualized, taking into account the patient's characteristic and molecular biology of the tumor.*
3. Lo S, Mumby PB, Norton J, Rychlik K, Smerage J, Kash J, Chew HK, Gaynor ER, et al. J Clin Oncol. 2010;28:1671–6. *Validation of the recurrence score through analysis of 21 genes (Oncotype) by 17 oncologists and 89 patients regarding their power to alter the adjuvant therapeutic decision. There was a change in the treatment of oncologists in 31.5% of cases and by patients in 27%. Interpretation: multigene analysis has an impact on the recommendation of adjuvant treatment.*
4. Masuda N, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376:2147–59. *Patients with negative Her2 neoplasia who have residual disease after neoadjuvant treatment have a worse prognosis than patients with complete pathological response. In this context, the addition of Xeloda adjuvant was evaluated. Interpretation: Xeloda adjuvant predicts a 5-year progression-free survival benefit with HR 0.7 (95% CI 0.53–0.92) and overall survival at 5 years with HR 0.59 (95% CI 0.39–0.9). This benefit was even more pronounced in triple-negative. However the study was performed exclusively with Japanese and Korean population.*
5. Sparano JA, et al. Long-term follow-up of the E1199 phase III trial evaluating the role of taxane and schedule in operable breast cancer. J Clin Oncol. 2015;33(21):2353–60. E1199. *A prospective study comparing four cycles of AC followed by four distinct schemes of taxane: paclitaxel and docetaxel weekly and every 3 weeks. Interpretation: increased progression-free survival for the weekly paclitaxel and docetaxel groups every 3 weeks.*

Anti-HER2 Adjuvant Therapy

Carlos Barrios and Alessandra Morelle

Introduction

HER2-positive breast cancer is defined by the presence of overexpression of the human epidermal growth factor receptor type 2 (ErbB2), also known as HER2. This receptor belongs to the receptor tyrosine kinase family, it is stimulated by growth factors, and it exerts its effects through the activation of signaling pathways that are in charge of cell proliferation, differentiation, and survival; these include the MAPK and PI3K/Akt pathways. There is an increase in HER2 expression in approximately 15–25% of breast cancers, and this is commonly associated with a more aggressive profile and a worse prognosis of the disease with higher recurrence rates and higher mortality.

Diagnosis

The HER2 status of the tumor can be assessed by several methods, including immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), silver in situ hybridization (SISH), and chromogenic in situ hybridization (CISH).

More commonly used, the diagnosis of HER2 overexpression is performed by immunohistochemical analysis. The evaluation of HER2 overexpression is mandatory for patients with invasive breast carcinoma. The result is important because it significantly impacts the treatment and evolution of the disease. HER2-positive

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tumors exhibit some resistance to endocrine therapy and less benefit with some chemotherapeutic regimens, such as those containing no anthracyclines or taxanes. In 2007, the American Society of Clinical Oncology (ASCO) along with the American College of Pathologists (ACP) issued detailed guidelines on how the test should be performed. These recommendations were reviewed in 2013 and some modifications were made. The classification of immunohistochemistry (IHC) was modified by defining as +3 (positive test) the complete and intense staining of the circumference of the cell membrane; +2 (indefinite test) incomplete staining and weak to moderate intensity in more than 10% of the invading cells or complete and intense in equal to less than 10% of the invading cells; +1 (negative test) incomplete and weak staining in more than 10% of invading cells; and 0 (negative test) when no staining is observed or when membrane staining is incomplete and weak in less than 10% of invading cells. If the score is 2+, the result is considered ambiguous and it requires confirmation by FISH or SISH test.

It should be noted that a significant percentage (10–40%) of the tests evaluated in general clinical practice may be incorrect when repeated in central laboratories of greater experience. Patient selection has paramount importance for treatment with target HER2 therapies, and therefore it is crucial that the HER2 test be performed adequately to avoid false-positive and false-negative results. Because of the significant benefits observed in studies, the high cost and potential risk of cardiotoxicity with trastuzumab, testing for HER2 requires maximum accuracy and should be performed in experienced pathology laboratories, which perform the test sufficiently frequently and participate in quality control programs.

Adjuvant Treatment of HER2-Positive Disease

The management of breast cancer has evolved a lot in recent decades with the development of several target therapies against the HER2 receptor. The benefits have been observed in both adjuvant and metastatic disease. The available agents for clinical use are trastuzumab (Herceptin; Genentech), lapatinib (Tykerb; GlaxoSmithKline), pertuzumab (Perjeta; Genentech), and ado-trastuzumab emtansine (T-DM1) (Kadcyla; Genentech).

Trastuzumab

Trastuzumab was the first agent to be developed with HER2 as a target, and in 1998 it was approved by the US Food and Drug Administration (FDA) as a therapy against metastatic breast cancer with increased HER2 expression. Its introduction

in the treatment of breast cancer represents a milestone in the history of oncology. Trastuzumab is a humanized monoclonal antibody that acts by binding to the extracellular domain IV of HER2. When interacting with the outside of the receptor, trastuzumab exerts its activity through mechanisms not yet fully known. There is evidence that the antibody inhibits tumor growth via a variety of mechanisms, including decreased receptor expression, antiangiogenesis, and antibody-dependent cytotoxicity. Trastuzumab disrupts signaling through the PI3K pathway and interferes with cell cycle progression mediators such as cyclin D1. It is known that primary resistance to trastuzumab, when administered as a single agent, occurs in about 70% of malignant neoplasms of breast HER2+, with most developing resistance during treatment. The main mechanisms of resistance proposed include:

- Overexpression of other erbB receptors and/or other EGFR ligands
- Activation of different signaling pathways through the loss or inactivation of the *PTEN* tumor suppressor gene
- Activating mutations of PI3K
- Dependence or signaling through recipients of alternative growth factors, leading to hyper-activation of the PI3K/AKT/Mtor signaling pathway
- Alterations of antibody binding sites or masking of binding epitopes
- Increased circulating HER2 extracellular domain
- Altering immune mechanisms affecting ADCC response (antibody-dependent cell-mediated cytotoxicity)
- Hypo-activation of P27 and high CDK2 activity

After demonstrating benefits in metastatic disease in combination with chemotherapy, several studies have shown that the addition of trastuzumab to chemotherapy in adjuvant treatment generally results in a 50% reduction in the risk of recurrence and a 30% reduction in mortality risk. In 2006, based on these results, the FDA approved its incorporation in combination with chemotherapy for adjuvant treatment in patients with HER2-positive breast cancer.

Neoadjuvant Trastuzumab Chemotherapy Treatment

Patients with HER2-positive breast cancer who respond to neoadjuvant chemotherapy and achieve pathological complete response (pCR) have better progression-free survival rates and overall survival. The benefit of trastuzumab in the neoadjuvant scenario was demonstrated in the analysis of two randomized trials in which the addition of trastuzumab to the treatment regimen showed increased pCR rates when compared to the control group. Trastuzumab reduced rates of relapse and mortality without increased cardiac toxicity (Table 1).

Table 1 Neoadjuvant studies with trastuzumab

Studies	Treatment branches	pCR
Techno	EC → P + H	38.7%
Noah	(a) AP → P → CMF (b) AP + H → P + H → CMF + H (c) (HER2-) AP → P → CMF	(a) 19% (b) 38% ($p = 0.0007$)
GeparQuattro	EC → docetaxel +/− cap +/− H	31.7% with H vs. 15.7%
Buzdar et al.	(a) P → FEC (b) P → FEC + H weekly	(a) 26% (b) 65% ($p = 0.016$)
ABCSG-24	(a) ED ± cap (b) ED ± cap +H	(a) 26% (b) 40% ($p = 0.369$)

A Adriamycin, *ABCSG* Austrian Breast and Colorectal Study Group, *C* cyclophosphamide, *Cap* capecitabine, *D* docetaxel, *E* epirubicin, *F* fluorouracil, *GeparQuattro* German Breast Group/Gynecologic Oncology Study Group, *H* trastuzumab, *M* methotrexate, *Breast and NOAH* Neoadjuvant Herceptin, *P* paclitaxel, *TECHNO* Taxol Epirubicin Cyclophosphamide Herceptin Neoadjuvant

Adjuvant Chemotherapy Treatment with Trastuzumab

A meta-analysis of eight randomized controlled trials involving 12,000 patients with HER2-positive initial breast cancer showed that trastuzumab-containing regimens resulted in better progression-free survival regardless of duration of treatment or type of administration over non-trastuzumab regimens. Patients who received trastuzumab for 12 months had a statistically significant improvement in overall survival when compared to regimens lasting below 6 months. The benefit of overall survival was associated with concomitant administration of trastuzumab with chemotherapy but not with sequential treatment of chemotherapy followed by the single trastuzumab agent.

Several chemotherapy regimens combined with trastuzumab have been studied. The role of this agent in the adjuvant treatment of HER2-positive breast cancer has been evaluated in several clinical trials, which are described below.

The HERceptin Adjuvant (HERA) trial study was an international study that evaluated the effect of sequential addition of trastuzumab after completing standard adjuvant chemotherapy. A total of 5090 breast cancer patients with overexpression of HER2, lymph node (LN) positive or negative LN with $T > 1$ cm, were randomized into three groups: QT chosen by the investigator without trastuzumab, conventional QT followed by trastuzumab for 1 year (dose of attack of 8 mg/kg EV and after 6 mg/kg EV every 3 weeks), or QT followed by trastuzumab for 2 years. After 8 years of follow-up, a 24% reduction in the risk of recurrence and risk of death for trastuzumab treatment was demonstrated. There was no significant difference between treatment for 1 year and treatment for 2 years (see discussion of the controversies below).

In the Scandinavian study (FinHer), 1010 patients were randomly assigned to receive either three cycles of docetaxel (100 mg/m^2; D1 every 21 days) or vinorel-

bine (25 mg/m^2 at D1, D8 and D15 every 21 days) followed by fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, and cyclophosphamide 600 mg/m^2 (FEC) at D1 every 21 days. A second randomization was performed for HER2-positive patients receiving or not trastuzumab weekly (first dose of 4 mg/kg and the other 2 mg/kg) for 9 weeks along with docetaxel or vinorelbine. Although the initially reported results demonstrated benefit for this short-course treatment after a follow-up of 62 months, it was observed that for women with HER2 overexpression, treatment with trastuzumab for 9 weeks had no significant impact on distant disease-free survival or risk of death when compared to chemotherapy alone. At the other randomization, docetaxel treatment presented better results with respect to distant disease-free survival when compared to vinorelbine.

The French study, PACS04, evaluated two chemotherapy regimens with sequential administration of trastuzumab or only observation for HER2-positive patients. In this study, 3010 women were randomly assigned to receive six cycles of fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 (FEC) or epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 on D1 every 21 days. Patients with HER2 positivity were again randomized to receive trastuzumab for 1 year or remain under observation. This was a negative result in which a non-significant reduction of only 14% in the risk of relapse was observed despite the administration of 1 year of trastuzumab.

In the BCIRG 006 study, the use of two chemotherapy regimens with trastuzumab, one without anthracyclines, was explored. The study included 3222 patients in three groups: doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles, followed by docetaxel 100 mg/m^2 with or without trastuzumab for 1 year (ACTH and ACT), or docetaxel 75 mg/m^2 and carboplatin AUC 6 every 3 weeks for six cycles concomitantly with trastuzumab and, after, trastuzumab for 34 weeks (TCH). The results demonstrated a decreased risk of recurrence and death with ACTH and HCT (the two groups that included trastuzumab). There was no significant difference between these two groups, suggesting comparable efficacy for the two regimens. However, lower cardiotoxicity was observed for treatment with TCH. Therefore, this scheme is an alternative for adjuvant treatment of HER2-positive disease. There is intense controversy in the medical literature among those who consider that anthracyclines may or may not be excluded from the adjuvant treatment of HER2-positive patients. Our position is that in the absence of specific contraindications, anthracyclines still play an important role in the treatment of these patients, probably with a positive balance when considering risks and benefits. Future studies may clarify this situation.

The NCCTG study 9831 and the NSABP study B31 were conducted separately, but because they approach similar treatment groups, they were analyzed together. In summary, patients with HER2-positive breast cancer were randomized to receive 60 mg/m^2 doxorubicin and cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles followed by paclitaxel 80 mg/m^2 weekly for 12 weeks. The other two branches, experimental ones, included the same chemotherapy with sequential or concomitant administration (with paclitaxel) of trastuzumab for 1 year of treatment. Disease-free

survival was significantly better in women who received 52 weeks of trastuzumab when compared to that in the trastuzumab group. Treatment with trastuzumab concomitantly with paclitaxel demonstrated a statistically non-significant advantage, but with indications that in the absence of contraindication to concomitant use, they recommend this type of regimen as a standard treatment.

The summarized treatment schemes can be seen in Table 2, adapted from Parakh et al. (2017). There is no doubt that the consistent benefits demonstrated in most of these studies represent a significant advance in the treatment of patients with HER2-positive disease.

Table 2 Adjuvant studies with trastuzumab for breast cancer HER2-positive

Study	Length trastuzumab	Mid-term follow-up	Outcome	Overall survival
BCIRG006	52 weeks	10.3 years	DFS AC-TH: HR 0.70 TCH: HR 0.76 $P < 0.001$	AC-TH: HR 0.64 ($P < 0001$) TCH: HR 0.76 ($P = 0.0081$)
NSABP B-32 NCCTG9831 Final analysis	52 weeks	8.4 years	DFS 62.3% vs. 73.7% HR 0.60 $P < 0.001$	75.2% vs. 84% HR 0.63 $P < 0.001$
HERA	1 vs. 2 years	8 years	DFS 75.8% vs. 76% HR 0.99 $P = 0.86$	86.9% vs. 88.7% HR 1.05 $P = 0.63$
FinHER	9 weeks	5.2 years	DFS 73.7% vs. 62.3% HR 0.65 $P = 0.12$	82.3% vs. 91.3% HR 0.55 $P = 0.09$
PACS04	52 weeks	3.9 years	DFS 77.9% vs. 80.9% HR 0.86 $P = 0.41$	96% vs. 95% HR = 1.27 (P = NS)
PHARE	6 vs. 12 months	42.5 months	DFS 92.1% vs. 93.8% HR 1.28 $P = 0.29$	94.5% vs. 96.1% HR = 1.46
Meta-analysis	–	36 months	DFS HR 0.60 $P < 0.0001$ favoring regimens with trastuzumab	HR 0.66 $P < 0.0001$ favoring regimens with trastuzumab

ABCSG Austrian Breast and Colorectal Study Group, *BCRIG* Breast Cancer International Research Group, *CALBG* Cancer and Leukemia Group B, *DFS* progression-free time, *FinHER* Finland Herceptin trial, *H* trastuzumab, *HERA* Herceptin adjuvant study, *HR* hazard ratio, *NS* not significant, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *NCCTG* North Central Cancer Treatment Group, *OS* overall survival, *PACS* Protocol Adjuvant dans le Cancer du Sein, *PHARE* Protocol for Herceptin as adjuvant therapy with reduced exposure

Adverse Effects of Trastuzumab

Like other antineoplastic agents, trastuzumab is also associated with adverse effects. Among the most common ones are mild allergic reactions associated with infusion, headache, arthralgia, fatigue, nausea, diarrhea, abdominal pain, muscle weakness, and skin rash. Allergic reactions are found in a minority of patients, especially in the first few applications with a tendency to disappear with continuity of treatment. In general, less than 10% of the patients present these effects that have a mild degree, and less than 1% of cases can be classified as grade 3 or 4. These adverse events are symptomatically easy to manage and are not generally associated with the need to discontinue treatment with trastuzumab.

Cardiotoxicity may also be observed with trastuzumab treatment and is a para-effect that deserves special attention. The use of trastuzumab raises the risk of myocardial dysfunction and its use should accompany the Left Ventricular Ejection Fraction routinely. Therefore, caution should be exercised when trastuzumab is administered in patients with heart problems and especially if the patient previously used anthracyclines as part of their treatment. A reported cardiac dysfunction rate was observed in the adjuvant studies reported 0.4 (TCH) to 3.37%. A small percentage of these cases present symptomatology (<1%) and the dysfunction is usually reversible. Even so, it is recommended to perform periodic monitoring during treatment and also after completion. The use of imaging methods is essential for detecting changes in ventricular function, with echocardiography being the most accepted method for monitoring patients receiving trastuzumab. Radioisotope ventriculography (MUGA) is another method used. Patients should be screened prior to initiating treatment with trastuzumab, every 3 months during treatment or at any time if clinical suspicion of heart failure presents, and also after termination. It is suggested that the monitoring method used be the same throughout the treatment period, since the measures provided by the different techniques are not interchangeable. The incidence of myocardial dysfunction increases with prolongation of treatment beyond 12 months as presented in the 2-year arm of the HERA study.

Controversial Topics on the Adjuvant Treatment of HER2-Positive Disease

As many questions have been answered with the identification of this subgroup of breast cancer patients and with the development of agents targeting this abnormality, many questions remain unanswered. Some of these questions are generating important controversies in the literature, mainly because they frequently impact on situations of clinical practice that were not included in the studies carried out so far.

The first situation is the treatment of tumors smaller than 1 cm. Most of the adjuvant studies performed so far did not include a significant number of patients in this

group, who are more and more frequently found in practice. The literature is poor and generally descriptive and retrospective as to the prognosis of patients with tumors smaller than 1 cm and HER2-positive disease. The two largest series (MDACC and Milan) indicate that patients with small tumors and increased HER2 expression appear to have a worse prognosis (higher rate of recurrence and less distant disease free survival) than tumors of the same size but without HER2 overexpression. A more detailed analysis was not performed separating patients T1a (up to 0.5 cm) and T1b (0.5–1.0 cm). Recently, the National Comprehensive Cancer Center Network (NCCN) reviewed its database and reported a 5-year overall survival over 95% in patients with pT1a/bN0 HER2-positive who were not treated with chemotherapy or trastuzumab.

Another American tumor registry – the Kaiser Permanent Northern California (KPNC) – also identified 171 untreated HER2+ pT1a/bN0 patients. A shorter free range of distance progression (FRDP) was identified in T1bN0HER2+ patients when compared to smaller tumors. The 5-year LLPI was 99% (95% CI, 93–99.9%), 100% and 93.3% (95% CI, 75.9–98.3%) for T1a, T1b with less than 1 cm, and T1b with 1 cm, respectively. None of the four pivotal studies included patients with T1a/bN0, with the exception of BCIRG-006, which included patients T1a/b. Although not specifically mentioned, these tumors most likely had positive lymph nodes.

A retrospective French study reviewed 276 cases of patients with breast cancer pT1a/bN0 HER2+. Of these, 129 patients (47%) were treated with adjuvant chemotherapy associated with trastuzumab, 19 with chemotherapy alone, only 5 with trastuzumab, and 123 (45%) did not use chemotherapy or trastuzumab. Patients receiving chemotherapy and trastuzumab were significantly associated with tumors with negative hormone receptors and higher tumor grade. Despite this selection bias, only two relapses occurred in the group that received chemotherapy and trastuzumab. In the group that did not perform either chemotherapy nor trastuzumab, there were 13 relapses with a mean follow-up time of 44 months. Progression-free time at 40 months was 99% and 93%, respectively ($p = 018$).

The Dana-Farber Cancer Institute group designed a prospective non-randomized phase II study with weekly paclitaxel in combination with trastuzumab followed by maintenance with trastuzumab for 1 year in patients with N0 HER2-positive breast cancer and tumor with 3 cm or less. A total of 201 patients from the 406 participants had pT1a/bN0 breast cancer. The 3-year progression-free time of this group was 99.5%. This proportion was significantly higher than the historical data from the MD Anderson series. Another ongoing randomized phase II trial of Dana-Farber is the ATTEMPT Trial, which is comparing the weekly paclitaxel plus trastuzumab with the immune-conjugate ado-trastuzumab emtansine (T-DM1) every 3 weeks for 17 cycles in patients with breast cancer HER2-positive clinical stage I.

In practice, managing these patients remains currently controversial and recommendations necessarily include the informed discussion with each patient of the elements available in the literature and their implications. Our recommendation is to consider treatment for patients with T1b tumors and discuss the indication of the same treatment for smaller tumors. In our opinion the potential biological risk of the disease should weight more than the size of the tumor.

The optimal duration of treatment with trastuzumab is also not fully understood. The definition of a year of treatment was arbitrary. From the studies from the past decade, only the HERA explored this issue by randomizing patients to receive 1 or 2 years of treatment. Recently, results were presented after 8 years of follow-up. There were no significant differences with prolonged treatment of trastuzumab. A French study has also been presented (PHARE) exploring the possibility that the duration of treatment may be less than 1 year. In this study, researchers randomized patients to receive either 6 or 12 months of treatment. The study had a non-inferiority design with very strict criteria for interruption of randomization. Briefly, the results indicate that it was not possible to demonstrate that 6 months of treatment were not inferior to 12 months. In fact, the statistical trend of the analysis indicates favoring the conventional treatment of 12 months. There are other studies that address the issue of duration of treatment that are still in the recruitment and follow-up phase. Until further information is presented in this regard, the 12-month adjuvant treatment with trastuzumab remains the standard.

Other Anti-HER2 Agents

Parallel to the development of trastuzumab other agents directed to this signaling pathway have been developed and are found in different stages of evaluation. Lapatinib is a tyrosine kinase inhibitor that blocks the inner part of the receptor. It demonstrated combined efficacy with capecitabine in metastatic disease and also demonstrated efficacy when combined with trastuzumab in a "double-blind" regimen without chemotherapy. This agent was evaluated in adjuvant treatment in combination with trastuzumab or as a single agent in the ALTTO study published in 2015. Adjuvant treatment with lapatinib did not significantly improve the progression-free time compared to trastuzumab and also increased toxicity in this setting.

The other agent, HER2 tyrosine kinase inhibitor that has been tested in the adjuvant setting is neratinib. In the ExteNET study, patients who completed 1 year of treatment with trastuzumab were randomized to receive an additional 12 months of neratinib versus placebo. The treated patients showed an improvement in invasive disease-free survival (HR: 0.67, 95% CI: 0.50–0.91, $p = 0.0091$). Without a definitive explanation, the group of women with hormone receptor positive was the one who benefited the most from treatment with neratinib. Overall survival results are still awaited. Neratinib had a significant incidence of grade 3 and 4 diarrhea. The interpretation of this study is that even conventional treatment with trastuzumab still leaves a group of patients destined for recurrence of the disease. Complementation with a second, sequential anti-HER2 treatment with a different mechanism of action has a positive impact on the chance of recurrence of the disease. The challenge is to identify which patients need this complementary treatment. This is particularly important given the potential toxicity associated with the drug. Regrettably, we do not yet have biomarkers that will assist us in clinical practice in this regard.

Another agent developed against HER2 is pertuzumab, which binds to a different receptor domain on the outside of the membrane. This agent blocks dimerization, a process that is critical for receptor activation and triggering of signaling. Pertuzumab has shown benefit in metastatic disease in a regimen with chemotherapy and trastuzumab. Pertuzumab was evaluated in neoadjuvant setting in two randomized studies: NEOSPHERE and TRYPHAENA. Both evaluated the safety and efficacy of trastuzumab and pertuzumab together with different chemotherapies. In both, the addition of pertuzumab significantly improved the rate of pathological complete response (pCR), although few occurred in tumors with hormone receptor positive, in addition to HER2 + 3.

Pertuzumab was tested in the adjuvant setting in combination with trastuzumab and chemotherapy in the recently published APHINITY study.

After 3 years of follow-up, 94.1% of patients using trastuzumab and chemotherapy combined with pertuzumab and 93.2% of patients using trastuzumab alone and chemotherapy were free of disease progression. In lymph node-positive patients, progression-free survival was 92% in the pertuzumab group versus 90% in the control group (HR: 0.77, $P = 0.02$). The result in the negative lymph node patients was 97.5% in the pertuzumab group versus 98.4% in the placebo group (HR: 1.13, $P = 0.64$). These results indicate the need for a better follow-up of this patient population, since the number of events of the negative lymph node subgroup has been low so far. The results of this study clearly demonstrate that there is a small group of patients with poor prognosis (LN positive, for example) who benefit from double-block adjuvant treatment.

The elements available to identify these patients are limited and a definitive recommendation is challenging. In our opinion, the information should be discussed between doctor and patient, and considering all the elements of each case before, an informed treatment decision can be made.

Finally it is appropriate to explain that T-DM1 is a conjugate of a cytotoxic (DM-1) and antibody (trastuzumab), in which the two agents are associated through a linker molecule. The KRISTINE study evaluated T-DM1 in the neoadjuvant setting in combination with pertuzumab. Despite being better tolerated, patients treated with chemotherapy, trastuzumab, and pertuzumab more frequently undergo conservative surgery and achieved higher rates of pCR. Studies evaluating the efficacy and safety of T-DM1 as monotherapy and in combination with pertuzumab in adjuvant therapy include studies in progress: KATHERINE (NCT 01772472) and KAITLIN (NCT 01966471), respectively.

Conclusion

Identification of the HER2 molecule and the development of anti-HER2 therapy represent a milestone in the history of breast cancer treatment. This group of patients, who usually had a poor prognosis and high rates of relapse, nowadays

receives a target-directed treatment with excellent results, as shown in the studies described in this chapter. Adjuvant treatment with trastuzumab should be considered in all patients with overexpression of the HER2 molecule. Although the results are expressive, it is important to remember that there are limitations that we still have to face. A small number of patients still relapse after chemotherapy and trastuzumab. There are tumors with primary resistance and those that develop resistance during or after treatment.

Our understanding of the mechanisms of resistance is still rather insufficient for us to select patients and intervene rationally in the individualized management. New agents and new strategies for anti-HER2 drug combinations, which have shown efficacy even in previously treated patients, are expected to further improve outcomes.

Recommended Reading

1. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol. 2009;27:5700–6. *Fehrenbacher L, Capra AM, Quesenberry CP Jr, Fulton R, Shiraz P, Habel LA. Distant invasive breast cancer recurrence risk n human epidermal growth factor receptor 2-positive T1a and T1b node-negative localized breast cancer diagnosed from 2000 to 2006: a cohort from an integrated health care delivery system. J Clin Oncol. 2014;32(20):2151–8.*
2. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012;4:CD006243. *Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353:1659–72.*
3. Piccart-Gebhart M, Holmes E, Baselga J, de Azambuja E, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. J Clin Oncol. 2016;34(10):1034–42. *Chan A, Delaloge S, Holmes FA, Moy B, Iwata H, Harvey VJ, Robert NJ, Silovski T, Gokmen E, von Minckwitz G, Ejlertsen B, Chia SK, Mansi J, Barrios CH, Gnant M, Buyse M, Gore I, Smith J 2nd, Harker G, Masuda N, Petrakova K, Zotano AG, Iannotti N, Rodriguez G, Tassone P, Wong A, Bryce R, Ye Y, Yao B, Martin M; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentric, randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2016;17(3):367–77. https://doi.org/10.1016/S1470-2045(15)00551-3.*
4. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365:1273–83. *Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol. 2011;29:3366–73.*
5. Untch M, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. J Clin Oncol. 2010;28(12):2024–31. *Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2–positive operable breast cancer. J Clin Oncol. 2005;23(16):3676–85.*

6. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, Suter T, Arahmani A, Rouchet N, Clark E, Knott A, Lang I, Levy C, Yardley DA, Bines J, Gelber RD, Piccart M, Baselga J, APHINITY Steering Committee and Investigators. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med. 2017;377(2):122–31.

Neoadjuvant Therapies

Max S. Mano and Rudinei Diogo Marques Linck

Definition and Background Facts

Neoadjuvant therapy consists of preoperative administration of systemic treatment in patients with nonmetastatic breast cancer (BC). The term neoadjuvant chemotherapy (neoChT) does not adequately reflect the wide range of possibilities for systemic treatment that can be employed in this setting—such as endocrine therapy and new target therapies—being "technically more appropriate" to use neoadjuvant systemic therapy (NST); see Table 1.

Although the first generation of randomized trials of neoChT failed to demonstrate survival gains relative to adjuvant chemotherapy (ChT), there was also no negative impact on prognosis. In addition, other important data were extracted from these studies (discussed later) and eventually led to the recognition of neoChT as a standard treatment for patients with locally advanced BC (LABC). It is also worth remembering that these studies (from the molecular pre-classification era of BC) did not evaluate important issues such as the possibility of having a positive impact on the prognosis in biologically more aggressive subtypes—especially with modern therapies, much more effective than those from the years 1980–1990.

Definition of Response, Downstaging, and Progression

For the clinical/radiological evaluation, the RECIST criteria are frequently applied (only as a general guide, with no need to be applied in the everyday practice with excessive rigidity as to the numbers proposed in this system) (Table 2).

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Table 1 Main therapeutic schemes in the neoadjuvant systemic treatment

Scheme	Duration	Comment	Contraindication	Reference
Her2 negative[a]				
AC-T AC (EC/FEC) ×4 q3w → T ×12 q1w or AC (EC/FEC) ×4 q3w → D ×4 q3w	24 weeks	Paclitaxel used weekly tends to be better tolerated than docetaxel, though its administration is less practical	Clinically relevant cardiac disease	J Clin Oncol. 2008;26(5):778
TAC ×6 q3w	18 weeks	It demands the use of prophylactic growing factor	Clinically relevant cardiac disease	Breast Cancer Res Treat. 2013;142(3):549
TC ×6 q3w	18 weeks	It is a better option for contraindication to anthracycline It demands the use of prophylactic growing factor	It is not contraindicated, but it is difficult to be administered in elderly patients	Breast Cancer. 2017;24(1):63
Her2 positive[a]				
AC-TH AC (EC/FEC) ×4 q3w → T ×12 q1w + TZM → TZM or AC-DH AC (EC/FEC) ×4 q3w → D + TZM ×4 q3w → TZM	ChT: 24 weeks TZM: total 1 year	Paclitaxel used weekly tends to be better tolerated than docetaxel, though its administration is less practical	Clinically relevant cardiac disease	N Engl J Med. 2005;353(16):1673
TCH D + C + TZM ×6 q3w → TZM	ChT: 18 weeks TZM: total 1 year	It is the best option for patients with high risk of cardiotoxicity		J Clin Oncol. 2009;27(15s):e11557

FEC-DHP FEC ×3 q3w → D + TZM + PZM ×3 q3w → TZM	ChT: 18 weeks TZM: total 1 year		Clinically relevant cardiac disease	Ann Oncol. 2013;24(9):2278
TCHP D + C + TZM + PZM x6 q3w → TZM	ChT: 18 weeks TZM: total 1 year	It is the best option for patients with high risk of cardiotoxicity Diarrhea and neutropenia are frequent toxicities		Lancet Oncol. 2012;13(1):25
Neoadjuvant endocrine therapy				
Letrozole, anastrozole or exemestane	4–12 months	Post-menopausal with "less chemo sensitive" tumors Absence of response: consider the use of ChT (adjuvant or neoadjuvant)		J Clin Oncol. 2011;29(17):2342

AC doxorubicin + cyclophosphamide, *EC* epirubicin + cyclophosphamide, *FEC* epirubicin + cyclophosphamide + 5-fluorouracil, *T* paclitaxel, *D* docetaxel, *TAC* docetaxel + doxorubicin + cyclophosphamide, *TC* docetaxel + cyclophosphamide, *TZM* trastuzumab, *PZM* pertuzumab, *C* carboplatin, *ChT* chemotherapy, *q1w* weekly, *q3w* every 3 weeks

[a]Only the most used schemes in our practice and environment are mentioned here, though there are many other variations

Table 2 Definitions of response to treatment

Partial response[a]	Tumor regression in ≥30% (measured by its largest diameter at the basal evaluation)
Complete response[a]	Tumor completely disappeared
Progression of the disease	Increase in ≥20% of tumor (in relation to the largest size reached by the tumor after treatment has begun—widest diameter) or upcoming of new lesion
Stable disease	Any result that does not qualify as response or progression
pCR	Absence of tumor cells in the breast or in the lymph nodes in the surgical anatomopathological report Two definitions are mostly accepted: one admits persistence of foci of in situ tumor, the other does not (they seem equivalent)
Downstaging	Regression of the stage of the disease, in case of good response The term is more frequently used to describe cases with initial indication of mastectomy in which performing conservative breast surgery has become possible

pCR pathologic complete response
[a]Clinical response (palpation) or radiologic

Prognostic Markers

Early neoChT studies suggested a correlation between treatment response and prognosis—modest correlation for clinical and radiological response but better for pathologic complete response (pCR). More recently, we have learned that the prognostic value of pCR is higher in ER- (triple-negative or "Pure" Her2) and "luminal B" tumors. However, the prognostic value of pCR is probably absent in less proliferative tumors ("luminal A"). In addition, pCR is not an appropriate outcome for neoadjuvant endocrine therapy (neoET) studies—it is rarely observed even in patients with an excellent prognosis (alternative methods are being validated, such as early re-excision for re-evaluation of Ki67 or Preoperative Endocrine Prognostic Index—PEPI).

Main Schemes

The schemes used in NST are the same as those used in adjuvant therapy (Table 3). In the case of neoChT, the addition of a taxane should be strongly considered, since the LABC are by definition high-risk diseases; in addition, tumor response is another crucial treatment objective. Based on some randomized phase II studies, there has been some discussion as to the role of adding carboplatin to the standard regimen. However, since there is no evidence of improvement in prognosis—and there is an increase in toxicity—the opinion of the authors of this chapter is that at least for the time being, there is no such indication. The duration of treatment for neoChT correlates with the final response, and should not be less than 5–6 months. Sandwich

Table 3 Indications of neoadjuvant chemotherapy

Indication	Comments
T3–T4 or "bulky" axillary lymph nodes	Possible exceptions: Phenotype is not very sensitive to chemotherapy (G1–2 in luminal A subtype and the majority of classical lobular) Low risk from genomic test
Inflammatory carcinomas	Neoadjuvant chemotherapy is almost always recommended
T2	Especially if: Boderline for conservative surgery and/or cosmetic result could be better in case of a favorable response Phenotype is "chemo sensitive" (G3, HER2 positive, triple-negative or luminal subtype with high risk according to genomic signatures)
Less clear indications but could be considered: True multifocal/multicentric (no tumor mass can be evaluated)	

HG histological grade, *IHCh* immunohistochemistry

regimens (chemotherapy split in "before and after" surgery) should be avoided. In Her2 positive tumors there is a need to add target therapy. For trastuzumab, the ideal duration is 12 months, which should be initiated concomitantly with ChT, and not interrupted during the surgical and adjuvant radiotherapy. The addition of pertuzumab in the neoadjuvant treatment of HER2-positive tumors continues to be debated; two phase II studies showed a significant increase in response rates, but no benefit has yet been demonstrated in terms of improvement in prognosis.

Regarding neoadjuvant endocrine therapy (neoET), the optimal duration of treatment is not well defined—ranging from 4 to 12 months. The author suggests that, within the abovementioned period, the best time to perform surgery is the first evaluation with a "stable disease" (i.e., at a time when there appears to be no further tumor regression). In menopausal women, aromatase inhibitors are superior to tamoxifen. In premenopausal women the role of neoET was not adequately evaluated.

Indications

Once the indication for systemic therapy has been established, regardless of the stage of the disease, its administration can be considered in the preoperative period. In the case of very early tumors (T1N0), the role of NST is less clear and may increase the risk of overtreatment, especially for neoChT. Examples include the following:

1. LABC of luminal profile with final pathological classification up to T3 or N1 may not require adjuvant ChT if they have a genomic signature showing low risk.
2. HER2-positive BC with final pathological classification up to T2 (≤3 cm) and N0 can receive a simplified and less toxic scheme of adjuvant ChT with weekly paclitaxel for 12 applications + trastuzumab for 12 months.

Nowadays, the biology of the disease must be one of the pillars of the NST decision. The tumors that best respond to neoChT are histological grade (HG) 3, ER-, HER2 positive or ER + with strong proliferative activity (for example, HG3 or high risk for genomic signature). Predictors of poor response include: classic lobular histology (rich in ER and low HG); luminal profile A or HG 1 (in these cases, the choice for neoET or even initial surgery should be considered).

Other situations in which initial surgery may be the choice include:

1. "Hygienic" complications (ulcerated tumors with suppuration, fetid, or bleeding odor)
2. Any uncertainty regarding the indication of chemotherapy or the diagnosis (for example, doubts about the presence of stromal invasion or inconclusive immunohistochemistry)
3. Some cases of "true" multicentricity, in which there may be interest in better assessing the biological profile of all outbreaks of the disease

They do not constitute a contraindication to NST: uncomplicated ulceration (without suppuration, foul smell, or bleeding); multicentricity; or "unavoidable" indication of mastectomy.

It should also be remembered that the decision to indicate NST in a patient implies, in the vast majority of cases, the need for adjuvant radiotherapy.

Advantages and Disadvantages of NST

Potential advantages of NST include:

- Improvement of surgical options, since 80–90% of patients respond to the treatment;
- Obtaining important prognostic information;
- For the researcher, NST provides the perfect setting for testing innovations, since the outcome (clinical response, pCR) is immediately available and there is no need for "maturing" of the data over years or decades.

Among the potential disadvantages are the loss of detailed prognostic information on the surgical pathology, which in cases of borderline ChT and adjuvant radiotherapy could lead to overtreatment, as well as making it difficult to determine the irradiation fields.

Response Monitoring

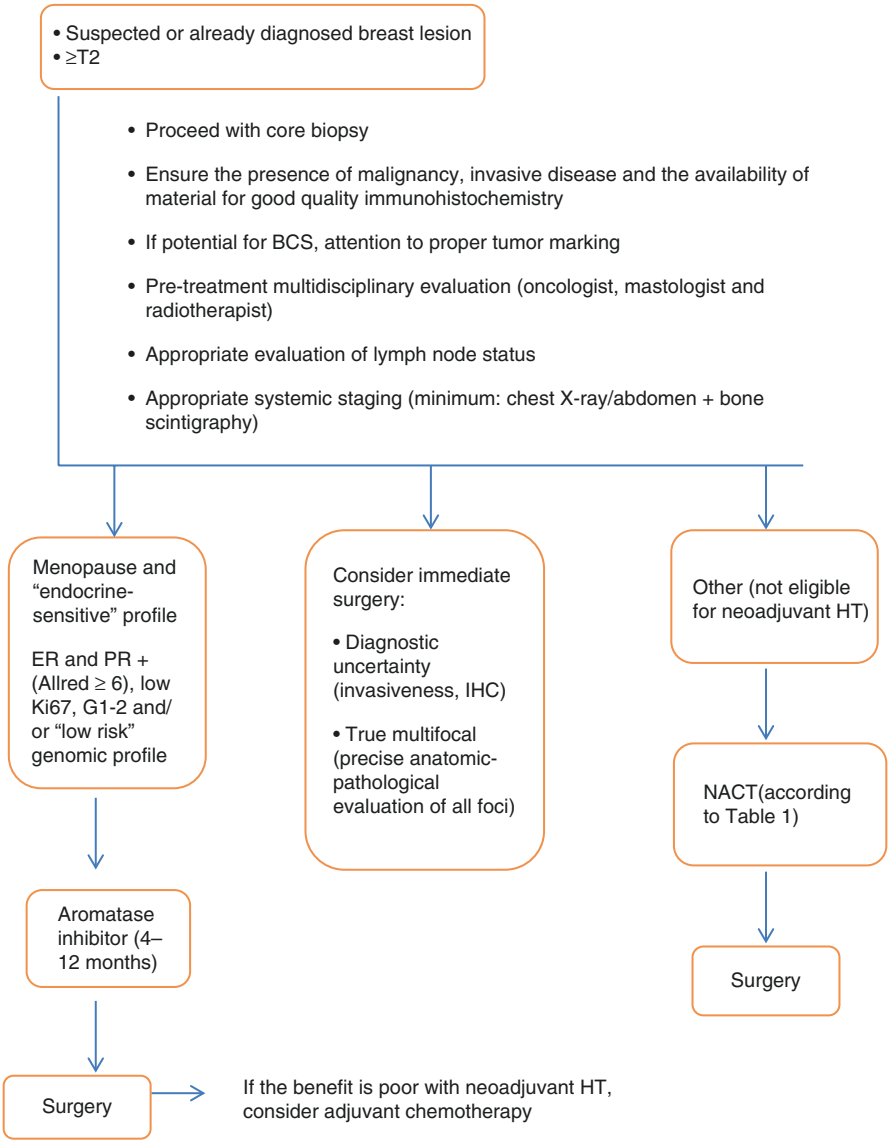
Monitoring of the response is performed primarily through physical examination, which must be regular, accurate, and well documented in the medical record. Visible skin lesions should be additionally photographed and images should be stored on the patient's chart. In some cases (such as full-breast or multicentric tumors with no "palpable mass"), imaging tests play a more important role, and magnetic resonance imaging (MRI) is considered the gold standard. Regardless of the method of response evaluation, performing MRI before and after treatment may be of great assistance in the surgical planning.

The oncologist should remember that the patient must always be evaluated by the surgeon before starting NST. The tumor marking method (skin tattooing and/or intra tumor clip placement) also needs to be defined in cases with potential for conservative surgery, as the complete clinical and radiological response occurs in up to 30–40% (twice as much in HER2 positive tumors), which may hinder the surgical procedure. Currently, with the greater acceptance of more conservative axillary treatments after neoChT, some services have been using compromised axillary lymph node marking methods.

Patients with no response to the first two to three cycles of neoChT present a worse prognosis; however, there is no indication of altering the treatment plan yet. In these cases it is not possible to discard at least some impact of the treatment on the micro-metastatic disease. In addition, some patients may present a good response to the second phase of the chemotherapy.

In case of frank disease progression, the prognosis may be even worse, with some patients already presenting with micro or macro metastatic disease. In the case of sequential two-stage chemotherapy schemes (e.g., anthracyclic followed by taxane), the start of the next phase is usually a best option (adding or not adding carboplatin to the taxane). However, indicating immediate surgery in these patients may also be an acceptable course of action.

Flowchart



Flowchart 1 Definition of the best LABC treatment. (*NACT* neoadjuvant chemotherapy, *HT* hormonal therapy)

Recommended Reading

1. Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res. 2007;13(1):228–33. *A small randomized institutional study showing that the addition of trastuzumab to neoChT elevates pCR to the expressive rate of 60%. Although trastuzumab was administered concomitantly throughout ChT (including anthracycline), there was no apparent increase in cardiotoxicity.*
2. Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. Ann Oncol. 2001;12(11):1527–32. *A randomized study that established the advantage of the letrozole aromatase inhibitor versus tamoxifen when administered for 4 months as neoET for menopausal patients with CM ER +. The gains were seen in terms of response rate and conservative breast surgery.*
3. Mauri D, Pavlidis N, Ioannidis JP, et al. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst. 2005;97(3):188–94. *A meta-analysis of nine studies comparing neoChT with adjuvant ChT, showing no impact on the prognosis. At the same time, it demonstrated the negative impact of the omission of definitive surgery on the rate of local recurrence.*
4. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol. 2008;26(5):778–85. *Mature joint analysis of NSABP studies B18 and B27. In the first one, there was no improvement in the prognosis with neoChT in relation to adjuvant ChT in the general study population, but a strong trend in the population under 50 years. In study B27, the addition of docetaxel doubled pCR, but did not impact conservative breast surgery rate or prognosis.*
5. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012;30(15):1796–804. *Analysis of seven studies (n = 6.377) from the German Breast Group (GBG) showing the excellent correlation between pCR and prognosis in ER-, pure Her2 and luminal B tumors; however, a low correlation in luminal A and "triple–positive".*

Other Systemic Treatments for Breast Cancer

Mário Alberto D. L. da Costa and Rodrigo Moura de Araújo

Introduction

With the advent of information on molecular biology, receptors and cell signaling pathways, new agents are being developed and the expectation of improved results is great.

Following is a list of some of the major new and active breast cancer treatments. The biggest investment has been made on target-molecular drugs. Today, we have drugs that act on the HER2 pathway, angiogenesis inhibitors, cyclin-dependent kinase inhibitors, PARP inhibitors, PI3K/AKT/m-TOR pathway drugs. Immunotherapy, already applied in the treatment of several neoplasias, has also been tested in breast cancer.

There is a trend in new studies and treatments to block multiple signaling pathways simultaneously and to more personalized treatment and taking into account the presence of biomarkers.

Anti-Body Conjugate Drugs (Immunoconjugates)

Sacituzumab Govitec

This immunoconjugated drug with antineoplastic activity contains a humanized monoclonal antibody hRS7 against TACSTD2 or TROP2 (tumor-associated calcium signal transducer 2) linked to an active metabolite of irinotecan (SN-38).

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The sacituzumab govitec (SG) molecule selectively binds to TROP2, and, after internalization and proteolytic cleavage, SN-38 stabilizes covalent DNA-topoisomerase I complexes resulting in DNA breaks, inhibition of DNA replication, and apoptosis. TROP2 (also called glycoprotein-1) is overexpressed in several neoplasms including triple-negative breast cancer. This antigen is related to cell adhesion, increased growth, aggressiveness, and metastasis.

Bardia et al. studied SG in 69 patients with previously treated triple-negative breast cancer (median 5 previous therapies). The OR rate was 30% (RP $n = 19$; RC $n = 2$) and the clinical benefit was 46%. Median PFS of 6 months and median OS of 16.6 months were observed. The drug was well tolerated with grade ≥3 adverse events including neutropenia (39%), leukopenia (16%), febrile neutropenia (7%), anemia (14%), and diarrhea (13%). Most tumors exhibited moderate or intense TROP2 expression (88%) by immunohistochemistry. SG appears to be an important alternative in the treatment of patients with triple-negative breast cancer and is being evaluated for approval by the FDA.

PI3K/Akt/mTOR Pathways Inhibitor

Activation of signaling pathways such as MAPK, ERK 1/2, and PI3K/Akt/mTOR may contribute to resistance to endocrine therapy in breast cancer, and the use of agents that block these pathways has been shown to be a promising strategy in the treatment of breast cancer. On the other hand, the development of biomarkers for better patient selection for treatment with PI3K/Akt/mTOR inhibitors is a priority.

Everolimus

Everolimus is an antineoplastic agent that inhibits mTOR (mammalian rapamycin target), which is a pathway located below the PI3K/Akt pathway and is dysregulated in many human malignancies. Everolimus binds to an intracellular protein (FKBP12), acting on the mTOR1 complex (mTORC1) with consequent inhibition of mTOR activity. Subsequently, there is a reduction in the activity of S6K1 (S6 ribosomal protein kinase) involved in protein synthesis and required for cell cycle progression, inhibition of ligand-independent activation of estrogen receptor (S6K1 acts on domain 1 of the ER leading to the activation of the ligand-independent receptor), and inhibition of the expression of HIF-1 (factor induced by hypoxia 1) and VEGF (vascular endothelial growth factor). Inhibition of mTOR by everolimus (E) results in reduced cell proliferation, angiogenesis, and glucose uptake in vitro and in vivo.

Phase II studies combining mTOR inhibitors with endocrine therapy have shown efficacy in the treatment of advanced breast cancer following progression with aromatase inhibitors. In the randomized phase II trial of TAMRAD, 111 patients with

breast cancer resistant to aromatase inhibitor were treated with tamoxifen and E or tamoxifen exclusively. The clinical benefit was 61% versus 42% ($p = 0.045$), the time to progression (TTP) increased from 4.5 to 8.6 months, and the risk of death was reduced by 55% (HR 0.45; $p = 0.007$) with the combination. The greatest benefit occurred in patients with better response to previous hormone therapy.

The BOLERO-2 study was a double-blind, multicenter, phase III study of 724 women with post-menopausal advanced breast cancer with ER positive, HER2-negative and presenting with recurrence or disease progression after letrozole therapy or anastrozole. Patients were randomized (2:1) to E 10 mg/day associated with exemestane 25 mg/day ($n = 485$) or placebo associated with exemestane ($n = 239$), without everolimus crossing in case of progression of the disease. The PFS was 7.8 months and 3.2 months with E and placebo, respectively (HR 0.45; $p < 0.0001$). All subgroups analyzed benefited regardless of age, race, visceral disease, and sensitivity to previous hormonal therapy. The objective response rates were 12.6% and 1.7%, respectively. OS was 31.0 months with E and exemestane and 26.6 months with placebo and exemestane (HR 0.89; $p = 0.1426$).

Adverse effects were evaluated in 720 patients, and the most common (>30%) were stomatitis, infections, rash, diarrhea, asthenia, edema, and decreased appetite. Grade three and four (≥2%) reactions were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonia, and diarrhea. Noninfectious pneumonitis may occur, and the physician should monitor the clinical symptoms and radiological changes and may need to reduce the dose or discontinue treatment with E in addition to the use of corticosteroids. Fatal adverse reactions occurred in 2% of patients in the E arm compared to 0.4% with placebo. Permanent treatment discontinuation occurred in 24% and 5% of everolimus and placebo cases, respectively, and was more frequent in patients aged ≥65 years (33% vs 17% for patients <65 years).

Everolimus is indicated for the treatment of advanced ER positive, HER2-negative breast cancer in postmenopausal patients after failure of letrozole or anastrozole. The recommended dose is 10 mg/day orally. The dose should be adjusted for patients with impaired hepatic function. Concomitant use of strong CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, saquinavir, indinavir, and others should be avoided. Caution is also advised (reduction to 2.5 mg) in patients taking moderate inhibitors of CYP3A4 and/or PgP (e.g., fluconazole, aprepitant, diltiazem, etc.). Concomitant use should be avoided with strong CYP3A4 inducers such as phenytoin, phenobarbital, carbamazepine, and rifampicin.

Everolimus is being tested in the adjuvant treatment of ER high-risk patients and HER2-negative breast cancer. Everolimus has been tested in combination with anti-HER2 agents in patients with HER2-positive tumors. Other studies seek to overcome the potential development of resistance to mTOR inhibitors. One of the possibilities is the combination with compensatory pathways (e.g., mTORC2) or parallel blockers such as IGF-1R inhibitors (insulin-like growth factor receptor 1).

Buparlisib (BKM-120)

Buparlisib is an oral pan-inhibitor of PI3K (phosphatidylinositol 3-kinase), which acts on class 1 (α, β, γ, and δ) isoforms in the PI3K/Akt signaling pathway. This may result in inhibition of tumor cell growth and survival in populations of susceptible tumor cells. Activation of the PI3K signaling pathway is often associated with tumorigenesis. Deregulated PI3K signaling may contribute to tumor resistance to a variety of antineoplastic agents.

The BELLE-2 study was a randomized, double-blind, multicenter study in post-menopausal women with HER2 negative, inoperable or metastatic locally advanced disease and progression after treatment with aromatase inhibitors and receiving up to one line chemotherapy. It included 1147 patients who received fulvestrant 500 mg on days 1 and 15 of cycle 1 and on day 1 of subsequent cycles every 28 days, and oral buparlisib (100 mg/day) or placebo from day 15 of cycle 1. Median PFS was 6.9 months in the buparlisib group versus 5 months in placebo (HR 0.78; $p = 0.00021$). In patients with activation of the PI3K pathway, the PFS was 6.8 months versus 4 months. The most common grade 3–4 adverse events were increased PGT (25% vs. 1%), hyperglycemia (15% vs. <1%), and cutaneous rash (8% vs. none). Important psychiatric symptoms such as depression and anxiety have also been reported.

Although active, buparlisib was considered relatively toxic, and novel PI3K therapies with more selective blockers (e.g., PI3K-alpha isozyme blockers) may be as effective and better tolerated.

PARP (Poly (ADP-Ribose) polymerase-1) Inhibitors

Poly (ADP-ribose) polymerase-1 (PARP1) is a DNA-binding protein involved in detecting and repairing breaks in DNA strands. It is activated by the occurrence of DNA damage, which may be the result of normal cell metabolism or exposure to harmful agents. To participate in the molecular events that lead to the recovery of damaged DNA, PARP1 binds to breakpoints and attracts other repair enzymes. Its action occurs, predominantly, through mechanisms of repair by excision of bases. When PARP1 is sustained in an inhibited fashion, breaks in the double strand of DNA accumulate during its replication and, under normal conditions, are repaired by the BRCA1/2 pathway-dependent homologous recombination mechanism (a process that restores the original nucleotide sequence).

Therefore, cells with mutations of the BRCA genes appear to be particularly sensitive to inhibition of PARP, since homologous recombination is deficient in these cells and DNA repair occurs through other pathways with a greater tendency for errors to occur. Thus, PARP inhibition is a strategy to selectively eliminate cells with dysfunctional homologous recombination.

PARP1 inhibitors may be more useful in the treatment of BRCA1/BRCA2 mutation breast cancer and in triple-negative tumors with pathological and molecular characteristics similar to those with BRCA1 mutations, which are characterized as occurring in individuals with defect in homologous repair of DNA. These tumors appear to be particularly sensitive to inhibition of PARP1, which in this situation is the only functioning repair pathway—BRCA-deficient cells are a thousand times more sensitive to inhibition by PARP-only agents than BRCA 1 and 2 wild-type cells.

Olaparib

Olaparib (Ola), an oral PARP1 inhibitor, has been used in women with advanced breast cancer with BRCA1 and/or BRCA2 mutations. Of these, more than 50% had triple-negative tumors. In a single-branch phase II study, an overall response rate of 41% and progression-free survival of 5.7 months was obtained. The drug was well tolerated, exhibiting as its main adverse effects fatigue, nausea and vomiting. In another study, Ola activity was not demonstrated in patients without BRCA mutations.

The OlympiAD phase III study compared Ola with standard treatment in patients with BRCA, HER2 negative germ mutation and evolving with metastatic breast cancer previously treated with 2 or more chemotherapy lines. Three hundred two patients were randomized (2:1) to Ola 300 mg twice daily or chemotherapeutic treatment (capecitabine, eribulin, or vinorelbine). The PFS was significantly higher with Ola (7 vs. 4.2 months, $p < 0.001$). The OR was 59.9% and 28.8%, respectively. There were also fewer grade 3 adverse events (36.6% vs. 50.5%).

Olaparib is already indicated in the treatment of ovarian cancer and should be rapidly incorporated in the treatment of patients with breast cancer and BRCA mutation.

Cyclin-Dependent Kinases (CDKs) Inhibitors

Cyclin-dependent kinases (CDKs) are serine/threonine kinases that play a key role in regulating cell cycle progression, allowing the transition between their different phases. For activation, they depend on molecules that are synthesized and degraded during each cell cycle—cyclins. The interaction of cyclin D with CDK4 and CDK6 facilitates hyper phosphorylation of the retinoblastoma gene product (Rb) which in turn leads to progression of G1 to S phase of the cell cycle. Alterations in the cyclin-D-CDK4/6-Rb pathway occur in many malignancies and are associated with endocrine resistance in breast cancer. Inhibitory drugs of CDKs are capable of interfering with cell proliferation and inducing apoptosis of neoplastic cells.

Palbociclib

Palbociclib (Pal) is an oral selective inhibitor of CDK4 and CDK6, thus inhibiting the phosphorylation of the Rb protein at the start of the G1 phase, leading to cell cycle arrest. This suppresses DNA replication and decreases the proliferation of tumor cells.

The PALOMA-2 phase III study compared (in the first line of treatment) in 666 postmenopausal patients with positive ER, Pal (125 mg/day for 3 weeks every 4 weeks) and letrozole (2.5 mg/day) with placebo and letrozole. The PFS was 24.8 months in the Pal-letrozole group, compared to 14.5 months in the placebo-letrozole group (HR 0.58; $p < 0.001$). The OR rate was 42.1% vs. 34.7%, and clinical benefit was observed in 84.9% versus 70.3% of patients. OS data is not yet available. Adverse events with Pal were neutropenia (66.4%), leukopenia (24.8%), anemia (5.4%), and fatigue (1.8%). Febrile neutropenia was reported in only 1.8% of patients. Permanent discontinuation of any study treatment as a result of adverse events occurred in 43 patients (9.7%) in the Pal group and in 13 patients (5.9%) in the placebo group.

For the second line of treatment, the PALOMA-3 study was performed, with 521 patients being randomized to Pal (125 mg/day for 3 weeks every 4 weeks) and fulvestrant (500 mg D1, D15, and D29 and then every 28 days) or placebo and fulvestrant. The PFS was 9.5 months vs. 4.5 months, respectively (HR 0.46; $p < 0.0001$).

Palbociclib has been rapidly incorporated into both the first and the second line post-menopausal patients with positive ER, and is also being tested for adjuvant treatment.

Ribociclib

Ribociclib (Rib) is also a CDK4/6 inhibitor. The study MONALEESA-2 with 668 patients evaluated the incorporation of Rib in the first line of treatment in ER positive HER2 negative premenopausal patients. Patients were randomized to Rib 600 mg daily for 21 days every 28 days and letrozole or placebo plus letrozole. There was a significant increase in PFS (HR 0.56; $p = 3.29 \times 10–6$). At 18 months, 63% of patients with RIB remained without signs of progression versus 42.2% with placebo. The OR was 52.7% vs. 37.1% ($p < 0.001$). Grades 3 and 4 neutropenia were reported in 59.3% of patients with ribociclib.

Ribociclib has already been approved by the U.S. FDA for initial treatment of advanced or metastatic breast cancer in patients with ER positive and HER2 negative tumors associated with aromatase inhibitor.

Abemaciclib

Abemaciclib (Abe) is a potent and selective inhibitor of CDK 4 and 6. It is a structurally distinct compound of palbociclib and ribociclib and it is 14 times more potent against cyclin D1/ CDK4 and cyclin D3/CDK6 in enzymatic assays. Abe was

active in phase I study both as monotherapy and associated with fulvestrant. In the phase II study MONARCH-1, exclusive Abe was tested in patients with ER positive, HER2 negative evolving with refractory hormone disease at the dose of 200 mg twice daily continuously. The OR occurred in 19.7% of patients with clinical benefit in 42.4%.

The phase III MONARCH-2 study evaluated Abe in patients previously treated with hormone therapy in metastatic disease. 669 patients were randomly assigned to Abe (150 mg twice daily) and fulvestrant or placebo plus fulvestrant. There was an increase in PFS (median of 16.4 vs. 9.3 months, HR 0.553; $p = 0.001$). In patients with measurable disease, OR was 48.1% compared to 21.3% in the control arm. The toxicity profile is somewhat different from the other CDK inhibitors with more volume of diarrhea, which does not appear to be difficult to control, and less neutropenia. Compared with placebo, there were diarrhea (86.4% vs. 24.7%), neutropenia (46.0% vs. 4.0%), nausea (45.1% vs. 22.9%), and fatigue (9% vs. 26.9%).

Angiogenesis Inhibitors

The process of angiogenesis plays an important role in the progression of breast cancer. Multiple angiogenic factors are expressed in invasive breast cancer, including vascular endothelial growth factor (VEGF). VEGF stimulates endothelial proliferation and migration, inhibits endothelial apoptosis, induces remodeling of the extracellular matrix, increases vascular permeability and vasodilation, and inhibits dendritic cells, among other actions. There are several isoforms of VEGF, but VEGF-A is a potent inducer of vasodilation and pathological angiogenesis.

Bevacizumab

Bevacizumab (Bev) is a humanized monoclonal antibody against VEGF-A. By binding to VEGF, it prevents its binding to the VEGF receptor, thus preventing the growth and maintenance of tumor blood vessels.

The E2100 phase III study evaluated 722 patients with metastatic breast cancer who were treated on the first line with either paclitaxel alone or paclitaxel plus Bev. The doses used were paclitaxel 90 mg/m^2 on days 1, 8, and 15 with or without Bev 10 mg/kg on days 1 and 15 every 4 weeks. There was an increase in PFS from 5.9 months to 11.8 months ($p < 0.001$) and from OR (from 21.2% to 36.9%, $p < 0.001$). OS was similar in both groups (HR 0.88; $p = 0.16$). The main side effects with Bev were grade 3 and 4 hypertension (14.8%), proteinuria (3.6%), headache (2.2%), and cerebral ischemia (1.9%). The risk of infection was higher with paclitaxel and Bev (9.3% vs. 2.9%, $p < 0.001$), but febrile neutropenia was uncommon (<1%).

In the RIBBON-1 study (Regimens in Bevacizumab for Breast Oncology) 1237 patients were treated on the first line with chemotherapy (capecitabine, taxane or

anthracyclic regimen). PFS was also significantly superior with Bev, although with no impact on OS.

Another phase III study (TURANDOT) compared Bev plus paclitaxel with Bev plus capecitabine. Despite showing a higher PFS for the paclitaxel arm, there was no difference in overall survival (median OS 30.2 months and 26.1 months, respectively) and the association with capecitabine may be useful for patients with early recurrence after adjuvant with taxanes or even taking into account the difference in the profile of toxicity among chemotherapeutic agents.

Although studies with Bev on the first line do not show OS gain, the impression is that the combination, particularly with weekly paclitaxel or capecitabine, is well tolerated, brings about a response gain and PFS, and may be interesting for some patients with metastatic disease.

Although Bev is approved in Brazil for use in the first line of treatment, there is also evidence of benefit with the use in the second line. The RIBBON-2 study with 684 patients shows an increase in PFS from 5.1 to 7.2 months ($p = 0.0072$).

Immunotherapy

Immune responses to cancer are initiated when the immune system recognizes proteins expressed in neoplastic cells called tumor-associated antigens (TAAs). The final immune response is regulated by a balance between immunostimulant and immunosuppressive mechanisms, which prevent uncontrolled inflammation and autoimmune disease.

Most immunotherapies under development for breast cancer involve the use of vaccines that trigger and direct immune responses against TAAs, or agents that act on immune regulation (assuming the presence of an endogenous antitumor immune response), as checkpoint inhibitory antibodies that inhibit suppressor mechanisms of the immune system acting on pathways mediated by CTLA-4 (cytotoxic T lymphocyte associated antigen 4), PD-1 (programmed death 1), and PD-L1 (programmed death ligand 1), or the combination of these two strategies.

Vaccine

Breast cancer is usually less immunogenic compared to other malignancies such as melanoma and lung cancer. Therefore, the use of vaccines capable of inducing an immune response may be an interesting strategy. Several vaccines have already been tested, including monovalent, polyvalent, and cellular vaccines. The monovalent vaccines aim to facilitate immune responses against a single antigen of interest like HER2, while polyvalent vaccines deliver multiple TAAs simultaneously. A third class of vaccines uses whole cell preparations or cellular products to improve the delivery of TAAs.

The most investigated antigen for vaccination in breast cancer is HER2. The most studied HER2 vaccine is E75, called nelipepimut-S. Combined with GM-CSF (granulocyte-macrophage colony-stimulating factor) it was safe in phases I and II studies. In a phase II study, 5-year DFS increased from 80.2% to 89.7% ($p = 0.08$) in tumors with low HER2 (1 or 2+) expression, with no benefit in HER2 3+ (induction of antigen tolerance?). The nelipepimut-S/GM-CSF association is being compared with exclusive GM-CSF in phase III study. Other monovalent vaccines are under development against the mucin 1 and Globo-H antigens.

PANVAC (Pancreatic Vaccine) encompasses several antigens such as CEA, MUC1, LFA-3 (lymphocyte function-associated antigen 3), and ICAM1 (intercellular adhesion molecule 1). In phase II study, the association of PANVAC with docetaxel showed a trend toward superiority over exclusive docetaxel with PFS of 7.9 vs. 3.9 months ($p = 0.09$).

GVAX is an irradiated human breast cancer cell vaccine that is being tested in combination with cyclophosphamide at low dose +/− trastuzumab in patients with HER2-negative tumor.

Checkpoint Inhibitors

Given the relatively modest immunogenicity of breast cancer, studies with checkpoint inhibitors are still at an intermediate stage of development and more focused on triple-negative tumors that exhibit a greater number of mutations, are usually richer in TILs (tumor-infiltrating lymphocytes), and most often express PD-L1. These inhibitors are being tested as monotherapy and as part of strategies that combine checkpoint blocking with therapies that lead to increased exposure of cellular antigens such as tumor ablation, radiation therapy, and chemotherapy.

The most advanced results available are pembrolizumab and atezolizumab, but several studies are underway with other inhibitors such as nivolumab, durvalumab, and durvalumab/tremelimumab.

Pembrolizumab (Pembro) is a humanized monoclonal antibody directed against PD-1, which is an inhibitory signaling receptor expressed on T cells. When activated, PD-1 drives T cell negatively and plays a key role in tumor immunity evasion of the host. Following administration of Pembro PD-1 blockade occurs, and that prevents its binding and activation by its ligands, resulting in increased T-cell mediated immune system activity and responses against tumor cells. Binders for PD-1 include PD-L1 expressed on certain tumor cells, and PD-L2 which is expressed on APCs (antigen-presenting cells).

The phase II KEYNOTE-086 study included 170 patients with metastatic triple-negative tumors and with progressing disease after 1 or more treatment lines receiving Pembro 300 mg i.v. every 3 weeks. There was CR or PR in 4.7% and DE in 20.6% of the cases. It is important to note that PD-L1 was not predictive of response and median OS has not yet been achieved in patients with OR or SD, whereas in patients with PD it was 7.1 months. At 9 months 100% of patients with CR or PR

were alive versus 89.6% of those with ED and only 39% of those with PD. The treatment was well tolerated.

In the I-SPY-2 study with adaptive randomization design, Pembro 200 mg i.v. every 3 weeks was associated with paclitaxel chemotherapy 80 mg/m^2 weekly for 12 weeks ($n = 69$) and compared with paclitaxel exclusive ($n = 180$) in the neoadjuvant treatment of breast cancer. After 12 weeks the patients followed with four more AC cycles (doxorubicin and cyclophosphamide) only. The probability of RPC rose from 16% to 46%. In patients with triple-negative tumor the probability of RPC was 20% with paclitaxel and 60% with association, while in patients with ER positive/HER2 negative RPC increased from 13% to 34%. Adrenal insufficiency ($n = 5$), hepatitis ($n = 2$), colitis ($n = 1$), and hypothyroidism ($n = 1$) were observed with Pembro.

Atezolizumab is a monoclonal antibody against PD-L1. By binding to PD-L1, it blocks its binding to receptor 1 (PD-1) expressed on activated T cells, which may increase the T cell-mediated immune response.

The phase Ib study associated nab-paclitaxel with atezolizumab in 32 patients with metastatic triple-negative breast cancer. Overall OR was 38% and in patients treated in the first line of 46%. In addition, responses were similar in tumors with and without PD-L1 expression. A phase III study is underway with this combination.

Osteolysis Inhibitors

Zolendronic Acid

Zolendronic acid (Zol) is synthetic third generation bisphosphonate with anti-reabsorption activity. It binds to hydroxyapatite crystals in the bone matrix, retarding their dissolution and inhibiting the formation and aggregation of these crystals. This agent also inhibits farnesyl pyrophosphate synthase, with consequent inhibition of osteoclast activity. Decreased bone turnover and stabilization of the bone matrix contribute to the analgesic effect of Zol in painful osteoblastic lesions. It also reduces the serum calcium levels associated with hypercalcemia. It is a more potent bisphosphonate than clodronate and pamidronate.

Osteonecrosis of the mandible may occur, so periodic dental monitoring is recommended and dental implant or extraction should be avoided. Symptomatic hypocalcemia is uncommon, but calcium monitoring and replacement is important. In the presence of vitamin D deficiency it should be corrected. The dose of Zol should be adjusted for renal function, which must be monitored because nephrotoxicity may occur. Musculoskeletal pain and fever are common, especially after the first dose.

Zolendronic acid is indicated for the treatment of hypercalcemia and for patients with bone metastases and consequent reduction of Skeletal-Related events (SREs), pain, fractures, spinal compression, and improvement of the quality of life. The

dose approved to reduce the frequency of SREs is 4 mg every 3–4 weeks. More recently, new studies have evaluated administration every 12 weeks. CALGB (Alliance) 70,604 studied 1822 patients with bone, prostate, or multiple myeloma bone metastases at the same Zol dose every 4 or 12 weeks for 2 years, starting with the first dose. There was no difference in the proportion of patients who developed at least one SRE (29.5% vs. 28.6%). Usage every 12 weeks resulted in less renal dysfunction and mandibular osteonecrosis. Two other studies also tested the use with longer intervals (OPTIMIZE-2 and ZOOM) after an initial period with monthly treatment, concluded by the safety of the application every 12 weeks. We believe that a dosage every 4 weeks, at least initially for patients with extensive or highly symptomatic bone metastases, is preferable, and it may be considered at greater intervals after neoplastic control.

Zolendronic acid is also indicated for the treatment of osteoporosis and as prevention of bone loss associated with the use of aromatase inhibitors and corticosteroids. Several studies have shown benefit in the use of bisphosphonates, especially clodronate and Zol, in the adjuvant treatment of breast cancer. There is strong evidence of reduced risk of bone recurrence and increased survival, especially in the adjuvant treatment of postmenopausal patients. Zol (4 mg i.v. every 6 months) and clodronate (1600 mg/day v.o.) were approved by ASCO in the adjuvant treatment of postmenopausal patients.

Denosumab

Denosumab (Den) is an osteoclast inhibitor that binds to RANKL (receptor activator of nuclear factor kappa beta ligand), blocking its interaction with RANK, which is a receptor located on the surface of osteoclasts, leading to inhibition of osteoclast activity, decreased bone reabsorption, and potential increase in bone mineral density. There may be hypocalcemia and osteonecrosis of the jaw, but the risk of nephrotoxicity is lower than that of Zol, and there is no need for adjustment according to renal function.

Den is indicated for the treatment of hypercalcemia associated with malignancy at 120 mg s.c. every 4 weeks; in the first month it may be necessary to repeat the dose on days 8 and 15.

In the treatment of bone metastases there is a reduction of SREs, so the dose of 120 mg s.c. every 4 weeks is recommended. A meta-analysis of three phase III trials comparing Zol versus Den concluded that Den was superior to Zol in reducing the risk of a first SRE (HR 0.83) and by delaying the time to SRE or hypercalcemia (median 26.6 vs. 19.4 months). OS and disease progression rates were similar with the two treatments. Consequently, Den may be the drug of choice for patients with bone metastasis.

The duration of treatment with osteolysis inhibitors is not accurate, but it can be kept indefinitely, especially in patients with extensive disease and good tolerability.

Denosumab is also indicated in the treatment of osteoporosis and bone loss induced by aromatase inhibitors at a dose of 60 mg s.c. every 6 months.

Table 1 lists some of the most promising agents being tested in breast cancer.

Table 1 Promising agents tested in breast cancer

Name	Mechanism of action	Main studies
Utidelon	Epothilon inhibitory function of microtubes	Phase III, 405 pts refractory to anthracyclics and taxanes, utidelon, and capecitabin vs. capecitabin; increase in PFS (HR 0.58; $p < 0.0001$); well tolerated
Tucatinib	Anti-HER2 TK inhibitor with CNS activity	Anti-HER2 TK inhibitor phase II randomized (HER2CLIMB) capecitabine/trastuzumab e ticatinib or placebo with CNS activity
Margetuximab	Anti-HER2 antibody active in tumors already treated with trastuzumab and other anti-HER2 agents	Phase III (SOPHIA): margetuximab and chemotherapy (ChT) vs. trastuzumab and ChT in metastatic breast cancer
MM-302	Immunoconjugated anti-HER2 with liposomal doxorubicin	Randomized phase II (HERMIONE): trastuzumab and ChT vs. trastuzumab and MM-302 on non-anthracyclic exposed pts
Veliparib	PARP inhibitor	Phase II randomized veliparib/carboplatin (C) and paclitaxel (P) vs. placebo/C/P in patients with BRCA mutation. Increased OR. Tendency to increase PFS and OS
Talazoparib	PARP inhibitor	Phase II in patients with BRCA mutation after platinum (OR 21% and BC 38%) or multiple cytotoxic (OR 37% and BC 66%)
Glembatumumab vendotin (Gv)	Immunoconjugated ant-glycoprotein NMB	Randomized phase II (EMERGE) in pretreated patients. Gv vs. ChT: pts with triple-negative (TN) OR 18% vs. 0% and positive tumors for gpNMB OR 40% vs. 0%
Divotinib	FGFR inhibitor	Phase II, HER2-, RE+, divotinib/fulvestrant vs. fulvestrant: 97 pts, PFS 5.5 months (m) vs. 5.5 m; for FGFR amplified PFS 10.9 m vs. 5.5 m
Ipatasertib	Akt inhibitor	Phase II randomized (LOTUS) 124 pts with TN tumor, first line; paclitaxel and ipatasertib or placebo; SLP 6.2 m vs. 4.9 m; SLP in pts with alteration of PI3K/Akt/PTEN 9 m vs. 4.9 m. Well tolerated. Phase III in progress
Enzalutamide	Androgenic receptor (AR) blocking	Phase II AR+, TN, androgen-targeting (Dx): 43 pts, PFS 32 weeks for Dx + and 9 weeks with Dx-; 2 pts CR and 5 PR
ANG 1005	Taxane-peptide conjugate	Phase II, cerebral metastasis ± trastuzumab in progress

TK tyrosine kinase, *FGFR* fibroblast growth factor receptor, *PI3K* phosphatidylinositol 3-kinase, *mTOR* mammalian target of rapamycin, *CB* clinical benefits (RC + RP + DE), *SD* stable disease, *CR* complete response, *PR* partial response

Recommended Reading

The studies listed below are recent reviews about the medicaments mentioned in this chapter.

1. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375:1925–36.
2. Guerrero-Zotano A, Mayer IA, Arteaga CL. PI3K/AKT/mTOR: role in breast cancer progression, drug resistance, and treatment. Cancer Metastasis Rev. 2016;35:515–24.
3. Loibl S, Gianni L. HER2-positive breast cancer. Lancet. 2017;389:2415–29.
4. McArthur HL, Page DB. Immunotherapy for the treatment of breast cancer: checkpoint blockade, cancer vaccines, and future directions in combination immunotherapy. Clin Adv Hematol Oncol. 2016;14:922–33.
5. Robson M, Im S, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017;377:523–33. https://doi.org/10.1056/NEJMoa1706450.

Follow-Up After Breast Cancer

BBSG – Brazilian Breast Study Group

Introduction

The number of breast cancer survivors has increased steadily due to early diagnosis and advances in treatment. It is estimated that there are 3,000,000 women with a history of breast cancer in the United States, which corresponds to 41% of all women with cancer in that country. These patients are exposed to the appearance of a new tumor, local recurrence, other types of cancer, and adverse effects of the treatment received. There are differences in the literature on the best way to follow up such patients, which contributes to a variation of conduct among entities that guide daily practice.

Definition and Objectives

Follow-up can be defined as the period from the time of diagnosis/treatment to the occurrence of a relapse or death. The objectives of the follow-up are to diagnose a local or contralateral relapse early, to evaluate and resolve possible treatment-related complications, and to provide psychological support and information necessary to restore a normal life.

BBSG – Brazilian Breast Study Group (✉)
BBSG, Sao Paulo, SP, Brazil

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https://doi.org/10.1007/978-3-030-13636-9_63

Table 1 Frequency of physical exam follow-up

Physical exam	ASCO	ESMO	NCCN
First year	3–6 months	3–4 appointments/year	1–4 appointments/year
Second year	3–6 months	3–4 appointments/year	1–4 appointments/year
Third year	3–6 months	Annually	1–4 appointments/year
Fourth year	6 months	Annually	1 to appointments /year
Fifth year	6 months	Annually	1–4 appointments/year
Sixth year on	Annually	Annually	Annually

Clinical Follow-Up

There is no evidence from randomized studies regarding the periodicity and time of patients follow-up. The recommendations of the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and European Society of Surgical Oncology (ESMO) are summarized in Table 1.

During the appointment, anamnesis must be targeted at the symptoms and signs of local recurrence or distant metastasis.

- Pain or breast lumps
- Headache, altered visual acuity, and behavioral changes
- Coughing and dyspnea
- Nausea, vomiting, and change in appetite
- Genital bleeding and hematuria
- Osteoarticular pain

During physical examination and skeletal muscle, lung, cardiac, genital and abdominal evaluation should be performed

Complementary Exams

Mammography

Post-treatment mammography for breast cancer shows a decrease in mortality in all age groups. This practice is aimed at the detection of ipsilateral cancer after conservative surgery and contralateral breast disease. In patients undergoing conservative surgery, the first mammogram should be performed between 6 months and 1 year after radiotherapy is completed and continued annually.

Ultrasonography

The indication of mammary ultrasonography at follow-up is restricted to the mammography complement. There is no evidence to justify its routine use in the follow-up of patients with breast cancer. A study comparing mammography and

ultrasonography versus isolated mammography showed an increase in the diagnosis of local recurrence from 8 to 12 cases per 1000 but with a false-positive increase from 4.4% to 10.4%.

Magnetic Resonance Imaging (MRI)

The use of MRI in post-treatment follow-up deserves prospective studies. Evidence shows an increase in unnecessary procedures due to high sensitivity and low specificity. However, in women at high risk of local recurrence, genetic mutation carriers or high risk family history, they benefit from the MRI at follow-up.

Systemic Follow-Up

In the follow-up of asymptomatic patients, there is no evidence that routine radiological examinations and early diagnosis of metastases result in improved survival. Routine use of these tests will result in high rates of false-positive and false-negative results, with a significant financial impact.

For patients using aromatase inhibitors, attention should be given to bone density, indicating bone densitometry.

Regarding the use of tamoxifen, especially in extended therapy, evaluation of the endometrium with transvaginal ultrasound should be performed only in cases of abnormal bleeding. This routine examination should not be used because of the increase in false-positive results, which will result in unnecessary invasive exams (hysteroscopy or uterine curettage).

Genetic Counseling

The NCCN suggests that patients diagnosed with invasive carcinomas, triple-negative tumors and who are younger than 60 years be investigated for mutation of Brca1 and Brca2 genes. Especially in young patients with a suggestive family history, one should consider the genetic tests.

Treatment Complications

Patients with childbearing potential should be advised of the possible reproductive consequences of adjuvant treatment. An evaluation with a reproduction specialist is recommended to evaluate the best way to preserve fertility before starting chemotherapy.

The possible side effects resulting from systemic treatment are usually managed in a multidisciplinary team, but we must remember specially the cardiac effects of some drugs, especially anthracycline and trastuzumab.

The most common complaints following treatment are due to the early menopause caused by chemotherapy drugs and treatment with prolonged hormone therapy.

Among patients who use tamoxifen, hot flushes represent one of the most common complaints. Venlafaxine and desvenlaflaxine are the drugs of choice, with about 50% efficacy. In refractory cases, the use of gabapentin and clonidine is described in the literature but with a high incidence of side effects.

Osteopenia should be managed in association with lifestyle guidelines (exercises, adequate diet, exposure to sun) and with calcium and vitamin D replacement. In patients at risk for osteoporosis development and with AI, bisphosphonates can be used.

Currently, there is a growing use of denosumab, a monoclonal antibody that inhibits osteoclast activity with a subcutaneous half-yearly application. The drug most commonly used in our environment is zoledronic acid, intravenously every 6 months. It acts on the inhibition of osteoclast action. Its main side effects are increased risk of osteonecrosis of the jaw, hypocalcemia, and renal failure.

Other symptoms that deserve attention are the following:

- Sexual dysfunction (loss of libido, dyspareunia, genital atrophy)
- Depression and anxiety
- Cognitive dysfunctions
- Fatigue
- Symptoms resulting from surgical treatment (lymphedema, paresthesia, movement limitations) and radiotherapy (radiodermity, edema, actinic pneumonitis, cardiopathy)

Physical Activity and Life-Style Habits

Recently, more attention has been given to regular physical activity and life style habits in the prevention of recurrence of breast cancer. It is up to the mastologist to recommend and supervise that the patients follow these recommendations.

A 2005 study published in JAMA showed that those who walked for at least 30 min, on average five times a week at speeds of 5–6 km/h (or performed equivalent exercises), had about 60% reduction in the risk of disease recurrence, as well as lower mortality from breast cancer and lower probability to die from other causes.

Potential risk reduction is associated with physical exercise, reduced levels of insulin-like growth factor (IGLF), as well as other factors associated with carcinogenesis.

Overall Guidelines

In premenopausal patients, contraception with hormone contraceptives is contraindicated, regardless of the receptors; so non-medicated intrauterine devices, barrier methods, or tubal ligation/vasectomy are recommended.

It is strongly advised that smoking, alcohol consumption, and sedentary life style habits be avoided, while keeping the body mass index below 25 is recommended.

Recommended Reading

1. Ellegaard MB, Grau C, Zachariae R, Jensen AB. Women with breast cancer report substantially more disease- and treatment-related side or late effects than registered by clinical oncologists: a cross-sectional study of a standard follow-up program in an oncological department. Breast Cancer Res Treat. 2017;164(3):727–36. *A prospective study showing that intensive post-treatment investigation does not diagnose early-stage metastases. More important than research is the management of complications of long-term treatment, according to questionnaires answered by patients.*
2. Khatcheressian JL, Hurley P, Bantug E, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(7):961–5. *Recommendations of the American Society of Clinical Oncology, not indicating complementary radiological and biochemical exams in asymptomatic women. However, it concludes that patients with tumors of worse prognosis (triple negative) need better studies to evaluate the impact of intensive follow-up.*
3. Lash TL, Fox MP, Buist DS, et al. Mammography surveillance and mortality in older breast cancer survivors. J Clin Oncol. 2007;25(21):3001. *Prospective study with over 1800 women above 65 y-o, with breast cancer at stages I and II, showing that continuation of tracking after treatment led to lower rate of specific death cases.*
4. Quinn EM, Coveney AP, Redmond HP. Use of magnetic resonance imaging in detection of breast cancer recurrence: a systematic review. Ann Surg Oncol. 2012;19(9):3035. *Meta-analysis including 10 studies and 494 patients, aiming to evaluate the impact on magnetic resonance imaging in recurrence of breast cancer. It showed the high sensitivity, but low specificity of this test, determining a greater number of interventions.*
5. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v8–30. *Recommendations of the European Society of Oncology as to post-treatment follow-up.*

Survivorship: Life After Breast Cancer

Mariana Tosello Laloni and Adriana Paula de Castro Barrichello

Introduction

The concept of survivorship includes the long-term follow-up of patients who have had breast cancer and have undergone treatment. These survivors should be followed up to monitor the risk of disease recurrence, second neoplasm screening, assessment, and management of long-term physical and psychosocial side effects related to treatment and health promotion. Such actions may impact not only the quality of life but also on the progression free survival or overall survival.

Implications

The number of breast cancer survivors has increased dramatically in the past two decades. This is due to early detection in screening programs, improvement in technology, better awareness of the population on health education, and the incorporation of new surgical, radiotherapeutic and systemic treatments.

Data from 2014 show that in the United States more than three million women had a history of breast cancer; this corresponds to 41% of the female population of cancer survivors.

The treatment of breast cancer depends on the stage, location of the tumor, and its biological characteristics. Patients with stages II and III usually receive multidis-

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ciplinary treatment with a combination of therapeutic modalities that aim to increase their chances of cure, but which unfortunately increase the severity of the impacts of acute and chronic side effects.

The international guidelines for follow-up of patients treated with initial breast cancer are controversial and in fact there is still no consensus. The guideline produced by the American Cancer Society in association with the American Society of Clinical Oncology used correct methodology; however, only 11% of the 1073 articles had evidence levels I and II.

It is mandatory for all treated patients to be monitored for local recurrence and for the possibility of developing a new primary breast tumor.

Side Effects

The risk of physical and psychological side effects secondary to treatment depends on the association of several factors: type of treatment; duration and dose of treatment; type of chemotherapy; hormonal treatment; and age of the patient during treatment.

All surviving patients are expected to have a better quality of life after treatment, but this does not always happen. About one-third of patients keep symptoms after cessation of treatment, and such symptoms are similar to those presented during treatment.

Physical and psychic sequels include fatigue, pain, peripheral neuropathy, sexual dysfunction and infertility, increased risk of cardiovascular and skeletal diseases, sleep disturbance and depression, often leading to psychosocial difficulties, affecting work and social relationships. Symptoms of pain, fatigue, and sleep disorders are the physical symptoms most frequently observed after 5 years of diagnosis (61%). In addition, studies show that 37.5% of survivors also present with depression and 80% of them experience moderate to severe attention deficit in the long term.

Fatigue is one of the most common side effects of cancer treatment, and depending on the degree it can lead to a significant drop in functional status and significant worsening of quality of life. During the treatment of radiotherapy and/or chemotherapy in breast cancer, some level of fatigue was reported in 99% of the women; in 60% fatigue was reported as moderate to severe, and in 30% the condition remained moderate to severe 2 years after treatment. Of all the symptoms, fatigue was considered the most distressing side effect of treatment in patients with breast cancer who received adjuvant chemotherapy. Before assuming that fatigue is related to prior treatment for breast cancer, treatable causes should be ruled out, including anemia, thyroid dysfunction, cardiac dysfunction, pain, depression, and sleep disorders. Patients should be advised to perform regular physical activity and, if necessary, seek cognitive behavioral therapy. There is no evidence of improvement of the fatigue related to chemotherapy with drug treatment.

Bone Health

Bone health and maintenance of bone integrity are important components of cancer patients' care. Among postmenopausal women who underwent breast cancer treatment around 60% have osteopenia and 20% experience osteoporosis. Loss of bone mass should be monitored because of adjuvant hormone therapies, such as aromatase inhibitors. The progression to osteoporosis can be rapid and asymptomatic. Risk factors for osteoporosis in post-breast cancer patients include early menopause induced by chemotherapy, suppression of GnRH and gonadal function, antiestrogen therapies, and glucocorticoid. These risk factors are cumulative with other factors known as age, low calcium diet, vitamin D deficiency, previous frailty fracture, family history of hip fracture, smoking, excessive alcohol consumption, and prior history of rheumatoid arthritis. Much of the morbidity and mortality associated with bone loss can be prevented by means of appropriate screening, lifestyle interventions, and drug therapy. Patients should be encouraged to maintain healthy lifestyle habits such as adequate diet with good calcium supplementation and regular physical activity.

Screening with initial bone densitometry every 2 years should be performed in postmenopausal women treated with aromatase inhibitors, premenopausal women taking tamoxifen and/or a GnRH agonist, and those with early chemotherapy-induced menopause.

For post-menopausal women or for those with other associated risk factors it is suggested to intake 800 IU of vitamin D per day and 1200 mg of elemental calcium (ideally from diet, in addition to supplements if necessary).

The selection of patients that are candidates for pharmacological therapy should consider an estimate of fracture risk as determined by a combination of bone densitometry and clinical risk factors. The risk of fracture can be calculated using the Fracture Risk Assessment Tool (FRAX). The National Osteoporosis Foundation (NOF) recommends pharmacological therapy in patients with osteopenia (T-score between -1.0 and -2.5 in the neck of the femur, hip, or lumbar spine) if there is an estimated 10-year probability of hip fracture of $\geq 3\%$ or large osteoporotic fracture $\geq 20\%$ and in those with osteoporosis (T-score lower than -2.5).

Bisphosphonates and denosumab are potent inhibitors of osteoclast activity and are approved for the prevention and treatment of osteoporosis. Estrogen receptor modulators (SERMs), such as raloxifene and tamoxifen, also play a role in the prevention of bone loss, in addition to reducing the recurrence of breast cancer. However, SERMs should not be used in the prevention of osteoporosis in women who are using aromatase inhibitors.

Cardiotoxicity

Chemotherapy (e.g., anthracyclines, fluoropyrimidines), anti-HER2 therapy (e.g., trastuzumab), and hormone therapy (e.g., aromatase inhibitors) have been associated with an increased risk of cardiovascular disease in breast cancer patients.

Cardiac complications include dilated cardiomyopathy, arrhythmias, vasospasm, or vessel occlusion resulting in chest pain or myocardial infarction, increased cholesterol levels, and the risk of diabetes caused mainly by aromatase inhibitors.

This risk is increased in a patient with a known history of cardiovascular disease and in a post-menopausal patient, since endogenous estrogens in younger women contribute to the low prevalence of cardiovascular diseases in this population. The incidence of heart disease is higher in patients with cumulative exposure to anthracycline and the risks of heart disease related to this class of drug range from 0.2% to 100% at cumulative doses ranging from 150 to 850 mg/m^2 respectively.

In general, the risk of cardiovascular toxicity and the need for treatment increases gradually if patients do not receive primary and secondary prevention measures. For all patients receiving potentially cardiotoxic therapies, primary prevention of cardiovascular risk reduction should be initiated.

Management of preexisting comorbidities (hypertension, systolic or diastolic heart dysfunction, arrhythmias, metabolic disorders) should be optimized and an encouraged healthy lifestyle (such as cessation of smoking, optimal weight maintenance, increased exercise) before and after exposure to chemotherapy.

In the absence of specific guidelines for cardiac monitoring of a potentially cardiotoxic agent, evaluation and monitoring of ejection fraction with echocardiogram should be considered. Secondary prevention measures require that patients be monitored during and after treatment and managed when the signal of toxicity appears.

Thromboembolic Events

Of the patients with breast cancer who received adjuvant chemotherapy, 1.2% had hospitalization or an emergency room visit due to thromboembolic phenomena (deep vein thrombosis or pulmonary embolism), but it is not known whether this greater risk is associated with the cancer itself or with the treatment.

In contrast, the use of tamoxifen is demonstrably associated with an increased rate of venous thromboembolic events and that there is a significant additional procoagulant effect when tamoxifen is added to chemotherapy.

Neuropathy

Peripheral neuropathy induced by chemotherapy (PNICh) is a common adverse effect of cancer therapy that can have a profound impact on quality of life and survival. PNICh may also adversely affect cancer outcomes, forcing dose reduction and/or premature treatment discontinuation.

PNICh has some unique characteristics: it is typically dose dependent and cumulative; it usually has a symmetrical, distal, sock-and-glove distribution.

Autonomic neuropathy is rare, and has a predominantly sensitive pattern, since motor nerve function usually remains unchanged during treatment, with the exception of paclitaxel, which may also be associated with motor neuropathy (mainly proximal) in up to 14% of patients.

Patients receiving paclitaxel may develop an acute pain syndrome, commonly classified as arthralgia and myalgia associated with paclitaxel, suggesting a form of acute neuropathy. The pathophysiology of this syndrome is unknown and has not been shown to be associated with any structural changes in muscles or joints. With docetaxel this phenomenon can occur, but it is rarer. After completing paclitaxel treatment, approximately 50% of patients improved over a period of 4–6 months, but one study reported that neuropathy may persist in up to 80% of patients within 2 years of treatment.

Symptomatic improvement of PNICh can be achieved with the use of antidepressants (duloxetine) and anticonvulsants (gabapentin/pregabalin).

Depression, Anxiety, and Cognitive Loss

The most problematic changes that affect the quality of life in the psychological scope are anxiety, fear of recurrence and metastasis, and concern with reexamination tests. This feeling of uncertainty is manifested by anxiety, mood swings, and depression and can persist for years, often being the most difficult part of the patient's recovery.

The risk of having major depression after a breast cancer diagnosis is higher among younger patients, patients with a history of previous psychiatric illness, patients with low socioeconomic status, and those who are unemployed. Among breast cancer patients, decreased libido, lower self-image, and marital relationship issues were common among those who were depressed.

All patients should be assessed for distress, depression, and/or anxiety. A more in-depth evaluation should be conducted in patients at higher risk of depression (e.g., young patients with a history of prior psychiatric illness, patients with low socioeconomic status), and counseling and/or pharmacotherapy and/or referral should be offered to psycho-pedagogical and mental health resources.

Chemotherapy may produce cognitive decline that, while subtle, may have changes in attention, memory, and functionality. They may last 2–10 years after treatment. This can negatively affect work skills and educational activities. However, no effective treatment has been proposed so far.

Sexual Dysfunction

Sexual activity may become less pleasant and even painful after the treatment of breast cancer. The psychological sequelae of a breast cancer diagnosis can lead to strain on the marital relationship and change in body image that may further hamper sexual activity.

Sexual complaints may include decreased sex drive, libido, arousal, orgasm, and dyspareunia.

Psycho-pedagogical support, group therapy, sexual counseling, marital counseling, or intensive psychotherapy should be offered to all breast cancer survivors with sexual complaints that present anxiety, stress, and mood swings.

Women who report dyspareunia, usually related to the use of aromatase inhibitors, may benefit from local hormone therapy, vaginal dilators, vaginal lubricants, and moisturizers.

Infertility and Pregnancy After Breast Cancer Treatment

The risk of amenorrhea related to chemotherapy, menopause, and infertility can be caused by injury to the hypothalamic-pituitary-gonadal axis, and it seems to be related to age, since the female ovarian reserve is not renewable and decreases with age.

Cytotoxic drugs, radiotherapy, surgery, and the disease process itself can cause infertility, which can be temporary or permanent. When it does occur, it can have a profound psychosocial impact especially on the woman who wants to become pregnant.

There are options available for preservation of fertility that include cryopreservation of embryos, oocytes, ovarian tissue prior to treatment, and ovarian suppression during chemotherapy.

While some experts recommend that patients wait 2 years after the end of treatment to attempt pregnancy (in order to avoid pregnancy during the period of greatest risk of recurrence), some data suggest that pregnancy after 6 months of termination of treatment is safe.

Women treated with trastuzumab should use effective contraception for at least 6 months after termination because of the risk of trastuzumab-related oligo-amniotic fluid. In addition, due to the risks of teratogenicity, women treated with tamoxifen should be advised to wait at least 3 months after cessation of tamoxifen before attempting to conceive.

For women with breast cancer who wish to preserve fertility and would like to maintain a contraceptive method, the safety and efficacy of hormonal contraception have not been well studied in women with breast cancer since these women are traditionally excluded from contraceptive studies on hormones. It is advisable to avoid hormonal contraception in women with prior or current history of breast cancer (particularly those with hormone receptor positive disease) and to guide women about other contraceptive methods such as copper IUD and barrier methods.

Second Neoplasia

Breast irradiation, adjuvant chemotherapy, and tamoxifen are associated with an increased risk of second primary cancers that may manifest decades after treatment. Although it is very small, it is important for doctors and patients to be aware of the risk.

Adjuvant radiotherapy is associated with a small increased risk of developing sarcoma or lung cancer after 10 years of treatment. Modern treatment approaches with lower dose and radiation limitation preserving normal tissues reduce the risk of developing cancer associated with radiation.

The incidence of development of acute myeloid leukemia and myelodysplastic syndromes related to adjuvant chemotherapy is generally less than 1%, but it corresponds to a twofold increased risk compared to the general population. Normally, chemotherapy-related leukemia is refractory to conventional anti-leukemia therapy, and it has a worse prognosis.

Tamoxifen is associated with a two to threefold increase in the risk of developing endometrial cancer, but the benefit of adjuvant therapy outweighs this risk. Endometrial cancer that occurs after tamoxifen therapy does not appear to be different, or it has a worse prognosis for endometrial tumors in the general population.

Changes in Life Habits

Promotion of Health

Quality of life is a multidimensional aspect that takes into account the physical, mental, social, economic, and spiritual factors of life.

Observational data suggest that exercise, weight control, cessation of smoking, and decreased alcohol intake are associated with a lower risk of recurrence of breast cancer and death in cancer survivors. Healthy habits are also the key to reducing the risk of second cancer, comorbidities, obesity, and recurrence, leading to improved prognosis, improved cancer-related symptoms, and consequently lowering mortality.

Dieting

Several observational studies have evaluated the relationship between dietary factors, the risk of recurrence of cancer, and death in women diagnosed with early-stage breast cancer. Nevertheless, there were no consistent relationships between

any food pattern or intake of a particular nutrient and the decrease of the risk of recurrence in breast cancer, especially after adjusting for body weight and other related factors.

Some evidence suggests that reducing dietary fat intake following a cancer diagnosis may improve treatment outcome, but the data are not consistent, and diet modification is not a standard part of adjuvant therapy for women with breast cancer currently.

Although there is no convincing evidence that soy affects the risk of recurrence, the theoretical risk that phytoestrogens may stimulate breast cancer growth raises concern that high soy intake can be dangerous. Thus, moderation of soy intake is generally suggested.

Physicians should advise survivors to achieve a dietary pattern that is rich in vegetables, fruits, whole grains and legumes, low in saturated fats and limited consumption of alcohol because it causes a decreased risk of death from other causes, even though its effect on recurrence of breast cancer has not been proven.

Obesity

Obesity is a well-established risk factor for many types of cancers. A number of studies have also linked obesity to an increased risk of recurrence and cancer mortality, especially in patients with breast cancer.

Observational studies consistently associate obesity at the time of breast cancer diagnosis with higher rates of recurrence, breast cancer-related mortality, and overall mortality. However, weight gain after diagnosis may be associated with an increased risk of recurrence, although available data do not demonstrate this association.

The etiology of the poor outcomes observed in obese women with breast cancer is not well understood. In the past many oncologists used ideal body weight or limited the doses of chemotherapy administered to obese patients because of fear of increased toxicity. Further studies have shown that these practices produce inferior results, leading the American Society of Clinical Oncology to develop guidelines recommending the use of full doses of chemotherapy based on the actual weight of obese individuals.

Even when taking into consideration the correct chemotherapy dosage and the relationship between weight on diagnosis and the prognosis of breast cancer, adjuvant clinical trials continue to show a negative impact on the prognosis, especially in women with breast cancer hormone receptor positive.

Complementary Therapies

Although there is no evidence that complementary therapies decrease breast cancer recurrence, acupuncture and meditation can be used in conjunction with conventional treatment as they can help improve quality of life by reducing pain, stress, anxiety, fatigue, vasomotor symptoms, and improvements in sleep quality.

Conclusion

Breast cancer survivors face potentially significant impacts of cancer and its treatment and deserve comprehensive and multidisciplinary follow-up care. They should receive support with the aim to decrease pain, depression, anxiety, cognitive deficits, concerns about body and sexual image, functional changes, physical disabilities, changes in the marital relationship, job stability concerns, and financial problems, among others.

They also need to be counseled through health promotion strategies with healthier lifestyle habits that include following a healthy diet, starting or maintaining a physical exercise program, minimizing alcohol intake, and stopping smoking, thereby improving overall health conditions, increasing survival, and improving quality of life.

Recommended Reading

1. Bodai BI, Tuso P. Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. Perm J. 2015;19(2):48–79.
2. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. CA Cancer J Clin. 2016;66(1):43–73.

Physical Rehabilitation After Breast Cancer Treatment

Fernanda Alaite Zambelli and Alessandra Tessaro

Despite the decrease in morbidity with the evolution of breast cancer treatment, many patients have functional sequelae. Physical therapy and some medications can prevent or treat most of these limitations.

Side Effects from Treatments

The main physical problems arising from breast cancer treatments are shown in Table 1.

Apparently, the risk of complications is proportional to the size of the intervention, be it surgery or radiotherapy (RT). The site of treatment with the highest risk is the axillary region.

Harris et al. [4], observed more limitation after mastectomy than after conservative breast surgery.

The number of lymph nodes removed (or irradiated) is directly proportional to the risk of sequelae, mainly lymphedema, as shown in Fig. 1.

Sentinel lymph node biopsy (SNB) techniques have reduced surgical morbidity, but are not risk-free (Fig. 2).

A review by Boughey et al. (2007), reported a mean lymphedema rate of 6.8% after SL biopsy versus 31.4% after axillary dissection.

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Table 1 Main sorts of sequelae from breast cancer treatment, with pathophysiology, clinical condition, and time of evolution

Sequelae	Pathophysiology	Clinical condition	Onset/evolution
Lymphedema	Lymphatic drainage blocking with damping and extravasation of lymph	Accumulation of lymph in the interstitial tissue, with edema and subsequent functional limitation	6–12 months after surgery; slow and progressive worsening
Axillary cords (*web syndrome*)	Lymphatic and superficial thrombosis, with lower elasticity	Restricted arm abduction	1 week up to 1 year after surgery; slow improvement
Pain and paresthesia	Lesions of minor nerves, mainly the intercostal brachial nerve	Feeling of numbness or stabbing in the surgical scar or in the medial side of the arm	Immediate after surgery; slow and progressive improvement
Winged scapula	Lesion in the long thoracic n., resulting in paralysis of m. serratus and dislocation of the scapula	Lifting the lower portion of the scapula and limitation of abduction	Immediate after surgery; Persistent
Lymphocele and seroma	Accumulation of lymph in the surgical site after removal lymph drainage	Blurring of the operated area or in the axilla by means of accumulation of liquid	1 week after surgery, with spontaneous regression in 1–3 months

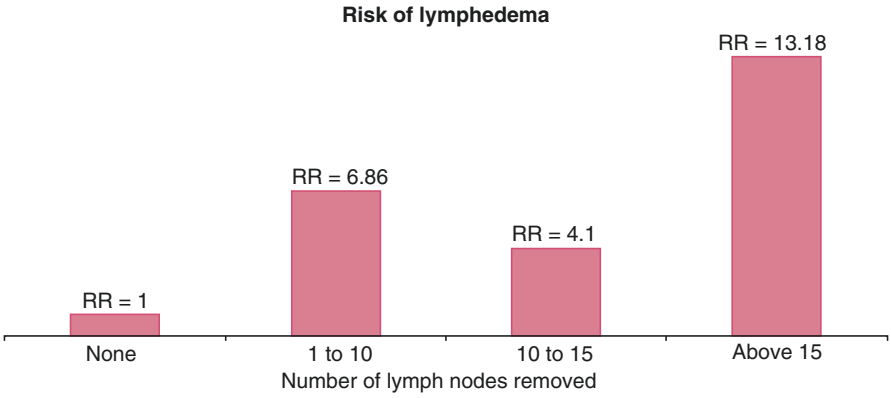


Fig. 1 Risk for lymphedema proportional to the number of lymph nodes removed. (Adapted from Kiel KD, Rademacker AW. Radiology. 1996;198:279–83)

Radiation therapy also increases the risks. Some authors have already demonstrated a decrease in lymphatic permeability, including in the contralateral breast. Others reported that patients submitted to radiotherapy present greater impairment in daily activities (40% vs. 31%).

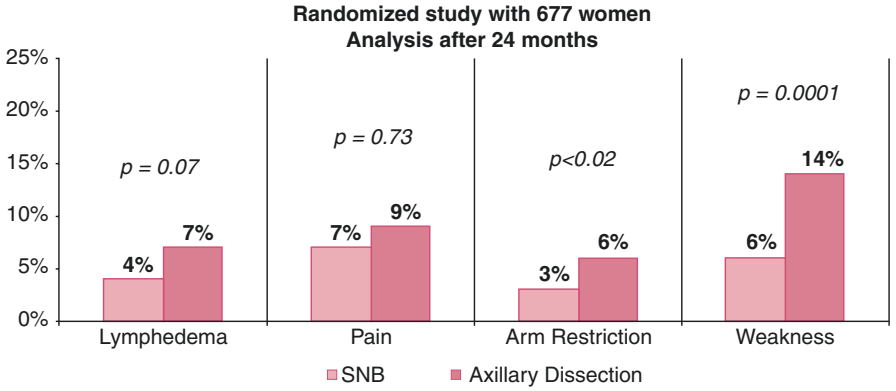


Fig. 2 Study comparing sequelae after different types of axillary surgery. (Adapted from Del Bianco P, et al. Eur J Sur Oncol. 2008;34(5):508–13)

Evaluation and Diagnosis

Whenever possible, it is suggested that the preoperative evaluation be performed to diagnose previous comorbidities and elucidate the physiotherapeutic treatment.

In the first evaluation, risk factors should be observed for possible complications. In the case of lymphedema, the main ones are:

- Age
- Number of lymph nodes removed (type of axillary surgery)
- Radiotherapy (especially axillary)
- Overweight
- Chemotherapy infusions in the ipsilateral arm
- Infection
- Lymphocele, seroma, or arm edema on the first 6 months P.O

Detailed physical evaluation is the best way to diagnose the main problems, from limitations of upper limb amplitude (ULA) to surgery, presence of pain, postural changes, winged scapula or web syndrome. Strength and sensitivity tests can be easily performed without the need for specific equipment. However, detailed examinations, such as electromyography, may be necessary in some situations.

The evaluation of lymphedema can be easily obtained through diagnosis: subjective symptoms of the patient (feeling of heaviness), inspection, palpation, skin changes, skin coloration and tissue fibrosis, and also the use of measures of arm circumference every 7 cm – the differential diagnosis is obtained with a difference greater than 2 cm compared to the other arm.

Other forms of evaluation are volumetric (difference greater than 200 ml) and bio impedance. However, they require more apparatus and are not always used on a daily basis. Lymphoscintigraphy may be valid in specific situations, such as treatment-refractory lymphedema, with suspicion of total obstruction of the lymph flow.

Guidance and Preventive Measures

The guidelines should be performed according to the postoperative period.

Immediate Postoperative Guidance

- Keep arm elevated, resting on pillows, while lying down;
- Early de-ambulation;
- Respiratory re-education;
- Return to everyday basic activities, except for vigorous efforts;
- Restrict maximal abduction of the arm up to 90° in the first week, or while stitches and drain are still present.

Late Postoperative Guidance

- Avoid venous punctures in the ipsilateral arm.
- Protection of the ipsilateral arm.
- Beware of minor injuries, infections.
- Perform regular physical activities (gradually and under supervision).
- Control the body mass index.
- Do self massage.

Physiotherapeutic Treatment

Motion Restriction

Exercises aim to gradually increase the range of motion (flexion and abduction), respecting the bearable limits for the patient. Axillary nerve syndrome should be treated with stretching exercises, manual stretching exercises, and pressure training. Physiotherapy also plays a fundamental role in pre, during, and after RT, through the gain and maintenance of range of motion of the upper limb.

Pain and Paresthesia

Techniques of sensorineural improvement with different tactile stimuli, besides massages and stretches are helpful. Electrical stimulation (TENS) may aid in pain control.

Winged Scapula

The use of analgesic resources, kinesiotherapy (postural exercises), mobilization of the shoulder girdle, electrostimulation, cervical relaxation, and overall stretching are recommended.

Lymphedema

Complex Physical Therapy (CPhT) is the form of conservative treatment that presents more consistent results for most patients. The CPhT results depend fundamentally on the stage of the disease when the treatment is started, regardless of the age of the patient and the time of evolution of the clinical condition.

CPhT is composed of manual lymphatic drainage, compression, exercise, and skin care.

Manual Lymphatic Drainage

Its fundamental principles are the physiotherapist's detailed knowledge of the anatomy and physiology of the lymphatic system, the performance of maneuvers with low pressure, slow and rhythmic manual activity, and the initial treatment of normal and proximal areas of the lymphatic region. Maneuvers should be performed at low pressure because the purpose of lymphatic uptake and transport is directed to superficial vessels but also by demonstrating that pressures above 40 mmHg can lead to lymphatic endothelial cell damage. The initial approach to distant areas of edema is to prepare lymph nodes and proximal vessels to receive volume overload from the affected limb.

Compression

This technique is essential to obtain adequate results and it varies according to the treatment phase. In the decongesting phase, compression with little elasticity is used by means of multilayer packing. In the maintenance phase, compression using compression sleeves is used. These are only prescribed when all movable fluid is no longer present in the affected limb, which can be evaluated by the disappearance of Godet's signal. The degree of compression to be chosen is the maximum supported by the patient, usually proportional to the degree of tissue fibrosis. For the upper limb the compression used is about 30–40 mmHg and custom tailoring is rarely required.

Physical Exercises

The movement of the limb increases the regional lymphatic flow and causes contraction of the smooth muscle of the collecting vessels wall. Besides the direct action on lymphatic drainage, the prescription of the exercises aims at the functional recovery of the limb, since lymphedema decreases joint function by edematous infiltration of the capsule and ligaments and also by the external restriction to the joint due to tissue fibrosis and edema. They are active exercises performed by the patient, which mobilize the joints and muscle groups in a centrifugal way, following the sequence of manual lymphatic drainage. For the upper limbs, that involves initially neck and shoulders. They are performed slowly and progressively, mimicking the frequency of vessel contractions, about eight to ten cycles per minute.

Skin Care

Patients with lymphatic drainage deficiency present decreased lymphocyte circulation and delayed immune response, resulting in regional immune deficiency.

Skin lesions cause loss of the protective barrier of the epidermis, facilitating bacterial invasion and acute infectious conditions, with additional lymphatic vessel injury and progressive worsening of edema.

The prevalence of interdigital fungal lesions is high in patients with lymphedema, mainly dermatophytes and yeasts. Local hygiene measures and antifungal application should be taken. Intermittent pneumatic compression is used in some centers as a complementary therapy for lymphedema. There are several devices available for clinical application, but there is no consensus on the efficacy of this method.

Usually, the CPhT is divided into two phases: decongestant phase and maintenance phase. In the decongestant phase, in which most of the edema is reabsorbed and the regression of fibro sclerotic tissue changes begins, manual lymphatic drainage sessions must be done daily and tissue compression is performed by means of bandaging. This phase usually lasts 6–8 weeks. In the maintenance phase the lymphatic drainage is occasional and the result of the first phase is maintained or improved by use of compression with compression sleeves. The maintenance phase can last for a lifetime.

During the 2017 AsBrs, the following recommendations were made regarding the prevention/treatment of lymphedema:

- Educate and inform the patient as to risks;
- Early detection (perimeter, volume);
- Stimulate physical activity (low reps, low weights, gradual increases);
- Multidisciplinary team (treatment);
- Rigorous baseline and follow-up.

Clinical and Surgical Treatment of Lymphedema

Diuretics are not indicated for patients with lymphedema, except for treating other concomitant conditions, such as systemic arterial hypertension or heart failure.

Antibiotics are used to treat infectious complications such as erysipelas and cellulites. As these are important factors of worsening the prognosis, there is concern about prophylaxis. The most appropriate methods of infectious prevention are skin care and edema reduction. Prescription of antibiotics such as benzathine benzylpenicillin at the dose of 1,200,000 IU IM every 3 weeks or sulfamethoxazole 400 mg + trimethoprim 80 mg IU every 12 h for 1 week a month is effective and recommended in the 6 months following one infectious outbreak or patients with unsatisfactory skin care.

The use of benzophenones and diosmin is the subject of discussion in the literature, and there is no consensus about its actual indication. These drugs have a demonstrated effect in vitro by enhancing tissue proteolysis by macrophages, contractility of lymphatic vessels, and reduction of capillary permeability. However, clinical studies in patients with post-mastectomy lymphedema have shown discordant results. At the present time the role of these drugs is not defined for the treatment of lymphedema, including which formulations and doses would be adequate and cannot be considered alternatives or substitutes for CPhT. Surgery is considered the exception course for the treatment of lymphedema.

Surgical procedures currently used are divided into resection surgery (dermolipectomy, liposuction, and amputation) and bypass surgery (lymphovenous anastomosis by microsurgical technique).

Dermolipectomy

It is not intended to cure lymphedema but rather to remove excess skin and subcutaneous tissue, being an alternative to giant lymphedema after clinical treatment, in a limb that has maintained the measurements for at least 1 year and did not present lymphangitis. In this way the affected limb acquires a more physiological form and can be better manipulated by the CPhT, presenting better functionality. It consists of the removal of a spindle of skin and subcutaneous cellular tissue with primary closure, avoiding large detachments so that there is no excessive lymphatic damage.

Liposuction

This technique has been used to treat lymphedema with good results. It consists of the removal of edema and hypertrophied fat, interstitial fluid, and accumulated proteins. It should be performed delicately for the same indications of dermolipectomy,

resulting in low infection rate and decreased limb volume. As it is for CPhT, in this technique patients should maintain strict and long-term follow-up.

Amputation

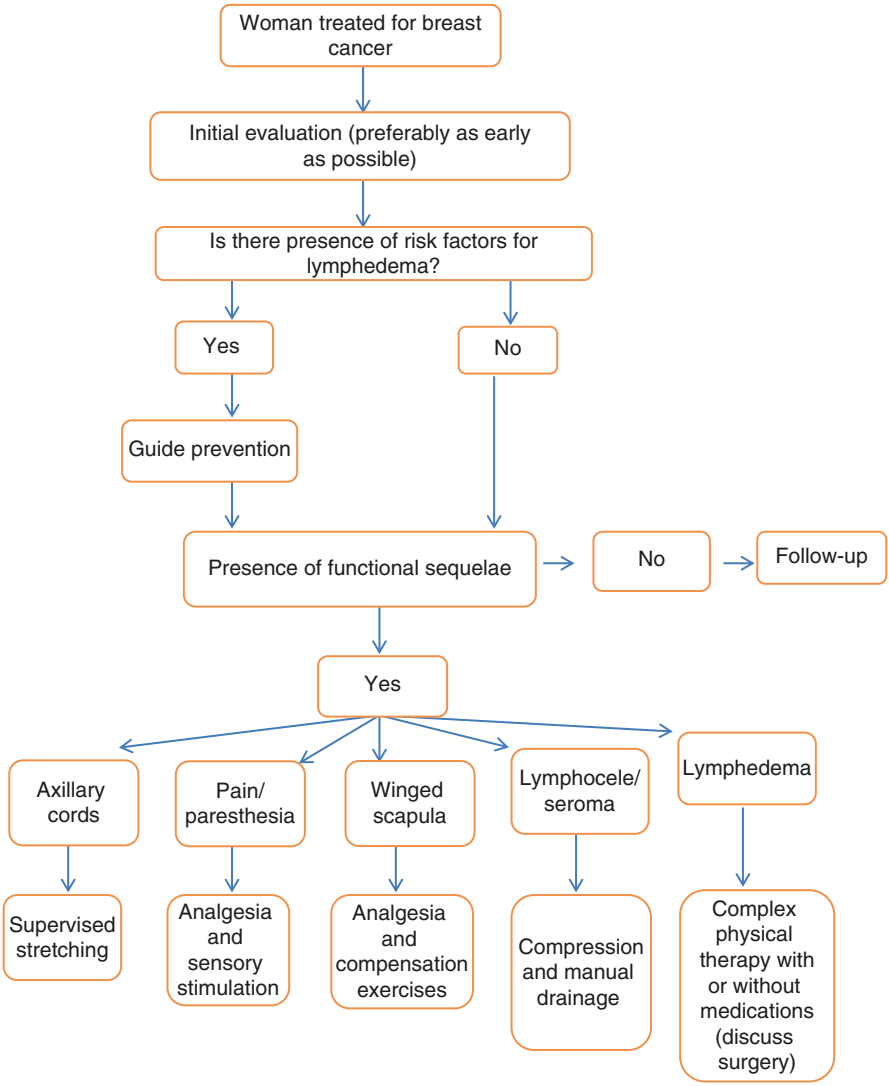
Cases of malignant lymphedema with transformation into lymphangiosarcoma are rare. This is an immature neoplasm of very aggressive character, with a high mortality rate. One should be aware of the formation of an ulcer in the limb with lymphedema and indicate biopsy early. Treatment is early amputation of the involved limb, with extensive lymph node dissection.

It is important to make the precise differential diagnosis between lymphangiosarcoma after mastectomy (Stewart-Treves Syndrome) and subcutaneous nodule adenocarcinoma of the upper limb, since the latter is less aggressive and respond reasonably to local excisions and chemotherapy.

Lymphovenous Anastomosis

It is indicated in rather selected cases: in lymphedemas in an initial phase, in which there was still no lesion of the lymphatic capillary. Three to six anastomoses are performed with a microsurgical technique between superficial lymph collectors with some vein, which may be superficial or deep, either main or even a tributary. Lymphoscintigraphy done after 6 months is the test indicated to document the functionality of the anastomosis.

Flowchart



Flowchart 1 Summary of the ideal sequence of functional rehabilitation

Recommended Reading

1. Bevilacqua JL, Kattan MW, Changhong Y, Koifman S, Mattos IE, Koifman RJ, Bergmann A. Nomograms for predicting the risk of arm lymphedema after axillary dissection in breast cancer. Ann Surg Oncol. 2012;19(8):2580–9. *Prospective cohort study with 1054 Brazilian women treated for breast cancer. The incidence of lymphedema at 5 years was 30.3% and the risk factors were: age, body mass index, chemotherapy infusions in the operated arm, level of axillary emptying, radiotherapy field, seroma, infection and early edema. Nomogram for calculating individual risk is available at www.lymphedemarisk.com/.*
2. Ferguson CM, Swaroop MN, Horick N, et al. Impact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer. J Clin Oncol. 2016;34(7):691–8. https://doi.org/10.1200/JCO.2015.61.5948.
3. Fukushima K, Carmo L, Borinelli A, Ferreira C. Frequency and associated factors of axillary web syndrome in women who had undergone breast cancer surgery: a transversal and retrospective study. Springerplus. 2015;4:112. Published online 2015 Mar 5.
4. Harris SR, Schmitz KH, Campbell KL, McNeely ML. Clinical practice guidelines for breast cancer rehabilitation: syntheses of guideline recommendations and qualitative appraisals. Cancer. 2012;118(8 suppl):2312–24. *Summary of consensus recommendations after systematic review on breast cancer rehabilitation in the following areas: limb restraint, lymphedema, pain, fatigue, chemotherapy-induced neuropathy, cardiotoxicity, bone health, and weight control.*
5. Oremus M, Dayes I, Walker K, Raina P. Systematic review: conservative treatments for secondary lymphedema. BMC Cancer. 2012;12:6. *A systematic review of 44 articles on the treatment of secondary lymphedema, most cases of upper limb lymphedema after treatment of breast cancer. It is not possible to establish comparisons between the different therapies, but apparently all of them have some degree of efficacy.*
6. Paskett ED, Dean JA, Oliveri JM, Harrop JP. Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. J Clin Oncol. 2012;30(30):3726–33. *Review of lymphedema secondary to the treatment of breast cancer, with details of physiotherapeutic, pharmacological and surgical treatments.*
7. Scaffidi M, Vulpiani MC, Vetrano M, Conforti F, Marchetti MR, Bonifacino A, et al. Early rehabilitation reduces the onset of complications in the upper limb following breast cancer surgery. Eur J Phys Rehabil Med. 2012;48(4):601–11. *A clinical study comparing 83 patients submitted to breast cancer treatment. Group A (25 women) did not undergo physical therapy during hospitalization and Group B (58 women) started therapy immediately. The results after 180 days demonstrated a superiority by far of the early onset of physiotherapy in relation to the mobility of the upper limb.*
8. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, Bryan CJ, Williams-Smith CT, Greene QP. Weight lifting in women with breast-cancer-related lymphedema. N Engl J Med. 2009;361(7):664–73. https://doi.org/10.1056/NEJMoa0810118.

Contraception and Infertility

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Introduction

The use of contraception by women is common. Birth control pills and other hormonal methods are used by millions of women around the world. The need to evaluate the influence of these methods on the genesis of the breast tumor is clear.

On the other hand, more than ever younger women have been treated for breast tumors. They will maintain their sex life and must be guided on the methods of contraception that they are allowed. These women at reproductive age, must get attention to their preservation of fertility, since the chemotherapy used in the treatment can jeopardize the reproductive function.

Contraception

Approximately 60% of women at reproductive age use methods of contraception. The method of choice is usually made on an occasional basis, without a thorough analysis of the history of the woman, with evaluation of associated diseases, habits, personal antecedents, and mainly family history. Contraceptive methods have an effect on the ability to prevent unwanted pregnancy. We can choose medications that bring other benefits to the woman, such as treating and preventing some diseases. On the other hand, the inadequate choice of the method may imply an increased risk of some diseases, such as breast cancer.

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Contraception and Risk of Breast Tumor

Assessing a woman's family history is a key step when choosing a contraception method. In this chapter, we will cover only the aspects related to breast tumor. Twenty to thirty percent of women with breast tumors have at least one relative with the disease. However, only 5–10% have proven hereditary predisposition.

There are many papers pointing out that the use of oral contraceptives brings protective effect to ovarian tumors, though the data are inconclusive in relation to breast tumors.

Three large epidemiological studies have shown no association between oral contraceptive use and breast cancer. In one study, which followed nearly 50,000 women on average for 24 years, the risk of breast cancer was similar in users and non-users of the pill (RR: 0.98, 95% CI: 0.87–1.10). In the *Nurses Health Study,* women over 40 years of age had no increased risk was seen when they had a history of hormonal contraception use. In a case-control study comparing 4574 women with breast cancer with 5682 controls between 35 and 64 years, no association between disease and estrogen dose, duration of use, onset of use among women below 20 years, or race was found. The relative risk of breast cancer in this study for prior hormonal contraception use was 0.9 (CI 95%: 0.8–1.0).

A meta-analysis in 2015 [21] evaluated the risk of oral contraceptives and the risk of death from breast tumors, but found no association.

On the other hand, a new publication of the Nurses Health Study [1] suggests that using oral contraceptives would increase the risk of breast cancer.

Some meta-analyses also indicated an increased risk. One of them, with 53,297 women with breast tumors and 100,239 controls (Lancet 1996), published before the three studies that indicated the opposite, showed an increased relative risk in contraceptive users (RR: 1.07). It should be noted that users are young, so they would incur in a small increase in absolute risk. It is also important to note that only 40% of these women used oral contraceptives. A more recent meta-analysis [3] also indicated this slightly increased but significant risk (RR: 1.08, CI 95%: 1.0–1.17) and concluded that although this increased risk is small due to the high incidence of breast tumors; this can contribute to a substantial number of new breast cancers.

Another meta-analysis [17] evaluated only contraceptives with progesterone, and did not indicate an increase in breast cancer risk.

In patients with a family history of breast cancer we also have conflicting data. In the aforementioned case control study [10] the risk was not increased with the use of contraceptives in those patients with a family history of breast cancer. In contrast, there is a review (Gabrick et al. 2000) that indicates increased relative risk (RR: 3.3) in women who used contraceptives before 1975; therefore, a high dosage was used.

In BRCA1 and 2 mutation-carriers, oral contraception could increase the risk of breast cancer [2, 13, 19] but is still a controversial issue. In a control case study [13] in patients with BRCA 1 mutation, those who used oral contraceptives for at least 5 years had a small increase in the risk of breast cancer (OR: 1.33, 95% CI: 1.11–

1.60) compared to those who never used the pill. In a more recent meta-analysis [12], there was no statistically significant difference between users of oral contraceptives and BRCA 1 and 2 mutation carriers (OR: 1.21, 95% CI: 0.93–1.58).

Contraception After Breast Cancer

During the treatment of breast cancer, pregnancy should be avoided, so that contraception is a priority. In general, we can say that after breast cancer, oral hormone contraceptives are contraindicated, although it is not easy to establish the real risks of their use under these conditions.

Currently the intrauterine device is available with levonorgestrel, which releases high local doses of progesterone, but with a low systemic effect. It is known that Mirena® may reduce the risk of endometrial changes in patients undergoing breast cancer treatment with tamoxifen (Chan et al. 2007; Dominick et al. 2015). The studies, however, are small and cannot define risk of recurrences or novel cancers. Analysis in a retrospective cohort study reported a trend toward increased recurrence of breast cancer in Mirena users at the time of diagnosis and who continued to use the device. But this was not observed in patients who started to use Mirena® after cancer diagnosis (Trinh et al. 2008). Therefore, the real safety of Mirena® after breast cancer has not yet been established. Thus, up to now, patients should be informed that the safety of Mirena® is unknown, and it is recommended that some non-hormonal contraceptive method be prescribed.

Infertility

We define a couple as infertile when they do not get pregnant after a year of active sexual life without the use of contraception. Marital infertility affects 10–15% of couples at reproductive age, with a tendency to increase these rates nowadays. The supposed reasons for this increase are various, and they include the postponement of maternity by the modern woman. It is clear that with modernity, women entered the labor market and acquired greater sexual freedom with access to contraceptive methods. The result is clear: more and more women are seeking to have children after the age of 35 or 40, which is indeed an age there is already a significant reduction in fertility. In this scenario, there is also an increase in the incidence of breast cancer in women who have not yet had children.

During the breast tumor treatment, these women are expected not to become pregnant, delaying motherhood. Aggression to the ovaries caused by chemotherapy, which is usual in many treatments, is more severe. The result is a radical impairment of the woman's fertility, since a large proportion of patients will survive the treatment. It is mandatory to address this problem, and include fertility preservation in the treatment protocols.

We cannot say that a patient exposed to chemotherapy will become infertile. Many women who receive chemotherapy become amenorrhoeic, usually with high serum gonadotrophin levels. Erroneously, such women can be diagnosed as menopause and infertile, but many of these will recover their fertility and menstrual regularity, months or even years after the end of treatment.

Alkylating drugs such as cyclophosphamide are the most potent inducers of ovarian failure. The effects are dose, drug, and age dependent. Older women, especially over 40 years of age, are more likely to have amenorrhea and definite impairment of their fertility. Two usual chemotherapy protocols for early breast tumors include cyclophosphamide, methotrexate and 5-fluoracil (CMF) and doxorubicin and cyclophosphamide (AC). The risk of ovarian failure appears to be higher with CMF compared to the AC protocol (Bines et al. 1996). It is clear that the ideal measure would be to modify the protocols for those who have the least aggression to the ovaries, but we must not forget that the main objective of the treatment is to maximize the cure of neoplasia.

Preservation of Fertility

Exposure of alternatives for preserving fertility to patients at risk should be encouraged. These risk situations can only be defined by the woman's age (above 35 years) as well as by exposure to chemotherapy or radiotherapy. There is no defined formula. The decision of which method to be employed will depend on several factors such as age, presence of partner, tumor type and staging, radiotherapy protocol or chemotherapy used, and time available before the treatment.

Placing age as the first factor to be assessed seems obvious, but many are unaware of the limitations of assisted reproduction techniques. Regardless of the treatment employed, the pregnancy rate is close to zero for ova obtained from women over 45 years of age. Even in those women over 40 years of age, success rates do not exceed 20% per cycle, no matter that freezing techniques are not used.

The time available before the start of chemotherapy has great importance for determining if there is a possibility of induction of ovulation and collection of the eggs, so that they are frozen or fertilized, with consequent freezing of embryos. During stimulation, it is not advisable to stimulate ovulation. Usually, it takes 2–5 weeks for ovulation induction, starting at the menstrual period and collecting the ovules after approximately 10 days of gonadotrophin use. When it is not possible to wait for menstruation, the ovarian stimulus can start at any point in the menstrual cycle. In the breast tumor, there is usually the 6-week interval between surgery and chemotherapy, a period suitable for ovarian stimulation. In those situations where there is not enough time to perform ovarian stimulation, there are other options such as collection of immature ova or freezing of ovarian tissue (see management flowchart).

Breast tumors that have estrogen receptor may be especially impaired with the high estradiol levels obtained with ovarian stimulus. Situations such as this can be

avoided by the freezing of immature eggs and/or ovarian tissue, or with ovarian stimulation through aromatase inhibitors or tamoxifen.

Aromatase inhibitors, such as letrozole, have shown good results associated with gonadotrophins in the freezing of ova or embryos in breast tumor patients. Letrozole allows a reduction in the use of gonadotrophins and levels of estradiol close to physiological levels, besides being theoretically safer for these patients [9, 14, 15]. Likewise, tamoxifen may also stimulate ovulation for being a selective modulator with antiestrogen properties.

Ovarian suppression seeks to reduce ovarian function during the treatment period, which in theory would reduce ovarian tissue damage. GnRH agonists or contraceptive pills are used during chemotherapy. This is still subject to debate. However, there are three small randomized studies, one in mammary tumor [6] and a recent review [18], which did not show proven efficiency of the use of GnRH agonists in the preservation of fertility in patients undergoing chemotherapy. The safety of GnRH agonists is also questioned because they could theoretically reduce the efficiency of chemotherapy.

Cryopreservation

Embryo freezing is the most important technique to preserve fertility. Ovules usually obtained by means of ovarian stimulation are fertilized in the laboratory and the resulting embryos are frozen. Gestation rates from frozen embryos are close to those resulting from embryos transferred fresh (not frozen) [8, 18, 20]. The main disadvantage is previous fertilization of the egg, thus not allowing the woman to later define the "biological father" of her offspring. That is, the woman who undergoes this technique must have an already defined partner or use donated sperm.

Egg freezing is a promising technique and it has become an option, especially for those women who do not have a partner. Ovules, however, are more sensitive to freezing, leading to even lower pregnancy rates.

Ovarian stimulation with gonadotrophins is usually employed to obtain the growth of more follicles, so that more mature eggs can be obtained. The standard protocol starts at the beginning of menstruation, when, after ultrasonography and hormonal dosages, gonadotrophins are applied subcutaneously. After approximately 10 days of gonadotrophin use, the follicles are aspirated transvaginally under sedation. As mentioned previously, in many situations ovarian stimulation is not possible, either due to lack of time for the procedure or the presence of ovarian metastasis or even due to the patient's fear of using hormones. For all of these cases, we have the option of freezing immature eggs, however, emphasizing that there are reports of few births resulting from this technique.

Ovarian tissue can also be frozen, but it is an experimental method. The ovary or part of it is removed by laparoscopy and then it is frozen.

The potential benefit of this technique is the need for ovarian stimulation, but the result is very poor or even absent (especially for the entire ovary).

Difficulties and Limitations

There are no large controlled trials that evaluate most of the methods mentioned above. Nor can one lose focus of the goal, which is to enable women to have a healthy child in the future. Knowing the percentages of live births for each method used is the main variable to be compared when evaluating results. Many may claim that having embryos, ova, or ovarian tissue will already bring comfort to the patient, and that is really important, but false expectations should not be encouraged.

The most consecrated method that presents the best pregnancy rates is embryo freezing, but the patient will need a partner or sperm donated. The best pregnancy rates also require ovarian stimulation to extract the largest number of mature eggs. The time lapse for the procedure and the estradiol levels are also important factors to consider.

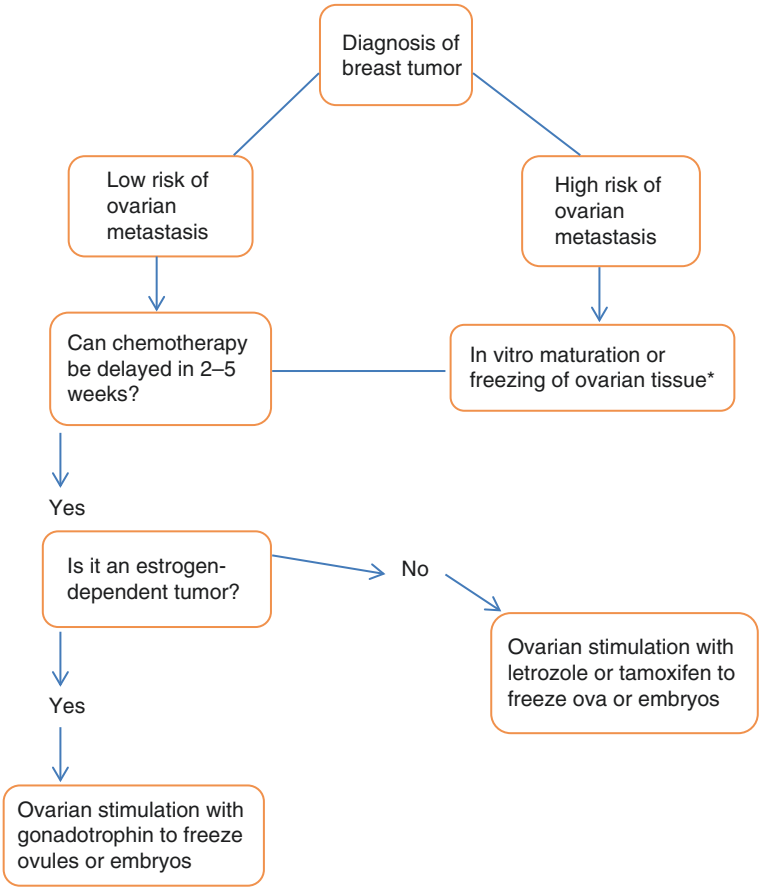
Assisted Reproductive Treatments

Faced with a couple with infertility, the first stage of treatment is to seek the cause and, if possible, to treat it. It is mandatory to search for the easiest and safest treatment to obtain a pregnancy. For women who have undergone some fertility preservation treatment because of breast tumor but still wish to become pregnant, we have as a first step the aproval by the mastologist and the oncologist. With this consent we must start with an analysis of the fertility of the couple, considering mainly the age of the woman, menstrual regularity, time trying to conceive and also any possible cause of infertility unrelated to the treatment of the tumor. Frozen ova or embryos should be viewed as a reserve or insurance, which will only be used if we find no other way to enable pregnancy.

In the diagnosis of infertility, it is sought to find the cause and treat it specifically, whether with medication or surgery. When this is not possible, one starts for methods of assisted reproduction such as induction of ovulation, artificial insemination, or in vitro fertilization. The fertility preservation methods presented above will be used in the treatment of in vitro fertilization in cases of conjugal infertility where the other techniques do not fit or have been tried without success. It is quite possible that the woman who froze her eggs or embryos will never use them, because she may become pregnant naturally or by means of simpler treatments.

In the worst reproductive scenario after breast tumor, the patient will not have viable eggs. In this situation, the options are the use of donated eggs (egg donation) or the adoption of a child. In egg donation, eggs from an anonymous donor are obtained, which are fertilized in the laboratory with the sperm of the partner or donor. The embryos formed are then transferred to the uterus of the recipient. Pregnancy rates are usually similar to those of young women with reduced risk of aneuploidies such as Down syndrome and miscarriages, all of which are compatible with the age of the egg donor. It is a consecrated and safe technique.

Flowchart



Flowchart 1 Management for fertility prevention. (Note: ∗Still experimental treatment)

Recommended Reading

1. Bhupathiraju SN, et al. Exogenous hormone use: oral contraceptives, postmenopausal hormone therapy, and health outcomes in the Nurses' Health Study. Am J Public Health. 2016;106(9):1631–7.
2. Brohet RM, Goldgar DE, Easton DF, et al. Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS Collaborating Group. J Clin Oncol. 2007;25:3831.
3. Gierisch JM, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2013;22(11):1931–43.

4. Hankinson SE, Colditz GA, Manson JE, et al. A prospective study of oral contraceptive use and risk of breast cancer. Cancer Causes Control. 1997;8:65.
5. Hannaford PC, Selvaraj S, Elliott AM, et al. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. BMJ. 2007;335:651.
6. Ismail-Khan R, Minton S, Cox C, Sims I, Lacevic M, et al. Preservation of ovarian function in young women treated with neoadjuvant chemotherapy for breast cancer: a randomized trial using the GnRH agonist (triptorelin) during chemotherapy. J Clin Oncol. 2008;26:524.
7. Jain JK, Paulson RJ. Oocyte cryopreservation. Fertil Steril. 2006;86(Suppl 4):1037.
8. Kosasa TS, McNamee PI, Morton C, Huang TT. Pregnancy rates after transfer of cryopreserved blastocysts cultured in a sequential media. Am J Obstet Gynecol. 2005;192:2035.
9. Lambertini M, et al. Controversies about fertility and pregnancy issues in young breast cancer patients: current state of the art. Curr Opin Oncol. 2017;29(4):243–52.
10. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med. 2002;346:2025.
11. Massarotti C, et al. State of the art on oocyte cryopreservation in female cancer patients: a critical review of the literature. Cancer Treat Rev. 2017;57:50–7. *Studies evaluating the efficiency of egg freezing. INTERPRETATION: Freezing of eggs is a promising technique, but results are still lower than results on embryo freezing.*
12. Moorman PG, et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol. 2013;31(33):4188–98. *Four studies (cohort, control case and a meta-analysis) that evaluated BRCA1 or 2 mutation carriers and the use of oral contraceptives are discussed here. INTERPRETATION: In BRCA1 or 2 mutation carriers, oral contraception may increase the risk of breast cancer.*
13. Narod SA, Dube MP, Klijn J, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst. 2002;94:1773.
14. Oktay K. Further evidence on the safety and success of ovarian stimulation with letrozole and tamoxifen in breast cancer patients undergoing in vitro fertilization to cryopreserve their embryos for fertility preservation. J Clin Oncol. 2005;23:3858.
15. Oktay K, Buyuk E, Libertella N, et al. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. J Clin Oncol. 2005;23:4347. *Studies evaluating the efficacy of letrozole and tamoxifen for ovarian stimulation. INTERPRETATION: Letrozole and tamoxifen are valid options for ovarian stimulation and embryo freezing.*
16. Oktay K, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a meta-analysis. Fertil Steril. 2006;86:70.
17. Samson M, Porter N, Orekoya O, Hebert JR, Adams SA, Bennett CL, Steck SE. Progestin and breast cancer risk: a systematic review. Breast Cancer Res Treat. 2016;155(1):3–12. https://doi.org/10.1007/s10549-015-3663-1. Epub 2015 Dec. *The first three studies are epidemiological studies. The first one (Hannaford et al.) with nearly 50,000 women followed on average for 24 years. The incidence of breast cancer was similar in users and non-users of pills. The fifth indicates otherwise. The fourth, sixth and seventh ones are more recent meta-analyses. The fourth one concludes that oral contraceptives are not related to breast tumor deaths. The sixth study assesses the risk of oral contraceptives and concludes a small increase in risk. The seventh one indicates that progesterone-only formulations do not increase the risk of breast tumor. INTERPRETATION: This subject is still controversial, but it is known that combined oral contraceptives could increase the risk of breast tumor.*
18. Taylan E, Oktay KH. Current state and controversies in fertility preservation in women with breast cancer. World J Clin Oncol. 2017;8(3):241–8. *Randomized study evaluating the effect of GnRH agonist on preservation of fertility in patients submitted to neoadjuvant chemotherapy for breast tumor, and review on the subject. INTERPRETATION: Ovary blockade with GnRH agonist has no proven benefit for preservation of fertility in patients undergoing chemotherapy.*

19. Ursin G, Henderson BE, Haile RW, et al. Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? Cancer Res. 1997;57:3678.
20. Veeck LL, Bodine R, Clarke RN, et al. High pregnancy rates can be achieved after freezing and thawing human blastocysts. Fertil Steril. 2004;82:1418. *Pieces of work comparing the rate of implantation of fresh and frozen embryos and revision. INTERPRETATION: Embryo freezing methods are effective at implantation rates similar to unfrozen embryos.*
21. Zhong GC, Cheng JH, Xu XL, Wang K. Meta-analysis of oral contraceptive use and risks of all-cause and cause-specific death. Int J Gynaecol Obstet. 2015;131(3):228–33.

Approaching Climacteric Issues

Luciano de Melo Pompei, Nilson Roberto de Melo, and César Eduardo Fernandes

Introduction

The climacteric (perimenopause) causes clinical manifestations in the great majority of women, bringing serious damages to their quality of life. Hormone therapy (HT) is a very effective treatment for such manifestations; however, just like any treatments, it offers risks and benefits that must be carefully analyzed.

When HT is not the treatment of choice, other forms of treatment may be employed, usually less effective than HT, but they may be sufficient to resolve the clinical condition presented.

Most Usual Complaints

Excluding menstrual changes, hot flushes or heat waves are the most frequent manifestations in the climacteric, reaching 75–80% of women. About half of them report such manifestations for more than 4 years postmenopausal, and about 10% report such complaints for more than 12 years.

Often, heat waves are accompanied by perspiration, palpitation, and facial flushing and may be associated with significant impairment of quality of life. Sleep may also be disjointed, resulting in problems to focus and to the ability to work the following day.

Mood changes, emotional lability, melancholy or depression, anxiety, irritability, and reduced libido often occur at this stage.

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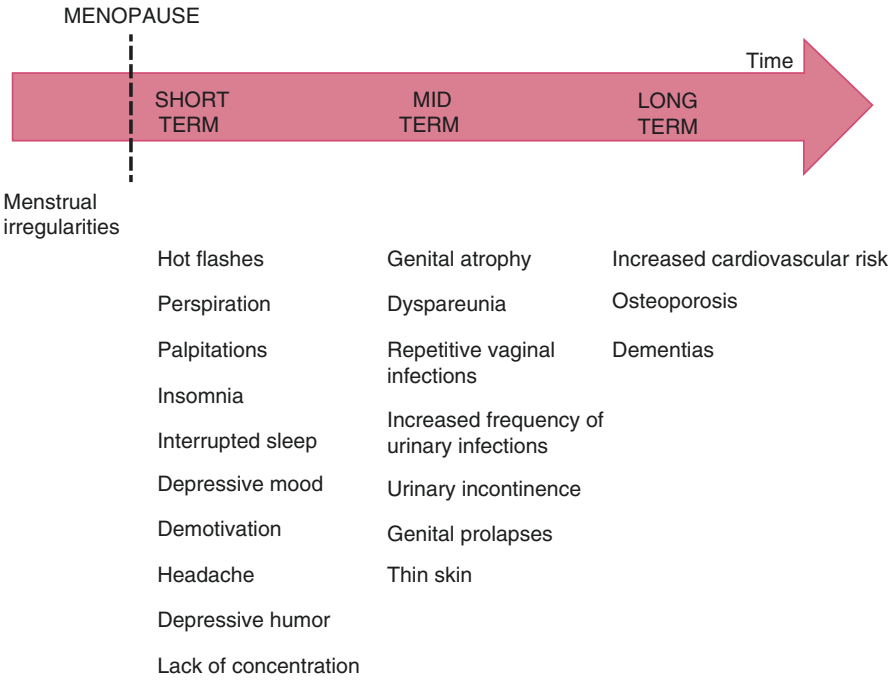

Fig. 1 Manifestations related to hypoestrogenism

In the medium term, the characteristic of postmenopausal hypoestrofenism causes atrophic urogenital phenomena. At this time, complaints of vaginal dryness or lack of lubrication, pain in intercourse, occurrence of vaginal infections, and propensity to low urinary tract infections are common. The greater looseness of connective tissue can be associated with urinary losses, characterizing urinary incontinence with or without any effort.

In the long term, there is an increase in rates of cardiovascular events, osteoporosis, and dementias.

Figure 1 represents graphically the short-, medium-, and long-term manifestations related to hypoestrogenism that characterize the climacteric.

Non-pharmacological Treatments

In general, studies on non-pharmacological treatments for vasomotor symptoms are very limited.

Physical exercises may improve psychological health and quality of life in women with vasomotor symptoms; however, a systematic review by the Cochrane Library informs that existing studies do not provide sufficient evidence to determine the effectiveness of physical exercises for the treatment of hot flushes.

On the other hand, aerobic physical exercises improve cardiorespiratory fitness and are beneficial to the cognitive function of the elderly, as well as improving motor function and balance and, thus, contributing to impede falling down and to reduce the risk of fractures.

Exercises for the pelvic muscles are known to be effective in the treatment of urinary incontinence and urge incontinence.

The effect of acupuncture was analyzed in a Cochrane systematic review published in 2013, including 16 studies and 1155 individuals. According to the authors, there was insufficient evidence of efficacy of acupuncture in relieving vasomotor symptoms.

It has also failed to prove that Yoga is effective in treating symptoms of climacteric.

Treatment with Non-hormonal Medication

There is sufficient evidence that antidepressants in the families of selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, fluoxetine, sertraline, and also serotonin and noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine and desvenlafaxine, are effective in the treatment of vasomotor symptoms of the climacteric. Relief rates are quite variable according to the study, but there is demonstration of superiority over placebo.

It should be remembered that the drugs in this family still have significant emotional effects with reduction of anxiety and relief of depressive symptoms, which can be very useful in the climacteric, even after cancer.

In cases of treatment after breast cancer using tamoxifen, most SSRIs should be avoided because they may reduce the effect of tamoxifen by inhibiting its conversion to endoxifen through enzyme CYP2D6. Paroxetine and fluoxetine are among the most potent inhibitors of this enzyme, duloxetine moderately inhibits it and the others weakly or non-inhibit. In this situation, venlafaxine is one of the options considered appropriate, since its effect in this enzymatic system is small.

Gabapentin, an anticonvulsant drug, is effective in treating vasomotor symptoms and is an alternative for breast cancer. It presents as a disadvantage the need to divide the dose into three daily doses and the possibility of side effects, such as dizziness and changes in appetite.

Clonidine, an alpha-adrenergic receptor agonist used as an antihypertensive, is superior to placebo in the control of hot flushes; however, side effects may hinder its use.

Phytoestrogens comprise a category encompassing various substances obtained from plants and have, at least in part, an effect similar to that of endogenous estrogens. In fact, some authors prefer to call them phyto-SERMs, since such authors believe they would have properties more similar to tamoxifen and raloxifene than to the estrogens themselves. Isoflavones are the best-known representatives in this category and include substances such as daidzein and genistein, among others.

There is great diversity of study results regarding the effects on night sweats and hot flushes. Some show relief of such manifestations regarding frequency and severity with superiority to placebo, while others do not. Nevertheless, many of these studies are at a low-quality level and have small sample power. Commonly, studies with these substances reveal high rates of symptom reduction in the placebo group.

There seem to be no stimulatory effect of phytoestrogens on the endometrium. In the same line, there also appears to be no significant proliferative effect on the breast; however, the safety of such substances after breast cancer is unknown, so they are generally contraindicated in this situation.

Due to the insufficient evidence on the safety of phytoestrogens after breast cancer, Sobrac (*Associação Brasileira de Climatério* – Brazilian Association of Climacteric) and SBM (*Sociedade Brasileira de Mastologia* – Brazilian Society of Mastology) considered that such herbal medicines cannot be recommended as being safe to women who have had breast cancer, according to consensus meeting held in 2012.

Cimicifuga racemosa (St. Christopher's apple) is another herbal medicine used for the treatment of heat waves. Its predominant effect disregards estrogenic action; however, the significance of phytoestrogens present in such extracts is discussed. It seems that the use of extract of this plant is safe after breast cancer, but there is the need for further studies so that such safety can be guaranteed and, therefore, there is no official recommendation of its indication in this circumstance, according to the aforementioned consensus of the Sobrac and the SBM.

Hormone Therapy

Postmenopausal HT is considered the most effective treatment of climacteric symptoms. Estrogen, even at low doses, is quite effective in treating heat waves, night sweats, emotional manifestations, atrophic urogenital disorders, and skin alterations. It is also effective in the maintenance of bone mineral density, showing a lower occurrence of osteoporotic fractures in users of this type of treatment.

Women who have a uterus, that is, not hysterectomized, need a progestogen to counteract the proliferative effect of estrogen on the endometrium. Thus, there are several HT regimes available, which can be grouped as follows:

- Pure estrogen
- Estrogen and associated progestogen (HT combined)
- The combined sequential HT (continuous estrogen and progestogen administered in sequences of generally 10–14 days per cycle or month)
- Continuous combined HT (estrogen and progestogen administered daily)
- Tibolone
- Local (vaginal) estrogens

One of the biggest concerns with HT refers to the risk of developing breast cancer. After 3–5 years of combined HT use, there is an increase in the number of diagnosed cases of breast cancer.

According to the Women's Health Initiative (WHI) study, in the only randomized study that evaluated the risk of breast cancer related to HT, five or more years of combined HT were associated with the addition of eight new cases per 10,000 women/year. It is not possible to tell if there is a difference between the continuous and sequential schemes in this question. It is relevant to mention that these results refer to the US population, known to be at higher mammary risk, under the use of HT composed of conjugated estrogens and medroxyprogesterone acetate. In other populations, the risk should also increase, but it is difficult to say if the same magnitude would be found. Other oestro-progestative HT compositions, as well as alternative routes of hormonal administration other than oral, were not evaluated by the WHI study.

It is important to point out that unlike the endometrium, progestogen does not protect the breast against cancer; on the contrary, it increases the risk. Proof of this is that the same WHI study did not reveal an increased risk of developing breast cancer with estrogen alone. Indeed, in the isolated estrogen branch of the WHI there was a reduced risk of developing breast cancer when the analysis was restricted to women adhering to the treatment.

This does not mean that estrogen alone does not cause increased breast risk, since observational studies showed a small increase in risk. The Million Women Study (MWS), for instance, showed that estrogen alone also causes an increased risk of breast cancer, but of a magnitude lower than the combined HT. According to this study, the cumulative rate of breast cancer at age 65 increased from about 50 to 51.5 per 1000 women as a result of estrogen therapy alone for 5 years and from about 50 to 56 per 1000 women due to HT combined also for 5 years.

HT after breast cancer is still a controversial issue, as two important studies have shown opposite results, one revealing an increased risk of recurrence of the disease using HT and another not, both of which were interrupted before the originally planned duration. Therefore, there is insufficient safety to indicate the use of this treatment after breast cancer and, therefore, international and national societies contraindicate HT in this situation.

On the other hand, cervical cancer is less frequent in HT users. Endometrial cancer also presents a lower risk in users of HT combined.

Regarding general (all-cause) mortality, the WHI study itself showed a trend toward a reduction in both estrogen alone and combined HT of around 30%, although not statistically significant, for women who started treatment shortly after menopausal women under 60 years of age.

Tibolone, in turn, is a form of HT, but with peculiar characteristics. This substance is a weak progestogen; however, its metabolites have estrogenic and androgenic actions, and, of course, the progestogenic effect itself. In addition, they may interfere with enzymes associated with the formation of estradiol from weaker estrogens in some tissues, for instance, in the breast. Several studies have shown the absence of stimulating effects of breast tissue on this steroid, which has raised the

possibility of its use after breast cancer. Nevertheless, a study published in 2009, known as *Livial Intervention following Breast Cancer: Efficacy, Recurrence, And Tolerability Endpoints* (LIBERATE), revealed a higher rate of relapse of the disease in the group of users of this steroid. Therefore, its use should be contraindicated for women who have had breast cancer.

In contrast, another randomized study with this drug, published in late 2008, the Long-Term Intervention on Fractures with Tibolone (LIFT), which primarily evaluated the fracture rate in women over 60 years of age with osteoporosis treated with low-dose tibolone, revealed a reduced risk of developing breast cancer in the steroid group. However, years earlier, the MWS observational study had shown increased risk.

Combining the results, one cannot be sure if tibolone is actually associated with a lower risk of developing breast cancer in women of medium population risk. On the other hand, if the cancer has already occurred, its use promotes higher rates of recurrence of the disease and its use is contraindicated in this circumstance. Nothing can be said if women who are at risk for breast cancer above the population mean would have some benefit or an increased risk from using the substance.

Topical vaginal estrogens are used primarily for the treatment of atrophic urogenital manifestations. In Brazil, there are two substances that can be used by this route:

(a) Estriol
(b) Promestriene

Once there were conjugated estrogens for vaginal use, it was discontinued, though.

It is necessary to differentiate the three substances, because conjugated estrogens are well absorbed through the vaginal route, providing systemic levels with endometrial effects. As a result, there may be endometrial proliferation and even uterine bleeding. Thus, if there is contraindication to systemic estrogen, for instance, as it occurs after breast cancer treatment, estrogens conjugated vaginally should not be used.

The effect of estriol on the improvement of urogenital trophism is well known. But when administered vaginally it can be detected systemically, that is, absorption will occur. That does not seem to stimulate the endometrium when administered by this route, though. Due to is absorption and if you do not know your breast safety after breast cancer, it is recommended to avoid it.

Promestriene is a synthetic estrogen derived from estradiol, but its absorption through the vaginal route is considered negligible, which causes its effects to be eminently local. In the literature there is contraindication of vaginal permethrin in contraindication to systemic estrogens—for instance, after breast cancer and endometrial cancer. It is important to report the inexistence of studies with such populations that attest security.

Due to the need to treat atrophic genital manifestations and contraindications to systemic estrogens, such as the cases they occur after breast cancer, the use of non-hormonal vaginal moisturizers is preferred. They are substances that adhere to the

vaginal mucosa and are able to retain moisture. They are usually applied twice a week and, unlike vaginal lubricants, their use does not coincide with sexual intercourse. Currently there are three compositions available:

(a) Polyacrylic acid
(b) Polycarbophil
(c) Hyaluronic acid

Recommended Reading

1. Baber RJ, Panay N, Fenton A. 2016 IMS recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016;19(2):109–50.
2. Kenemans P, Bundred N, Foidart JM, Kubista E, Schoultz B, Sismondi P, et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol. 2009;10(2):135–46.
3. North American Menopause Society. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24(7):728–53.
4. Pompei LM, Brenelli FP, Araújo Neto JT, et al. Tratamento dos sintomas da menopausa na mulher de risco para câncer de mama. In: Associação de Obstetrícia e Ginecologia do Estado de São Paulo. Recomendações SOGESP, vol. 3. São Paulo; 2016. p. 215–28.
5. Wender MCO, Pompei LM, Fernandes CE. Consenso brasileiro de terapêutica hormonal da menopausa. Associação Brasileira de Climatério (SOBRAC). São Paulo: Leitura Médica; 2014.

Metastatic Disease: Therapy and Palliative Care

Pedro Henrique de Souza and José Bines

Definition

According to the World Health Organization, palliative care is defined as: "Total and active care of patients whose disease is no longer responsive to curative treatment. Some factors are of the utmost importance: the control of pain and other symptoms, such as psychological, spiritual and social."

Currently, the concept of palliative care is based on a multidisciplinary approach to the quality of life of the patients with metastatic disease, in order to contemplate their diverse needs from the moment of diagnosis of advanced disease, and not only in terminal situations. Randomized clinical trials comparing standard oncologic care versus standard oncologic care associated with palliative care show gains in several domains, including overall survival, incidence of depression, improved quality of life for patients and caregivers, reduced use of resources, and reduced costs resulting from fewer hospitalizations for end-of-life care.

In the treatment of the patient with metastatic neoplasia, the main objectives are:

1. To optimize the quality of life, with adequate palliation of symptoms
2. To increase survival, which in recent years has been achieved due to significant advances in cancer diagnosis and treatment, including chemotherapy, hormone therapy, and biological therapies

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Approaching Metastatic Disease

Whenever possible and safe for the patient, confirmation of metastatic disease through biopsy is advisable. The biopsy of the metastatic disease can alter both the prognosis and the treatment, making it possible to direct the treatment according to the characteristics of the metastatic disease.

Several studies show discordance between the primary tumor and relapsed disease, with changes in the hormone receptor profile ranging from 3% to 60% (change in estrogen receptor from negative to positive), 7% to 31% (change in estrogen receptor positive to negative), and up to 11% discordance for HER2. The NCCN's latest Guideline recommends that biopsy, hormone receptor retesting, and also HER2 status should be done in first-relapse patients, especially in patients with either unknown or negative hormone and HER2 status. Less commonly, biopsy of the potential metastatic site may reveal a non-malignant disease or even a second primary tumor, especially if single lesions are found.

The profile of some tumors also favors more specific behaviors on recurrence. Lobular carcinoma, for instance, tends to recur more often on serous surfaces, presenting with pleural effusion, ascites, or leptomeningeal carcinomatosis; HER2-positive and triple-negative tumors usually have early relapses and present a higher incidence of cerebral metastases. Triple-negative tumors have the lungs as the first site of distant metastasis, while bones are the most usual site of distat mestastases in the non-triple-negative tumors. The biological behavior of the disease should always be considered for the choice of systemic treatment. In more aggressive disease and with visceral metastases, systemic treatments that induce faster responses are sought whenever possible.

Median survival in stage IV breast cancer is 18–24 months, but more current studies have shown increased survival in recent years with the use of systemic treatment. The 5-year survival of patients with stage IV breast cancer at initial presentation is 22%. Young patients, with good performance status, without comorbidities, and with few metastatic sites (oligometastasis) may have a longer survival. It should also be noted that selected patients with metastatic disease should be evaluated for primary tumor surgery, although the literature is controversial in this regard.

Supporting Therapy for Metastatic Cases: Locorregional and Distant Metastases (Bony, Pulmonary, Hepatic, and Cerebral)

Patients with advanced disease may present with a wide variety of clinical conditions. The most common sites for distant metastases from breast cancer include the bone (more frequent), lung, liver, lymph nodes, chest wall, and brain. The symptoms of metastatic cancer are related to the location and extent of the tumor.

Table 1 Karnofsky scale

Rating	Performance status
100	Normal, no complaints
90	Able to carry on normal life, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most of his personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Table 2 ECOG scale

Grade	Performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Palliative treatment should include both systemic therapies (chemotherapy, hormone therapy, and target therapy) with early supportive care.

It is important that there is a homogenous language, both for therapeutic evaluation and for prognostic determination. Karnofsky (KPS) performance status scales Table 1 and Eastern Cooperative Oncology Group (ECOG) scales Table 2 (simplified version) are often used. Patients with KPS below 70 or ECOG PS greater than 2 have a more reserved prognosis.

Locorregional Disease

Local metastasis is common in breast cancer. The surgical approach should be encouraged for both diagnosis and local control. There is evidence of greater disease-free survival when relapse is amenable to complete resection. Whenever a local surgical approach is not indicated, systemic treatment and radiotherpy should

be discussed. In selected cases of locoregional advanced disease, resection of isolated sternal and chest wall involvement can be evaluated in order to provide good local control, pain palliation, prevention of bleeding, and infection.

Distant Metastases

Bone Metastasis

In bone metastasis, pain control with analgesics is essential. In addition to radiotherapy assessment, bisphosphonates such as pamidronate (90 mg IV every 3–4 weeks) or zoledronic acid (4 mg IV every 3–4 weeks) should be considered in order to avoid complications such as hypercalcemia and bone events (pathological fractures, bone pain, orthopedic surgery, and spinal cord compression syndrome). It is important to consider the possible side effects of bisphosphonates such as jaw osteonecrosis (rare event), renal failure, hypersensitivity reactions, muscle pain, and fever (usually within 24 h after infusion). More recently, denosumab (120 mg every 4 weeks) has been incorporated into the therapeutic arsenal for the treatment of bone metastases. Denosumab is a monoclonal antibody, RANKL inhibitor, subcutaneously administered and when compared to zoledronic acid it showed superiority in delaying or preventing bone events with a favorable toxicity profile, but at an increased cost.

Patients with severe bone pain or spinal cord compression syndrome should be evaluated for radiation therapy. Spinal cord compression syndrome is an oncologic emergency and should be treated immediately. Patients may present with pain, paresthesia with sensory level, fecal/urinary retention, and paresis of lower or upper limbs. The success of the results is related to the early diagnostic and the speed of the interventions. The usual treatment includes dexamethasone (4 mg of 6/6 h), analgesia, and radiotherapy. It should be emphasized that recent studies have demonstrated benefits in incorporating early surgery in the approach of spinal cord compression syndrome in selected patients.

Pleural and Pulmonary Metastasis

Neoplastic pleural effusions are commonly associated with breast neoplasm and the main symptoms are dyspnea, cough, and chest discomfort. Diagnostic and therapeutic thoracentesis should be considered, with a cytopathologic examination. Pleurodesis can be discussed after diagnostic confirmation, since recurrence of pleural effusion is high. Successful pleurodesis is able to prevent new interventions and control pleural effusion in 68–78% of cases.

Breast carcinoma has the capacity to spread to the lungs through the hematogenous and lymphatic pathways. Resection of pulmonary nodule(s) can be considered in selected cases. Carcinomatous lymphangitis has a reserved prognosis. Opiates, oxygen therapy, and corticosteroids may favor patient comfort.

Upper vena cava syndrome may be associated with metastatic breast neoplasm. The main symptoms include dyspnea (more common), cough, and chest pain; signs include facial edema, venous distention in the neck and thorax, cyanosis, and facial plethora. Treatment may include external beam radiotherapy and placement of endovascular stent for patients with severe symptoms.

Brain Metastasis

Another diagnosis that requires special care is brain metastasis. Factors associated with increased risk of brain metastases include young age, bulky tumors at initial diagnosis, increased number of axillary lymph nodes involved, high grade tumors, negative hormone receptors, HER2 positivity, and presence of lung metastases.

In the evaluation and definition of the treatment of patients with brain metastases, one must always consider factors related to the patients performance status, symptoms and whether the patient is able to tolerate surgery, as well as factors concerning the disease such as aggressiveness, estimated median overall survival, presence of extracranial disease, previous systemic treatments, number and size of lesions, location of lesions, extent of cerebral edema.

Surgery followed by irradiation used to be limited to patients with single brain metastasis. More recently, stereotactic radiosurgery (radiosurgery technique with a higher localized dose) extended the definition of limited disease up to four metastatic lesions. In these patients with “limited” disease, one should offer the greatest benefit of local control with stereotactic surgery associated or not with whole brain radiotherapy. In patients with multiple brain lesions, there is a preference for whole brain radiotherapy. Stereotactic radiosurgery may also be indicated in the presence of recurrence or small lesions localized in areas where surgery is more difficult. Recent studies have explored the broadening of the use of radiosurgery even in patients with more than four lesions and the suppression of whole brain radiotherapy (after surgery or radiosurgery).

In addition to the control of peri-tumor edema and intracranial pressure with corticosteroids (dexamethasone), seizures should be treated. There is, however, no indication for the use of primary prophylaxis with anticonvulsants routinely.

Breast neoplasm may also spread to the meninges with an extremely dire prognosis, a clinical condition called meningeal carcinomatosis. The main symptoms include mental confusion, behavioral change, seizure, and headache. Treatment includes palliation of symptoms and in selected cases, intrathecal chemotherapy or radiotherapy may be used.

Table 3 Evaluation and localized treatment of distant metastatic sites

Lung/ pleura	Dyspnea, pain, cough	Pleural effusion – thoracocentesis + or − pleurodesis Pulmonary nodule: surgery, in selected cases
Bone	Pain, paresthesia, paresis	Radiotherapy Surgery Bisphosphonates Denosumab
Liver	Nausea, fatigue, anorexia, fever, pain in the right hypochondria	Hepatic nodule(s): surgery/radiofrequency ablation in selected cases
Brain	Mental confusion, seizures, headache, paresthesia	Single lesion: surgery/radiosurgery +/− followed by whole brain radiation therapy "Limited disease" (up to four lesions): +/− radiosurgery followed by whole brain radiotherapy Multiple lesions (≥5 lesions): whole brain radiation therapy

Liver Metastasis

Liver metastases usually present as a disseminated disease and its treatment is systemic. Thus, resection of hepatic nodule(s) is an exceptional approach. When the clinical condition is symptomatic, possible complaints include anorexia, weight loss, nausea, abdominal pain, pain that irradiates to the right shoulder, fatigue, and fever. It is important to provide nutritional support and treatment with antiemetics, analgesics and, eventually antidepressants and neuroleptics.

In cases of liver failure, in addition to general care, prevention of infections and bleeding is important. Hepatic encephalopathy may be managed with lactulose (oral 90–150 mL/day) and adequate hydration.

Table 3 summarizes local approach to patients with metastatic breast cancer.

Oncologic Pain Treatment

Pain is a common symptom in patients with neoplasia. Approximately two-thirds of advanced cancer patients experience moderate to severe pain at some point in the course of their disease and up to 50% of patients report inadequate pain management. The main causes are the tumor itself (most common), followed by locoregional factors associated with neoplasia (e.g., muscle spasm, lymphedema, constipation) and treatment (surgery, chemotherapy, and radiotherapy). The knowledge of the types of pain, which are defined by neuroanatomical and neurophysiological mechanisms, allows a better therapeutic approach:

- Visceral pain: associated with damage to the nociceptors of the abdominal, pelvic, and thoracic viscera. It is poorly localized and associated with autonomic

symptoms (nausea, vomiting, and sweating) and usually has a good response to opiates.

- Neuropathic pain: a result of injury to the central or peripheral nervous system due to various causes, such as tumor infiltration (e.g., spinal cord compression), chemical injury (e.g., chemotherapy and radiotherapy), infection and ischemia. Symptoms may range from hypersensitivity, explosive pain, and burning sensation. Adjuvant analgesics (such as corticosteroids, anticonvulsants, and antidepressants) are needed in addition to opiates.
- Somatic pain: it is well localized and is due to the activation of cutaneous nociceptors or deep tissue. Common examples are musculoskeletal pain and postoperative pain.

Besides its origin, pain can be divided by its timing into *acute pain*, characterized by a definite time of initiation and by activation of the autonomic system (tachycardia, tachypnea, psychomotor agitation), and into *chronic pain*—when it becomes persistent and poorly delimited, usually associated with depression and anxiety.

The patients are the best ones to measure their pain and the best approach is based on the information they provide. The Visual Analogue Scale (VAS), in which zero corresponds to the absence of pain, 5 to moderate pain and 10 to the highest pain level, represents an excellent model in the follow-up of pain treatment (Fig. 1). It should be used at every appointment.

The World Health Organization (WHO) has laid the foundations for pain management and recommends that the treatment must be done incrementally according to the pain intensity (Fig. 2), in a strategy best known as WHO pain ladder. The control is preferably orally, on a regular basis, with the use of adjuvant analgesics and always considering the characteristics of the individual. It is important to emphasize that in patients with chronic pain analgesia should be done continuously and not only when there is increased pain. Constant reevaluation of response to medications is mandatory and the guidelines include rescue doses of short-acting analgesics in addition to regular medications. As an example, patients with severe pain may be instructed to receive strong opiates regularly, such as slow release morphine, and short-acting opioids for rescue doses (usually corresponding to 10% of the total daily dose).

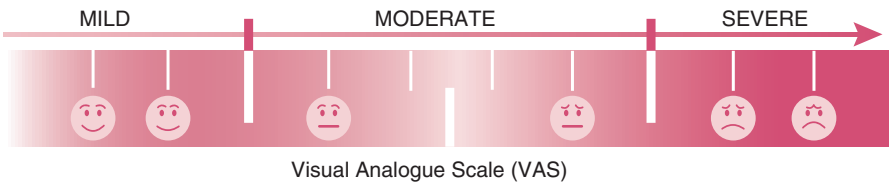

Fig. 1 Visual Analogue Scale (VAS)

Severe pain

Strong opioid (morphine, methadone, fentanyl, oxycodone) + adjuvant

Moderate pain

Non-opioid + weak opiates (codeine and tramadol) + adjuvant

Mild of moderate pain

Non-opioid (dipyrone, paracetamol, acetylsalicylic acid and non-hormonal anti-inflammatory – diclofenac sodium, diclofenac potassium and Tenoxicam) + adjuvant treatment (anticonvulsants, antidepressants and steroids)

Fig. 2 Treatment scale by WHO

Adjuvant analgesics include antidepressants such as amitriptyline, sertraline, and citalopram; anticonvulsants such as gabapentin (useful for neuropathic pain) and carbamazepine (lancinating neuropathic pain), as well as corticosteroids (cord compression, cerebral and hepatic metastases), and antispasmodics such as hyoscine (Table 1). Occasionally, patients may benefit from interventions such as neural blocks.

The prescription should include guidelines for the main side effects of analgesic medications such as the use of laxatives and antiemetics to control constipation and nausea/vomiting, often present with the use of opiates.

In recent years, other therapies have been studied such as the use of local anesthetics in trigger points, acupuncture, TENS (transcutaneous electrical nerve stimulation), anesthetic techniques (such as infiltration of anesthetics into nerve plexuses, placement of an continuous epidural catheter), and even the thalamic stimulation. These methods can aid in the well-being of the patient.

The oncological pain approach is multidisciplinary. In addition to the treatment directed to the cause (with systemic treatment, surgery, and radiotherapy) and directed drug treatment, the psychological evaluation should be considered, emphasizing the treatment of concomitant c, insomnia, and depression.

Analgesia for oncologic pain

Class	Types	Dose	Features	Side effects
Non-opiate analgesics	Non-steroidal anti-inflammatory drug (NSAID). Examples: tenoxicam, diclofenac sodium or potassium naproxen, ibuprofen	Tenoxicam 20 mg/day OR Diclofenac: 100–150 mg/day divided by 2 to 3×/day OR Naproxen: OR or RC 250–500 mg 2×/day to 1 g/day Ibuprofen: OR or RC 300 mg, 2 to 3×/day, up to 2400 mg/day	No tolerance produced	Gastric ulcer, gastrointestinal bleeding, renal failure, allergic reaction
	Basic analgesics: Paracetamol and Dipyrone	Paracetamol: 500–750 mg VO up to 4/4 h or 4000 mg/day Dipyrone: 1 g suppository RC up to 4×/day, 500 mg tablet or 1 mL = 50 mg – 500–750 mg OR up to 4×/day	No tolerance produced	Paracetamol: Rare acute liver failure Dipyrone: Agranulocytosis, rare allergic reaction
Soft opiates	Tramadol	200–400 mg/day OR and EV up to 600 mg/day. Divided in 4–6 h	There is an oral form associated with simple analgesic	Nausea, vomiting, dry mouth, headache and vertigo
	Codeine	15–60 mg every 3–6 h Maximum: 120 mg/day OR	There is an oral form associated with simple analgesic	Constipation and drowsiness

(continued)

(continued)

Class	Types	Dose	Features	Side effects
Strong opiates	Morphine	OR: Start 5–10 mg of 4/4 h. Increase according to need SC IV	Psychological dependence occurs rarely. Physical dependence is observed, but prevented with the orientation of non-abrupt discontinuity OR = 3 mg SC = 1 mg IV = 1 mg	Drowsiness, constipation, urinary retention, dry mouth, blurred vision, gastroparesis, pruritus, mental confusion, nausea, vomiting
	Fentanyl	TD: Changed every 3 days. Minimum 25 μg	When beginning, keep using morphine until effect starts, 12–24 h (100 × more potent than oral morphine)	Effects similar to morphine
	Methadone	2.5–10 mg a day every 3 or 4 h OR	Caution in elderly patients for long half-life (use of morphine less than 100 mg/day, conversion of methadone 1:5, use of morphine greater than 100 mg/day, conversion of methadone is 1:10)	Effects similar to morphine
	Oxycodone	10–40 mg 12/12 h OR	(1.5–2 times more powerful than morphine used orally)	Effects similar to morphine

TD transdermal, *IV* intravenous, *SC* subcutaneous, *OR* oral route, *RC* rectal

Palliative Measures for Terminal Patients

At this critical point in the course of the disease, the direct and empathetic communication to the patient and to his/her family is fundamental. In addition to the use of continuous infusion morphine, benzodiazepines such as midazolam or haloperidol may be added if the patient is confused or agitated. When the patient is on the verge of death, with difficult-to-manage pain or significant dyspnea, the use of terminal sedation should be considered. It is noteworthy that, unlike assisted suicide, sedation is intended to produce enough sleepiness to alleviate suffering, being potentially reversible. There is no evidence that sedation in patients in imminent death shortens life. No patient should die without adequate relief of their symptoms.

Recommended Reading

1. Bickel K, McNiff K, et al. Defining High-Quality Palliative Care in Oncology practice: an American Society of Clinical Oncology/American Academy of Hospice and Palliative Medicine Guidance Statement. J Oncol Pract. 2016;12(9):821–38. *Defining aspects needed for the operationalization of palliative care for oncological practice.*
2. Cuidados Paliativos Oncológicos – Controle da Dor- Instituto Nacional dos Importantes aspectos do cuidado paliativo com foco no tratamento da dor e da terminalidade. Câncer. 2001. http://www1.inca.gov.br/publicacoes/manual_dor.pdf.
3. Ferrell B, Temel J, et al. Integration of palliative Care Into Oncology care: American Society of Clinical Oncology Practice Guideline Update. J Clin Oncol. 2017;35(1):96–112. *Recommendations of the American Society of Clinical Oncology to integrate palliative care with standard oncology care.*
4. Guia com algoritmo de cuidados paliativos realizado por painel de experts no tema. Versão 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf.
5. Guidance for the treatment of oncologic pain in adult patients. Versão 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
6. Hawley P. Barriers to access to palliative care. Palliat Care. 2017;20(10):1–6. *An article describing barriers of access to the best palliative care and how to overcome them.*
7. Morrison E, Meier DN. Palliative care. N Engl J Med. 2004;350:2582–90. *Practical approach for palliative care based on a clinical case.*

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https://doi.org/10.1007/978-3-030-13636-9