



Breast cancer
OncoGuia
Update 2008



Clinical Practice Guidelines in Cancer in Catalonia



Breast cancer
OncoGuia
Update 2008



Agència d'Avaluació
de Tecnologia i Recerca Mèdiques



Pla Director
d'Oncologia



CatSalut

Servei Català
de la Salut

The Catalan Cancer Plan (CCP) is based on a comprehensive approach to cancer care, integrating the whole health care system and trying to meet all the health care and psychosocial needs of cancer patients.

In this way, the development and continuous updating of the OncoGuias, as a key element to use scientific evidence for clinical decision-making, is one of the strategies used by the CCP in order to promote both therapeutic equity and the best quality of cancer care.

The updating of this OncoGuia has been developed through an agreement with The Health Department of Catalonia and in collaboration with the Catalan Agency for Health Technology Assessment and Research (CAHTA), within the framework of the Plan de Calidad para el Sistema Nacional de Salud.

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PART I. ONCOLOGY CLINICAL PRACTICE GUIDELINES: PROCESS AND METHODOLOGY

PROCESS

General aims

The Department of Health of Catalonia has implemented the CCP in order to reduce the impact of cancer in Catalonia. The CCP states the promotion, planning, coordination as well as the evaluation of strategies and actions that have to be developed for different cancer areas. In this framework, the CCP develops measures for improvement of cancer care based on the best scientific evidence.

The OncoGuies are the key element used by the Catalan Cancer Plan (CCP) in order to promote equity of therapeutic access and quality cancer care. On the other hand, The Catalan Agency of Health Technology Assessment and Research (CAHTA), which is also a public institution of the Catalan Health Service (CatSalut), aimed to generate evidence based cancer care in order to ensure that those responsible for clinical decision-making can do so through the Catalan Health system. In this way, the CAHTA has a wide experience in the development and assessment of clinical practice guidelines.

These aims and goals were developed through an agreement to launch a joint program –the Clinical Practice Guidelines Program (OncoGuies) - defined by the basic attributes of quality, efficiency and transparency.

Contributors and users

The *OncoGuies* are intended to promote that patients with cancer receive treatments recommended by scientific studies and experts worldwide. To achieve this goal, it was decided that although CatSalut and the CCP would coordinate the *OncoGuies* project, health care professionals would be responsible for their content.

Participants in the project are selected as follows: representatives of tumor boards and medical oncology, hematology, radiotherapy and surgery specialists; medical specialists in respiratory diseases and digestive diseases, endoscopy, gynecology, plastic surgery, and thoracic surgery fields; and specialists from centralized services and pathology, radiology and nuclear medicine departments belonging to the network of subsidized hospitals for public utilization (*Xarxa Hospitalària d'Utilització Pública*). Participants contribute with clinical experience embodied in existing protocols for the main tumor types, and, in the *OncoGuia* development process, discuss and review the design of the clinical algorithms and the content of the guidelines until a consensus is reached in the final document. This part of the process is fundamental to establishing the interactive participation and consensus that ensures that the final document is the outcome of all the participants' inputs and that ownership is as much of the experts as of the institutions in charge of developing the project.

The *OncoGuies*, which are shaped and adapted to the Catalan health care context, are based on state-of-the-art scientific knowledge, reviews of international expertise, and the contributions of experts. They guarantee to the patients the best available treatment, irrespective of where they live; noteworthy in this regard, is the innovative aspect of standardized treatment. The *OncoGuia* reflect the values of equity of access to the best health care, protection of the best interest of the patient, and expert consensus.

Contents

The Breast OncoGuia, which covers clinical aspects of diagnosis, treatment, and follow-up, is for use with patients with suspected or diagnosed breast cancer.

The updated OncoGuia provides information as follows:

- ▭ Information on the support and methodology team and participating experts
- ▭ Table of contents
- ▭ Diagnostic, treatment, and follow-up care algorithms
- ▭ Explanatory text
- ▭ Information for patients
- ▭ References
- ▭ Appendices

This document forms part of the Breast OncoGuia, which includes:

- A full version
- A quick guide.

Changes to the previous version

Changes in explanatory text content with respect to the version for 2003 are indicated by a gray background. Modifications to algorithms are indicated by a pale yellow background.

Update

The general aim of this new Breast OncoGuia was to update the November 2003 version.

Specific aims were as follows:

- To update the recommendations of the November 2003 version of the Breast OncoGuia.
- To update evidence supporting recommendations and add quality ratings.
- To improve general layout and enable key recommendations to be easily identified.
- To propose a series of indicators.
- To include a section providing explanations and advice for patients with breast cancer.

None of the participants in the updating process have declared any conflict of interests, for both the period of involvement in drawing up the clinical practice guidelines and for the year prior to their declaration in this regard. The declarations were made by completing a standard form.

A committee of breast cancer experts has been appointed to oversee future updates to the Breast OncoGuia based on emerging scientific evidence. This committee will meet every 6 months, at the request of any of its members, or when necessary to

discuss any relevant developments.

Evaluation

Implementation of the recommendations will be assessed as follows:

- By evaluating adherence to hospital protocols.
- Evaluating cancer care practice processes and results using the cancer care indicators designed by the Institut Universitari Arideis Donabedian (Autonomous University of Barcelona) in conjunction with agencies for the evaluation of technology for medical research in Catalonia (AATRM), Galicia, and the Canary Islands (in a study commissioned by the Spanish Ministry of Health and Consumer Affairs to develop indicators and standards based on clinical practice guidelines aimed at improving cancer care processes and results (1). Of all the indicators developed in the above study, we chose those that correspond to the recommendations included in this guide (see Appendix 1).
- By evaluating in greater depth processes and results concerning particularly relevant issues and recommendations in cancer care such as the OCG recommendation on sentinel node biopsy.

METODOLOGY

Linking recommendations to available scientific evidence

The OncoGuia algorithms describe a series of diagnostic, preventive, and therapeutic interventions for different kinds of tumors. In deciding on intervention recommendations, account was taken of existing protocols, current clinical practice in Catalan hospitals, and opinions and arguments expressed by members of working groups in a series of open, scheduled meetings forming part of a structured work plan. The basic working methodology was the preparation, for debate, of preliminary drafts that were not considered definitive until a consensus was reached by the group of experts. The members of each working group made amendments to their draft recommendations (at or after their meetings) and these changes were further discussed at scheduled meetings.

For certain recommendations selected as being particularly relevant, two additional tasks were performed by the working groups. Firstly, each working group evaluated consensus in regard to the recommendation and then rated this consensus. Secondly, each group assessed available scientific evidence supporting the intervention and assigned it a category reflecting its quality, as agreed on by 2 experts.

Thus, the selected recommendations include a code that indicates the degree of consensus within the working group and occasionally a callout to a summary of the evidence. Included also is the result of an independent evaluation of the quality of the evidence by the 2 experts who reached a consensus.

Described below are the categories for consensus and for the quality of the scientific evidence available. The consensus categories were devised bearing in mind currently valid recommendations of the National Cancer Institute, the National Comprehensive Cancer Network, the Scottish Intercollegiate Guidelines Network, the Institute for Clinical Systems Improvement, and the Fédération Nationale des Centres de Lutte Contre le Cancer.

Table 1. Consensus categories

Category S	Standard. When the entire working group agrees on recommending a particular intervention within the specific context of the algorithm.
Category CO	Consensus option. When the majority (at least 90%) of the working group agrees on recommending a particular intervention within the specific context of the algorithm.
Category O	Option. When there are major discrepancies as to whether a particular intervention should be recommended or not and no majority consensus was reached by the working group.

Classification of available scientific evidence

Most of the classification systems currently in use rate quality of evidence according to potential sources of bias in any study that supports the efficacy of a proposed intervention. In broad terms, the strongest evidence is awarded to studies in which patients have been randomly assigned to different groups (typically, randomized controlled trials or meta-analyses of such trials), whereas the weakest evidence is awarded to studies reporting expert opinions but no hard evidence. Intermediate levels of evidence are assigned to analytical observational epidemiologic studies that include a control group (for example, cohort and case control studies), and observational studies without a control group (for example, case series).

Given the many scales available for grading existing evidence and the absence of unanimity in terms of establishing any one particular scale as a gold standard, we chose to use the widely used guidelines manuals drawn up by the National Institute for Health and Clinical Excellence (2). The instruments used were the Scottish Intercollegiate Guidelines Network (SIGN) scale to evaluate therapeutic intervention studies and the Centre for Evidence-Based Medicine (CEBM-OXFORD) scale to evaluate diagnostic intervention studies.

Occasionally the working groups were unable to identify evidence supporting important clinical aspects that are considered to be good practice point (GPP).

Table 2. SIGN scale for intervention studies

1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High-quality systematic review of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well-conducted case control or cohort studies with a low risk of bias and with a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Nonanalytic studies, e.g., case reports, case series.
4	Expert opinion.

Table 3. CEBM-OXFORD scale for diagnostic studies

Ia	Systematic review of level 1 studies.
Ib	Level 1 studies.
II	Level 2 studies and systematic reviews of level 2 studies.
III	Level 3 studies and systematic reviews of level 3 studies.
IV	Expert opinion.
Level 1	Blind comparison of the test with a validated reference standard in a suitably sized sample of patients.
Level 2	One of the following criteria is fulfilled: The population is not representative. The reference standard is unsuitable. Unblinded comparison of the test with the reference standard. Case control study.
Level 3	Two or more of the above criteria are fulfilled.

ONCOGUIA review

The final drafts of the OncoGuies were reviewed externally by the private cancer foundation ONCOLLIGA (Fundació Privada Lliga Catalana d'Ajuda Oncològica) and the AGATA GROUP (Associació Catalana de Dones Afectades de Càncer de Mama), who also reviewed the last version of this OncoGuia. The suggestions and contributions of these two entities were taken into account in the definitive versions.

AATRM implemented an external quality review of the OncoGuies using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument. Nonetheless, their agreement with the final content, which, ultimately, is the responsibility of the authors, was not necessarily implied.

Limitations of the methodology

Consensus classification

Generally speaking, no formal voting took place in the working groups; rather, the degree of consensus was assessed by the group coordinator, who noted the consensus for each intervention in turn. These provisional consensus categories were endorsed—or modified as appropriate—in subsequent meetings of the working group.

No specific method for interpreting the classification of available scientific evidence in terms of an actual recommendation for each intervention was defined, and no explicit criteria were defined for considering issues such as, for example, the extent of the benefit, iatrogenic risk, etc. Furthermore, no criteria were defined for costs or aspects related to the appropriateness of the interventions (for example, the complexity or the need for special monitoring). Some of these issues were, nonetheless, discussed by the working groups on the basis of occasionally contradictory evidence and this had a bearing on the final consensus. In the future, an appraisal will be made in regard to whether there is a need to modify the method for classifying available evidence in terms of recommendations and for classifying the degree of consensus.

Classification of available evidence

Susceptibility to bias was the main factor evaluated when rating the quality of a study supporting a particular intervention. The focus was on efficacy, but magnitude of benefit or doubts regarding the reliability of the system used to evaluate efficacy

(measurement accuracy) were not formally taken into account. Nor was a formal evaluation of the iatrogenic or toxicity risk associated with the intervention considered. Many of these issues, nonetheless, were raised in working group discussions and had a greater or lesser bearing on the final consensus in regard to recommendations for particular interventions. An appraisal will be made at some point in the future in regard to formally taking into account any or all of these issues in terms of classifying evidence or adjusting the strength of recommendations.

Another limitation of the methodology was that no explicit criteria were defined for identifying and selecting the scientific evidence supporting each intervention. For each intervention, members of the group of experts drew up a summary of scientific evidence supported by references, for discussion—and modification if appropriate—by the group. In some cases, scientific evidence compiled in other published clinical practice recommendations or guidelines was taken into account; in other cases, a systematic search was made of the literature.

SOURCES

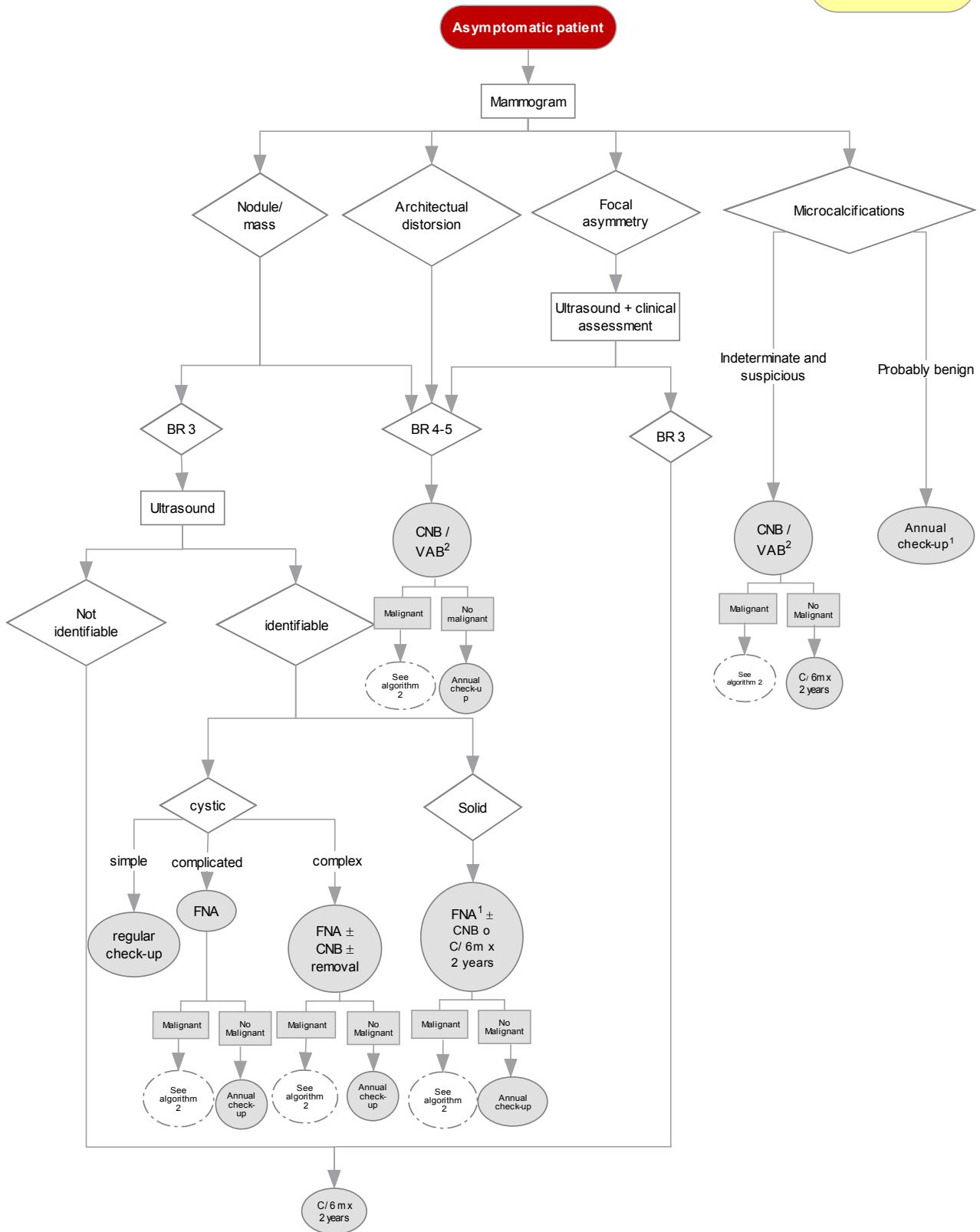
- Fédération Nationale des Centres de Lutte Contre le Cancer (www.fnclcc.fr/)
[FNCLCC]
- Institute for Clinical Systems Improvement (www.icsi.org) **[ICSI]**
- National Cancer Institute (www.cancer.gov/cancerinfo/pdq/) **[NCI]**
- National Comprehensive Cancer Network (www.nccn.org/) **[NCCN]**
- Scottish Intercollegiate Guidelines Network
(www.sign.ac.uk/guidelines/published/index.html) **[SIGN]**
- National Institute for Health and Clinical Excellence (www.nice.org.uk/) **[NICE]**
- European Society for Medical Oncology (www.esmo.org/) **[ESMO]**
- American Collage of Radiology (www.acr.org) **[ACR]**
- European Society of Breast Imaging (www.eusobi.org) **[EUSOBI]**
- American Joint Commission on Cancer (www.cancerstaging.org) **[AJCC]**
- International Union Against Cancer (www.uicc.org) **[UICC]**
- Cancer Care Ontario (www.cancercare.on.ca) **[CCO]**

PART II. BREAST ONCOLOGIA

ALGORITHMS

ALGORITHM 1A. INITIAL ASSESSMENT OF BREAST CANCER

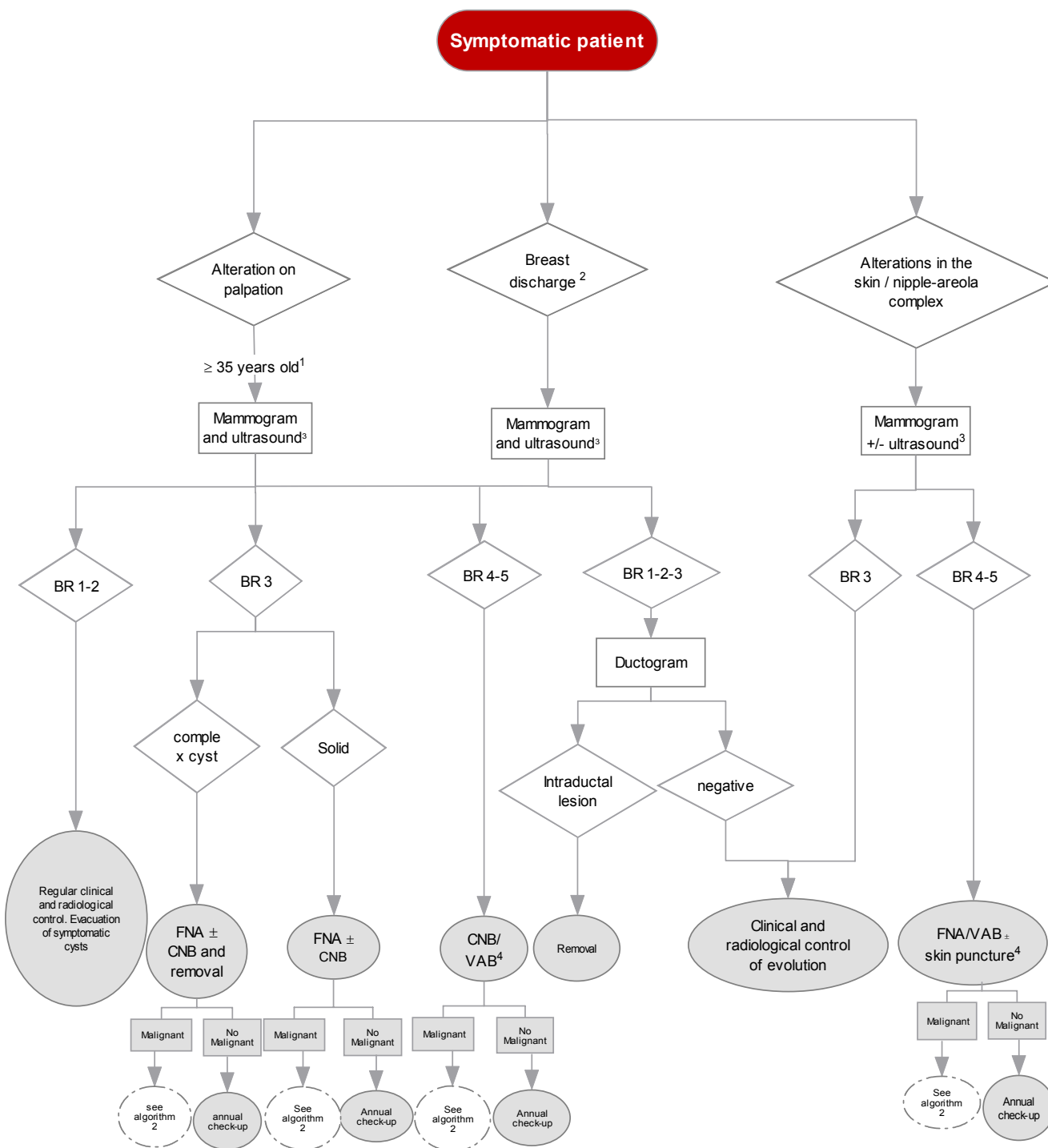
MODIFIED



Abbreviations: CNB, core needle biopsy; VAB, vacuum-assisted biopsy; FNA, fine needle aspirate cytology

1 Consider biopsy according to personal and history and the patient's clinical situation.

2 If the radiological and histological results do not concur, the histological study will be repeated and the use of magnetic resonance will be considered.



Abbreviations: CNB, core needle biopsy; VAB, vacuum-assisted biopsy; FNA, fine needle aspirate cytology

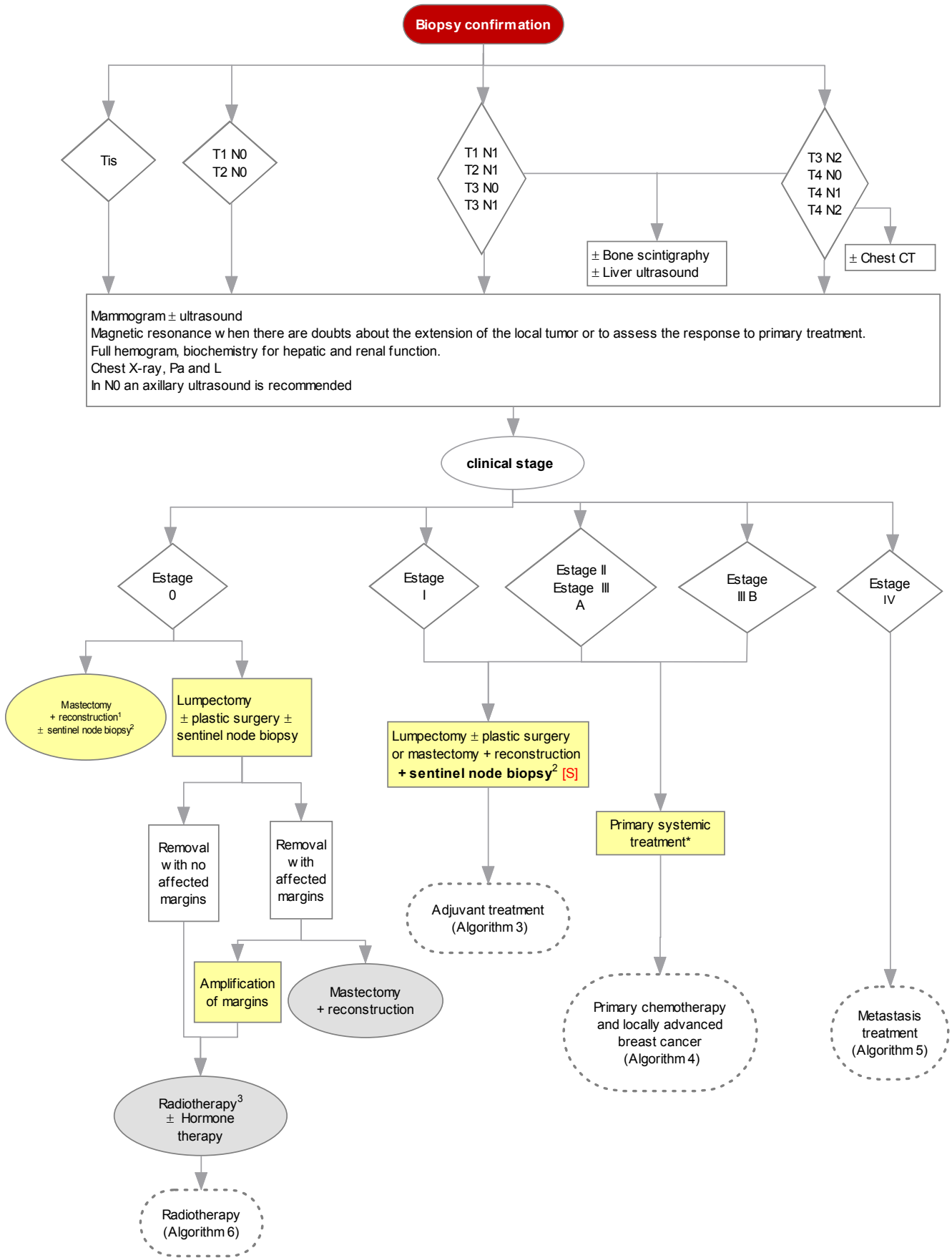
1 < 35 years. Initial ultrasound. BR 1-2, regular control; BR 3, c/ 6m o FNA; BR 4-5, include mammogram.

2 Breast discharge with study criteria

3 In all cases, the degree of clinical suspicion and the need for additional examinations (biopsy or magnetic resonance) will be assessed, if the normal imaging studies are negative.

4 If there is no concordance between the suspected cancer as diagnosed by clinical and radiological examinations and the histological result, the histological study will be repeated and magnetic resonance will be considered.

ALGORITHM 2. STAGING AND TREATMENT OF BREAST CANCER



Abbreviations: CT, computerized tomography, S, standard.

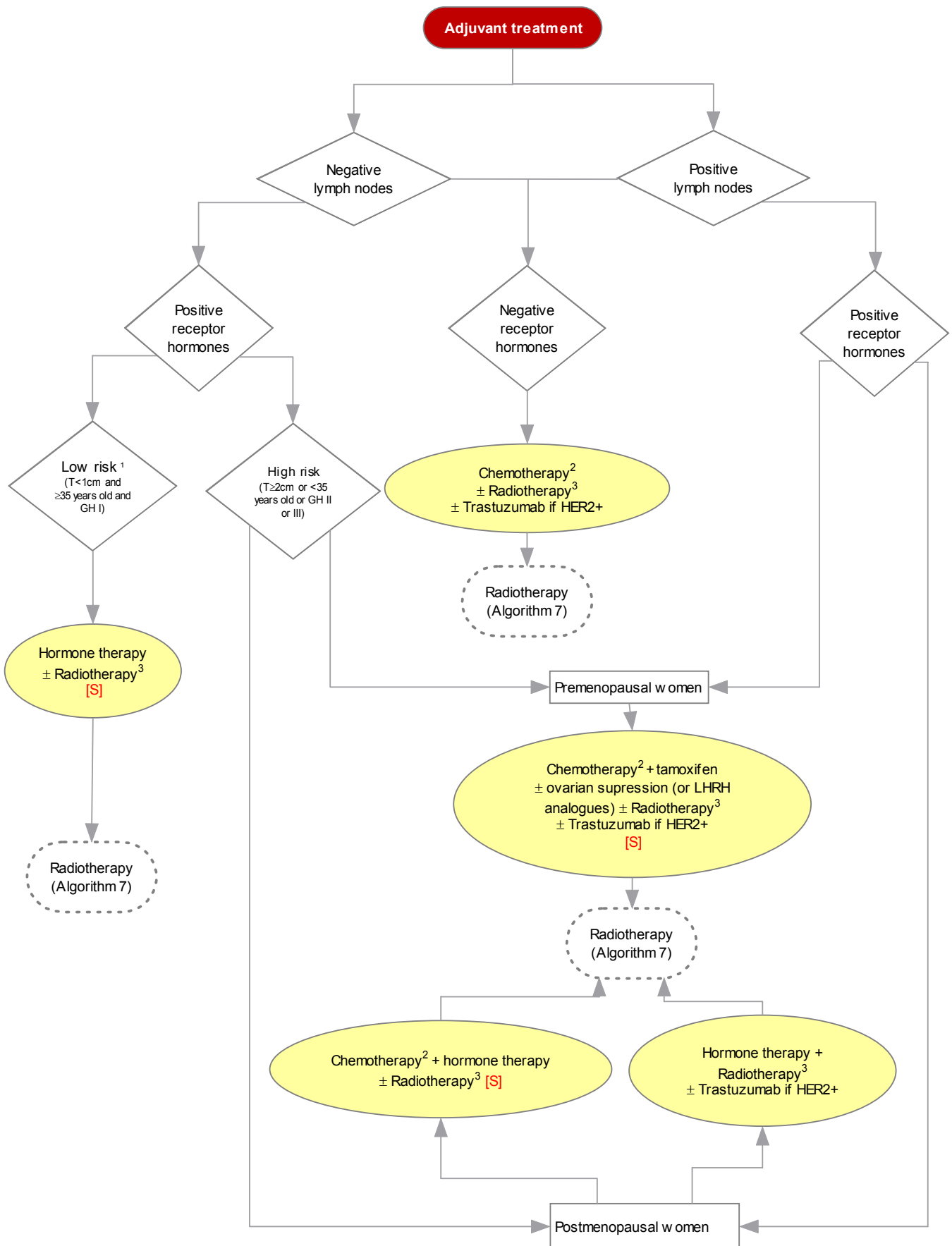
1 Preferably immediately

2 See text on indication criteria

3 See radiotherapy guidelines

* Consider carrying out a sentinel node biopsy before primary systemic treatment as a randomized clinical trial.

ALGORITHM 3. ADJUVANT TREATMENT

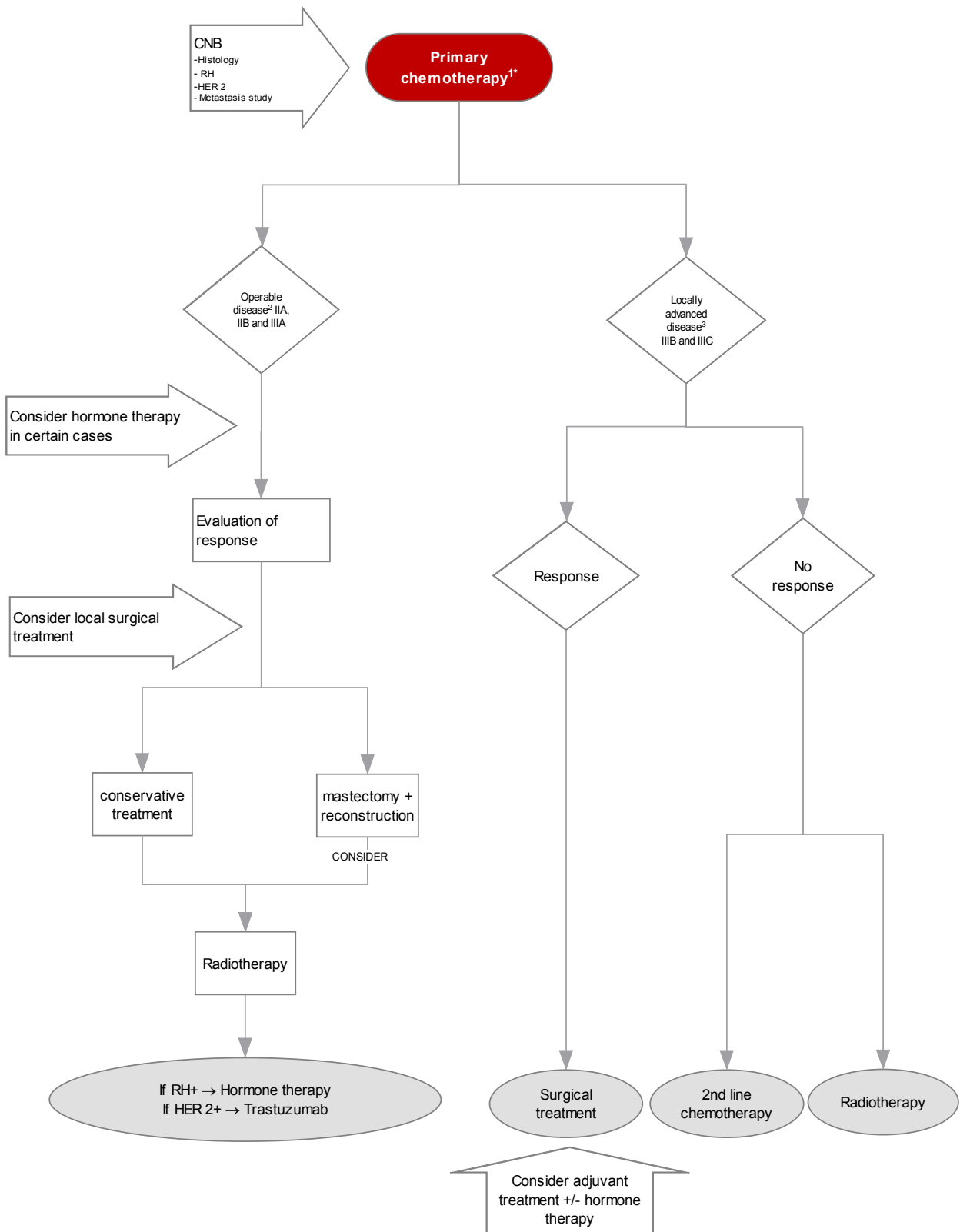


Abbreviations: S, standard.

¹ In pure papillary, colloid and tubular tumors, the risk is low

² See chemotherapy text

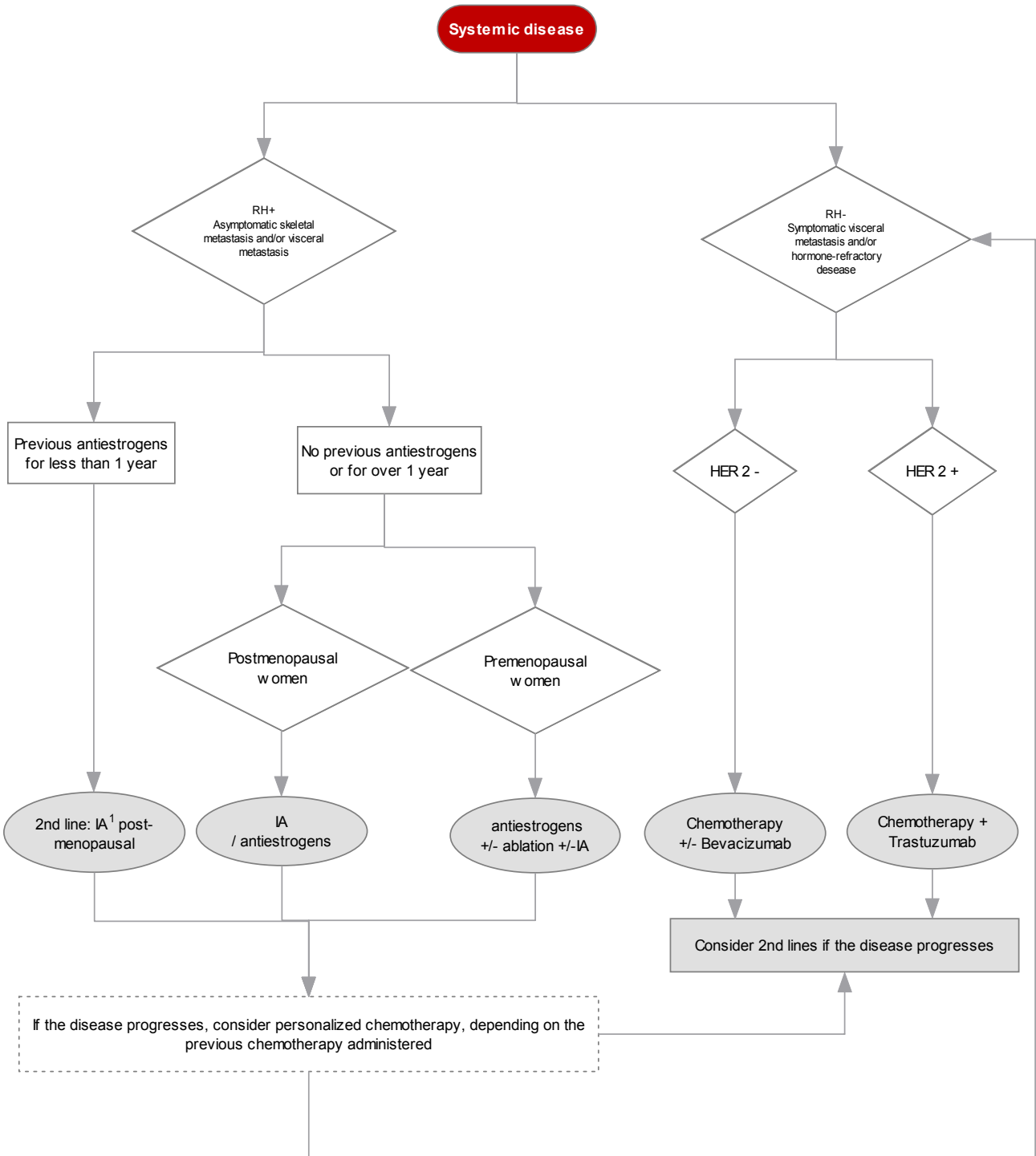
³ See radiotherapy text



1 Type of chemotherapy (see text); preferably sequential A-T (8 cycles) or combination A-T (6 cycles)
 2 Aim: conservative treatment
 3 Aim: operability
 *Sentinel node biopsy can be considered before systemic primary treatment in randomized clinical trials.

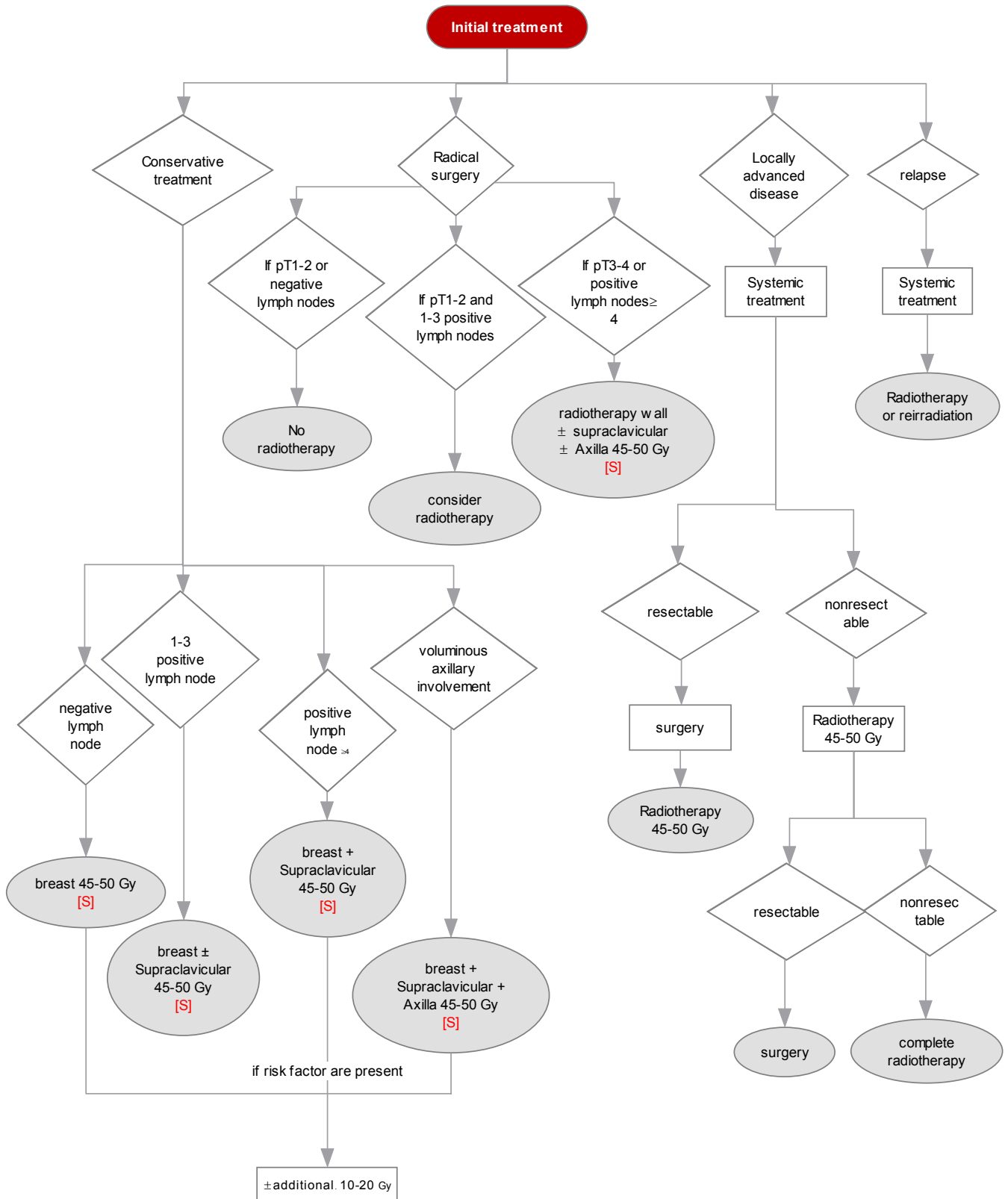
ALGORITHM 5. ADJUVANT TREATMENT

MODIFIED



1 Aromatase inhibitors

ALGORITHM 6. RADIOTHERAPY FOR BREAST CANCER



Abbreviations: S, standard.

¹ In case of (+) sentinel lymph nodes in the internal mammary, consider irradiating this chain.

INTRODUCTION AND EPIDEMIOLOGY

Breast cancer is the most frequent neoplasia among women and represents 30% of all cancers. In Catalonia in 2002, the crude incidence rate was 116.5/100,000 women and the age-adjusted incidence rate in the world standard population was 70.9/100,000 women. Breast cancer is the main cause of cancer death in women. Mortality increased until 1991-1992, and then decreased up to the present. The adjusted mortality rate rose from 17.8 cases/100,000 women in 1985 to 18.8 in 1995. It then dropped to 15.3 cases/100,000 women in 2002. There are several reasons for this change, including therapeutic advances and the introduction of measures for the early diagnosis of breast cancer. Five-year survival from breast cancer increased significantly to 75.9% in 1990-1994 and to 80.9% in 1995-1999 (3-5).

The main risk factors for breast cancer are related to hormonal, reproductive, sex, age and family history factors. Between 15 and 20% of new cancer cases are estimated to occur in a family with a history of cancer and from 5 to 10% of cases could be related to the inheritance of a genetic predisposition to the disease. The discovery of cancer-related genes has enabled carriers of an inherited predisposition to cancer to be identified, so that the risk can be defined and prevention behavior encouraged. In addition, specific screening can be undertaken in order to make early diagnoses (6-8).

GUIDELINES FOR SUSPECTED CANCER

The main aim is to obtain a pathological diagnosis of the lesion before therapy begins.

Studies of patients with suspected cancer should include the following tests: clinical examination, imaging and biopsy [S].

Evidence shows that the combination of these three investigations (the triple test) leads to higher diagnostic accuracy (9) [II], [SIGN] (10).

A. Clinical examination

A clinical examination is important, not only when clinical signs are the first evidence of a tumor, but also when imaging has detected suspected breast cancer in asymptomatic patients.

A clinical examination should consider the following (11):

- ▮ Breast cancer risk factors (personal, including obstetrics and gynecology; hereditary; and family).
- ▮ An assessment of pathological history and concomitant diseases that could influence the choice of therapy (12;13).
- ▮ A study of the clinical characteristics of the tumor: its size, the ratio between the size of the tumor and the size of the breast, the evolution time, localization, invasion of neighboring structures, multicentricity and the presence of adenopathy.
- ▮ Correct staging of the disease.

B. Imaging

Imaging begins with a standard bilateral mammogram [S].

This is complemented by additional views, ultrasound or other image analyses, if required (14-17) [III], [ACR(18)].

The assessment of the lesion should include the following parameters:

- Morphological description of the lesion
- Tumor size and localization
- Multicentricity/multifocality
- Degree of suspected malignancy

In order to standardize the language found in mammography reports, we will use the Breast Imaging Reporting and Data System (BI-RADS) [ACR](18). In this system, the lesion is classified into one of six categories and guidelines are provided on the action to be taken:

Table 1. BI-RADS categories

	Mammography	Action to be taken
1	Negative, no findings, normal	Usual monitoring
2	Benign. Benign finding	Usual monitoring
3	Probably benign	Follow-up after 6 months*
4	Suspicious abnormality	Undertake a biopsy of the lesion
5	Highly suggestive of malignancy	Undertake a biopsy of the lesion.
6	The biopsy results indicate malignancy.	

* A biopsy can be undertaken if the patient cannot attend the 6-month follow-up, is anxious or presents a high risk of breast cancer.

When the lesion under study is palpable, a radiological examination should be carried out before a needle biopsy is undertaken, to ensure that the morphological characteristics of the tumor are not altered (hematoma) [S].

The following radiological examinations should be undertaken: mammogram and ultrasound (19-21) [II] [ACR].

In patients under 35 with palpable lesions, the radiological examination should begin with ultrasound [S].

Due to the low incidence of cancer in patients under 35, the lower sensitivity of mammography for detecting malign lesions and the higher risk of developing malign lesions due to radiation, some authors and scientific societies such as the ACR recommend beginning a radiological examination with ultrasound. If necessary, a mammogram can be carried out subsequently (21-23) [III] [ACR].

In cases of breast discharge (from one orifice, spontaneous and unilateral) that can be studied, a cytology sample of the secretion is taken and a radiological examination is carried out with a mammogram, ultrasound and ductogram of the affected duct (24;25) [II].

C. Biopsy

[ESMO(26)], [SIGN(10)]

The aims of biopsy are to characterize the tissue in a lesion, using cell samples that are obtained by fine needle aspirate cytology (FNA), and to study the histology of tissue that is attained by means of core needle biopsy (CNB) or a vacuum-assisted biopsy (VAB) [S].

CNB is more sensitive and specific than FNB in the diagnosis of breast lesions. However, in the hands of expert cytopathologists, the low cost, the rapid diagnosis and the fact that it is one of the triple test assessments make FNA a valid diagnostic tool.

VAB is more sensitive and specific to microcalcifications and parenchymal distortions than the other techniques.

FNA can be complemented by CNB/VAB if the sample is inadequate, if there is variance in the triple test assessments, suspected carcinoma in situ, presentations of microcalcifications and parenchymal distortions and when prognostic tissue factors need to be assessed to establish the treatment (27-29).

Ultrasound is preferentially used to guide biopsies of lesions that are apparent with this technique.

Stereotactically guided CNB/VAB is used in lesions that are not apparent using ultrasound, such as microcalcifications, some nodules and distortions.

Magnetic resonance is used as a guidance method for lesions that are only apparent using this technique (30).

Assessment of the axilla

The state of the axilla at the time of the breast cancer diagnosis has significant prognostic value and can condition the initial therapeutic attitude (31-33).

The first assessment should be made by means of a systematic and thorough palpation.

An ultrasound examination of the axilla ipsilateral to the breast lesion is carried out in all diagnosed cases of extensive invasive carcinoma and carcinoma in situ. This represents another technique in the diagnostic algorithm of patients with suspected breast cancer [GPP] [S].

If an adenopathy is palpated, an axillary ultrasound should be carried out and a FNA guided by image techniques (34).

If the FNA is negative and the patient is a candidate for a sentinel node biopsy, this technique can be undertaken to diagnose node staging (35;36).

D. Pathological study

A cytological examination of samples obtained by fine needle aspiration biopsy (FNA) leads to a reliable diagnosis. Thus, surgical interventions are only required for treatment purposes. Cytology enables a rapid diagnosis of malignancy to be made, although it is not possible to distinguish between a carcinoma in situ and an invasive carcinoma. Depending on the sample, a study of different parameters can also be undertaken, including the nuclear grade, the hormone receptors (estrogens,

progesterone), proliferation (Ki 67) and the HER2 (immunohistochemistry and in situ hybridization of material in extensions or in the cell block), among others (37-39).

The cytology report should classify the lesion into one of the following groups:

- Cannot be assessed / insufficient material to make a diagnosis
- Benign
- Atypia
- Suggestive of carcinoma
- Indicative of carcinoma

Core needle biopsy enables a histological diagnosis to be undertaken. The following can also be assessed: tumor invasion into the stroma, the tumor histotype, the histological grade, the estrogen and progesterone receptors, the nuclear proliferation and molecular factors, such as overexpression and amplification of HER2 (CB-11, Herceptest, FISH, CISH), the amplification and detection of topoisomerase II, and the overexpression of Bcl-2 (40-47).

The histology report (see appendix) should be classified within one of the following groups (pending international consensus on standardization):

- Material of uncertain representativeness (an indication for a new biopsy).
- Specific negative (definitive diagnosis: fibroadenoma, fat necrosis, adenoma, granular cell tumor, etc).
- Non-specific negative (requires appropriate correlation between radiology and pathology: fibrosis, fibrocystic changes with microcalcifications, etc).
- Non-conclusive benign diagnosis (need for subsequent surgical biopsy not agreed by consensus: benign papillary lesions, fibroepithelial polyps with stromal hypercellularity, radial scars, columnar cell alterations and mucocele-like lesions).
- Atypical proliferative lesions (need for subsequent surgical biopsy agreed by consensus, apart from some exceptions: atypical ductal hyperplasia and intraductal carcinoma, lobular neoplasia, atypical adenosis).
- Diagnosis of specific malignancies: invasive carcinoma with histological subclassification, sarcoma, lymphoma, melanoma, metastasis, etc.

.....

PRETHERAPEUTIC EVALUATION AND STAGING

A physical examination is essential in determining the stage of the disease [GPP].

Firstly, for a primary tumor, a thorough inspection of the breast skin should be performed to assess the presence of skin disorders [S].

A radiological study of the breast by means of mammography, ultrasound and magnetic resonance (if this technique is available at the health centre) will aid assessments of the localization, volume and extension of a tumor. In addition, such analyses will enable the presence of multicentric lesions to be identified.

Indications for mri in preoperative studies

There is controversy in the literature on the indications for MRI in patients diagnosed with breast cancer, due to the advantages and disadvantages of the test. The advantages include the following:

- Very high sensitivity, close to 100% (48) [II]

- Better definition of tumor size than that obtained by mammography or ultrasound, which often underestimate the size of tumors that are larger than 2 cm (49;50) [II]
- Detection of ipsilateral focal carcinoma that are not apparent with other techniques in 10 to 30% of patients (51-53) [II]
- Better definition of the presence of an intraductal component than that provided by mammography (54;55) [III]
- Detection of contralateral disease in 5 to 24% of patients diagnosed with breast cancer (56-58) that is not apparent in other examinations (mammogram and ultrasound) in 75% of cases (59) [II]

The disadvantages of MRI are as follows:

- Low specificity (this is the greatest disadvantage), which leads to a high rate of false positives (53;60;61) [II]
- The possibility of overdoing the surgical treatment of disease, as focuses detected by MRI alone can be controlled with radiotherapy of the breast after a conservative treatment (62) [III]
- The high cost of the technique (62;63)
- The lack of availability in many health centers of the technique used to perform MR-guided biopsies
- The lack of randomized studies that demonstrate an increase in disease-free survival or overall survival due to systematically undertaking NMI when breast cancer is diagnosed (59)

Until randomized studies are published that define the role of NMI in patients diagnosed with breast cancer, the current conclusion, after a review of the existing literature, is as follows:

A preoperative MRI is recommended in patients diagnosed with breast cancer when a MR-guided biopsy can be undertaken after the test (59;62;64) [S].

The initial surgical strategy should not be changed if the suspicious focuses identified by MRI have not been confirmed histologically (59;60;65) [II] [S] [EUSOBI], [NCCN], [FNCLCC].

A preoperative MRI should be undertaken in patients diagnosed with breast cancer in cases in which a mammogram diagnosis would be difficult. This includes the following situations [S]:

- Dense breasts (59;60) [II]
- Diagnosis of invasive lobular carcinoma (59;66) [III]
- Paget's disease of the nipple (60;65) [IV]
- Axillary adenopathies that are positive for carcinoma, with no apparent disease using the normal diagnostic techniques (59;60;64) [II]

A study of the spread of cancer includes all of the complementary tests required to reject the possibility of metastatic disease. The risk of finding metastatic disease from the outset is related to tumor size (T) and lymph node involvement (N). Therefore, tumors larger than < 20 mm with no lymph node involvement have a low probability of metastatic disease at outset and there is no need to request a comprehensive metastasis study. However, in locally advanced breast cancer, the probability of metastatic disease is very high. In these cases, it is essential to undertake a complete metastasis study (see Tables 2 and 3). (67;68) [AJCC], [UICC].

Therefore, in all stages, a preoperative analysis is required that includes ALT, AST, gamma-GT and alkaline phosphate levels [NCCN](60). From stage IIA, a simple chest radiography (frontal and lateral) is justified, as well as a liver ultrasound and bone scintigraphy, regardless of the results of the preoperative analysis [NCCN](60).

In stages 0 and I, these tests will only be required in the case of clinical or analytical alterations that indicate metastasis.

Table 2. TNM definitions of breast cancer

PRIMARY TUMOR (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, ductal carcinoma in situ, lobular carcinoma in situ or Paget's disease of the nipple with no associated tumor. [Note: Paget's disease associated with a tumor is classified according to the size of the tumor.]
T1	Tumor 2.0 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1.0 cm in greatest dimension
T1c	Tumor more than 1.0 cm but not more than 2.0 cm in greatest dimension
T2	Tumor more than 2.0 cm but not more than 5.0 cm in greatest dimension
T3	Tumor more than 5.0 cm in greatest dimension
T4	Tumor of any size with direct extension to: a) chest wall or b) skin, only as described below
T4a	Extension to chest wall, except the pectoral muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
REGIONAL LYMPH NODES (N)	
Nx	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph nodes
N2	Metastasis to ipsilateral axillary lymph nodes fixed or matted or in clinically apparent (detected by imaging studies) ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes matted or fixed to other structures
N2b	Metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph nodes with or without axillary lymph node involvement, or in clinically apparent ipsilateral internal mammary lymph node and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph nodes with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph nodes with axillary lymph node involvement
N3b	Metastasis in ipsilateral internal mammary lymph nodes with axillary lymph node involvement
N3c	Metastasis in ipsilateral supraclavicular lymph nodes
PATHOLOGICAL CLASSIFICATION (pN)	
pNx	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathological study)
pN0	No regional lymph node metastasis histologically, and no additional examination for isolated tumor cells (ITC)
pN0 _(y-)	No regional lymph node metastasis histologically, negative immunohistochemistry
pN0 _(y+)	No regional lymph node metastasis histologically, positive immunohistochemistry, and no ITC cluster larger than 0.2 mm
pN0 _(mol-)	No regional lymph nodes metastasis histologically, and negative molecular findings (RT-PCR)
pN0 _(mol+)	No regional lymph nodes metastasis histologically, and positive molecular findings (RT-PCR)
pN1	Metastasis in one to three axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN1mi	Micrometastasis (larger than 0.2 mm but not larger than 2.0 mm)
pN1a	Metastasis in one to three axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by SNL dissection but not clinically apparent
pN1c	Metastasis in one to three axillary nodes and in internal mammary nodes with microscopic disease detected by SNL dissection but not clinically apparent
pN2	Metastasis in four to nine axillary lymph nodes or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph nodes
pN2a	Metastasis in four to nine axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastasis in clinically apparent internal mammary nodes in the absence of axillary lymph node metastasis
pN3	Metastasis in ten or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes or metastasis in the ipsilateral supraclavicular lymph nodes.
pN3a	Metastasis in ten or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent in internal mammary lymph nodes.
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes
Distant metastasis (M)	
Mx	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 3. Stage groupings

Staging	
Stage 0	Tis N0 M0
Stage I	T1 N0 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
Stage IIIB	T4 N0 M0 T4 N1 M0 T4 N2 M0
Stage IIIC	Any T N3 M0
Stage IV	Any T Any N M1

TREATMENT OF BREAST CANCER: STAGES I - III

Breast cancer can be divided into two groups: intraductal carcinoma, in which the growth of neoplastic cells is confined to the ducts and there is no stromal invasion, and invasive carcinoma, in which stromal invasion is observed and therefore there is a risk of metastasis in the axillary lymph nodes and other organs.

Carcinoma in situ

- **Lobular carcinoma**

The recommendation is removal of the lesion and patient follow-up [S].

Lobular carcinoma in situ is currently considered an indication of a risk of developing breast cancer (in any quadrant and in either breast, regardless of the where the lesion is located). It is also considered a preneoplastic lesion. The overall 15-year risk of developing breast cancer is 21%, both in the form of invasive lobular carcinoma and invasive ductal carcinoma. However, invasive carcinomas have a good prognosis and rarely lead to death [SIGN](10).

One option that should be considered is the administration of tamoxifen for a five-year period [S].

Evidence shows that the administration of tamoxifen can reduce the risk of developing malignancy in patients with risk factors. The reduction in risk has been estimated as between 44 and 56%, according to the age group and the risk factors (69) [1+].

- **Ductal carcinoma**

The group of experts recommends removal of the lesion and radiotherapy [S].

Ductal carcinoma in situ is characterized by a proliferation of malignant epithelial cells within the ducts and lobules, with no stromal invasion observed in a routine study using an optical microscope. Ductal carcinoma in situ can present as a palpable nodule or as a non-palpable lesion that is detected by mammography, usually in the form of microcalcifications. Palpable nodules are rare and usually cannot be distinguished from invasive carcinoma. They were the most common clinical presentation before the widespread use of mammography as a method of early diagnosis. Currently, the most common presentation is non-palpable, which has

led to an increase in the use of mammography and the establishment of screening programs [SIGN](10).

For many years, mastectomy was the treatment of choice, as surgical removal of the lesion had a high percentage of local recurrence. However, several randomized studies have shown that the percentage of local recurrence is significantly reduced if radiotherapy is used in combination with lumpectomy [SIGN](10).

The most important prognostic factor for local recurrence is the resection margin. Margins with tumor involvement are linked to a high percentage of recurrence. In 50% of cases, recurrence occurs in the form of intraductal carcinoma, which should not affect the prognosis of the patient. However, in the other 50% of cases, the recurrence is in the form of invasive carcinoma.

In the case of extensive disease, a mastectomy followed by reconstruction is recommended, or a lumpectomy with plastic surgery techniques and radiotherapy [S].

Radiotherapy in combination with local removal reduces the number of invasive and non-invasive recurrences in the ipsilateral breast (70) [1+].

The axilla should be studied by sentinel node biopsy in cases of extensive carcinoma in situ (larger than 4 cm) and/or high-grade carcinoma in situ. [S]

Axillary dissection is not indicated for carcinoma in situ, given that an intraluminal lesion cannot invade the lymphatic space. However, around 5% of axillary lymph nodes are metastatic, due to carcinoma in situ of the breast and infiltration focuses that were probably not detected in the pathological study. Therefore, the study of the axilla by sentinel node biopsy is justified in cases of extensive carcinoma in situ (larger than 4 cm) and/or high-grade carcinoma in situ, as the likelihood of axillary involvement is highest in these cases (see sentinel node biopsy).

Complementary treatment with tamoxifen should be considered to prevent local recurrence and the appearance of contralateral cancer, as it has been shown to reduce the percentage of local recurrence, but not to improve survival in patients with overexpression or amplification of HER. (69;71) This decision should be taken in accordance with the patient and the risk and benefits should be assessed, taking into account the good prognosis of this disease.

Invasive carcinoma

• Surgical treatment

1. Conservative treatment

The randomized studies that compare modified radical mastectomy (removal of the mammary gland and axillary dissection) with conservative treatment (removal of the breast lesion with negative margins, axillary lymphadenectomy and radiotherapy) show that a conservative approach is the treatment of choice in any stage of the disease. Indications depend on the relationship between tumor size and breast volume. After a lumpectomy, the breast must be aesthetically correct. Lumpectomy is performed with a safety margin of at least 1 mm (microscopic).

The group of experts recommends conservative treatment for tumors under 50 mm, when the breast volume is such that surgery is likely to have a positive result [S].

Long-term results demonstrate that there are no differences in overall survival up to 20-year follow up. Local recurrence appears to be higher in the conservative treatment group, although the authors of a meta-analysis state that confounding factors may exist (72-76) [1++].

2. Lumpectomy with plastic surgery techniques

In cases in which a conventional conservative treatment cannot be performed, the option of preserving the breast with the assistance of plastic surgery techniques (oncoplasty) will be considered. In this situation, close collaboration is required between the radiologist, oncologist, pathologist, the radiation oncologist and the plastic surgeon. The aim of plastic surgery is to facilitate the preservation of the breast in cases in which a large lumpectomy or a hemi-mastectomy needs to be performed. These techniques obtain better aesthetic results than mastectomy with immediate reconstruction and morbidity is lower. The oncological criteria prevail, and the aim is to remove the tumor with wide safety margins. The resulting loss of volume is corrected by means of plastic surgery techniques. These techniques include patterns for breast reduction, breast remodeling and dorsal muscle or rectus abdominis flaps (77;78). Subsequently, radiotherapy is administered to the remaining breast tissue, according to the indications for conservative treatment.

3. Mastectomy

Over the years, the indications for mastectomy have been limited to a decreasing number of situations. With the knowledge that a mastectomy is not advantageous in terms of survival or local control of the disease, it is now only indicated in cases in which the treatment has not led to control of the disease or cases in which breast reconstruction would represent a risk for the patient's life.

3.1. Mastectomy with immediate reconstruction

When mastectomy is undertaken, immediate reconstruction can be performed in order to reduce the psychological impact.

Mastectomy with immediate reconstruction can be undertaken when the tumor affects a significant volume of the mammary gland, due to the ratio between tumor size and breast volume. This technique can also be performed in cases of multicentric disease, or other indications such as the possibility of avoiding radiotherapy, difficulty in radiological control or the wishes of the woman. It is also indicated when the skin or the nipple-areola complex is affected.

The most commonly used reconstruction methods are the transverse rectus abdominis muscle (TRAM) flap, tissue expanders, the wide dorsal muscle flap and microsurgical flaps of perforating vessels (DIEP(79)).

Expanders cause technical difficulties with radiotherapy.

3.2. Delayed breast reconstruction

This option should be offered to all patients who have undergone a mastectomy [S].

[NCCN], [SIGN](10)

There are no cancer stage-related contraindications for breast reconstruction. Contraindications are related to the patient's age and underlying pathology. There is no defined period of time after the primary treatment in which breast reconstruction can be performed.

The type of technique used depends on the individual case, and varies from fitting an expander that will later be replaced by a silicone prosthesis, to the use of an abdominal flap or mixed techniques that combine the use of a silicone prosthesis with a dorsal flap.

4. Surgery of lymph node areas

4.1. Sentinel node biopsy (80-82)

In recent years, the sentinel node technique has emerged as a valid option before axillary dissection. This approach to the axilla can be used in combination with a mastectomy or a lumpectomy. Axillary dissection can involve false negatives and significant morbidity (83-96)

Sentinel lymph node biopsy, which has a high negative predictive value, is indicated for tumors up to 3 cm, with certain exclusion criteria (recent axillary or breast surgery, previous radiotherapy or chemotherapy, multicentricity and multifocality of the tumor), according to the Spanish Salamanca and València consensus (2001) and that of Philadelphia (USA) (2001). It must be performed by multidisciplinary teams that are appropriately trained and have proven results (97-105). This option depends on the availability of a nuclear medicine center in the vicinity. One solution could be to create "itinerant" teams, made up of approved professionals who can guide staff in centers that have just introduced this technique. Another alternative is to allocate catchment areas to the centers that currently perform this technique.

Postoperative morbidity after sentinel node biopsy is much lower than that of lymphadenectomy. In health centers with experience, the rate of false negatives is below 5%. The real value of the sentinel lymph node in the internal mammary chain still has to be determined (although some cases have emerged in which there is metastatic involvement in this localization alone). The alternative to sentinel node biopsy is an axillary lymphadenectomy. However, within the aforementioned parameters (tumors < 3 cm), this is not considered the best option, as it may involve false negatives and the postoperative morbidity can cause lasting disabilities (92;106-109).

The sentinel node technique is recommended in patients with invasive carcinomas up to 3 cm in diameter **[S]**.

In the consensus meeting on selective sentinel node biopsy for breast cancer, held in Murcia on 24 November 2006 and presented with the support of Spanish Society of Senology (SESPM) in Madrid on 2 March of the same year, the following criteria were accepted for performing the aforementioned technique:

Indications for selective sentinel node biopsy

- 1) Invasive carcinoma of up to 3 cm in diameter (acceptable in T2 patients with negative axilla that who have been diagnosed clinically and with ultrasound, with or without fine needle biopsy).
- 2) It is possible in multifocal tumors and acceptable in multicentric tumors, although there is still limited evidence.
- 3) In cases of large intraductal tumors (> 4 cm) and/or high grade tumors and/or with comedonecrosis and/or tumors that require a mastectomy.
- 4) In male breast cancer, this technique has the same indications as in female breast cancer.
- 5) A prior excisional biopsy does not contraindicate this technique, if there are no exclusion criteria and if it is carried out after a month has elapsed.
- 6) It is acceptable, with sufficient supporting evidence, before primary systemic treatment, for rescue purposes in conservative treatment.

Exclusion criteria or contraindications for selective sentinel node biopsy

- 1) Preoperative verification of lymph node involvement by means of imaging studies (ultrasound) and, at least, cytology that indicates metastases of suspicious lymph nodes.

- 2) Previous surgery and/or radiotherapy.
- 3) Inflammatory carcinoma.
- 4) It is NOT indicated before primary systemic treatment in locally advanced carcinoma with therapeutic intent, or after primary systemic therapy, except in the case of specific clinical trials for studying and validating this technique.
- 5) There is NO evidence to recommend the test in pregnant women.
- 6) There is NO evidence to recommend the technique in cases of previous breast augmentation or reduction surgery.
- 7) There is NO evidence to recommend the technique in cases of previous conservative surgery with sentinel lymph nodes.

4.2. Axillary dissection

Axillary dissection is recommended in the following situations [GPP]:

- ~ When the axilla is positive for malignancy.
- ~ When sentinel node biopsy cannot be performed.
- ~ When sentinel node biopsy reveals metastasis.

In any case, axillary dissection will include at least levels I and II. [GPP]

According to various national clinical practice guidelines (CPG) on breast cancer, there is no consensus on how to treat the axilla in breast cancer patients. The NCCN (60) guidelines consider that axillary dissection is an option, but are awaiting data that demonstrate an impact on survival. This is in contrast to the SIGN group (10), which recommends this technique.

- **Systemic treatment**

1. Primary systemic treatment

The administration of primary chemotherapy is of benefit in Stages II, IIIA and IIIB and is considered a valid option [CO].

In the past, systemic treatment has been administered as an adjuvant. Likewise, although the correct sequence of breast cancer treatments has not been defined, in recent years the trend has been to begin systemic treatment before surgery.

Randomized studies have been published for Stages II, IIIA and IIIB and have shown the following (110-112):

1. Primary systemic treatments lead to an increase in the percentage of conservative surgical treatments [1+].
2. There are no differences in disease free survival between primary chemotherapy and adjuvant chemotherapy [1+].
3. After primary chemotherapy, patients have a lower rate of metastatic axillary nodes than patients who have not received this treatment.
4. Patients who have a complete pathological response to primary systemic treatment have better survival rates than those who do not respond. Therefore, response to such treatment is a prognostic factor.
5. Systemic primary treatment enables the study of different factors for predicting response that may be useful when the best systemic treatment is selected for each patient.

The most common scheme of treatment is sequences or combinations of anthracyclines and taxans. In postmenopausal diseases and in tumors with positive hormone receptors, primary treatment with hormone therapy does not decrease survival, but

increases the rate of conservative surgery (113-117) [1+] [CCO].

In the case of overexpression and amplification of HER2, several phase 2 studies have shown that the antitumor activity of trastuzumab increases when it is administered in combination or in sequence with chemotherapy (118;119) [1++].

Surgery is the indicated treatment once the response to primary treatment with chemotherapy or hormone therapy has been assessed. The most appropriate type of surgery (either lumpectomy or mastectomy) is selected on an individual basis. When feasible, a lumpectomy will be performed with an axillary dissection. Lumpectomy after systemic treatment must be adapted to the volume of the residual tumor, rather than the tumor size at the start of treatment. A metal clip can be inserted at the beginning of the treatment. In cases of a complete response, the clip will aid dissection of the area in which the initial tumor was located. If a complete response is shown by imaging, the breast segment indicated by the metal clip will be resected. In multifocal cases, a conservative treatment can be undertaken when the tumors are close together and the expected aesthetic result is good. In contrast, in multicentric cases, mastectomy and reconstruction are recommended.

2. Treatment of locally advanced breast carcinoma

Chemotherapy must be performed in patients with locally advanced carcinoma [S].

The aim of the treatment is to rapidly control the systemic disease and to improve control of the local disease, which facilitates the role of surgery and radiotherapy. The treatment involves sequences or combinations of anthracyclines and taxan (117) [CCO].

In the case of overexpression and amplification of HER2, several phase-2 studies have shown an increase in the antitumor activity of trastuzumab when it is administered in combination or in sequence with chemotherapy. (118;119)

Before surgery, the response to chemotherapy must be assessed with a mammogram or ultrasound. The same assessment technique will be used as in the initial study. The type of surgery that is indicated depends on the state of the tumor after chemotherapy. (120) The feasibility of preserving the breast using plastic surgery techniques will be assessed. If the response to treatment is not good or is insufficient to preserve the breast, the need for a second-line treatment before surgery should be assessed. This should be administered before surgical treatment so that the response to this second line can be evaluated. Subsequently, the surgery will be performed. At the end of chemotherapy, radiotherapy will be started to ensure local disease control (121).

After chemotherapy in patients with tumors that have positive hormone receptors, sequential treatment will be carried out with tamoxifen and aromatase inhibitors or aromatase inhibitors followed after 2/3 years by tamoxifen up to 5 years. [S]

3. Adjuvant systemic treatment

Adjuvant systemic treatment is recommended in breast cancer patients [S].

Several randomized studies and meta-analyses have conclusively shown the benefit of systemic treatments on the survival of breast cancer patients. [S]

This benefit has been demonstrated in tumors with positive lymph nodes [1+] and tumors with negative lymph nodes [1+].

Several conclusions can be drawn from these studies. With respect to the administration of adjuvant chemotherapy (122-125):

- The administration of polychemotherapy is more effective than monotherapy.
- The optimum duration of chemotherapy has to be adapted to the type of treatment chosen.
- Anthracycline regimens are slightly more active than CMF.

- Combinations and/or sequences of anthracyclines and taxans are clearly indicated in cases of positive lymph nodes. The indications in cases of negative lymph nodes still have to be defined (126).
- The doses of anthracyclines used do not lead to excessive cardiac toxicity in the long-term.
- The benefits of high dose chemotherapy in breast cancer have not been proved.
- There is little information on the benefits of adjuvant chemotherapy in patients over 70.
- The administration of hormone therapy after chemotherapy improves survival in tumors with positive hormone receptors (93;123) [1+].

Hormone therapy is recommended after chemotherapy in patients with tumors that have positive hormone receptors. [S]

- The recommended chemotherapy treatment includes the following standard alternatives:

Combinations that do not contain trastuzumab:

- FAC: 5-fluorouracil, doxorubicin and cyclophosphamide (127-129)
- CAF: cyclophosphamide, doxorubicin and 5-fluorouracil (130)
- FEC: 5-fluorouracil, epirubicin and cyclophosphamide (131)
- AC: doxorubicin and cyclophosphamide (125)
- AC followed by paclitaxel (132;133)
- EC: epirubicin and cyclophosphamide (134)
- TAC: docetaxel, doxorubicin and cyclophosphamide (135)
- A followed by CMF: doxorubicin followed by cyclophosphamide, methotrexate and 5-fluorouracil (136)
- E followed by CMF: epirubicin followed by cyclophosphamide, methotrexate and 5-fluorouracil (137)
- CMF: cyclophosphamide, methotrexate and 5-fluorouracil (138)
- AC with a stronger dose followed by paclitaxel (138)
- A-T-C with a stronger dose: doxorubicin followed by paclitaxel, followed by cyclophosphamide (139)
- FEC followed by docetaxel
- TC: docetaxel and cyclophosphamide (140)

Combinations that contain trastuzumab:

- AC followed by paclitaxel with trastuzumab (141)
- Docetaxel and trastuzumab followed by FEC (142)
- TCH: docetaxel, carboplatin, trastuzumab (143)
- Approved combinations of chemotherapy for at least 4 cycles followed by trastuzumab (144)
- AC followed by docetaxel with trastuzumab (142)

- Systemic treatment should begin preferably less than 6 weeks after surgery. [S]

With respect to the administration of adjuvant hormone therapy: (145-150)

- The decision to administer hormone therapy is taken when there are hormone receptors in the original tumor. Hormone therapy is not effective in tumors with negative hormone receptors.
- Immunohistochemistry is used to determine the presence of hormone receptors.

Results are considered positive when they are equal or higher than 10%.

- Tamoxifen is the most commonly used drug in adjuvant hormone therapy. Aromatase inhibitors (anastrozole, exemestane and letrozole), administered from the start or in sequence after tamoxifen, have shown greater benefits in reducing the risk of a relapse than tamoxifen alone in postmenopausal women with hormone-dependent tumors (116) [CCO].
- Ovarian ablation has benefits that are similar to chemotherapy treatments without anthracyclines in premenopausal patients. However, there is no evidence that the association of chemotherapy and ovarian ablation increases benefits. Combinations of adjuvant hormone treatments have not been studied.
- A tamoxifen treatment must last 5 years.
- The recommended hormone treatment options are as follows:
 - ~ In premenopausal patients, the following alternatives can be used as standards:
 - Tamoxifen: 20 mg/day for 5 years
 - Temporary ovarian ablation with LHRH analogues, administered for 2 years ± tamoxifen for 5 years
 - Definitive ovarian ablation with pelvic radiation techniques or surgery
 - ~ The following options apply to postmenopausal patients:
 - Tamoxifen: 20 mg/day for 3 or 5 years, followed by an aromatase inhibitor for 2 to 5 years (exemestane, letrozole, anastrozole)
 - Anastrozole or letrozole for 5 years (151-153)

In patients who undergo chemotherapy, hormone treatment will begin when the chemotherapy has been completed. In patients who receive chemotherapy and have tumors with positive hormone receptors, hormone treatment can be a valid alternative and, in premenopausal women, goserelin is recommended for 2-3 years with tamoxifen for 5 years. In postmenopausal women, aromatase inhibitors, as specified above, are recommended.

In patients with tumors who have overexpressed or amplified HER, treatment with trastuzumab and chemotherapy is recommended. **[S]**

In cases of overexpression or amplification of HER2, the addition of trastuzumab significantly reduces the risk of relapse and death. This benefit has only been demonstrated in women who have received adjuvant chemotherapy (141;142;144) [1+].

Trastuzumab should be administered for one year. However, the results of phase III studies will determine whether varying the duration of treatment increases the benefits (141;142;144).

Radiotherapy

Additional radiotherapy is recommended after conservative surgery in all patients, and after radical surgery in patients with a poor local prognosis. **[S]**

Several studies have shown that radiotherapy in addition to surgery reduces the relapse rate in the breast and the lymph node areas, and increases survival (154-157) [2++].

Additional radiotherapy must begin within six months of surgical treatment. (158;159) [2++]

If no adjuvant chemotherapy is administered, radiotherapy can begin from 15 day to a maximum of 2 months after surgery (160;161).

If systemic treatment is administered, it will depend on the scheme of treatment used:

↪ Anthracycline schemes. These begin 2-4 weeks after the last anthracycline cycle. Exceptionally, they can be administered concomitantly (162-164) [2++].

↪ Schemes without anthracyclines: these can be administered concomitantly (165;166) [2++].

If radiotherapy is performed after primary chemotherapy, it will be based on the stage of the worst prognosis: TN initial (clinical) or pTN postsurgical (pathological) [S] [GPP].

If radiotherapy is performed after reconstructive surgery, it will be carried out according to the same indications as the previous surgical treatment, regardless of whether this was conservative or radical. In general, a boost should not be administered, due to the difficulty of localizing the surgical field (unless it has been marked). Boosts are contraindicated in pregnancy and relatively contraindicated in cases of previous radiation and autoimmune or collagen diseases. (167)

1. Ductal carcinoma in situ

Radiotherapy of the breast (45-50 Gy) is recommended as a standard after conservative surgical treatment (168) [2++].

A boost can be administered in cases of insufficient margins or patients who are under 45 years old (169-171) [2++].

In cases of radical surgery, radiotherapy is not recommended. However, if margins are insufficient, radiotherapy of the thoracic wall can be considered (45-50 Gy) [GPP].

2. Lobular carcinoma in situ

Given that there is only a minimal risk of local relapse of lobular carcinoma in situ, radiotherapy is not recommended. [S] (172) [2++]

3. Microinvasive and invasive carcinoma

A series of volumes have to be considered in radiotherapy of invasive breast tumors following surgery:

↪ **Breast**. In cases of conservative surgery, radiotherapy of the breast is recommended (45-50 Gy) [1++]. It is also indicated in patients with advanced tumors that cannot be resected after neoadjuvant chemotherapy (45-54 Gy).

↪ **Boost of the surgical field**. A boost (10-26 Gy) is recommended in patients who are under 60 years old, or if the margins are insufficient (< 1 mm), or if there is an extensive intraductal component.

↪ **Tumor boost**. A tumor boost (20-35 Gy) is recommended in inoperable patients.

↪ **Thoracic wall**. In the case of radical surgical treatment, radiotherapy of the thoracic wall is recommended (45-50 Gy) as a standard in T3 or T4 patients, with the involvement of 4 or more lymph nodes, or insufficient margins. In this last case, a radiotherapy boost of the surgical field is recommended (10-20 Gy). If the patient has from 1 to 3 positive lymph nodes, radiotherapy of the thoracic wall has to be considered on an individual basis (45-50 Gy).

↪ **Supraclavicular region**. Radiotherapy is recommended (45-50 Gy) in the case of involvement of 4 axillary lymph nodes or more in the absence of axillary

lymphadenectomy with no study of the sentinel lymph nodes. In cases of involvement of 1 to 3 lymph nodes or insufficient lymphadenectomy, radiotherapy will be assessed on an individual basis (173-175). In the case of involvement of supraclavicular lymph nodes, they must be radiated, and a boost will be considered (10-30 Gy).

▬ **Axillary region.** Radiotherapy of the axillary region is only recommended (45-50 Gy) in the case of extensive disease (when the percentage of lymph nodes involved is equal to or greater than 75% or the lymph nodes affected are bigger than 1.5 cm), persistent disease, if no axillary lymphadenectomy has been undertaken or the results have been insufficient, and if the sentinel lymph nodes have not been studied.

▬ **Internal mammary region.** Radiotherapy (45-50 Gy) will be considered in the case of lymph node involvement at this level or in locally advanced stages.

Notes:

Hypofractionation can be considered in elderly patients with significant comorbidity(176).

Partial radiation of the breast is only considered in the framework of a clinical trial [NCCN](60).

TREATMENT OF METASTATIC DISEASE: STAGE IV

The presence of metastasis at the time of breast cancer diagnosis is not common; it occurs in less than 5% of all cases. However, the spread of cancer beyond the breast may be observed several years after the first diagnosis and treatment of the primary tumor, even if a complementary treatment has been administered. The development of systemic disease is highly variable: in some cases, survival is very short (a few months); in other cases, the course of the disease is very slow, practically without symptoms and life expectancy is longer. In general terms, average survival is around 24-36 months after diagnosis. Patients are rarely cured, although a small fraction do have an excellent response to treatment and an absence of disease progression for many years. The survival of such patients is almost the same as that of women of the same age without neoplasia (177).

The objectives of treating metastatic disease are to palliate symptoms, to increase the time to disease progression and, if possible, to increase survival.

These objectives are obtained by means of different therapeutic methods: hormone therapy, chemotherapy, targeted therapy, radiotherapy or bisphosphonate treatment. However, the combination of these treatments depends on the characteristics of the patient and the disease.

The following set of variables condition the treatment response: a) hormone sensitivity (defined by the expression of hormone receptors and the previous response to hormone treatment); b) overexpression or amplification of the HER2 gene; c) the disease free interval; d) the extension and localization of metastasis; e) the patient's age; f) the type of treatment that has been administered to date, whether this was complementary or for disseminated disease, and the response obtained in this latter case.

Hormone treatment

Hormone treatment can be administered in women who have a tumor with hormone sensitivity and minimum visceral involvement or a tumor with involvement of the soft and/or bone tissues. Tolerance of this type of therapy is

usually good and the probability of a response is around 50-60%, with an average response after around a year (177). In patients in whom the response is short, a second line and even third line response may be observed.

In premenopausal women, the recommended treatment is ovarian ablation or the administration of LHRH analogues with tamoxifen **[S]**.

Recently, a meta-analysis that included few studies and a relative number of diseases showed that more benefit is obtained when analogues and tamoxifen are combined (149) **[1+]**. However, no studies compare tamoxifen in monotherapy with LHRH analogues and tamoxifen. Although there is no evidence from randomized trials involving premenopausal women, some guidelines have proposed the use of a combination of LHRH analogues and aromatase inhibitors.

In postmenopausal women with metastatic hormone sensitive cancer, first-line treatment with third-generation aromatase inhibitors is recommended. **[S]**

In postmenopausal women, third generation aromatase inhibitors (particularly letrozole exemestane) have been shown to be better than tamoxifen in first-line treatment of hormone sensitive metastatic cancer (152;178;179) **[1+]**.

In postmenopausal women who have disease progression during an antiestrogen treatment, the administration of fulvestrant is as effective as anastrozole. (180;181) **[1+]** Consequently, it has been proposed as an alternative second-line treatment, although there is less evidence of the activity of this drug when the neoplasia has progressed during aromatase treatment.

In diseases with severe symptoms or rapidly developing metastasis or after the progression of two or three lines of hormone therapy, the use of chemotherapy is recommended **[S]** **[NCCN](60)**.

Systemic treatment

Chemotherapy treatment is beneficial in patients with tumors that are not hormone sensitive or that have the aforementioned, more aggressive characteristics. **[S]**

In cytostatic treatments, patients whose tumors present overexpression of the HER2 gene should be differentiated from those in which this gene is not overexpressed. In this latter situation (HER2 negative), different schemes of first-line treatment have been shown to have an effect. The combination of different cytostatics has a higher response index, in terms of disease-free time, than the administration of one drug. A meta-analysis published several years ago corroborated this fact and indicated that the use of anthracyclines led to an increase in antitumor activity (182) **[1+]**. Most studies have shown that a combination of anthracyclines and taxans has greater benefits than monotherapy with anthracyclines alone. At least one randomized study has shown an increase in the response index with a drug combination, although this did not lead to an increase in probability of survival or disease-free time. In some cases the treatment failed. In addition, the combination was associated with a higher risk of toxicity (183) **[1+]**. In addition, a randomized study that compared the sequential administration of adriamycin and docetaxel to the combination of both drugs showed that the toxicity, particularly of medullary cells, was less in the sequential group than in the combination group. However, the risk of tumor progression was not higher in the combined treatment group (184).

Different schemes of treatment have demonstrated clear antitumor activity, such as the combination of taxans and anthracyclines. Other alternatives include combinations of taxans with gemcitabine or with other cytostatic drugs (185).

There is no clear evidence on the number of chemotherapy cycles that need to be administered. Most studies of chemotherapy have suggested that treatment should be administered until there is evidence of progression or toxicity. However, there is a certain degree of controversy about the role of maintenance chemotherapy. An Italian study that randomized patients who received weekly paclitaxel or observation found no significant differences in the maintenance treatment (186). However, a study by the GEICAM group indicated that the time to progression was 4 months longer in a group treated with the addition of six cycles of pegylated liposomal doxorubicin than in a group that had not received maintenance chemotherapy (187). Nevertheless, there is no clear recommendation on the use of cytostatic maintenance treatments. In addition, in patients with tumors in which hormone receptors are expressed, there is no evidence from randomized studies of the benefits of administering maintenance hormone therapy after cytostatic treatment, even though this is a common practice.

If the disease progresses after the first-line treatment, the cytostatics that were not used in the first-line should be administered. A randomized study demonstrated the role of capecitabine combined with docetaxel in cases of progression after first-line chemotherapy. The combination was beneficial (188) [1+].

Treatment in her2 positive tumors

A combined treatment of trastuzumab with chemotherapy is recommended for patients who have tumors with HER2 amplification [S].

Currently, the monoclonal antibody trastuzumab can be administered in cases of tumors with HER2 amplification. This antibody has been shown to have a high level of activity. When it is administered as a monotherapy, a 13-20% response index is obtained with a 10-month duration of response (189).

Two randomized studies have shown that the combination of trastuzumab and chemotherapy with anthracyclines or taxans leads to a response index and time to progression that are much higher than in patients who did not receive antibodies (190;191)[1+]. However, the combination of trastuzumab and anthracyclines has been associated with an increased risk of cardiotoxicity. Therefore, ventricular function should be monitored periodically and the administration of the aforementioned antibodies should be temporarily or permanently halted. In all of the studies, the administration of trastuzumab in combination with chemotherapy was maintained until disease progression. In clinical practice, once the maximum effect of the combination has been obtained, the patient can be treated with trastuzumab in maintenance monotherapy.

If the disease progresses, one recommended alternative is to introduce a different cytostatic drug such as vinorelbine or capecitabine, or platin derivatives, among others (192) [1+]. However, the benefits of this treatment have not been demonstrated in randomized trials. Despite this, one randomized trial that compared the administration of lapatinib-capecitabine with capecitabine alone showed clear benefits of the combination, which is currently considered a standard treatment (193) [1+].

Other targeted therapies

More recently, studies have shown the role of a combination of bevacizumab and weekly paclitaxel as a first-line treatment in HER2 negative disseminated breast cancer. An increase in the response index and its duration has been observed, although no differences in survival were found (194) [1+]. Likewise, the combination of docetaxel and bevacizumab has also been shown to have greater benefits than docetaxel monotherapy. Even though the differences are slightly smaller in this case, the reduction in risk of progression is higher in the combined treatment group (195). Currently, different randomized studies are being undertaken with drugs aimed at therapeutic targets. Such drugs could provide alternatives for patients who can be offered personalized treatment, according to the biological characteristics of each tumor.

Treatment of specific localizations of disseminated disease

As mentioned above, treatment of advanced disease should be adapted to its presentation, to the biological characteristics of the tumor and the state of the disease. Specific metastatic localizations can benefit from the administration of palliative radiotherapy in the base of multiple bone or brain metastases.

When only one metastatic lesion is detected, removal is recommended [S].

When only one metastatic lesion is detected, removal is recommended for two reasons: firstly, to reject the possibility of a second primary tumor (for example, a high proportion of single lung nodules in patients with a history of breast cancer); secondly, because exeresis can be associated with an increase in time to progression, although this aspect has only been demonstrated in a randomized study on single brain metastasis. In this study, patients with a single brain metastasis were randomized to surgery and radiotherapy or biopsy and radiotherapy groups (196) [1+].

Finally, in the treatment of bone metastasis, biophosphonates, particularly zoledronic acid, have been shown to reduce the incidence of complications related to the progression of bone disease, as they reduce morbidity and have palliative benefits.

The administration of biphosphonates, particularly zoledronic acid and/or radiotherapy, is recommended in the case of symptomatic metastasis [S].

The treatment duration is not clearly established. In fact, some guidelines have recommended maintaining drug administration for as long as the state of the disease permits. However, most of the studies do not prolong treatment for more than 2 years.

On an individual basis, removal of the local tumor can be considered to avoid subsequent complications of local or distant growth. Systemic disease must be controlled in such cases.

LOCAL RELAPSE

Local relapse is defined as the reappearance of neoplasia in a region that has been treated with radical or conservative surgery. The diagnosis of local recurrence has to be documented histologically by means of a FNB or a biopsy. In cases of local recurrence after conservative treatment, a second primary tumor should be identified. This situation can be distinguished according to the location of the tumor. Once local relapse has been confirmed, complete staging should be undertaken to rule out the

presence of distant dissemination. All patients with invasive relapse are at risk of systemic relapse and systemic adjuvant treatment should be considered [OC4].

Two situations must be distinguished:

- a) Local recurrence in the site of the lumpectomy after conservative treatment.
- b) Local recurrence in the scar after a mastectomy.

Local recurrence after conservative treatment

Treatment is based on a modified radical mastectomy (mastectomy and axillary lymphadenectomy) [S].
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In selected cases, a new lumpectomy can be undertaken, when permitted by the volume of the recurrence. In some cases further radiation can also be considered.

Local recurrence after a modified radical mastectomy

When the lesion is single or when permitted by the number of skin nodules, the first option to be considered is complete removal of the lesion, depending on the volume of the disease. Once the removal has been carried out and if the patient has not already received radiotherapy, radiation of the surgical field and the lymph node chains must be considered.

In cases of diffuse recurrence throughout the site of the previous mastectomy, systemic treatment should be initiated according to algorithm number 4.

Several studies have demonstrated that local recurrence is indicative of systemic relapse. However, to date, in patients with local recurrence, the administration of a systemic treatment has not been shown to delay the appearance of distant metastasis.

REGIONAL RELAPSE

This is defined by the reappearance of neoplasia in the axillary, supraclavicular and or internal mammary lymph nodes, with a negative metastasis study.

If the axillary relapse can be treated surgically, the lesion is removed. The surgery is followed by radiotherapy of the axilla and of the supraclavicular region if these areas have not been previously irradiated. In the case of previous radiation, a second course of radiation must be assessed. In all cases, systemic treatment should be considered.

SYSTEMIC RELAPSE

The recommendation is to follow the criteria in algorithm number 5 for metastatic disease.

PATIENT FOLLOW-UP

The aim of follow-up is to diagnose local and systemic relapse, secondary neoplasias or to detect complications and toxicity due to the treatments. To date, the early diagnosis of relapse has not been shown to increase survival in these patients. Therefore, complementary tests such as thoracic radiography, bone scintigraphy or seric tumor markers are not justified (CA15.3 i CEA) (197-199). These tests will only be undertaken if the patient has symptoms that indicate that the disease has reappeared. The treatment of local relapse and secondary neoplasias, both in the breast and in different localizations, could influence survival. Therefore, according to the criteria of ESMO, the following is recommended: (200)

- Case history and physical examination every 3-6 months for the first 3 years, then every 6-12 months up to the fifth year, then every 12 months.
 - Bilateral mammogram after conservative surgery and contralateral mammogram in the case of radical surgery, every 1-2 years.
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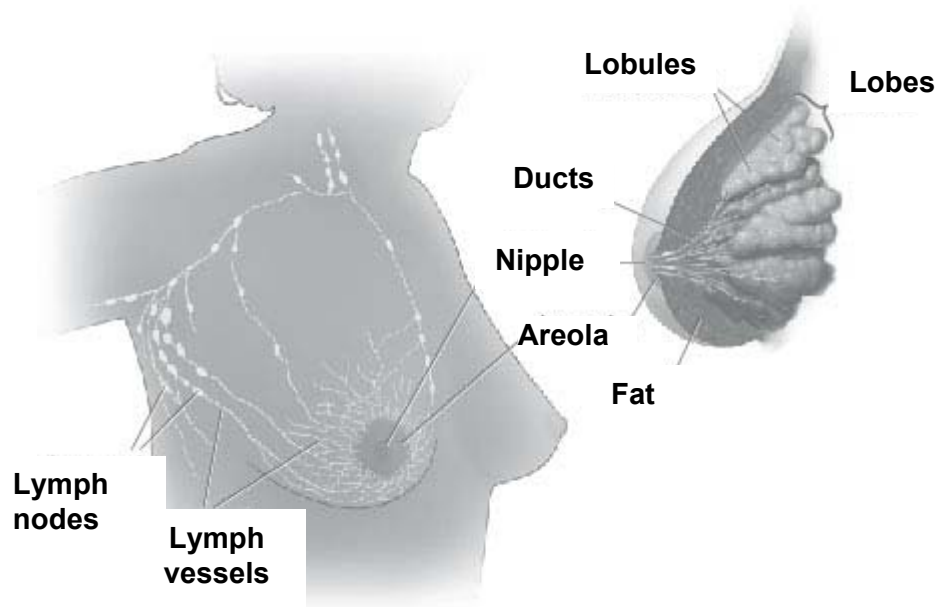
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PART III. INFORMATION FOR PATIENTS: BREAST CANCER

DEFINITION

Breast cancer is a malignant tumor that forms in the tissue of the breast.

The breast



The breast is located over the muscles that cover the ribs. It is mainly composed of adipose tissue (fat), which gives it consistency and volume. The breast is made up of lobes, which contain lobules, in which the milk-producing glands are situated. Small channels, called ducts, connect the glands, lobules and lobes. The ducts channel the milk to the nipple, which is in the centre of the areola (the darker area of skin that surrounds the nipple).

The entire breast is irrigated by blood and lymph vessels. The blood vessels carry blood to the cells. The lymph vessels form part of the body's defense system and are connected by lymph nodes, which trap bacteria, cancer cells and other damaging substances that are carried in the lymph, the pale liquid that circulates through the lymph vessels. The lymph nodes that are closest to the breast are in the axilla, the mammary artery and the supraclavicular area (above the collarbone at the base of the neck).

Breast cancer

The body's cells are the basic unit of life. They are grouped into tissues, which in turn make up the body's organs, such as the lungs, the liver, etc.

Normally, cells grow and divide to form the new cells that the body needs. When cells age, they die and are replaced by new cells. Sometimes alterations can occur in this cycle: the cells do not die when they should and go on to create new cells, so that the body ends up with more cells than it needs. These cells can form a mass or tissue that is called a tumor.

Tumors can be benign or malignant.

Benign tumors. These are not cancerous. Their cells do not invade other parts of the body. They can usually be removed and do not generally reappear.

Malignant tumors. These are cancerous. Cells in these tumors can invade nearby tissues or disseminate to other parts of the body. This dissemination from one part of the body to another is called metastasis.

Breast cancer can be found in different situations:

- **In situ.** This means that the tumor is located in the place where it arose, in the duct or the lobule.
- **Invasive.** In this type of cancer, the cells have broken through the duct or lobule and entered the breast tissue.
- **Lymph dissemination.** This occurs when cancer cells are transported to the lymph nodes via the lymph. The group of lymph nodes that is most commonly affected is that of the axilla.
- **Blood dissemination.** The blood transports the cancer cells to other organs. The most frequent are the bones, the liver the lungs and the brain. Thus, the cancer that is generated in these organs has the same type of cells as those in breast cancer. Therefore, such a disease is called breast cancer with bone metastasis. This is not a bone cancer. Therefore, it is treated in the same way as metastatic breast cancer.

CAUSES

The exact causes of breast cancer are unknown. Research shows that some women with certain risk factors have a greater probability than others of developing breast cancer.

A risk factor is any element that increases the chance of a person developing cancer. However, most risk factors are not the direct cause of the disease. Some can be controlled, e.g. smoking, whilst others cannot, e.g. age and hereditary aspects.

The following are considered to increase the risk of breast cancer:

Age. The risk of breast cancer increases with age. Most cases only appear around 50 years old. This disease is not common before menopause.

Family history. Women with a first-degree relative (mother, sister, daughter) who has or has had breast cancer are at greater risk of developing this disease. This risk may be higher if the woman has more than one first degree relative with breast cancer, particularly if the disease developed before menopause. These cases are related to genetic changes.

Genetic changes. Changes or mutations in certain genes increase the risk of breast cancer. BRCA1 and BRCA2 are the genes that are associated with greater risk. These mutations can be detected by a specific blood test. This test is not recommended for all women. It is only performed when requested by a doctor, particularly for women in families with the aforementioned characteristics.

Other risk factors are described below.

Personal history of breast cancer. Women who have had breast cancer are at greater risk of developing a tumor in the other breast over time.

Changes to the breast. Sometimes biopsy detects abnormal non-cancerous cells. This is called atypical hyperplasia and increases the risk of cancer.

Exposure to estrogen. Estrogen is a female hormone that controls the development of secondary sexual characteristics, such as breast development. The production of estrogen decreases after menopause. Some studies show that long-term exposure to estrogen can increase the risk of breast cancer.

- Women who had their first menstruation before they were 12 years old or menopause after they were 55 are at greater risk, as they have been exposed to estrogen for longer.
- Women who had their first child when they were over 30 years old.
- Women who have never had children.
- Women who use hormone replacement therapy during menopause.

Radiotherapy. In women under 30, the use of high doses of radiation for specific treatments increases the risk of developing breast cancer in later years. For example, the risk is higher in women who have been treated for non-Hodgkin lymphoma with chest radiation.

Lifestyle factors. As in other types of cancer, studies continue to show that various lifestyle factors can contribute to the development of breast cancer, such as:

- Excess weight or obesity after menopause
- Lack of physical exercise
- Overconsumption of alcohol

SYMPTOMS

There are rarely any symptoms in the early stages of breast cancer. These stages are normally diagnosed when a woman is in a screening program or when a mammogram is undertaken for a different reason.

The most common symptoms are as follows:

- The appearance of a lump in a breast that was not there before
- The appearance of a lump in an armpit
- A change in the size of one of the breasts
- An irregular breast outline
- Alterations in the breast skin: changes in color, orange peel skin, sores
- Changes in the nipple: inversion, fluid secretion
- Less mobility in one of the breasts when the arms are raised

These symptoms can be caused by other health problems. If they appear, consult your doctor so that a diagnosis can be made as soon as possible.

DIAGNOSIS

Diagnostic tests

Several different tests are used to diagnose cancer and to determine whether it has spread to other organs. Not all of the tests can be undertaken on every individual, as

they depend on factors such as age, state of health, the type of cancer, the severity of the symptoms and the results of previous tests.

The following tests can be used for breast cancer diagnosis:

Past health and physical examination. The doctor will ask you about your past health and that of your family. He or she will then examine your breasts to determine the presence or absence of lumps, the state of the skin and the nipple, the presence of lymph nodes in the armpit and to undertake a general physical examination.

Diagnostic mammogram. A diagnostic mammogram is similar to a screening mammogram, but more images are taken in more detail, particularly in the area in which the abnormality was detected. A mammogram is a simple test that uses X-rays.

Ultrasound. This test involves high frequency ultrasound waves that hit the structures under study and generate an echo that is recorded on a computer, which reproduces this echo in the form of images. Ultrasound can be used to distinguish between a solid mass and a liquid. It is a simple, painless test that is used in addition to a mammogram.

Magnetic resonance (MR). Magnetic fields are used to generate images, hence the name. This test has greater capacity to differentiate between the structures of the body, particularly soft tissues such as the brain, for example. In specific cases, doctors will request magnetic resonance imaging.

Fine needle aspiration biopsy (FNAB). This consists in introducing a fine needle into the nodule with the help of palpation or ultrasound. The needle is connected to a syringe and a small amount of liquid is extracted for analysis. This test is carried out in outpatient departments. It may be a little uncomfortable.

Biopsy. This test gives a definitive diagnosis. A biopsy consists of extracting a small amount of tissue for microscopic analysis. This provides information on the type of cells and the characteristics of the tumor. These data are essential to determining the prognosis and deciding on the most appropriate treatment.

Different types of biopsy can be performed:

- Stereotactic biopsy. This is also performed with a needle, but the nodule is located by means of a mammogram. It is carried out in the outpatient department.
- Surgical biopsy. This is minor surgery. Some of the tissue in the lump is extracted (incision biopsy) or the entire nodule is extracted (excision biopsy).

Determination of hormone receptors. When a tissue is analyzed, a test is undertaken to detect estrogen and progesterone hormone receptors (the female hormones). Cancer cells that have these receptors need hormones to grow. This helps to determine the prognosis and the treatment, as well as whether the cells are likely to respond to hormone therapy.

Determination of HER2/neu gene receptors. The tissue is also examined. The gene HER2/neu generates a specific protein, which participates in regulation of cell growth. From 15% to 20% of breast cancers are positive for this protein. A high presence of this gene indicates more rapid growth of tumor cells and more probability that the cancer will return after treatment. Currently, specific treatments aim to block

this gene.

Blood test. A complete blood test is carried out to assess general state of health.

- **Tumor markers.** The presence of proteins called tumor markers can be determined. In breast cancer, these markers are carcinoembryonic antigen (CEA) and CA 15-3. The presence of a tumor marker at higher or lower levels than normal indicates an abnormal process in the body, which could be due to cancer or to another disease. These markers can be used as a reference in the treatment follow-up.

Computerized axial tomography (CAT or CT). This test uses X-rays and enables parts of the body to be viewed in 3D. This is achieved by taking numerous images that are combined to produce the final three-dimensional image. Sometimes, a vein is injected with a substance called contrast, which is like a special dye. Some special details can be observed more easily after this.

Bone scintigraphy. This test is particularly used when cancer has spread to the bones. A radioisotope is injected intravenously and is taken up by the cells of the organ or tissue that we wish to study. After the administration of the radioisotope, a specific amount of time has to pass for the absorption to occur. Then, a special camera records the gamma rays emitted by the bones, and reproduces this information in images that show the healthy and diseased areas.

Positron emission tomography (PET). This consists of injecting a sugar substance that contains radioactive elements into a vein. The PET scanner takes images of how the cells use this substance, in other words, it identifies the metabolic activity of the cells. Malignant cells are usually identified as areas of high activity. This test provides complementary information.

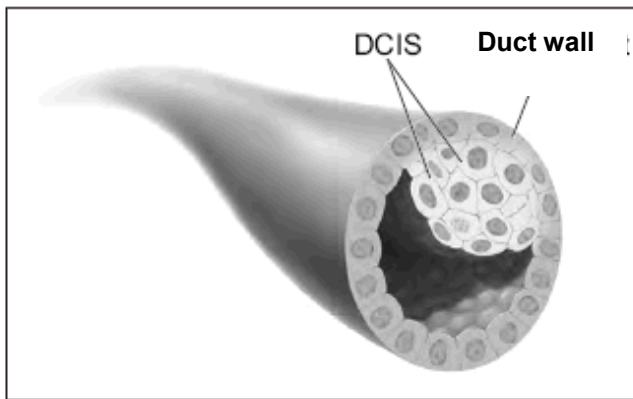
Spread of cancer (staging)

Once a diagnosis of breast cancer has been confirmed, it is essential to find out whether it has spread, in order to plan the most appropriate treatment. The degree to which a tumor has spread is also called the staging.

Breast cancer staging is described below.

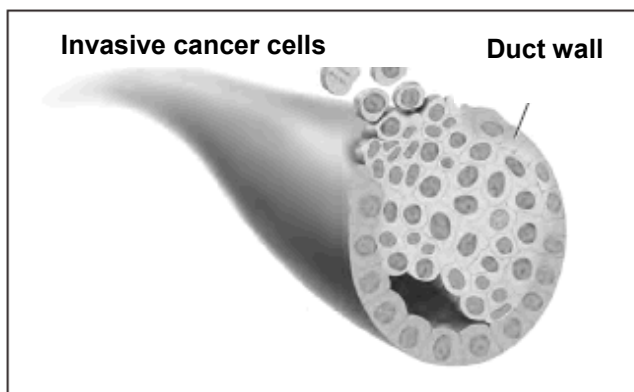
Stage 0: carcinoma in situ

- **Lobular carcinoma in situ (LCIS).** Cancer cells are found within the lobule. Such tumors are rarely invasive. However, their presence increases the risk of cancer in either breast.
- **Ductal carcinoma in situ (DCIS).** This is also called intraductal carcinoma. Cancer cells are found within the duct. In this stage, they do not invade adjacent structures. However, they could grow and become invasive carcinoma if they are not treated.



Stage I

This is the initial invasive stage of breast cancer. The tumor affects the adjacent structures, but has not gone beyond the breast. It measures no more than 2 cm and the lymph nodes are not affected.



Stage II

Several situations may exist:

- The tumor is no larger than 2 cm and has spread to lymph nodes in the armpit.
- The tumor is between 2 and 5 cm and may or may not have spread to the lymph nodes in the armpit.
- The tumor is bigger than 5 cm, but has not spread to the lymph nodes in the armpit.

Stage III

The tumor may be large and is disseminated in the same breast and in the lymph nodes and armpit. It is also known as locally advanced cancer. One of the following situations may have occurred:

- Stage IIIA
 - The tumor is smaller than 5 cm and has disseminated to the axillary lymph nodes, which are adhered to other adjacent structures.
 - The tumor is larger than 5 cm and has disseminated to axillary lymph nodes.
- Stage IIIB

- The cancer has grown and is in the skin or the chest wall.
 - The cancer has massively disseminated to the axillary lymph nodes.
 - The cancer has disseminated to the internal mammary lymph nodes or to the chest wall.
 - *Inflammatory breast cancer*: this is a very frequent form of stage IIIB. It is characterized by a reddish and inflamed breast, as the cancer cells obstruct the lymph vessels in the breast.
- Stage IIIC

A tumor of any size that has disseminated as described below:

 - To the lymph nodes of the chest wall and the axilla.
 - To the supraclavicular and infraclavicular lymph nodes-
 - Stage IV

Distant metastasis. The cancer has disseminated to other parts of the body.

 - *Recurrent* cancer. This occurs when, some time after breast cancer, the disease reappears in the breast, the thoracic wall and in another part of the body.

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TREATMENT

1. TYPES OF TREATMENT

Breast cancer treatment depends on the size, the staging and the biological type of the tumor (the degree of cell differentiation, the presence of hormone receptors and of HER2), as well as the specific state of health of each individual. As in other types of tumors, the treatment is multidisciplinary: different medical fields work together and therapies are combined.

1.1. Surgery

In general, the smaller the tumor, the greater the number of surgical options. Surgery is one of the most frequent breast cancer treatments. There are several types of surgery.

Conservative surgery

- Lumpectomy. This consists of removing the lump and a small margin of non-cancerous tissue from around the lump.
- Partial or segmental mastectomy. This involves removal of a quarter or a segment of the breast that contains the tumor.

In these cases, radiotherapy is applied to the affected area after surgery. The combination of surgery and radiotherapy is called conservative treatment. If chemotherapy is administered, radiotherapy is delayed until the end of the treatment.

Radical surgery

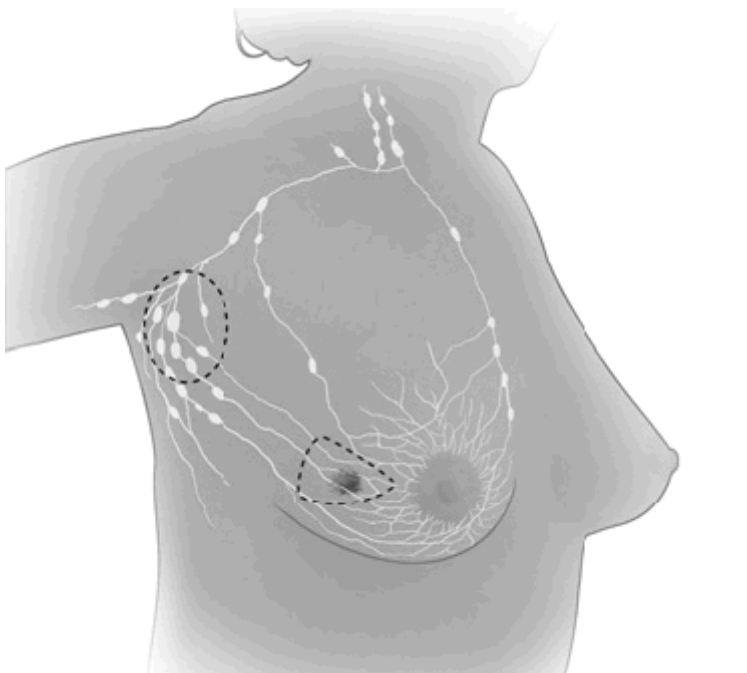
- Simple mastectomy. This consists of removing the entire breast, including the nipple, but not the lymph nodes.

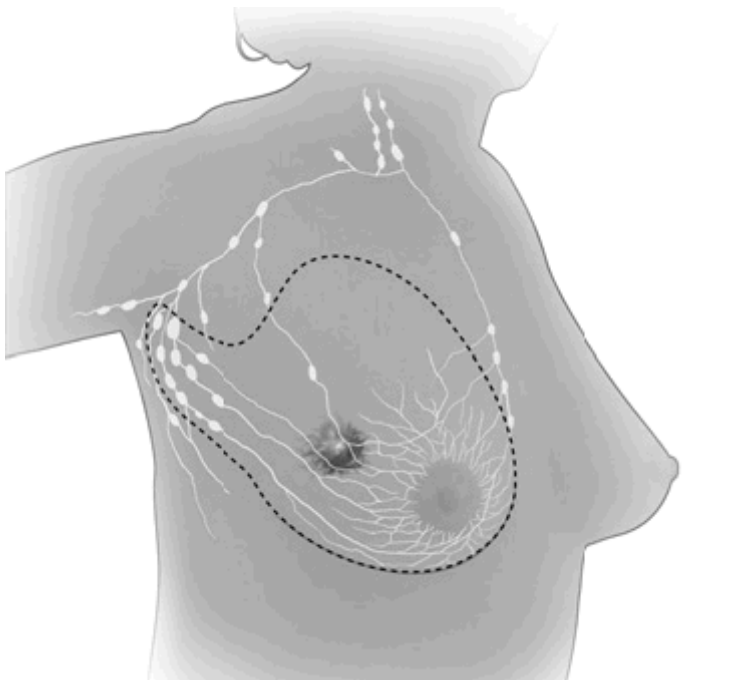
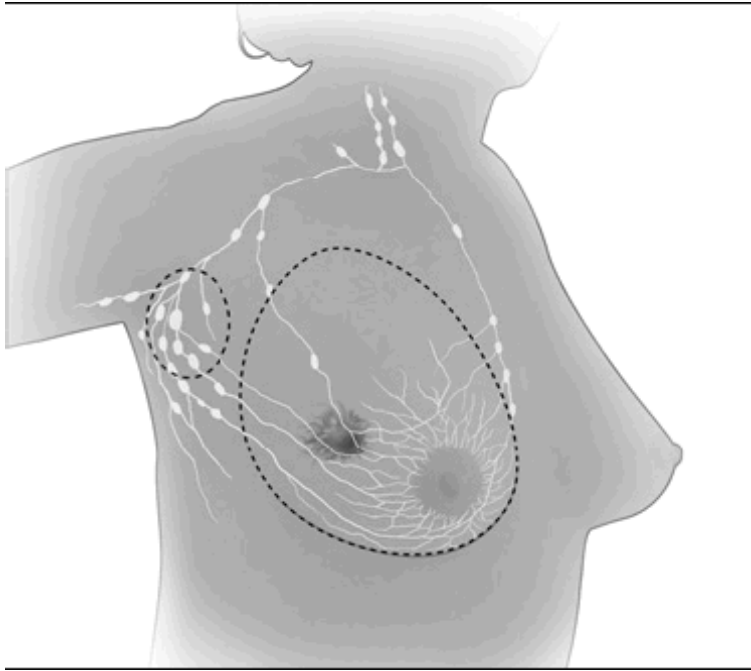
- Modified radical mastectomy. The breast and the axillary lymph nodes are removed.

Axillary lymphadenectomy. Regardless of the surgical technique, this consists of removing the axillary lymph nodes to analyze whether they contain cancer cells. The number of lymph nodes that are removed may vary. The aim is to remove them all to analyze whether they are affected and to avoid leaving cells that could lead to recurrence.

Sentinel node biopsy. The aim is to identify the first node that receives lymphatic drainage from the breast. If this node contains a tumor, the rest of the axillary lymph nodes must be analyzed and removed. If there is no cancer in the sentinel lymph node, a lymphadenectomy can be avoided, as well as the complications that this procedure may entail (lymphedema).

Breast reconstruction. The aim of this procedure is not to treat cancer, but to reestablish the shape of the breast after a mastectomy. It can be performed at the same time as breast removal (immediate reconstruction) or some time afterwards (delayed reconstruction). Reconstruction can be carried out using tissues from other parts of the body (skin grafts) or synthetic implants (internal prostheses). Alternatively, the reconstruction can be foregone and external prostheses used instead.





1.2. Radiotherapy

Radiotherapy uses high-energy rays to destroy cancer cells.

In breast cancer, radiotherapy is usually used after surgery, to kill any remaining cancer cells.

There are two types of radiotherapy:

External radiotherapy. The radiation comes from a machine outside the body and is directed specifically at the cancer. It is applied daily, five days a week. The treatment usually takes place over several weeks. Each application of the treatment lasts for a few minutes only.

Brachytherapy or internal radiotherapy. This consists of implanting narrow plastic tubes and using them to apply a radioactive substance directly or close to the site from which the tumor was removed.

1.3. Chemotherapy

Chemotherapy is the use of specific drugs that destroy cancer cells. The drugs are distributed around the body by the blood (see the section on treatment).

Chemotherapy can be administered in different ways:

Adjuvant or additional chemotherapy. This is administered after the surgical removal of the tumor and/or the lymph nodes to prevent recurrence and dissemination.

Neoadjuvant or primary chemotherapy. This is administered as the first treatment, before surgery, to reduce the size of the tumor and prevent dissemination.

Palliative chemotherapy. This is used in cases of disseminated disease to prolong survival and treat symptoms.

Chemotherapy that is used in breast cancer treatment can be administered orally or intravenously (through the veins), depending on which drugs are used. Generally, patients do not need to be admitted to hospital, and are treated in outpatient units.

1.4. Hormone therapy

Some breast tumors need hormones to grow. Hormone therapy can be used to control and treat tumors that are shown to have estrogen and progesterone receptors (see the section on diagnostic tests).

This therapy consists of administering hormones, usually orally, which block the action of estrogens on malignant breast cancer cells or prevent their formation. This slows growth and the tumor can even decrease in size or disappear.

Hormone treatment can be administered alone or in combination with chemotherapy.

1.5 Biological therapies: monoclonal antibodies

Biological therapies help the immune system (the body's defenses) to fight against cancer. They act on malignant cells rather than healthy ones. Therefore, there are fewer side effects and the therapies are usually well tolerated.

This treatment is indicated for high levels of the HER2/neu gene (see the section on diagnostic tests), which is involved in cell growth. The drug acts by blocking this gene, which reduces or stops the growth of malignant cells. The drug used in this therapy is trastuzumab. It can be administered alone or in combination with chemotherapy, and is administered intravenously.

2. SIDE EFFECTS

Both breast cancer and its treatment can cause side effects. Whether or not a patient develops side effects depends on many factors such as the type of surgery, the type

of chemotherapy or radiotherapy administered, dose levels and treatment duration, and the characteristics of the patient. Many side effects are temporary and can be easily controlled; others require more specific treatment. Regular checks are made throughout the treatment period to prevent side effects wherever possible and to treat unavoidable side effects.

2.1. Surgery

The length of time it takes to recover from an operation varies from person to person. The following may occur after surgery:

Immediate postoperative period. As in other surgical procedures, in the first few days the operated area is more delicate and small hematoma may appear. These problems generally disappear after two weeks.

Local changes in sensitivity. After the surgery, you may experience less sensitivity or the sensation of pins and needles in the operated area. Over time, this tends to disappear. Several months to a year after the operation the situation has usually returned to normal.

Postural imbalance. If one of your breasts has been removed, you may feel a little unbalanced, particularly if they are not small. This is a temporary situation, but could cause neck and back pain.

Arm mobility. If the axillary lymph nodes have been removed, the arm muscles may become rigid and weaker. Exercise is of great benefit and can begin gradually just after surgery, depending on your ability to move, in order to reduce rigidity and pain and to maintain arm mobility. The health care team will show you some exercises.

Lymphedema. The removal of lymph nodes can have an impact on the circulation of lymph. As lymph nodes have been removed, fluid may accumulate due to difficulties in drainage or circulation. The symptoms are swelling of the arm on which surgery has been performed (lymphedema). This is a chronic, progressive condition that may appear just after surgery or after months or years. Not all women develop lymphedema. However, certain specific actions can be undertaken to prevent or improve this condition. The main aim is to improve circulation in the arm and to prevent infections.

Recommendations

- Do not wear tight clothes, jewelry or a watch on the affected arm.
- Do not carry luggage or shopping bags on this arm.
- To shave, use creams or electric shavers. Do not use razors, in order to avoid cuts.
- Arterial pressure, blood extractions and intravenous injections, etc. should be performed on the unaffected arm.
- Use gloves to avoid infection when you are using detergents or gardening.
- Avoid cutting your cuticles in manicures.
- Protect your arm as much as possible to avoid cuts, knocks, burns, sunburn, etc.
- Do the exercises recommended by the health care team.

2.2. Radiotherapy

The side effects of radiotherapy vary depending on the type of therapy, the doses given, and the part of the body that is treated. The most common side effects in patients with breast are described below.

Local skin alterations. Radiotherapy often causes the skin around the area treated to become more sensitive, dry, and even a little red. These alterations will all disappear with time.

Recommendations

- Wear cotton clothing, including bras and other items of clothing that are in contact with your skin.
- Wear loose clothing that will allow air to circulate and that will not rub against irritated areas.
- Look after your skin. Check with your health care team before using any soaps, body milks, or antiseptic products, as certain products can interfere with radiation treatment or make your skin condition worse.
- Use mild soap and prevent anything from rubbing against your skin.
- Do not scratch your skin. If it is itchy, apply cold chamomile or ice wrapped in a cotton cloth to the affected area.

Fatigue or tiredness. Radiotherapy can cause you to feel tired, especially in the last few weeks of treatment. This feeling can persist for some weeks after treatment ends.

Recommendations

- Do regular exercise but adapt the level to your habits, your capacity, and to how you are feeling. A daily walk is an excellent way to exercise. People who exercise feel stronger and have a better appetite, more regular bowel movements, and a better body image.
- Maintain your energy levels and adjust activities to how you are feeling. You will feel more or less energetic at different times of the day. Make the most of the moments when you feel most energetic to do activities that require greater effort.
- Monitor any other side effects or problems that might increase your feelings of fatigue, such as difficulty in sleeping. Check with your health care team if you have any doubts.

2.3. Chemotherapy

Because chemotherapy targets cells that divide quickly, it affects healthy cells as well as cancer cells. This is why you may experience side effects, which will vary in type and severity depending on the drug used, the dose, and the duration of treatment. The possible side effects of chemotherapy are related to the location of rapidly dividing cells.

- Blood cells. When chemotherapy affects healthy blood cells, you have an increased risk of developing infections and of bruising or bleeding more easily. You are also likely to feel weaker or more tired than usual.
- Hair root cells. Certain chemotherapy drugs may cause hair loss or change hair color or texture.
- Digestive tract cells. When chemotherapy affects these cells—found in the mouth, stomach, and other parts of the digestive system—possible side effects are loss of appetite, nausea, vomiting, diarrhea, difficulty in swallowing, and mouth and lip sores.

The most common side effects are as follows:

Alterations of the mouth mucosa

- Dry mouth (xerostomia). Dry mouth occurs when the saliva glands do not produce enough saliva. This is a temporary side effect that disappears once the glands begin producing saliva again.
- Mouth sores (mucositis). Mucositis is an inflammation of the mucosa inside the mouth. Prevention is the best cure. If sores do appear, they should be treated as early as possible to minimize discomfort.

Mouth sores can make it difficult to chew, swallow, talk, and appreciate flavors.

Recommendations

- Maintain good oral hygiene. Brush your teeth 3 to 4 times a day with a soft brush. Wetting the brush first in warm water will make it softer.
- Rinse your mouth 4 to 6 times a day—for example, after meals—with a non-alcoholic mouthwash or a cold infusion of chamomile or thyme.
- Sip small amounts of water throughout the day and use artificial saliva to keep your mouth moist.
- Eat sugar-free chewing gum or sweets to stimulate the production of saliva.
- Eat soft foods that are cold or warm rather than hot. Use sauces and broths to make your meals juicier.
- Avoid rough-textured foods.
- Avoid very acidic or spicy foods.
- Avoid irritants such as coffee, tobacco, and alcohol.
- Avoid sweet, sticky food.
- If you have a metallic taste in your mouth, use plastic cutlery.

Nausea and vomiting

Nausea and vomiting can occur during different phases of treatment, as follows:

- Acute nausea and vomiting generally occurs within several hours of treatment
- Delayed nausea and vomiting occurs within 1 to 5 days of treatment
- Anticipatory nausea and vomiting occurs before treatment as a consequence of prior treatments. In this case, nausea and vomiting can be triggered by smells or even just by thinking about treatment.

Mild nausea and vomiting that are treated rapidly can cause discomfort but are not serious. When persistent, however, they can cause dehydration, electrolytic disturbance, weight loss, and even the desire to abandon treatment. Highly effective drugs are available to control nausea and vomiting.

Recommendations

- Eat small amounts of food 5 or 6 times a day.
- Chew slowly, taking all the time you need.
- If you feel nauseous, wait some time before eating.
- Avoid food odors.
- Avoid tight clothes, belts, etc.
- Sip small amounts of cold fluids throughout the day.
- Drink small amounts of liquid during mealtimes to make you feel fuller.
- Rest after each meal but do not lie down in the first hour.

Some people feel better when they do activities such as concentration, relaxation, or positive visualization exercises. These exercises help to reduce anxiety levels and thoughts about nausea and vomiting.

Diarrhea

Diarrhea is characterized by an increased frequency of watery stools. Consult your health care team if the diarrhea lasts for more than 24 hours as it may cause electrolytic disturbances and dehydration.

Recommendations

- Avoid caffeine, alcohol, fat, excessive amounts of fiber, orange and prune juices, and very spicy foods.
- Do not use laxatives unless told to do so by your doctor.
- Eat smaller amounts at more frequent intervals throughout the day.
- Drink plenty of liquid such as water, infusions, juice, and broth to avoid dehydration. Patients with severe diarrhea may need intravenous fluids to compensate for fluid and electrolyte losses.
- In certain circumstances, you might be prescribed anti-diarrhea drugs.
- Your doctor might also change treatment dosage if he/she considers this necessary.

Constipation

Chemotherapy can sometimes cause constipation but there are other contributory factors such as a reduction in normal activity levels and changes in diet. Consult your health care team if you are still constipated after 2 days. Under no circumstances take laxatives or other such products without first finding out if this is advisable.

Recommendations

- Do some exercise every day, for example, walking.
- Drink 1.5 to 2 liters of fluids (water, infusions, broth) a day and start the day with an infusion or a glass of warm water.
- Eat high-fiber foods such as fruit and vegetables.
- Try to establish regular bowel habits.

Fatigue or tiredness

Loss of energy and feelings of tiredness are among the most common side effects of chemotherapy and potentially have a major impact on daily life. Tiredness can start during treatment—especially towards the end—and last for several days afterwards.

Follow the same recommendations as indicated for radiotherapy.

Hair loss (alopecia). is quite a common side effect of chemotherapy. Hair loss may not occur at all, or it may be partial or complete, depending on the type of treatment. Sometimes hair loss does not occur, but hair may become drier and more opaque.

Hair loss is usually temporary, but may have a significant effect on an individual psychologically and in terms of their self-image and quality of life. By knowing what treatment you are going to receive, you can prepare as suits you best.

Recommendations

▪ Hair and scalp care

- Use a mild shampoo such as a baby shampoo.
- If the treatment you are going to receive causes complete hair loss, cut your hair very short before it begins to fall out. This helps to reduce the distress caused by seeing your hair fall out gradually.
- Moisturize your scalp regularly.
- Use a hat or scarf to protect your head from the sun and to retain body heat during winter.
- Do not blow dry your hair with hot air.
- Do not use chemical products such as hair dyes and straighteners (even if they are semi-permanent).

▪ Hair pieces and wigs

- By choosing a hairpiece or wig before your hair begins to fall out, you will be able to choose one that is similar to the color and style of your own hair.
- Go to a shop that is experienced in dealing with patients with cancer. Choose a good-quality wig to prevent irritation of the scalp.

▪ New hair

Your hair will start to grow back after treatment and will normally take about 12 months to return to normal. At the beginning, you might find that your hair is thinner, more fragile, and perhaps even a slightly different color. Follow the recommendations below while your hair is growing back:

- Wash your hair twice a week.
- Massage your scalp to remove dry skin and flakes.
- Brush your hair gently and as little as possible. Do not blow dry your hair with hot air.
- Use a soft hairbrush for new hair growth.
- Do not use any type of hair dye for at least 3 months after treatment ends.

Weakening of natural defenses

Infections develop when invading bacteria, viruses, or fungi are not rapidly destroyed by the body's immune (defense) system. This defense system is made up of the skin, the spleen, lymph nodes, bone marrow in long bones, and leukocytes (white blood cells). Neutrophils are a subset of white blood cells that destroy harmful bacteria. A fall in the number of neutrophils that weakens your defenses is called neutropenia.

When a person has neutropenia, there is a risk of a minor infection becoming serious. Symptoms of serious infection are as follows:

- A high temperature
- Shivering
- Inflammation of the throat or mouth
- Abdominal pain
- Pain or a burning sensation when urinating and increased urination frequency
- Diarrhea and/or irritation of the perianal area
- Reddening or inflammation around wounds or small cuts
- Abnormal vaginal discharge or itching.

Treatment options include antibiotics or antifungals (to fight fungi) and drugs that help

to build up your body's defenses. Patients with serious infection may need to be admitted to hospital for intravenous treatment.

Recommendations

- Consult your health care team if you have a temperature of 38°C or higher.
- Eat a balanced diet and make sure you get enough rest.
- Avoid crowds and people who are ill.
- Check with your doctor before a vaccination. Some vaccines (such as the flu vaccine) contain weakened viruses and can cause severe infections.
- For the same reason, avoid people, including children, who have been recently vaccinated with live weakened viruses (polio, flu, measles, etc.).
- Do not share personal items such as eating and drinking utensils or toothbrushes.
- Do not eat raw food such as meat, shellfish, or eggs. Wash fresh fruit and vegetables well before eating them.
- Wash your hands frequently throughout the day, particularly before mealtimes and after going to the toilet.
- Take a daily shower or bath and apply moisturizing creams or lotions to prevent dry, cracked skin.
- Take care when using sharp objects such as knives and scissors.
- If you have a pet, do not clean their eating or drinking utensils or pick up their poop, even with a plastic bag.
- When doing housework or gardening, use gloves to protect yourself from cuts or burns.
- Clean your teeth and gums with a very soft brush.
- Take care not to cut your cuticles when trimming your finger and toe nails.

Reduced platelet count (*thrombocytopenia*)

This condition, known as thrombocytopenia, occurs when there is a very low level of platelets in the blood. Platelets are also called thrombocytes and are involved in blood clotting. People with a reduced platelet count are more likely to bleed and bruise easily. Opinion on the best treatment varies.

Recommendations

- Do not drink alcohol or take any medication without first consulting your doctor. Some drugs can heighten the risk of bleeding.
- Clean your gums and teeth with a very soft brush.
- Blow your nose gently.
- Take care when handling sharp objects.
- Avoid shaving with razors or wax hair removal.
- Avoid contact sports or other activities that could cause injuries.

Reduced red blood cell count

People who produce too few red blood cells, otherwise known as erythrocytes, develop anemia. These cells are responsible for transporting oxygen from the lungs to the rest of the body. As there may be no symptoms, routine tests are conducted during treatment to detect possible decreases. The condition is easy to correct. Symptoms may appear if the red blood cell levels are particularly low. The most common symptoms are tiredness, weakness, difficulty breathing with minimal exertion, palpitations, dizziness, and pale skin.

Recommendations

- Get as much rest as possible.

- Sleep enough hours to feel refreshed.
- Only do activities you feel capable of doing. Avoid activities that cause additional tiredness.
- Spread your meals throughout the day to avoid heavy digestion.

Early menopause and infertility

Not all drugs have this side effect. Drugs that lead to a temporary (amenorrhea) or permanent (menopause) interruption in the menstrual cycle do this by acting on the ovaries. Age significantly influences this effect. Women who are close to menopausal age are more likely to present early menopause. Women who are under forty, could undergo a temporary period without menstruation (amenorrhea). Subsequently, a high percentage recover normal ovary activity. After this age, the percentage of recovery of the menstrual cycle is much lower.

2.4. Hormone therapy

The side effects of this treatment depend on the type of drug used, and on the patient's individual characteristics. The most general side effects are similar to the natural process of menopause, and are described below:

Hot flushes. These are mainly experienced by women who are close to menopausal age. Some non-hormonal drugs can reduce this side effect.

Vaginal changes

- Dryness. Dryness or vaginal irritation can cause discomfort and affect sexual relations.
- Spotting and irregular menstruation. These irregularities are not normal. You should consult your doctor if they appear.

Weight gain. You may gain some weight slightly.

Osteoporosis. This is a loss of calcium from the bones, which increases the risk of fracture. It can be prevented by exercise, a calcium-rich diet and specific drugs.

Recommendations

Hot flushes

- Try and stay in places that have a low temperature.
- Take deep breaths and do relaxation exercises.

Vaginal dryness

- You can use water-soluble lubricants. If these are not sufficient, consult your health care team to assess alternatives.

Weight increase

- You do not need to go on a diet. Regular physical exercise and a healthy diet should be sufficient, as only a small amount of weight is gained, in general.
-

2.5. Biological therapy

The side effects of biological therapy are similar to cold and flu symptoms: high temperature, shivering, weakness, and nausea. These symptoms tend to diminish

after the first treatment.

DAILY LIFE

Your daily routine will probably be affected during treatment. During this time, take good care of yourself, deal with needs as they arise, and adjust your daily routine to your new circumstances.

People adapt differently, depending on their capacities, priorities, and experiences. It is a time to think about how you can continue your daily routine without feeling overwhelmed and without allowing your illness to become the center of your life.

Taking care of yourself involves many aspects, but following a healthy diet and keeping active are key to ensuring a sensation of well-being.

Make sure that your daily intake of calories and proteins is sufficient to avoid weight loss and to keep you strong. Eating well will help you to feel better and more energetic.

Moderate regular exercise also helps. There are many activities to choose from, for example, walking, swimming, and yoga. Keeping active will help you to feel stronger, more energetic, and less stressed.

Talk to your health care team about what type of exercise is best for you.

RESOURCES/ASSOCIATIONS

The NCCN Patient Guidelines [online].
<http://www.nccn.org/patients/patient_gls.asp>

National Cancer Institute [online].
<<http://www.cancer.gov/cancertopics/pdq/treatment/breast/patient>>

Cancer Net URL [online].
<<http://www.asco.org/patient/Cancer+Types/Breast+Cancer>>

APPENDICES

APPENDIX 1. INDICATORS FOR IMPLEMENTING THE RECOMMENDATIONS

Indicator no. 1: BIOPSY

Indicator	PERFORMING A BIOPSY
Justification	A core needle biopsy (CNB) provides enough material to undertake immunohistochemical analyses that assess the state of hormone receptors and tumor suppressor proteins or provide results that can be used to predict response, for example in relation to HER2. Thus, open surgery is not needed to diagnose benign pathology. Malignancy can be diagnosed and an appropriate treatment program initiated.
Dimension	Effectiveness
Formula	$\frac{\text{Number of patients with a breast cancer diagnosis and CNB}}{\text{Number of patients with a diagnosis of breast carcinoma}} \times 100$
Explanation of terms	Core needle biopsy (CNB) = evidence of the histopathology report in the documents that are revised (health history in paper or digital format).
Population	All patients admitted in the study period with a principle diagnosis of breast carcinoma (Code ICD-9 = 174). Microcalcifications and non-palpable nodules are excluded.
Type	Process
Data sources	Clinical documentation ✓ Pathology reports ✓ Clinical course
Comments	Note: if there is a record of the request but the report cannot be found (in the health history or the Pathology Department), the criteria have not been met.

Indicator no. 2: RADIOLOGY REPORT

Indicator	IMAGING DIAGNOSIS
Justification	A radiological assessment is essential in cases of suspected breast cancer, to contribute to the diagnosis. Mammogram may be sufficient or additional imaging techniques may be required. In all cases, these techniques represent an initial study and the report will provide enough information to make the diagnosis or to assess the degree of suspicion.
Dimension	Effectiveness, health care continuity
Formula	$\frac{\text{Number of patients with breast cancer and a complete imaging diagnosis report}}{\text{Number of patients with an analysis that reveals breast cancer and an imaging diagnosis}} \times 100$
Explanation of terms	<p>Imaging diagnosis: any of the imaging tests carried out (mammogram, ultrasound, mammogram with air injection, ductography, positron emission tomography [PET] or magnetic resonance)</p> <p>Complete report: evidence in the health history (in paper or digital format) of the following elements:</p> <ul style="list-style-type: none"> ✓ ALWAYS: <ul style="list-style-type: none"> ◆ Morphological description ◆ Size of the tumor and localization ✓ IN CASES OF: <ul style="list-style-type: none"> ◆ Mammogram: degree of suspicion of malignancy using the Breast Imaging Reporting and Data System (BIRADS) ◆ If it is not the only lesion, record multicentricity / multifocality
Population	<p>All patients admitted in the study period with a principal diagnosis of malignant breast carcinoma. (Code ICD-9 = 174)</p> <p><u>Inclusion criteria:</u> mammographies undertaken in other health centers or in a screening program</p>
Type	Process
Data sources	<p>Clinical documentation:</p> <ul style="list-style-type: none"> ✓ Imaging diagnosis reports ✓ Comments of the Breast Cancer Committee (events or health history)
Comments	The indicator will only be considered complete if it includes all the parameters referred to in the Explanation of terms in the radiology report.

Indicator no. 3: PATHOLOGY REPORT

Indicator	CONTENTS OF THE PATHOLOGY REPORT
Justification	To treat cancer appropriately, clear, standardized and understandable information is required on the primary tumor, the surrounding tissue and the regional lymph nodes.
Dimension	Effectiveness, continuity of health care
Formula	$\frac{\text{Number of pathology reports for invasive breast cancer that include the internationally required elements}}{\text{No. of pathology reports for invasive breast cancer}} \times 100$
Explanation of terms	<p>Required elements. Documented evidence in the health history (in paper or digital format) of the following elements:</p> <ul style="list-style-type: none"> ✓ Macroscopic description ✓ Tumor size ✓ Histological type ✓ Histology grade ✓ Presence or absence of multifocality ✓ Presence or absence of involvement of surgical margins ✓ Presence or absence of vascular/lymph node invasion ✓ Lymph nodes: number and involvement of the sentinel lymph node (if required) <p>WHEN THERE IS NO PREOPERATIVE IMMUNOHISTOCHEMICAL STUDY, the report will also have to include hormone receptors (Re and Rp) and HER2 proteins.</p>
Population	All the reports of patients admitted in the study period with a principal diagnosis of malignant breast cancer (code ICD-9 = 174) who have undergone surgical tumor removal.
Type	Process
Data sources	Clinical documentation: <ul style="list-style-type: none"> ✓ Pathology report/s
Comments	The indicator is only considered complete if the radiology report contains all the parameters mentioned in the Explanation of terms.

Indicator no. 4: CONSERVATIVE SURGERY

Indicator	CONSERVATIVE SURGERY
Justification	Conservative surgery has been shown to have similar results to more radical surgery and represents the treatment of choice for most small breast cancers and those that are larger when (neoadjuvant) chemotherapy has reduced the tumor size.
Dimension	Patient-centered health care (satisfaction)
Formula	$\frac{\text{Number of patients with breast cancer submitted to conservative surgery}}{\text{Number of patients diagnosed with breast cancer}} \times 100$
Explanation of terms	Conservative surgery: primary surgery with complete removal of the suspicious lesion by segmentectomy, quadrantectomy, lumpectomy or oncoplastic techniques. Always in reference to primary surgery.
Population	All patients admitted in the study period with a principal diagnosis of malignant carcinoma of the breast (Code ICD-9 = 174)
Type	Process
Data sources	Clinical documentation: <ul style="list-style-type: none"> ✓ Surgical report ✓ Clinical course

Indicator no. 5: SENTINEL LYMPH NODE

Indicator	SENTINEL LYMPH NODE BIOPSY (SLNB)
Justification	SLNB is now considered a standard technique in the surgical treatment of breast cancer. It prevents unnecessary lymphadenectomies and reduces morbidity. A multidisciplinary team is needed for this procedure (surgery, pathology and magnetic resonance specialists). It has a high negative predictive value.
Dimension	Appropriacy
Formula	$\frac{\text{Use of a valid SLNB technique}}{\text{Number of centers assessed}} \times 100$
Explanation of terms	<p>SLNB: intrasurgical localization of the sentinel lymph node, using isotopic and/or colorimetric techniques.</p> <p>Validation: to meet a set of specific recommendations (these should be verified in each centre) to validate the technique.</p>
Population	The centre or centers that are under evaluation.
Type	Structure
Data sources	Centre address Surgical and nuclear medicine departments

Indicator no. 6: SYSTEMIC HORMONE TREATMENT

Indicator	SYSTEMIC HORMONE TREATMENT
Justification	Systemic hormone treatment is recommended in patients who have tumors with positive hormone receptors, once chemotherapy has been completed. Randomized studies of patients over 70 years old with positive hormone receptors suggest that survival is better with hormone treatment than with chemotherapy.
Dimension	Effectiveness and appropriacy
Formula	$\frac{\text{Number of patients with positive hormone receptors and hormone treatment}}{\text{Number of patients with positive hormone receptors}} \times 100$
Explanation of terms	<p>Determination of hormone receptors: immunohistochemistry or biochemistry</p> <p>Hormone treatment: includes any of the following:</p> <ul style="list-style-type: none"> ✓ Tamoxifen ✓ Letrozole (Femara®) ✓ Anastrozole (Arimidex®) ✓ Exemestane (Aromasin®) ✓ Zoloda
Population	All patients admitted during the study period with a principal diagnosis of malignant breast cancer (code ICD-9 = 174) and positive hormone receptors.
Type	Process
Data sources	<p>Clinical documentation:</p> <ul style="list-style-type: none"> ✓ Clinical course ✓ Pathology report ✓ Oncological documentation (CCEE)

Indicator no. 7: INTERVAL BETWEEN SURGICAL AND ADJUVANT TREATMENT

Indicator	INTERVAL BETWEEN SURGICAL AND ADJUVANT TREATMENT
Justification	Adjuvant treatment should begin in the period established in the protocols and clinical practice guidelines. This is essential from the perspective of the quality of health care. An interval of 6 weeks is considered appropriate. The length of the interval should be assessed by the Breast Cancer Committee and by the oncologist or radiotherapist.
Dimension	Effectiveness, risk
Formula	<p>Number of patients who had an interval between surgery and primary adjuvant treatment that was equal or less than 6 weeks or 30 working days</p> $\frac{\text{Number of patients who had an interval between surgery and primary adjuvant treatment that was equal or less than 6 weeks or 30 working days}}{\text{Number of patients who receive surgery for breast cancer}} \times 100$
Explanation of terms	<p>Surgery: last conservative surgery or conventional surgery (mastectomy)</p> <p>Adjuvant treatment: chemotherapy and/or radiotherapy</p> <p>Interval: the days between the date of surgery and the date of beginning the adjuvant treatment (chemotherapy and/or radiotherapy)</p>
Population	All patients admitted during the study period with a principal diagnosis of malignant breast cancer (code ICD-9 = 174).
Type	Results
Data sources	<p>Clinical documentation:</p> <ul style="list-style-type: none"> ✓ Surgical report ✓ Radiotherapy report ✓ Medical oncology report
Comments	In young patients with negative hormone receptors, the treatment should begin before three weeks.

APPENDIX 2. GENERAL RECOMMENDATIONS FOR DRAWING UP A BREAST CANCER PATHOLOGY REPORT

[Protocol Surgical Pathology Cancer Case Summary ACP](201)

Breast protocol /pathology report

IDENTIFYING DATA

Date obtained:	Date registered:	Health history no:	Biopsy no.:
Name:	Age:	Sex:	

CLINICAL AND MACROSCOPIC DATA

Localization:	↑ Right breast	↑ Left breast	
QUADRANT:	↑ QSE	↑ QSI	↑ QIE
UQ....	↑ QII	↑ Retroareolar	↑ Others/

Type of sample:

Needle biopsy:	CNB/ stereotactic	Direct	No. of cores
Surgical biopsy:	Palpable lesion	Needle localization	
Surgical treatment:	Lumpectomy	Quadrantectomy	
	Simple mastectomy	Modified radical mastectomy	
	Others (specify)_____		

Sample size _____ cm/mm Skin involvement Yes, _____ cm No

Size of the lesion / of the tumor _____ mm

Preoperative examination:-----
 Resection margin (distance and specified margins):-----

Macro photo: ↑ Yes ↑ No Tumor bank: ↑ Yes ↑ No

Key to sections: -----

MICROSCOPIC DATA

A. Malignant, non-invasive lesion of the breast	↑ Present	↑ Absent
Ductal	Nuclear grade: Low Intermediate High	With necrosis No necrosis

Size: _____ mm Growth pattern _____ Van Nuys Index _____
 Lobular Classic Undetermined Pleomorphic
 Paget's disease (with no underlying tumor)

B. Microinvasive lesion of the breast Present Absent

Microinvasive ductal carcinoma (≤1 mm)

C. Invasive malignant lesion of the breast Present Absent

Histological type of the invasive lesion

Ductal (NOS) Lobular Tubular Signet ring
 Medullary Mucinous Papillary Other: _____

Maximum diameter of the invasive lesion: _____ mm
 Total tumor size (including CDIS > 1 mm) _____ mm
 Amount of CDIS Equal or less than 25% Over 25%

Multiple tumor (including multifocal and multicentric tumors) Yes No

Distance between lesions: _____

Size of all of the lesions: _____ mm

Grade of the invasive component

				Total score
Tubular differentiation	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> Grade I (3-5 points)
Nuclear pleomorphism	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> Grade II (6-7 points)
Number of mitosis	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> Grade III (8-9 points)

Lymphatic/vascular invasion Present Absent

Tumor necrosis Present Absent

Calcifications Present Absent

Present, benign breast Present, benign and malignant breast
 Present, in situ tumor component Present, invasive tumor component
 Present, in situ and invasive tumor component

Skin involvement Present Absent

Invasion by direct or discontinuous extension of the tumor to the dermis, with or without the involvement of the epidermis and/or with neoplastic skin ulceration

í Invasion of the dermal lymphatics

í Paget's disease

Muscle involvement

í Present í Absent

PT (according to the latest edition of the UICC 2002):



D. Surgical margins

í Free

í Affected

Affected (contact with Chinese ink). Specify whether invasive component or in situ, the margin and the extension (mm):

Safety margin closest to _____mm.



E. Other lesions of the breast parenchyma

í Present

í Absent



í Ductal hyperplasia

í Not atypical

í Atypical

í Lobular neoplasia in situ

í Radial scar

í Columnar cell lesions

í Not atypical

í Atypical

í Other lesions (specify) _____



F. Lymph nodes

í Yes

í No

Total number of lymph nodes _____

Number of affected lymph nodes _____

Size of the largest metastasis _____



Sentinel lymph node

Name:

Size:

í Preoperative study

No

/

Yes:

Number affected /total number

í Molecular analysis

No

/

Yes:

Number affected /total number

í Definitive study

Number affected /total number

Size of the largest metastasis:

pN (according to the latest edition of the UICC, 2002)



G. Additional examinations (each hospital will specify which ones they perform)

- pN0 (i -) (negative lymph nodes histologically, negative immunohistochemistry)
 - pN0 (i +) (negative lymph nodes histologically, positive immunohistochemistry, deposits < 0.2 mm)
 - pN0 (mol -) (negative lymph nodes histologically, negative RT-PCR)
 - pN0 (mol +) (negative lymph nodes histologically, positive RT-PCR)
- î pN1 (metastasis in one to three axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent)
- pN1mi (micrometastasis, larger than 0.2 mm but not larger than 2.0 mm)
 - pN1a (Metastasis in one to three axillary lymph nodes, at least one larger than 2 mm)
 - pN1b (Metastasis in internal mammary nodes with microscopic disease detected by SNL dissection but not clinically apparent)
 - pN1c (Metastasis in one to three axillary nodes and in internal mammary nodes with microscopic disease detected but not clinically apparent)
- î pN2 (Metastasis in four to nine axillary lymph nodes or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph nodes)
- pN2a (Metastasis in four to nine axillary lymph nodes, with at least one tumor deposit larger than 2.0 mm)
 - pN2b (Metastasis in clinically apparent internal mammary nodes in the absence of axillary lymph node metastasis)
- î pN3 (Metastasis in ten or more ipsilateral axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes or metastasis in the supraclavicular lymph nodes)
- pN3a (Metastasis in ten or more axillary lymph nodes, at least one tumor deposit larger than 2.0 mm, or metastasis to the infraclavicular lymph nodes)
 - pN3b (Metastasis in clinically apparent internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or metastasis in more than three axillary lymph nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent in internal mammary lymph nodes)
 - pN3c (metastasis in supraclavicular lymph nodes)

Tumor assessment postchemotherapy (202)

Categories of therapeutic response:

Tumor:

- Complete response (absence of residual carcinoma / absence of residual invasive tumor with ductal carcinoma in situ)
- Partial response
- No evidence of response

Information should be obtained on the amount of the invasive or in situ component and the inflammatory or fibrosis changes that can be attributed to chemotherapy.

Lymph nodes

- 1. No evidence of metastatic disease or changes in lymph nodes
- 2. No metastatic tumor but evidence of down-staging
- 3. Evidence of metastatic disease and of down-staging
- 4. Evidence of metastatic disease with no response to therapy

Special cases of breast pathology

Phyllodes tumor

Benign Undetermined Malignant

Specify any elements with sarcosis _____

Margins:

Free Affected (marked with China ink). Specify _____ N/C

Sarcoma of the breast

Histological type _____

Grade I Grade II Grade III (according to sarcoma in the soft tissues)

No. mitosis (X10CGA) _____

APPENDIX REFERENCES

College of American Pathologists [online]. <http://www.cap.org/apps/capportal?_nfpb=true&_pageLabel=reference> [Consulted on 23 September, 2008].

Pinder SE, Provenzano E, Earl H, et al. Laboratory handling and histology reporting of breast specimens from patients who have received neoadjuvant chemotherapy. *Histopathology* 2007 Mar; 50(4):409-17.

