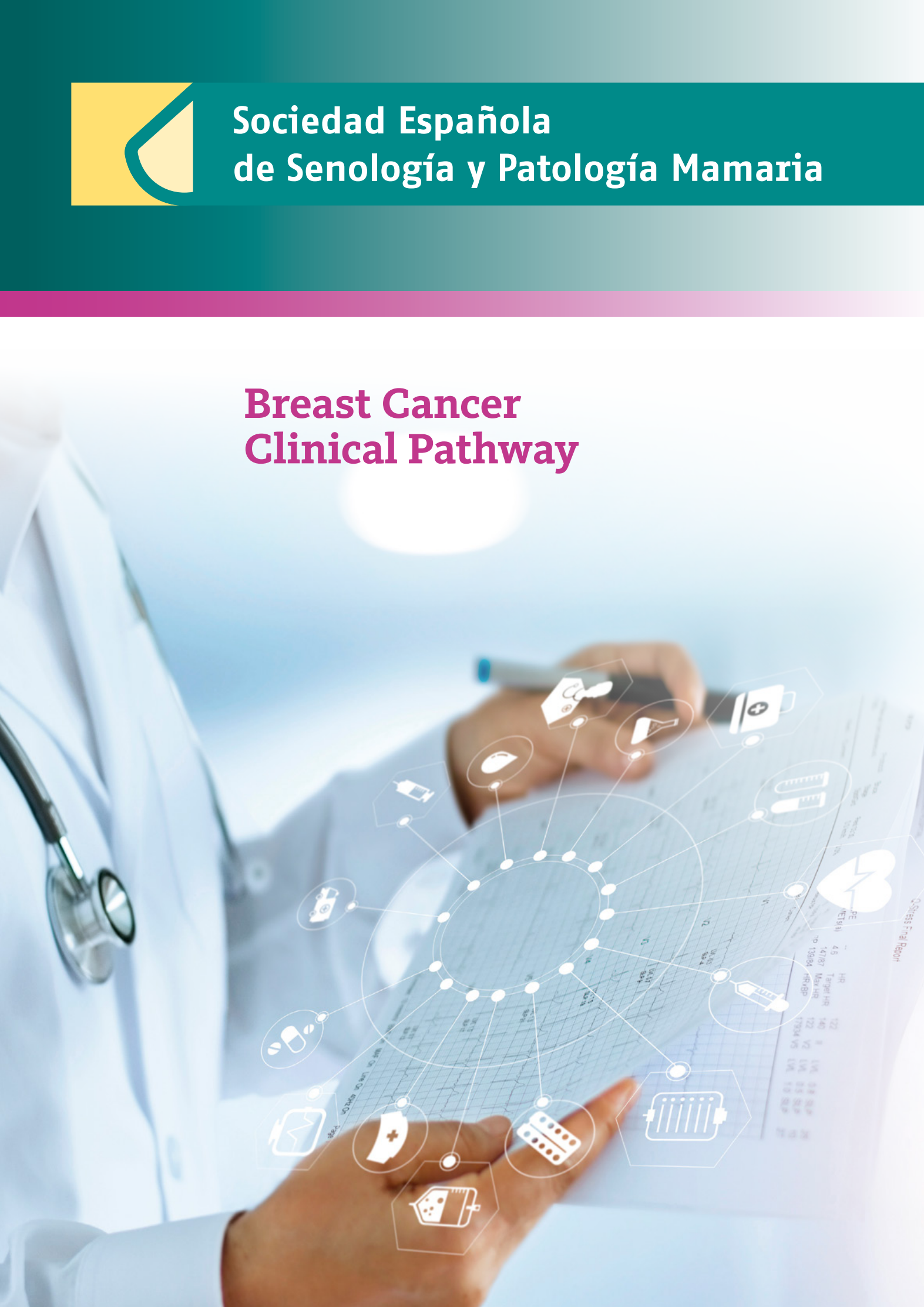
Sociedad Española
de Senología y Patología Mamaria

Breast Cancer
Clinical Pathway



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Breast Cancer Clinical Pathway 2020

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Foreword

More than two years ago, the Spanish Society Of Senology And Breast Disease (SESPM) considered the need to prepare a document that would not only include updates to scientific knowledge, such as the Clinical Practice Manual that we publish every two years, but also establish structured criteria for quality of care, for the first time in Spain.

These criteria, agreed upon by different state and international organizations, are based on the application of different paradigms arising from the continuous changes that fortunately occur in the evolution of knowledge and which include concepts such as evidence-based medicine at different levels, quality of evidence, degrees and quality of recommendation and evaluation indicators.

Furthermore, the entry of biological medicine replacing purely mechanical medicine has revolutionized the paradigms through which we had already improved the survival of breast cancer patients and has allowed the introduction of a concept that seemed very obvious but has taken too long to take hold: multidisciplinarity.

Its implementation through the Breast Units (BU) and its recognition by the Health Administration has been fundamental in promoting teamwork, facilitating collaboration in protocols, clinical trials and teaching at different levels, and eliminating many obstacles that, at personal or corporate level, had generally been created due to the rapid growth produced in the world of scientific medicine.

The SESPM has favored the creation of BUs practically since its creation 40 years ago and has managed to generate in our country the culture that they are essential to achieve excellence in care not only in technical terms but also in terms of quality. The accreditation by the Society of more than 35 Units implemented in different hospitals nationwide, through our Protocol, is a good example of this.

Our concern for the quality of patient care is linked to the indications of the European Commission Initiative on Breast Cancer (ECIBC) project. Some of their representatives have been present at the meetings of BU Coordinators in our country, which we hold annually at the Ministry of Health, giving us updates from the Quality Assurance Scheme Development Group (QASDG) and the Guidelines Development Group (GDG).

The combination of the method of tackling breast cancer through the BUs and the continuous improvement in patient care, with the periodic evaluation of these through the application of selected indicators included in this Clinical Pathway, is what guides us towards excellence, which is ultimately our goal.

Various circumstances have influenced the fact that there has been a notable delay in the publication of this Clinical Pathway. It is therefore necessary to thank the Coordinators and numerous professionals, members of SESPM, for their work and even for their patience in finally bringing it to fruition.

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All the authors have made a declaration of interest.
The authors and reviewers declare that they have no interests that could compete with the primary interest and objectives of this Breast Cancer Clinical Pathway and influence their professional judgment in this regard.

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Contents

Introduction

Cancer is one of the biggest health problems as indicated by studies based on the European Network of Cancer Registries (ENCR), the World Health Organization (WHO) database and the United Nations' population estimates, which establish cancer incidence and mortality figures for 2012 in 40 European countries. It is estimated that 3.45 million new cases appear each year (excluding non-melanoma skin cancer), of which 53% (1.8 million) are in men and 47% (1.6 million) in women[1]. In this study the most prevalent cancers were breast cancer in women (13.5%) followed by colorectal cancer (13%), while in men the most prevalent cancers were colorectal cancer (13%), prostate cancer (12.1%) and lung cancer (11.9%)[1]. In Spain, according to data from the aforementioned study, breast cancer was the leading cause of death in women (15.5%)[1].

In Spain, cancer is one of the main causes of morbidity, according to incidence estimates by the Spanish Network of Cancer Registries (REDECAN) for 2019, the most frequently diagnosed types of cancer will be colon and rectum cancer (44,937 new cases), prostate cancer (34,394), breast cancer (32,536) and lung cancer (29,503). In women, breast cancer is in first place and is followed by colorrectal cancer[2].

According to data provided by the GLOBOCAN 2018 Project on the estimated prevalence of tumours in Spain for 2018, the number of tumours among women is 358,434 and 414,419 cases among men. Breast cancer is the most prevalent neoplasm in women (36.2%)[3].

According to the data available from the National Statistics Institute (INE), in the year 2017 the number of deaths due to cancer was 113,266, globally constituting the second cause of death in Spain (26.7%). This same source describes that the mortality attributed to breast cancer was 6,573 deaths 4.

Given the relevance of this data, the convenience of the diagnosis and treatment of breast cancer patients has been verified in the context of Specialised Units[1], equipped with a multi- and interdisciplinary team of professionals that include both the specialties involved and those that may be involved at some point[5].

It is important that in order for these units to provide cross-sectional quality support, they follow standards in their operation and are monitored through indicators at all times. To this end, the European Commission is carrying out an initiative to develop, in a consensual manner, indicators for Breast Units that guarantee good practice and excellent patient care[6].

Objectives of the breast cancer clinical pathway

The objectives of the Breast Cancer Clinical Pathway are:

- To serve as a useful tool for the continuous improvement of patient care, to reduce unjustified clinical variability and to facilitate its regular evaluation, so that information is available on key indicators and the assessment and care provided to the patient.
- To describe the aspects related to the management of patients with suspected breast cancer, the diagnostic confirmation process and the therapeutic approach, in order to establish common and homogeneous points of care and their requirements according to the available evidence.

▼ STRUCTURE OF THE CLINICAL PATHWAY

The following documents make up the Breast Cancer Clinical Pathway:

1. Time matrix with all activities and interventions performed on the patient during the care process.
2. Treatment and nursing care record sheet.
3. Variation sheet.
4. Satisfaction Survey.
5. Evaluation indicators.

Of the documentation indicated, the first three documents must be completed by all the professionals involved in the patient's care, leaving a record of the activity carried out by recording date and signature of the person responsible.

Scope of the clinical pathway

Target population

1. People with clinical signs or findings of suspected breast cancer, referred from Primary Care or from population-based screening programmes.
2. Patients referred from the breast cancer early detection programme for suspected malignant lesions detected on the analog, digital or tomosynthesis mammography.
3. People with increased risk of breast cancer (personal history and risk factors), for their assessment and management of genetic risk.

Inclusion criteria

1. Presence of clinical signs or findings of suspected malignant breast cancer.
2. Referral from the population screening programme for suspected malignant lesions detected on the mammography.
3. Presence of increased risk of breast cancer due to personal history and genetic factors.

Exclusion Criteria

1. The performance of the population-based screening test, established as an activity of the Breast Cancer Early Detection Programmes, is not included in the Clinical Pathway
2. Advanced breast cancer in a palliative situation and receiving specific attention and care from the palliative care team.

Criteria for completion and exit from the Clinical Pathway

1. Patients in whom a lesion suspected of malignancy has been ruled out. Patient is discharged from the diagnostic process because it is a suspicious lesion that is classified as BIRAD2 or lower.
2. Patients who receive systemic treatment and after five years of follow-up there are no signs or symptoms of tumour recurrence, after the tumour has been excised and hormonal treatment given.
3. Patients receiving radiotherapy treatment, when no signs or symptoms of disease recurrence are observed five years after completion of other adjuvant treatments if needed (hormone therapy).
4. Patients who only receive surgical treatment without requiring other therapeutic measures (systemic treatment or radiotherapy) and who, after a 5-year follow-up, do not show signs or symptoms of disease recurrence.

▼ WHO THE CLINICAL PATHWAY IS AIMED AT

The Clinical Pathway is aimed at health professionals who are directly involved in the care of breast cancer patients, i.e. pathologists, radiologists, gynaecologists, surgeons, nuclear doctors, medical and radiotherapy oncologists and nursing professionals.

Also at all those professionals who are involved, in some way, in the diagnosis and interdisciplinary treatment of these patients, such as geneticists, psychologists, plastic surgeons, molecular biologists, primary care professionals, radiotherapy technicians, etc.

In addition, this document may be useful for clinical managers and professionals involved in quality of care.

Methodology

1

DEVELOPMENT OF THE TIME MATRIX OF THE CLINICAL PATHWAY AND THE RECOMMENDATIONS AND SOURCES OF EVIDENCE DOCUMENT.

The clinical pathway has been drafted by a group of 38 experts distributed in 6 working groups according to their specialty: Radiodiagnosis, Pathology, Nuclear Medicine, Surgery, Medical Oncology and Radiotherapy Oncology.

This group of experts drafted the time matrix, the document that summarises the recommendations and the evidence that supports the steps described in the time matrix. It was also in charge of prioritising indicators and drafting indicator sheets.

The drafting of the clinical pathway included the following steps:

A Literature review: Those clinical guidelines with a scope related to the clinical pathway were those mainly taken into account. Documents relating to the adequacy of diagnostic tests[7] and some relating to legislation on the topic[8,17] were also taken into account.

B Criteria for selection of revised sources: The guides selected were evaluated by two members of the group using the AGREE methodology II[9,10] so that the guides selected met a methodological rigour assessment of over 60%. (Annex 1).

C Design and development of the time matrix: A time matrix was developed for the diagnostic process and another for the therapeutic process. These columns show the different specialties involved in the process and the personnel, activities and documents involved in each one. In addition, the care time is considered for each stage. Finally, it is complemented by recommendation documents, supporting evidence sources and technical notes.

2

IDENTIFICATION, SELECTION, PRIORITIZATION, DEFINITION AND VALIDATION OF INDICATORS FOR THE EVALUATION OF THE CLINICAL PATHWAY.

All the experts participated in this process, again divided into the 6 working groups included in the clinical pathway.

As a background, a study led by the Spanish Society Of Senology And Breast Disease[11] was considered, in which the indicators used in the Breast Disease Units (SESPM) were established at state level. To this end, a survey designed through the bibliographic collection of indicators in breast pathology included in different international clinical practice guidelines12-17 was carried out and sent to 167 units, obtaining a response from 19 of them (11.3%).

The steps followed to establish the clinical pathway evaluation system were:

A Identification of indicators:

The guides or papers used in the SESPM[11-18] survey, proposed by the Scientific Societies to address general aspects[18-28], were considered.

The proposals for the statements of the indicators were grouped by areas of action to be evaluated by each group. The evaluation of an indicator by more than one working group was allowed, if necessary. Redundancies, repetitions and obsolete aspects were eliminated.

The number of indicators by area was:

- Pathology: 13
- Radiodiagnosis: 8
- Surgery: 22
- Nuclear medicine: 6
- Medical oncology: 18
- Radiation oncology: 8

The relevance of these indicators was evaluated by each group through an online survey (Surveymonkey), defining relevance such as: alignment with the contents of the time matrix, relative importance of the clinical impact of the application of the measure, aspects of the clinical pathway for improvement and feasibility of the measure.

B Selection and prioritisation of indicators:

The DELPHI[29-31] methodology was used, establishing the number of indicators to be prioritised by each group, which was 3 to 4.

Each expert made an assessment of each indicator, giving a score from 1 (not very relevant or relevant) to 9 (very relevant or relevant). The result was evaluated so that the selected indicators showed a median estimate with a value equal to or greater than 7 or an interquartile range equal to or less than 2. Three indicators were chosen in the Pathology, Radiodiagnosis, Nuclear Medicine, Medical Oncology and Radiotherapy Oncology groups and four in the Surgery group.

C Definition of the indicator and its standard:

A sheet was designed for each indicator which included: a description of the indicator formula (definition of numerator and denominator), the indicator standard, the inclusion and exclusion criteria, the source of information, a section for observations and a bibliography that supports the definition of the indicator.

D Validation of the indicator:

A face-to-face meeting with the coordinators of each group was held in October 2018 and it was considered a validated indicator if it received more than 75% of the votes with a score of 7 or more. Only in the medical oncology group was an indicator rejected and replaced with the next one in the prioritisation stage. The validated indicator sheets are detailed in the evaluation section of the breast cancer clinical pathway: Evaluation indicators.

3

UPDATING AND IMPLEMENTATION OF THE CLINICAL PATHWAY.

The clinical pathway will be updated every five years after its publication, and will include new evidence generated in the knowledge of breast cancer.

The implementation will be a multicentric process and, in addition, the design of the variation and verification sheets of the Clinical Pathway will be unified for all the participating Breast Units, although the specificities of each unit will be taken into account in the application.

The variation sheet is the document that reflects all the possible situations or circumstances that involve the departure of a patient from the Clinical Pathway before the process described therein has been completed.

The verification sheet is the document where all the activities of the personnel involved are recorded. Recording key activities as a checklist, and incorporating them into the patient's clinical history can help make implementation more successful.

Implementation will be carried out taking into account the following premises:

- **It should be distributed to all professionals in the Breast Unit.**
- **Its use will be facilitated by providing permanent and easy accessibility.**
- **There will be a person responsible in each unit or center for implementing the Breast Cancer Clinical Pathway. This person will guarantee:**
  - The distribution of the Clinical Pathway to all professionals involved.
  - That the documentation included in the Clinical Pathway is known and used appropriately by all the professionals involved.
  - Monitoring of the implementation of the Clinical Pathway, recording possible incidents, informing the rest of the team of professionals who use the Pathway and adopting corrective measures.
  - Updating the content of the Clinical Pathway.

Time matrix

TIME MATRIX FOR BREAST CANCER CLINICAL PATHWAY

STAGE 1. DIAGNOSTIC CONFIRMATION ON SUSPICION OF MALIGNANCY

Entry Criteria Clinical Pathway[1]	Diagnostic confirmation procedure

› TIME* Symptoms - Treatment (Maximum 3 months)
› TIME (First visit to the Breast Unit)- Treatment (Maximum 6 weeks)
› Time interval (decision to carry out histopathological study)- Result (Maximum 14 days)

UNIT	Surgery/Gynaecology	Radiodiagnosis
Staff involved	• Surgeon • Gynecologist • Plastic[2] • Administrative staff	• Radiologists • Technicians • Nurses (Case Manager) • Administrative staff
Clinical Evaluation	PH, FH, Treatments, allergies, careful PE (breast, axilla and Sc)	Mammography (be it analog, digital or tomosynthesis) and/or ultrasound sequentially according to clinical suspicion and findings. Figure 2.1 see page 26 Figure 2.2[3] see page 29 • MRI in selected cases[4] • Percutaneous VAB/CNB biopsy of BI-RADS 4 and BI-RADS 5 lesions[5] • Re-evaluation of the histological biopsy result
Nursing Care	Care of the patient, presence in the PE, material in case of cytology by nipple discharge	Support during and after interventionist processes
Techniques and equipment needed	Basic dressing material, syringes, intramuscular needles, carrier and fixation material	• Mammographer • Ultrasound Device • Sterotaxy biopsy system • Ultrasound-guided biopsy material • MRI • MRI biopsy system • Harpoons for location • Marker clips • Iodized contrast • Gadolinium • Galactography material
Information/ Documentation	• Consents to CNB and VAB • Mastalgia Documentation	• IC for interventionist procedures. • Previous studies
Activities management consultations / Tests requests	• Request for US, MMG, CNB or VAB as appropriate[3] Figure 2.1 see page 26 Figure 2.2 see page 29 Figure 2.3 see page 30 Table 2.3[9] see page 32 Table 2.4[10] see page 33	• BI-RADS 3 follow-up (Alternative to clinical follow-up + radiology). Inter-consultation to clinical, quick circuit activation • Request of PH • BI-RADS cases 0- Referral to Circuit or management of request for complementary diagnostic tests
Discharge criteria	BIRADS 2 or less	In case of concordant benign biopsy: Final radiological report[11] • BI-RADS Cases 1 or 2 • BI-RADS Cases 0

PH: Personal History; FH: Family history; Treatments: Treatment; PE: Physical Examination; US: Ultrasound; CNB: Core Needle Biopsy, VAB: Vacuum Aspiration Biopsy; IC: Informed consents; MMG: Mammography; MRI: BI-RADS Magnetic Resonance: Breast Imaging reporting and data System; IHC: immunohistochemistry; FISH: Fluorescence in-situ hybridization

	Extension Study
Pathology	**Radiodiagnosis**
• Pathologist • Technical • Pathology and cytology • Molecular Pathology • Administrative staff	• Radiologists • Technicians • Nurses • Administrative staff
• Diagnostic suspicion through image or clinical • Diagnostic Information (Hematoxylin-Eosin) • Diagnostic evaluation • Biomarker evaluation (IHC, FISH) • Genetic signature if applicable	**After biopsy-confirmed breast carcinoma:** • Staging MRI[6] Figure 2.3 see page 30 • Axilla Ultrasound. • Marker placement if neoadjuvant chemotherapy is considered.
	Support during and after interventionist processes
CNB, VAB • Fixation • Macroscopic study • Morphological study with H&E • Radiopathological correlation study. • Frozen study • Study of margins Note 4: on page 91 • Sectioning and staining of samples • Immunohistochemistry (IHC) and FISH. **Progesterone receptors, estrogen, HER2, Ki67,** **Establish fixing system and time** Note 8: on page 94 Note 10: on page 96	• Ultrasound Device • MRI
Pathology report • Report on sentinel lymph node and/or axillary lymphadenectomy. • Prognostic and predictive factors outcome report[8].	• IC for procedures
• Issuance of the final report including prognosis and predictive factors[8]	

CASE REPORT TUMOURS COMMITEE

⁖ **Multidisciplinary team**
- Pathologist
- Surgeon
- Gynecologist
- Plastic Surgeon
- Radiologist
- Radiation Oncologist
- Medical Oncologist
- Case Manager
- Psychologist

STAGING AND EXTENT OF THE DISEASE FOR THERAPEUTIC DECISION MAKING

Staging Results (TNM)
Extension Diagnosis
Prognosis Factors

*Genetic predisposition study[7]
Geneticist/Genetic Counseling Expert

1. TIME MATRIX:
STAGE 1: Diagnostic confirmation in case of suspected malignancy

01 Clinical Pathway Entry Criteria:

1] Person with clinical signs or findings in imaging techniques suggestive of breast pathology.

2] Person with increased risk of breast cancer (history/risk factors).

02 If a High Resolution Unit is available, patients are evaluated by Radiology on the same day as the Surgical Consultation. If they are discharged by BI-RADS<3, they return to the consultation and are discharged. If it is for revision by BI-RADS-3 from the surgery office, an appointment for revision is made for the US, MMG or MRI that Radiologist considers convenient

03 Indications for requesting radiological diagnostic tests:

Table 2.1 › Diagnostic management of breast pathology lesions.

Table 2.2 › BI-RADS radiological classification and its attitude towards the follow-up of breast lesions according to results.

Figure 2.1 › Sequence of imaging tests for suspected malignant lesions in the breast.

Figure 2.2 › Attitude in handling breast lesions according to BI-RADS classification.

04 MRI Indication in the presence of a lesion suspected of being malignant.

Figure 2.1 see page 26

1] Early detection in high-risk women:
Proven BRCA mutations and untested first-degree relatives.
Women with a history of chest irradiation between the ages of 10 and 30. (Start 8 years after irradiation).
Women with a risk of developing breast cancer equal to or greater than 20%, according to risk estimation models.

2] Suspicion of prosthesis breakage, after negative or equivocal conventional study.

3] Hidden breast cancer (histological diagnosis of metastasis, mainly axillary with negative conventional study).

4] Suspicious secretion, with negative conventional study.

5] Characterization of equivocal findings in conventional studies (only if biopsy orientation is not possible).

05 Indications for percutaneous biopsy of BI-RADS 4 and BI-RADS 5 lesions.

Figure 2.2 see page 29

- All lesions categorized as BI-RADS 4 or 5.
- In some cases of BI-RADS 3 (follow-up impossible, patient preference, high risk).
- No suspicious lesions should be surgically removed without verification by percutaneous biopsy.
- Precautions: anticoagulation and anti-aggregation should be discontinued, if possible. In the case of 14-gauge CNB, this is not always necessary. Local anesthesia is sufficient.

It can be done with ultrasound (more comfortable), stereotactic or by resonance control (in cases only visible with this technique).

Techniques:

- **FNAP** (its profitability is lower than other techniques. It is not possible to differentiate in-situ cancers from infiltrating cancers. It's only an alternative in expert hands. It is indicated for lymph node assessment).
- **Core needle biopsy (CNB).** The minimum desirable size should be 14G. Of choice in nodes and lymph nodes (in this case fine needle puncture is valid).
- **Vacuum-assisted biopsy (VAB).** Of choice in

  Microcalcifications (radiological verification of calcifications in the samples is essential).

  Distortions.

  As a second method after inconclusive result from CNB.

  MRI biopsy.

After biopsy, verification of results and agreement with the radiological findings is essential. It is advisable to place a clip on the bed, which is obligatory if the entire visible lesion is removed.

06 Staging magnetic resonance.

Figure 2.3 see page 30

No clinical guidelines recommend it systematically.

It may be indicated:

1] When the size of the lesion cannot be adequately assessed by mammography or ultrasound.

2] Infiltrating lobular carcinoma if conservative surgery is considered.

3] When partial breast irradiation is considered.

4] Carcinoma diagnosed in high-risk women.

07 Evaluation of genetic predisposition.

Table 2.18 see page 58

Table 2.19 see page 59

Table 18 › Risk assessment. Family study selection criteria.

Table 19 › Recommendations for the management of women who are mutation carriers in BRCA1 and BRCA2.

08 Clinical documentation:

] Pathology report.

Quality criteria and content.

09 Table 3. Recommendations on radiological and histopathological diagnosis in non-advanced localised disease.

Table 2.3 see page 32

10 Table 4. Recommendations related to imaging tests for extension studies in Metastatic Disease.

Table 2.4 see page 33

11 Clinical documentation:

] Radiology report.

Quality criteria and content.

TIME MATRIX FOR BREAST CANCER CLINICAL PATHWAY

STAGE 2. THERAPEUTIC APPROACH

STAGE	PLAN	SURGICAL TREATMENT	
UNIT	**TUMORS COMMITTEE**	**Surgery, Gynaecology, Plastic Surgery**	**Nuclear Medicine**
TIME	‣ Adjuvant chemotherapy (administered for 2-6 weeks post-surgery) ‣ Neoadjuvant Chemotherapy (Perform Surgery within 3-4 weeks of completion of CT)		
Staff involved	• Multidisciplinary Team[1]	• Surgeon • Gynecologist • Plastic Surgeon[2] • Administrative staff	• Nuclear Physician • Pharmaceutical Radio • Specialist Technician • Nurse • Administrative staff
Clinical Evaluation	THERAPEUTIC DECISION • ACCORDING TO STAGING (TNM) Note 1: on page 89 Note 5: on page 92 • Prognosis Factors Note 8: on page 94 Note 10: on page 96 • After going through the breast committee, you will be informed of the decision if it is surgical and the techniques that can be applied see corresponding column	• Inform the patient of the Radiology and Pathology outcome. • Report of decision of the breast committee • Offer alternatives according to IHC and her wishes. • Surgical treatment with its variants or CT • Answer questions and clearly explain surgical procedures • Subsequent appointment for patient if no decision is made at that time. • Schedule surgery. Table 2.6 see page 44 Table 2.8 see page 46 Table 2.9[17] see page 46 • Application checklist for surgical safety.	Short medical history and physical examination. Image processing. SSLNB procedure • Nodal marking system • Intraoperative collaboration Table 2.7[18] see page 45
Nursing Care		• Take care of patient. • If you are a specialised nurse, please call her to answer her questions. • Care and advice in surgical wound management.	
Techniques and equipment needed		• Measuring tape or ruler for size measurement in case of reconstruction to order suitable prostheses or expanders. • Marker for designing patterns	Diagnostic equipment: • Conventional gamma camera • SPECT (SPECTTC preferred) • Intraoperative Sentinel lymph node probe • PET/CT • Optional Intraoperative handheld camera Radiopharmaceuticals: • Albumin nanocoloids • (Tilmanocept if applicable) • Fluordeoxyglucose (FDG) • Diphosphonates (HDP)

	SYSTEMIC THERAPY	RESPONSE TO NEOADJUVANT THERAPY	RADIOTHERAPY
Pathology	**Medical Oncology**	**Pathology**	**Radiation Oncology**
• Pathologist • Technician in Pathological Anatomy and Cytology • Administrative staff • Molecular Biologist	• Medical Oncologist • Nurses • Administrative staff	• Specialist in Pathological Anatomy • Technician in Pathological Anatomy and Cytology • Administrative staff • Molecular Biology	• Radiotherapy Oncologist • Radiophysicist • Technicians • Nurses • Administrative
• SSLNB: Intraoperative pathological study Note 5: on page 92 • Evaluation of Pathological Response Note 6: on page 92	• Patient identification • Anamnesis and Physical Examination • Test evaluation • Relapse risk assessment and decision of treatment Table 2.10 [3] see page 47 • Prescription of treatment if: - Neo-adjuvant Table 2.15 [4] see page 53 - Adjuvant[5,6,7,8] Table 2.11 see page 48 Table 2.14 see page 51 - Metastatic Disease[9,10,11] Table 2.5 see page 34 Table 2.17 see page 55 Table 2.18 see page 58	• Study of Response. Post-Neoadjuvant • Post-neoadjuvant treatment response. • Evaluation of response to neoadjuvant treatment (Primary tumor as sentinel lymph node) Note 6: on page 92	• Anamnesis and Physical Examination • Patient Identification • Anamnesis and evaluation of patient tests • Treatment prescription Table 2.20 [12] see page 60 • Performing CT scans • Dosimetric calculation Table 2.20 see page 60 Table 2.21 [12,13] see page 61 • Dosimetric verification if Treatment with image verification is needed • Clinical and technical control of treatment
	• Care and appointments to answer her questions • Training in healthy habits and lifestyles		• Healthy habits advice. • Care and advice during and sometimes after radiotherapy
• Macroscopic and radio-pathological correlation study of surgical parts • Frozen study • Study of margins • Sectioning and staining of samples • Immunohistochemistry (IHC): Estrogen, progesterone, HER2, Ki67 receptors: Establish fixing system and fixing time **Sentinel lymph node study** • Molecular techniques (OSNA) • Conventional techniques (HE) (IHC) Note 1: on page 89 Note 10: on page 96	• CT Administration Device (Reservoir, PIC...)		• CT • Volume delineation and dose calculation system • Linear accelerator • High rate brachytherapy unit • Intraoperative radiotherapy unit

‣ Continued on next page

TIME MATRIX FOR BREAST CANCER CLINICAL PATHWAY

STAGE 2. THERAPEUTIC APPROACH

STAGE	PLAN	SURGICAL TREATMENT	
UNIT	**TUMORS COMMITTEE**	**Surgery, Gynaecology, Plastic Surgery**	**Nuclear Medicine**
⁖ Information/ Documentation		• Possible consents to SI • Surgical technique information brochures • Breast reconstruction information brochures • Mastalgia documentation	• Medical history • Informed Consent • Previous studies
⁖ Activities management consultations / Test request		• Inclusion on the surgical waiting list • Transfer to Medical Oncology • Coordination with Plastic Surgery	
⁖ Monitoring		• Postoperative (Visit after 10 days) • Remove stiches if applicable • Review of incisions • Give pathology outcome • Check oncology appointments if applicable • Expansion if applicable • Possible consents to SI • Surgical technique information brochures • Breast reconstruction information brochures	
⁖ Discharge criteria			

TT: Treatment; PE: Physical Examination; US: Ultrasound; IC: Informed Consents; MMG: Mammography; MRI: BI-RADS Magnetic Resonance: Breast Imaging reporting and data System; IHC: immunohistochemistry; FISH: Fluorescence in-situ hybridization; OSNA: One Step Nucleic Acid Amplification; HER-2: Human epidermal growth factor receptor 2; SSLNB: Selective Sentinel Lymph Node biopsy; OSNA: SI: Surgical Intervention.

	SYSTEMIC THERAPY	RESPONSE TO NEOADJUVANT THERAPY	RADIOTHERAPY
Pathology	**Medical Oncology**	**Pathology**	**Radiotherapy Oncology**
Pathological Report[14] • Lymph Node Status Report • Prognosis and predictive factors outcome report • Evaluation of pathological response Note 6: on page 92	**Pathological Report**[14] **Radiological Report**[15] • Medical history • Treatment prescription • CT treatment sheet • CT informed consent • Information leaflets on possible CT toxicities and advice and care	• Evaluation of pathological response Note 6: on page 92	• Pathology and Radiology Reports • Medical history • Informed Consent • Treatment prescription • Treatment Sheet[16]
• Safe, adequate and easily retrievable storage of the material for second opinions or further testing. • Consultation of cases to other centers.	• Clinical control of treatment • Monitoring • Management of chemotherapy adverse effects • Monitoring criteria according to cancer risk		• EXTENSION STUDY, disregard M1 (Abdominal US/CAT CT, GGO. Echocardio and Blood Work) • Diagnostic imaging tests, clinical or pathological analysis
	• Management of chemotherapy adverse effects • Monitoring criteria according to cancer risk		
• Issuance of final report including prognosis and predictive factors Note 1: on page 89 Note 10: on page 96	• No evidence of relapse after 5 years of follow-up after tumour removal and completion of hormonal treatment • Referral to another service for annual mammography, blood work and physical examination		• In principle, no discharge is possible • Royal Decree 1566/1998 of 17 July,

2. TIME MATRIX:
STAGE 2: Therapeutic Approach

01 Multidisciplinary team:

- Surgeon
- Gynecologist
- Nuclear medicine doctor
- Plastic Surgeon
- Pathologist
- Radiologist
- Radiotherapy Oncologist
- Medical Oncologist
- Case Manager
- Psycho-oncologist

] ***Genetic predisposition study:** Geneticist/Genetic Counseling Expert.

02 If the surgical procedure requires the collaboration of Plastic Surgeons and they are available at the centre or come as external surgeons, the surgical intervention will be coordinated with them. They will be evaluated by Plastic Surgery in advance to take action and explain the intervention, as well as to provide informed consent.

03 Assessment of relapse risk and treatment decision.

Table 2.10 see page 47

04 Neoadjuvant chemotherapy schemes for early breast cancer.

Table 2.15 see page 53

05 Recommendations for the complementary treatment of Early Breast Cancer.

Table 2.11 see page 48

Figure 2.5 see page 50

Complementary treatment algorithm for early breast cancer - HER2 Negative.

Figure 2.6 see page 51

Complementary treatment algorithm for early breast cancer - HER2 positive.

06 Hormonal therapy in the treatment of early breast cancer.

Table 2.12 see page 49

07 Recommendations for cytotoxic treatment.

Table 2.13 see page 50

08 Table 14. Anti-Her 2 Biological Agents Therapy.

Table 2.14 see page 51

09 Therapy of Metastatic Disease. Relapse study recommendations. PET-CAT Extension and Indication Study.

Table 2.5 see page 50

10 Hormonal therapy in the treatment of metastatic breast cancer. Pre-menopausal women.

Table 2.17 see page 55

11 Hormonal therapy in the treatment of metastatic breast cancer. Postmenopausal women.

Table 2.16 see page 54

12 Volumes, doses, treatment schemes. Treatment volumes.

Table 2.20 see page 60

] Annex 3. Radiotherapy treatment application procedures. Techniques

13 Dose of radiation to risk organs.

Table 2.21 see page 61

14 Pathology Report.

Quality criteria and content.

15 Radiology report.

Quality criteria and content.

16 Radiation Oncology Report.

Quality criteria and content.

17 Recommendations on surgical treatment.

Table 2.6 see page 44

Table 2.8 see page 46

Recommendations on excision/resection margins.

Table 2.9 see page 46

Recommendations related to reconstructive surgery.

18 Table 7. Recommendations related to selective sentinel lymph node biopsy.

Table 2.7 see page 45

Chapter 2

Recommendations and sources of evidence document

STAGE 1: DIAGNOSTIC PROCESS ON SUSPICION OF MALIGNANCY

1. RADIOLOGICAL AND PATHOLOGICAL DIAGNOSIS AND EXTENSION OF THE DISEASE.

1.1. MANAGEMENT OF LESIONS SUSPECTED OF MALIGNANCY: DIAGNOSTIC CONFIRMATION.

DIAGNOSTIC IMAGING TESTS IN IN BREAST DISEASE[32-38].

The exploratory signs of suspicion are:

- Presence of palpable nodes of new appearance (not previously studied).
- Pathological secretion (unilateral, uniorificial, and spontaneous).
- Changes in the skin or areola-nipple complex (retraction/ulceration).
- Axillary adenopathies.

The presence of one or more of these signs implies the need to request radiological tests.

Figure 2.1 shows the sequence of imaging tests for the management of lesions with suspected malignancy in the breast (Presence of Palpable Nodes) and/or Secretion.

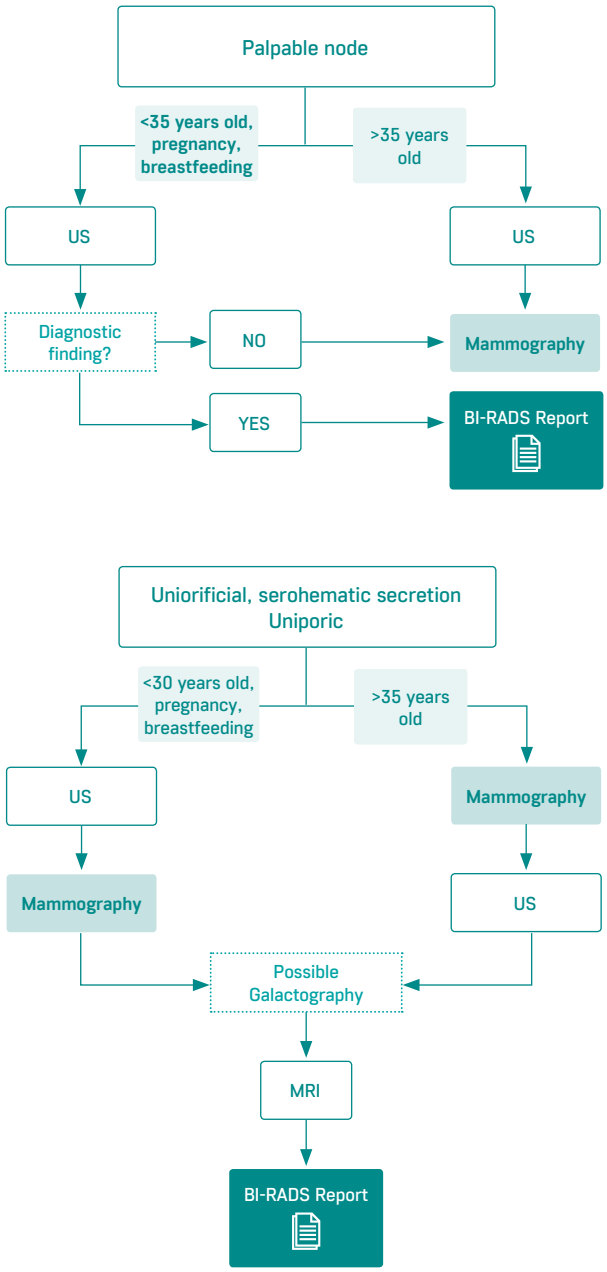


Figure 2.1. Sequence of imaging tests in the management of suspected breast malignancies.

BREAST DISEASE	IMAGING TESTS		HISTOLOGICAL SURVEY Histopathological confirmation or correlation
⁙ NODE and PALPABLE AREA Figure 2.1 see page 26	Women >35years or 30-35 years in case of high-risk FH	• **Bilateral mammography by double projection.** • **Complementary ultrasound in any case, even if mammography is negative.** • **Very important:** correlate the findings of both techniques.	**Percutaneous biopsy (CNB or VAB):** If histological study is necessary.
	Women <35 years old, pregnant, nursing or with signs of inflammatory pathology.	• **Ultrasound:** aimed at identifying the palpable lesion. • **Mammography:** if negative ultrasound or ultrasound signs of suspicion.	
⁙ SECRECTION Figure 2.2 see page 29	**Multimodality:** • **Mammography (if >30 years):** low sensitivity and specificity. If it is normal, it does not rule out injury. Other studies need to be done. • **Ultrasound:** Greater diagnostic cost-effectiveness when performed on the trigger point and/or lesions identified in galactography or MRI. If it is normal, it does not exclude the use of another image technique. • **Galactography:** If spontaneous, unilateral, uniorificial secretion. Technically complex. A normal result does not exclude pathology. • **MRI:** High sensitivity to detect lesion and less complexity than the previous one.		**Two possible scenarios:** diagnostic and therapeutic (Removal of intraductal papillomas with vacuum systems).
⁙ SKIN, AREOLA AND NIPPLE DISORDERS › Skin alterations	• **Ultrasound:** it is the initial technique in diagnostic management. • **Mammography:** conventional bilateral study in double projection. • **The correlation between both imaging techniques is very important.** • **MRI:** high sensitivity (98 100%) to detect lesions in inflammatory carcinoma, but it is not an initial technique in diagnostic management.		If it is necessary to confirm the diagnosis of inflammatory carcinoma. If no imaging lesion is detected, the biopsy will be performed on the area underlying the increased redness and/or skin biopsy.
› Areola and nipple alterations	• **Mammography:** (> 35 years): bilateral study by double projection and additional projections may be necessary for retroareolar area assessment. • **Ultrasound:** to complete the mammographic evaluation and as a biopsy guide if necessary. If clinical Paget's Disease is suspected, the absence of findings by both techniques does not exclude malignancy. • **MRI:** if you suspect clinical malignancy, with mammographic and ultrasound study		If you suspect malignancy, and negative image studies.
⁙ HIDDEN CANCER **	• **Sequentially, depending on the presence or not of findings:** bilateral mammography, breast and axillary ultrasound, MRI and 18FDG PET CT. The last two techniques are the most sensitive when mammography and ultrasound do not detect pathology.		
⁙ CANCER en the male	ADULT MALE: • **Bilateral double projection mammography:** generally sufficient to rule out neoplasia. If doubts arise: • **Ultrasound:** Very sensitive in the detection of benign pathology (epidermal lipomas and inclusion cysts) and high specificity for malignant lesions. YOUNG MALE: • **ULTRASOUND:** generally allows the diagnosis to be made without the need for any other type of test.		HISTOLOGICAL SURVEY If, after performing the imaging studies, it is not possible to rule out the presence of malignant pathology. CNB is the technique of choice.

* palpable lesions that are individualized either as a node, mass or indurated area.
** Hidden cancer: It is defined as primary breast cancer with palpable axillary node metastases, without breast lesion detected in the clinical examination or in the mammographic study.
PH - personal history; FH - family history; TT: treatment; CNB: core needle biopsy; VAB: vacuum-assisted biopsy; MRI: magnetic resonance imaging

Source: American College of Radiology ACR Appropriateness Criteria® Clinical Condition: Evaluation of the Symptomatic Male Breast. Includes revision on the subject from 1997 to 2014 Last revision date (2016)

Source: American College of Radiology ACR Appropriateness Criteria® Clinical Condition: Evaluation of the Symptomatic Male Breast. Includes revision on the subject from 1997 to 2014 Last revision date (2016)

Table 2.1. Diagnostic management of breast lesions and pathology.

The pathological diagnosis will be correlated with the radiological one to establish in a multidisciplinary way the most appropriate management for the patient. The radiological classification and management of breast lesions is shown on Table 2.2.

MANAGEMENT OF RESULTS.

Radiopathological correlation of all the results obtained is essential. In the event of an uncertain pathological result or one that is discordant with the radiological finding, the option of re-biopsiing the lesion should be considered. If the biopsy with the questionable result is a Core Needle Biopsy (CNB), it may be useful to repeat it as a Vacuum-Assisted Biopsy (VAB) [40].

BI-RADS	Diagnostic suspicion	Attitude
BI-RADS 0	Scanning with inconclusive results for technical defects	Need for other diagnostic tests for evaluation
BI-RADS 1	Normal breast	Mammography in 2 years
BI-RADS 2	Benign (probability of cancer similar to general population)	Mammography in 2 years
BI-RADS 3	Probably benign findings. (< 2% risk of malignancy)	Control 6, 12 and 24 months from initial study. If everything is normal (not pathological) Annual/biennial review Mammography
BI-RADS 4	Probably malignant (PPV for cancer between 29-34% up to 70%)	Consider biopsy Performance of histological diagnostic test (CNB/ VAB) Figure 2.2 see page 29
Categories	• **Category 4-A:** mammographic finding requiring biopsy but with a low suspicion of malignancy. • **Category 4-B:** intermediate suspicion of malignancy. • **Category 4-C:** moderate concern, but not classic malignancy (as in category 5).	
BI-RADS 5	Highly suggestive of malignancy (PPV for cancer greater than 70%)	Consider biopsy
BI-RADS 6	Malignant lesion confirmed by biopsy prior to imaging studies	Proceed with staging

CNB: Core Needle Biopsy, VAB: Vacuum-assisted biopsy.
PPV: Positive predictive value.
BI-RADS Breast Imaging Reporting and Data System.

Source:
D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.
Aibar L, Santalla A, López- Criado MS, González-Pérez I, Calderón MA, Gallo JL, Fernández Parra J. Clasificación radiológica y manejo de las lesiones mamarias. Clin Invest Gin Obst 2011;38(4):141-149.

Table 2.2. Radiological classification BI-RADS[39] and management of breast lesions.

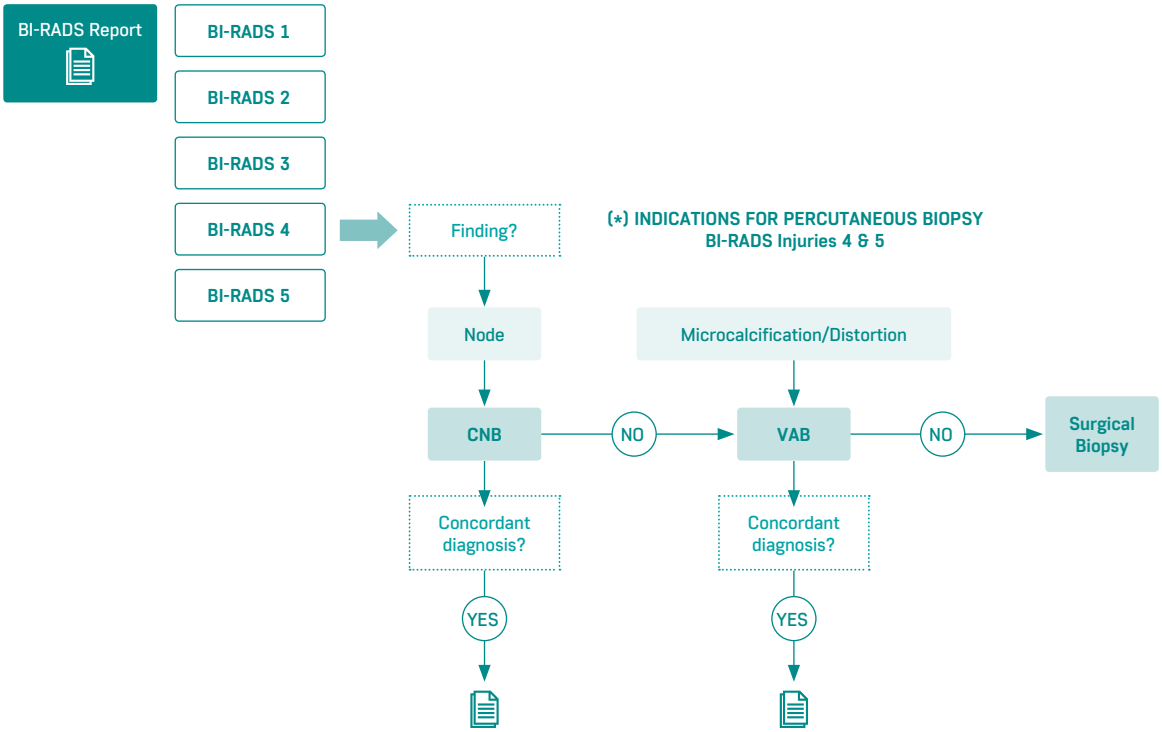


Figure 2.2. Breast lesion tracking attitude according to BI-RADS classification.

(*) PERCUTANEOUS BIOPSY INDICATIONS OF BI-RADS 4 and BI-RADS 5 LESIONS[39]

- All lesions categorized as BI-RADS 4 or 5.
- In some cases of BI-RADS 3 (inability to follow up, patient preference, high risk).
- No suspicious lesions should be surgically removed without a prior diagnosis with a percutaneous biopsy.
- Precautions: Anticoagulation and anti-aggregation should be discontinued, if possible. In the case of 14-gauge CNB, this is not always necessary.

  Local anesthesia is sufficient.

  It can be done with ultrasound control (more comfortable), stereotactic or by resonance (in cases only visible by this technique).
- Techniques:

  ❶ **FNAP.** Its cost-effectiveness is lower than other techniques. It does not allow differentiation between in-situ and infiltrative cancers. It is only an alternative in expert hands. It is indicated in the assessment of lymph node status.

  ❷ **Core needle biopsy (CNB).** The minimum desirable size should be 14G. It is the technique of choice for the study of nodes and lymph nodes (fine needle puncture is also valid in this case).

  ❸ **Vacuum-assisted biopsy (VAB).** Of choice in:

  a › Microcalcifications (radiological verification of calcifications in the samples is essential).

  b › Distortions.

  c › As a second method after inconclusive result from CNB.

  d › MRI biopsy.

After biopsy, verification of results and agreement with the radiological findings is essential. It is advisable to place a clip on the bed, which is obligatory if all the visible lesion is removed.

The **breast cancer diagnosis** is made by means of imaging techniques, mainly mammography, and by the macro-microscopic and molecular study of the affected tissue (pathological, histological and molecular diagnosis). Regional assessment of axillary nodes and distance extension study as shown in Figure 2.3 see page 30 is also needed.

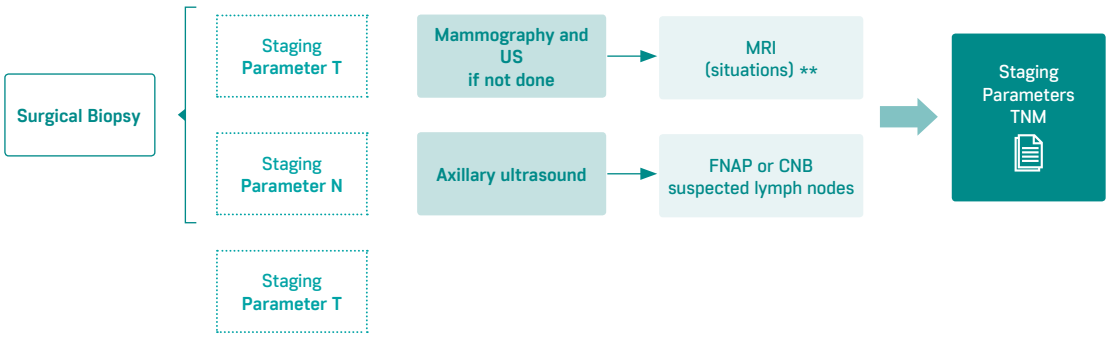


Figure 2.3. Locoregional and distant clinical staging in breast cancer.

(**) MAGNETIC RESONANCE IMAGING (MRI)[41-43]

It may be indicated:

1] When the size of the lesion cannot be adequately assessed by mammography or ultrasound.

2] Infiltrating lobular carcinoma if conservative surgery is considered.

3] When partial breast irradiation is considered.

4] Carcinoma diagnosed in high-risk women.

STAGING.

CLINICAL T-PARAMETER (T)

The assessment of the T parameter (tumour size, "TNM" staging system), from the radiological point of view, in the era of multimodality in which we find ourselves, is carried out by mammography, ultrasound and MRI.

Initially, the tumor size is evaluated by mammography and ultrasound, accepting as initial T the larger tumor size of the two techniques: the node is the finding with the best correlation between mammographic/ultrasound size (especially in predominantly fatty breasts) and histological size.

The maximum extent of microcalcifications is assessed by mammography.

In the case of distortions as a mammographic finding, the size is evaluated using this technique, considering the maximum extension of the spicules.

In general terms, mammography and ultrasound underestimate tumor size in a variable percentage range according to series between 14-37% and 18-40% respectively.

MRI is the technique with the best radio-pathological correlation for assessment. As mentioned above, parameter T should be completed for staging purposes.

Given the low specificity of MRI for the characterization of additional lesions, biopsy of such foci is a mandatory requirement before a change in therapeutic approach is made.

Ultrasound re-evaluation allows for the detection of such foci and the direction of the biopsy in most cases. When the lesion is only visible with MRI and presents suspicious characteristics, biopsy using this technique is recommended.

NODAL STAGING (N)[36,41,44-45]

The **pre-surgical regional lymph node study** in breast cancer should be directed at the axillary nodes and the infra- and supraclavicular nodes, as well as the study of the contralateral axilla against the primary tumour.

The preoperative test with the greatest safety and validity in the nodal study is ultrasound **followed by puncture (FNAP) or ultrasound-guided CNB** in cases of suspected metastatic nodal disease.

The **ultrasound-guided puncture** targets the nodes with metastatic semiology:

- Node visible by ultrasound of any size with rounded morphology.
- And/or absence of fatty hilum.
- And/or diffuse or focal cortical thickening.

Depending on the number and location of the suspicious nodes, the pN category is established by **ultrasound**:

- cN1: level I suspicious node with positive FNAP.
- cN2: adenopathic conglomerate more than three suspicious nodes with positive FNAP of the most suspicious node.
- cN3: suspicious node with positive FNAP in infra or supraclavicular territory.

The presence of metastasis in the contralateral axilla to the main tumor is considered distant metastasis, in the absence of bilateral tumor.

In case of bilateral breast cancer, both tumor size and axillary staging are performed independently for each breast.

For any tumor size the detection of metastatic nodes in infra and supraclavicular territory (N3) establishes the indication for neoadjuvant chemotherapy.

Axillary ultrasound allows the detection of rare axillary pathology in patients with clinical suspicion of metastatic breast cancer, with the consequent change in diagnostic and therapeutic approach: metastasis of extramammary tumors (melanoma), lymphoma, lymphoid hyperplasia, etc.

The territory of the internal breast is susceptible to study by ultrasound, with very low yield and with great difficulty to obtain a sample by FNAP.

MRI allows a suspicious approach, being the Selective Sentinel Lymph Node Biopsy (SSLNB) with tracer migration to this location and subsequent surgical node biopsy of these nodes the most cost-effective technique.

DISTANT METASTASIS (M)

The decision to extend studies for the detection of distant metastasis is established by the tumor staging (stage III) and the existence of symptoms:

Carcinoma in situ: no staging tests are recommended.

Stage I: radiological tests are not recommended. Complete blood work and Ca 153.

Stages II-III: chest x-ray, liver/CAT scan and bone scan. Complete blood work and Ca 153.

Stage IV: As in stage III, plus those indicated by the clinic.

The ^{18}F FDG PET CT is a technology based on the detection of neoplastic lesions with high glycemic consumption, a characteristic common to most tumors. For this reason, it has demonstrated greater sensitivity and specificity than radiological imaging techniques in the assessment of the distant extension of most neoplastic diseases, as it allows the location of tumor sites with little or no detectable anatomical alteration, as well as in the assessment of previously treated areas with a substantial secondary alteration of the anatomy, which is difficult to characterize radiologically.

For breast cancer, studies with ^{18}F FDG PET CT are potentially useful in the following situations[46,47]:

- Preoperative staging of patients at high risk of metastasis (upper stage IIIA).
- Patients with more than 4 affected axillary nodes in the post-surgical analysis.
- Patients with tumors T2N0M0 or higher in which neoadjuvant therapy for tumor size reduction is proposed.
- Pre-treatment staging in patients with inoperable tumors or locally advanced carcinomas.
- Patients with suspected recurrence, especially with negative or inconclusive imaging tests and increased tumor markers.
- Assessment of the response to primary systemic treatment.
- Initial study of inflammatory carcinomas.

At the time of diagnosis, detection of contralateral axillary metastases would classify patient as M1, even in the absence of systemic disease in other anatomical locations (once the possibility of synchronous contralateral breast cancer has been ruled out).

1.2. RECOMMENDATIONS RELATED TO DIAGNOSTIC CONFIRMATION WHEN THERE IS A SUSPICION OF BREAST CANCER MALIGNANCY.

RADIOLOGICAL AND PATHOLOGICAL DIAGNOSIS.

The following tests allow a correct diagnostic and prognostic approach for all patients in whom breast cancer is suspected.

Table 2.3

1.3. RECOMMENDATIONS IN METASTATIC BREAST CANCER ON DIAGNOSTIC TESTS FOR EXTENSION STUDY.

EXTENSION STUDY OF THE DISEASE.

The following table shows the recommendations for conducting the extension study, with regard to the indication of imaging tests and anatomical-pathological techniques[52,53].

Table 2.4 see page 33

	Recommendation	Level of Evidence / Strength of recommendation
⁘ Radiological diagnosis	• **Mammography and ultrasound:** an initial imaging test that also allows to take a biopsy of suspicious lesions[48] .	I/A
⁘ Pathological diagnosis	• **Initial biopsy:** essential for diagnosis and to obtain prognostic and predictive information. It is essential to study the estrogen receptor, progesterone receptor, HER2 and the determination of Ki-67[49] .	I/A
⁘ Staging: Imaging tests	• **Magnetic Resonance Imaging (MRI):** allows for a better staging of the disease by detecting disease foci not visible by other methods. Additional findings should be confirmed histologically due to the false positive rate. The use of MRI has not demonstrated a survival benefit, and therefore is not considered as a compulsory test[41,50].	I/B
⁘ Extension study: Imaging tests	• **Additional studies:** anamnesis, complete physical examination, laboratory tests with complete blood count, liver and kidney function tests, alkaline phosphatase and calcium. When abnormalities are detected on these tests or when advanced stage disease (stage III) is detected, a more extensive study is made using ^{18F} FDG PET-CT or thoracic-abdominal CT and bone scan (if there are bone symptoms, elevated alkaline phosphatase, LDH or calcium)[51].	I/B

Quality of evidence:

› I: Evidence from ≥ 1 correctly randomized controlled trial.

› II: Evidence from ≥1 well-designed, non-randomized clinical trial; from cohort or case-control analytical studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments.

› III: Evidence of opinions from respected authorities, based on clinical experience, descriptive studies or expert committee reports.

Strength of recommendation:

› A: Good evidence to support a recommendation for use.

› B: Moderate evidence to support a recommendation for use.

› C: Bad evidence to support a recommendation.

› D: Moderate evidence to support a recommendation against use.

› E: Good evidence to support a recommendation against use.

Source:

- Garcia-Saenz JA, Bermejo B, Estevez LG, Palomo AG, Gonzalez-Farre X, Margeli M, Pernas S, Servitja S, Rodríguez CA, Ciruelos E. Early and Locally Breast cancer. Clin Transl Oncol 2015; 17:939-945.
- Ayala de la Peña F, Andrés R, García-Sáenz JA, Manso L, Margeli M, Dalmau E, Pernas S, Prat A, Servitja S, Ciruelos E. SEOM clinical guidelines in early stage breast cancer (2018). Clin transl Oncol 2019; 21:18-30.

Table 2.3. Recommendations on radiological and histopathological diagnosis in non-advanced Localized Disease.

Metastatic disease	Recommendation	Level of Evidence/ Strength of Recommendation
⁙ **Extension study: Imaging tests**[54-56]	1] Assessing the presence and extent of visceral metastases using a combination of plain radiography, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI).	Moderate/ B
	2] Assessing the presence and extent of axial skeletal bone metastases using bone windows on a computed tomography or MRI scan or bone gammagraphy.	(*)
	3] Assessing the proximal bones of limbs for the risk of pathological fracture in patients with evidence of bone metastases elsewhere, using bone gammagraphy and/or plain radiography.	(*)
	4] Using MRI to evaluate bone metastases if other imaging is equivocal for metastatic disease or if more information is needed (for example, if there are lytic metastases invading the spinal canal).	(*)
	5] ^{18}F FDG PET-CT may replace traditional imaging for staging in high-risk patients who are candidates for neoadjuvant chemotherapy, as well as those with locally advanced disease and/or inflammatory carcinoma due to their high risk of metastatic disease[47].	Low / C
⁙ **Pathological diagnosis** Advanced disease	6] Pathological evaluation. At recurrence, consider re-evaluating estrogen receptor (ER) and status (HER2), tailoring treatment to results[57-59].	High / A
⁙ **Evolution monitoring** Advanced disease	7] Do not use the bone gammagraphy to monitor the response of bone metastases to treatment.	Low /C
	8] Do not use PET-CT to control advanced breast cancer.	Low /C

Level of Evidence:

- **High:** The available evidence generally includes consistent results from well-designed and well-conducted studies in representative populations. The studies evaluate the effects of the intervention on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
- **Moderate:** The available evidence is sufficient to determine the effects of interventions on health outcomes, but confidence in the estimation is limited by factors such as the number, size or quality of individual studies; inconsistency of findings in individual studies; limited generalization of findings to routine practice; or inconsistency in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect may change, and this change may be large enough to alter the conclusion.
- **Low:** The available evidence is insufficient to assess the effects on health outcomes. Evidence is insufficient due to: limited number or size of studies; major deficiencies in study design or methods; inconsistency of findings in the gaps of individual studies in the chain of evidence; findings not generalizable to routine practice; or lack of information on important health outcomes. More information may allow an estimate of the effects on health outcomes.

Strength of recommendation:

› A: There is a high certainty that the net benefit is substantial.
› B: There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
› C: There may be considerations that support the provision of the service in an individual patient. There is moderate to high certainty that the net benefit is small.
› D: There is moderate to high certainty that the service has no net benefit or that the harms outweigh the benefits.
› I: Evidence is missing, of poor quality or conflicting, and the balance of benefits and harms cannot be determined.

(*) Guidelines developed by the National Institute Clinical Excellence (NICE). Since 2015 it has stopped making a grading of the recommendations in its Clinical Practice Guidelines. The justification for this change is to avoid that the hierarchy previously used, linked to the quality of scientific evidence, is being confused with the degree of priority for implementing recommendations. And so the level of evidence and the strength of recommendation are not specified.

Source:
- National Institute for Health and Care Excellence (NICE) Update 2017. Advanced Breast Cancer (CG81) Update 2017 (Addendum August 2017).
- Gavilá J, Lopez-Tarruella S, Saura C, Muñoz M, Oliveira M, De la Cruz-Merino L, Morales S, Alvarez I, Virizuela JA. SEOM clinical guidelines in metastatic breast cancer 2015. Clin Transl Oncol 2015; 17:946-955.
- Chacón López-Muñiz JI, de la Cruz Merino L, Gavilá Gregori J, Martínez Dueñas E, Oliverira M, Seguí Palmer MA, Álvarez López I, Antolín Novoa S, Bellet Ezquerra M, López-Tarruella Cobo S. SEOM clinical guidelines in advanced and recurrent breast cancer (2018). Clin Transl Oncol (2019): 21:31-45.
- Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E et al. Primary Breast Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2015; (Supplement 5) 26: v8-v30.

Table 2.4. Recommendations related to the extension study in metastatic disease. Diagnostic tests.

RELAPSE EXTENSION STUDY.

Relapse Extension Study	Level of Evidence/ Strength of Recommendation
The relapse extension study should be carried out with: • Physical examination. • Blood work. • Body CAT. • Bone gammagraphy. Adding other complementary diagnostic tests oriented by the symptoms or results of those described above.	II/B
Indication 18F FDG PET-CAT	
In the case of metastatic or locally advanced breast carcinoma, 18F FDG PET-CAT can be used in this situation, replacing bone gammagraphy and diagnostic CT, especially when the results of other scans are equivocal[46,47,60].	II/B
Usefulness of tumor markers in recurrence	
The usefulness of tumor markers in recurrence is discussed both in their detection and in monitoring the response to treatment[61].	III/C
Histopathological re-evaluation location of relapse	
A new histopathological evaluation of the disease should be performed at the location of the relapse (if feasible).	I/A
Histopathological re-evaluation is recommended. Tumour phenotype changes have been demonstrated in relapse with respect to primary breast cancer.	I/A

Levels of evidence:

- I: Evidence from at least one large randomised controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity.
- II: Small randomised trials or large randomised trials with suspected bias (lower methodological quality) or meta-analyses of such trials or trials with demonstrated heterogeneity.
- III: Prospective cohort studies.
- IV: Retrospective cohort studies or case-control studies.
- V: Studies without a control group, case reports, expert opinions.

Grade of recommendation:

- A: Strong evidence of efficacy with substantial clinical benefit, highly recommended.
- B: Strong or moderate evidence of efficacy, but with limited clinical benefit, generally recommended.
- C: Insufficient evidence of efficacy or benefit does not outweigh the risk or disadvantages (adverse events, costs...) optional.
- D: Moderate evidence against efficacy or for adverse outcomes, generally not recommended.
- E: Strong evidence against efficacy or for adverse results, never recommended.

Source:

- Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, Andre F et al. 4th ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Annals of Oncology 2018;29(8):1634-57.
- García García-Esquinas M, Rodríguez Rey C, Ortega Candil A. Papel de la PET-TC en la estadificación del cáncer localmente avanzado de mama. Revisiones en cáncer, ISSN 0213-8573, Vol. 29, Nº3, 2015 (Ejemplar dedicado a: Carcinoma localmente avanzado de mama),2013;29 (3):101-108.

Table 2.5. Recommendations for a relapse extension study. PET-CAT indications.

1.4. CLINICAL DOCUMENTATION: REPORT.

1.4.1. RADIOLOGICAL REPORT.

The structure of the breast report should follow a similar scheme to that recommended for the rest of the radiological studies.

The use of the BI-RADS (Breast Imaging and Data System) [(1)] in breast radiology reports is widely spread in Spain, although there are no legal regulations requiring its use.

Structure of the report:

1. **Clinical justification for the study.**

   It should be included in the report because it determines the selection of the test and the interpretation of the findings.

2. **Description of the technique.**

   By listing the techniques used, the special explorations and the technical adjustments of the tests (particularly in resonance, because of the variability of sequences)

3. **Description of the characteristics of the breast tissue.**

   The density of the breast in mammography[(2)], the ultrasound pattern and the background capture in the resonance are included, because they express the limitation of the technique in the detection of lesions.

4. **Description of findings.**

   Lesions detected by imaging techniques should be described in the report as follows: the most relevant at the beginning, using standardized terms (BI-RADS), full description of all relevant data (number, size and location of the lesions). The location of lesions by quadrant should be detailed. The distance to skin, nipple and chest wall should be noted because it may be relevant to the clinician and because it helps in the correlation of findings between different imaging techniques and facilitates the macroscopic study of the surgical specimen, as well as the radio-pathological correlation.

5. **Comparison with previous imaging tests.**

   If compared with previous ones, it should be recorded in the report, especially if a category of suspicion is deduced from the comparison.

6. **Category of suspicion.**

   The adoption of the BI-RADS categories in the report makes the report easier to understand. Although the category of suspicion has a subjective component, it must be appropriate to the description of the findings. There is only one category per study, which will be the most suspected of the described lesions.

   Management recommendation: it must be included in all reports and must be appropriate to the category of suspicion.

1.4.2. PATHOLOGICAL REPORT.

The pathology report must contain, in a clear and concise manner, all the data describing the characteristics of the lesion, as well as the prognosis and predictive factors from which later therapeutic behaviours can be derived[62].

To make it easy to understand, it is recommended to use standardized guidelines that make the report uniform, reproducible and always expressing the same variables and in the same way[63,64].

It is also recommended that this be an integrated report, which includes the morphological characteristics and all those determinations that have been made to the primary and metastatic tumor(s) such as immunohistochemical techniques, molecular testing or genetic profiling.

Therefore, the main sections of the report will be:

- Macroscopic description.
- Microscopic description whenever the pathologist deems it necessary.
- Results of immunohistochemical and FISH techniques.
- Diagnosis.
- Genetic profile results.

Below is a model template detailing the variables to be recorded and specifying, by way of explanatory notes at the end of the template, the explanations of the variables that require them.

1] D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.
2] For asymptomatic women, with high mammographic breast density, in the context of an organised screening programme, the ECIBC's Guidelines Development Group (GDG) suggests screening with either digital breast tomosynthesis (DBT) (including synthesised 2D images) or digital mammography (DM).https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/dense-breast/DBT-alone.

1 MACROSCOPIC DESCRIPTION:

This section specifies the macroscopic characteristics of the specimen and the lesion:

- Type of procedure: Lumpectomy, Mastectomy...
- Node sampling: Sentinel lymph node, axillary lymphadenectomy...
- Laterality: Right, left, unspecified.
- Location of tumour: Indicate quadrant.
- Measurements of the surgical piece.
- Skin: Absent/Present (measures).
- References to orient the piece and marking "clips".
- Size of tumour.
- Location of tumour in case of mastectomy.
- Distance to the nearest margin: (specify margin).
- Other lesions detected macroscopically.
- Obtaining of sample for other tests: Identify whether tissue has been frozen for biobank, tissue in other conditions for RNA collection.
- Type of fixer used and specimen fixation time.

2 MICROSCOPIC DESCRIPTION:

This section details all the characteristics determined by microscopic observation of the lesion:

- **Histological Type** [63,65]**:** The primary histological type and any secondary histological type should be recorded.

Note 1: on page 89

- **Tumour size (mm):** Mark the maximum dimension of the infiltrating lesion obtained microscopically and correlate it with that obtained in the macroscopic examination. In the case of a multifocal tumour, specify the size of the different foci, or at least indicate that it is multifocal and the size of the largest focus.
- **Histological grade:**[63,64,66]

Note 2: on page 90

  - Formation of tubules: 1, 2, 3.
  - Nuclear pleomorphism: 1, 2, 3.
  - Mitotic index: 1, 2, 3.
- **Tumour focality:** Single focus or more than one focus. If there is more than one focus, indicate how many and the maximum dimension of each one.
- **Ductal carcinoma in situ:** Absent/ Present and no evidence of extensive intraductal component/ Present and with evidence of extensive intraductal component/ Present after neoadjuvant treatment / Paget's disease (intraductal carcinoma affecting the skin of nipple) / Others.
  - Ellis Histological Classification for CNB/VAB 67
  - Size (mm):
  - Architectural pattern: Solid/Cribriform/micropapillary/papillary/Comedo.
- **Nuclear grade**[68-70]**:** Low grade / High grade.

Note 3: on page 91

  - Necrosis: Absent / Present, focal (necrosis of isolated cells or small foci). / Present, central (expansive necrosis, comedo-type).
- **Lobular carcinoma in situ:** Absent / Present.
- **Skin:** Not evaluated / No evidence of infiltration / Infiltrating carcinoma invading the dermis and/or epidermis without ulceration / Infiltrating carcinoma invading the dermis and epidermis with ulceration / Angiolymphatic dermal invasion / Ipsilateral satellite skin node.
- **Margins**[71]**:**

Note 4: on page 91

  - Infiltrating carcinoma: Free. Distance from infiltrating carcinoma to the nearest margin: mm / Affected by infiltrating carcinoma (specify margin). And measure the extent of involvement whenever possible.
  - Ductal carcinoma in situ: Free. Distance from the carcinoma in situ to the nearest margin: mm / Affected by carcinoma in situ (specify margin).
- **Lymph nodes:**
  - Total number of lymph nodes examined (sentinel and non-sentinel).
  - Number of sentinel lymph nodes examined.
  - Lymph node involvement[72-73]:

Note 5: on page 92

    - Number of lymph nodes with macrometastases.
    - Number of lymph nodes with micrometastases.
    - Number of lymph nodes with isolated tumor cells.
    - Tumour burden (in case of using OSNA).
    - Size of the largest metastatic focus (mm).
  - Extranodal extension: Absent / Present.

  - Method of evaluation of the sentinel lymph node:
    - OSNA.
    - Hematoxylin-Eosin 1 level.
    - Hematoxylin-eosin various levels.
    - Immunohistochemistry (specify antibody used).
  - Regressive changes if there has been primary systemic treatment: Absent/Present.
- **Measurement of the surgical margin area is optional (unifocal, multifocal, or extensive).**
- **Lymphovascular invasion:** Absent / Present.
- **Perineural invasion:** Absent / Present.
- **Invasion of dermal lymphatic vessels:** No skin/Absent/Present.
- **Response to neoadjuvant therapy[74-77]:**

Note 6: on page 92

  - Miller and Payne's grade of regression.
  - Index and RCB Class.
- **Other pathological findings[64]**

Note 7: on page 93

- **Microcalcifications:** Unidentified/ Present in ductal carcinoma in situ/ Present in infiltrating carcinoma/ Present in non-neoplastic tissue.

3 IMMUNOHISTOCHEMICAL TECHNIQUES:

Indicate in this section if techniques have been used (apart from those used in the sentinel lymph node, hormone receptors, HER2 and Ki67) for the detection of myoepithelial cells, cytokeratins, neuroendocrine markers... Point out the type of antibody, the brand, the clone used and the result, as well as its interpretation if necessary.

4 DIAGNOSIS:

It is advisable to include in a paragraph the summary of the findings outlined in the previous sections so that the following is included:

- Histological type.
- Histological grade.
- Tumour size.
- Margin status.
- Node status.
- Other pathological findings.

5 PROGNOSIS AND PREDICTIVE FACTORS:

In a standardized way, the results of the determinations to establish the hormonal, HER2 and Ki 67 status of the tumor will be recorded in this section.

The type of antibody, the brand and the clone used, as well as the interpretation guide of each biomarker should be indicated.

- **Hormone receptors[62-66, 68-76, 78-81]:**

Note 8: on page 94

  - Estrogens: % of stained cells and intensity.
  - Progesterone: % of stained cells and intensity.
- **HER 2[82-83] (3+,3+,2+, 0/1+) after the result:**

Note 9: on page 95

  Positive (3+) /Equivocal (2+) /Negative (0/1+). For equivocal IHC, record ISH result Positive/negative; HER2/CEN17 Ratio; Her2/Cell signals; CEN17/Cell signals (In-situ hybridization).
- **Ki 67[84]:** % of stained nuclei.

Note 10: on page 96

6 GENETIC PROFILES:

The use of genetic signatures for determining the molecular profile of the tumour(s) is becoming increasingly common. These determinations, which usually require procedures not always available in the hospital[85] itself, are usually done on a deferred basis and it is convenient to add their results to the report, even if they are additional. The name of the test, the brand name, the variables it offers (high, moderate or low risk, recurrence rate...) and the evaluation of the concordance with the other methods must be indicated[80].

STAGE 2: THERAPEUTIC APPROACH TO BREAST CANCER

2. SURGICAL TREATMENT.

The paradigm of breast cancer treatment has changed from a disease-focused procedure to a patient-centered procedure, in which the psychosocial connotations, quality of life, potential co-morbidities and survival are increasingly important. This complexity provides an opportunity to improve quality, design more individualized treatments and bring together the patient's needs. In short, it allows for improved results.

In this way, multidisciplinary teams emerge as a real need for coordination between professionals from different specialties especially dedicated to a particular cancer, who work in a common physical space, to coordinate treatment at all stages of the process, and make evidence-based decisions, always involving the patient in the decision-making[86].

The European Parliament resolutions of 2003 and 2006 recommend that all cancers should be treated in a Breast Unit. Together with these, in the year 2013, EUSOMA, The European Society of Breast Cancer Specialist, updated the requirements for a breast specialized unit[8,7].

Composition of the Breast Committee.

The Breast Committee should have a minimum of components to be effective in the diagnosis and treatment of benign and malignant breast disease and should include:

- Specialist in Surgery/Gynaecology, with knowledge in oncoplasty.
- Specialist in Pathology.
- Specialist in Radiation Oncology.
- Specialist in Medical Oncology.
- Specialist in Nuclear Medicine.
- Specialist in Radiology.
- Nurse in charge of the Breast Unit.

The presence of other professionals is desirable, if possible:

- Specialist in Plastic Surgery.
- Specialist in Genetics.
- Psycho-oncologist.
- Rehabilitator.
- Physiotherapist.
- Data manager and secretary.

The meetings of the Breast Committee should be a recognized practice and be facilitated by the Hospital Directorates, which will provide the means for their members to attend.

In addition, the Tumours Committee must have rules of procedure specifying its composition and operation.

A Where to go for breast cancer treatment and surgery[87].

Breast cancer should be treated in a breast pathology center, from where a complete diagnosis and treatment of this disease can be made, including prevention, genetic study and primary treatment up to treatment of metastatic disease. The specialists involved in its diagnosis and treatment work there, forming a cohesive group that does not have to depend on a single hospital, but should be within an area to guarantee multidisciplinary work and access to all necessary services.

This centre must have updated and monitored databases of the patients who have undergone surgery, follow audits with multidisciplinary discussion of quality indicators to identify critical points and take corrective measures.

Likewise, multidisciplinary committees should be set up in which the members of the committee evaluate the therapeutic plan of each patient in each phase of their treatment, with a frequency that guarantees compliance with the temporary recommendations for the patient's care.

B Who should perform a breast cancer surgery.

Prior to surgery, diagnosis and staging should be performed by a breast specialist who is an accredited professional trained in breast diseases, especially cancer.

After the specialist in breast radiology has studied the disease with ultrasound or other tests with the relevant interventional tests, and after the complete

pathological diagnosis provided by the specialist in Pathological Anatomy, the surgery should be performed by the breast surgeon, who should be a general surgeon or gynecologist, with the collaboration of a plastic surgeon whenever necessary and possible in cases of breast reconstruction.

The entire process of diagnosis, staging and treatment should be performed by breast cancer specialists. Therefore, all treatments must be carried out under the supervision of the Breast Unit under the same protocol that ensures evidence-based decisions and according to recognized guidelines. All important decisions should be discussed and agreed upon in the Breast Committee.

C Requirements prior to surgery[19,88,89].

Recommended time standards:

Time from onset of symptoms to primary treatment: maximum 8 weeks.

Time from first visit to breast unit up to primary treatment: maximum 6 weeks.

Time from request for histopathological study up to diagnosis: maximum 2 weeks.

Presentation in a Committee:

In the multidisciplinary committee on tumours, > 90 % of cases must be presented both pre-surgically and post-surgically. In addition, all cases of surgical biopsies, and those cases without a final diagnosis, should also be discussed.

The committee will consider the three aspects that influence decision-making: patient-related factors, tumor-related factors, and options for treatment.

The Committee's decision must be immediately reflected in the patient's medical history, whatever its format, although it is preferable to draw up a record of the main clinical data of the case, the decision taken, the attendees and the degree of consensus among them, following the recommendation that there should be traceability of the decisions adopted both in the Medical History and in the committee's record, as contemplated in the Health National System's Strategy on Cancer[23].

Communicating the diagnosis:

It is recommended that the diagnosis be communicated to the patient within a maximum of 7 days after the case is presented to the committee. Although each specialist can give preliminary information to the patient, it is the clinician who must take responsibility for planning and communicating the primary treatment, in a comfortable physical environment. The nurse, after the medical communication, will be able to reinforce the information and give emotional support to the patient. If necessary, the collaboration of the psycho-oncologist will be requested.

Information to patient:

Patients should receive clear verbal information and, if possible, written explanatory brochures specifically designed by the Breast Unit, describing the diagnosis, the treatment options for their specific case and the possible complications that may arise from it.

Interval from diagnosis to first treatment:

The British Association of Surgical Oncologists (BASO) sets that time period at 3 weeks[88].

According to EUSOMA, primary treatment should be started within four weeks of the definite diagnosis of cancer or from the first visit to the breast center, if diagnosed at another center[19].

The English National Health Service (NHS) sets a maximum of 31 days from the decision to treat until the first treatment, or 62 days from referral to the Breast Unit until surgery is performed[89]

The expert panel considers a target of a maximum of 21 days from diagnosis up to primary treatment reasonable, and 42 days from referral to the Breast Unit up to that time[18].

Although it is true that there may be different causes for delaying surgery, due to factors associated with the patient, health providers or the health system itself, the real impact of delay in surgical treatment is uncertain. Despite this, there is evidence to suggest that delays in primary curative surgery may be associated with increased mortality. Shin et al[90], in a cohort study of 7,529 colorectal, breast, lung and thyroid cancer patients, concluded that delaying surgery in colorectal and breast cancer beyond 12 weeks is associated with increased mortality.

Both in Spain and internationally, a delay in diagnosis of 3 months or more is associated with a loss of opportunity, with the medical-legal implications that this entails.

2.1. SURGICAL QUALITY CRITERIA FOR BREAST CANCER.

There are different proposals for quality indicators in breast cancer. The American Association of Clinical Oncology (ASCO) [91] has proposed multiple quality indicators within the National Initiative for Cancer Care Quality (NICCQ)[92].

2.1.1. DIAGNOSTIC AND STAGING PROCESS: QUALITY CRITERIA[18,19].

- **Complete preoperative diagnosis.**

  Percentage of patients with suspected breast cancer, in whom the complete diagnosis is reached preoperatively. This should include: preoperative fine needle aspiration or core needle biopsy of breast with a conclusive diagnosis, ultrasound axillary study with puncture or biopsy of suspected adenopathies and complete preoperative pathology report, including diagnosis and prognosis factors. 90% of invasive carcinoma cases should go to the operating room with a histological diagnosis, that percentage should be 85% for non-invasive carcinomas. The British Association of Surgical Oncology (BASO) criteria set this in at least 90% of cases with a target that could reach up to 95%[88].

- **Pre-operative report of complete histological or cytological study.**

  The complete histological diagnosis includes at least: description of the morphological findings, histological type, histological grade, hormone receptors, proliferation index and over-expression of Her 2/neu. Some of these parameters can also be obtained from the cytological study if the material is sufficient.

- **Proper use of diagnostic imaging tests.**

  All patients with breast cancer should be studied with bilateral mammography and complementary breast ultrasound; an MRI will be reserved in selected cases according to the protocols of each center. In addition, axillary study with axillary ultrasound and cytological puncture or core needle biopsy should always be performed if indicated.

- **Extension study[46].**

  All Stage I patients should have at least one extension study that includes blood work with liver tests and chest x-ray. In Stage II, a bone gammagraphy should be added and, in locally advanced cancer, a thoraco-abdominal CAT including liver study.

The National Comprehensive Cancer Network's (NCCN) 2018 guidelines set out recommended extension studies for breast cancer treatment that can be viewed as its own[46].

The approach to the recommended tests is as follows:

- **Ductal carcinoma in situ:**
  - Medical history and physical examination.
  - Bilateral mammography.
  - Determination of estrogen receptors.
  - Genetic Counseling advise if the patient is at high risk for hereditary cancer.
  - Optional MRI.
- **Infiltrating ductal carcinoma:**
  - Medical history and physical examination.
  - Complete blood count.
  - Determination of liver enzymes and alkaline phosphatase.
  - Bilateral mammography and Ultrasound.
  - Determination of estrogen, progesterone and HER2 receptor levels.
  - Genetic Counseling in consultation in cases of high risk of familial hereditary cancer.
  - Optional MRI.
  - Fertility counseling in cases of pre-menopausal patients.
- **In stages I-II** more complete preoperative studies can be performed depending on the patient's signs and symptoms.
  - Bone gammagraphy in cases of localized bone pain or elevated alkaline phosphatase.
  - Abdominopelvic CAT or MRI in cases of elevated alkaline phosphatase, elevated liver enzymes, abdominal symptoms or pathological abdominal or pelvic examination.
- **In stages IIIA** consider the following:
  - Abdominopelvic CAT or MRI.
  - Thoracic CAT.
  - Bone gammagraphy.
  - ^{18}F FDG PET-CT - Clinical staging. cTNM.
  - Once the diagnosis is completed, the clinical staging should be established.

- **Presentation to committee and preparation of a multidisciplinary decision minutes.**

  The percentage of patients presented to the committee for multidisciplinary discussion, and the preparation of the corresponding minutes, is a relevant indicator, whose compliance must be 100%.

2.1.2. SURGICAL QUALITY CRITERIA FOR BREAST CANCER: CONSERVATIVE SURGERY, MARGINS, AXILLARY STAGING, RECONSTRUCTIVE SURGERY.

- **Surgical indicators.**

  All surgical excisional biopsies must be weighed. Over 90% of excisional biopsies for non-palpable lesions that later turn out to be benign should weigh less than 20 grams[93].

  Infection rate of Conservative and Reconstructive surgery. The incidence of infections in breast cancer surgery is in the range of 3% to 15%[94]. The 2009 Cochrane review recommends the use of antibiotic prophylaxis in breast cancer surgery. The 2014 review identified the group of patients undergoing immediate breast reconstruction as the most susceptible to infection, so antibiotic prophylaxis will always be indicated for these surgeries[95].

- **Conservative surgery.**

  Conservative surgery should be performed in 66% of patients operated for breast cancer[88]. This is a parameter for measuring overtreatment. For this reason, in those cases in which a mastectomy is performed, it should be stated whether it is a personal option for the patient and whether she has been correctly informed of the possibility of breast conservation with the relevant oncological results.

  A radiological study of the post-operative piece must be performed in 100% of ductal carcinomas in situ and non-palpable lesions that are associated with microcalcifications. The radiology report should be available within 20 minutes after the surgical specimen leaves the operation room[88].

- **Percentage of margin increase.**

  It is controversial that this is a parameter to measure the quality of conservative surgery, because there is no study that shows any difference between the number of surgeries to achieve free margins and local recurrence. In addition, this percentage can be very variable depending on when it is indicated (definition of free margin) and can range from 6 to 49%[96].

The consensus is that local recurrence increases if surgical margins are positive (tumor in contact with margin ink) and that one in four women with recurrence will die from the disease[97]. However, there is a lack of consensus on defining the appropriate margins in conservative surgery because the distance cut-off point for defining a negative margin (minimum residual tumor burden controllable with adjuvant therapies), does not modify the risk of local recurrence.

› For intraductal carcinoma.

The **National Institute for Care and Health Excellence (NICE) guide**[98] defines the distance of 2 mm as an appropriate minimum margin.

The **British Association of Surgical Oncology (BASO)**[99] proposes that breast units should have their own protocols and that each case should be examined separately by the Breast Committee. For the intraductal carcinoma it establishes a wider margin of 1 mm.

The 2018 NCCN [46] establishes the following concepts:

Margins greater than 1 cm can be considered as negative, but they can be excessive and lead to a worse aesthetic result.

Margins less than 1 mm are considered inadequate.

When margins are between 1-10 mm, wider margins are associated with a lower rate of recurrence. Likewise, margins of less than 1 mm on the anterior or posterior face (skin or chest wall) do not require re-intervention, but may be an indication for a higher dose of Radiotherapy or overdose (boost) in the area of the surgical bed.

› For infiltrating ductal carcinoma.

An expert panel led by Kaufmann and Morrow, established that the appropriate negative margin for infiltrating carcinomas was the absence of tumor cells in the margin painted with Indian ink [100].

- **Surgical axillary staging.**

  In infiltrating carcinomas, 90% of patients must undergo an axillary staging procedure, be it a sentinel lymph node or lymphadenectomy. The goal would be that 100% of cases undergo axillary staging. In cases where axillary staging is refused, the reason for this decision must be stated.

- **Quality of axillary staging.**

  At present, the technique of sentinel lymph node identification that offers the highest quality in terms of the highest rate of node detection and the lowest rate of false negatives is isotope lymphography, whether or not it is accompanied by vital dyes.74 This technique also allows, by means of the pre-surgical gammagraphy study, the detection of possible unexpected lymphatic drainage (intramammary, supraclavicular, internal mammary chain or axillary lymph nodes contralateral to the primary tumour). Therefore, the use of lymphatic isotope tracers should be considered as the technique of choice. The use of other alternative techniques (only vital or fluorescent dyes, magnetic particles) should be reserved for those Breast Units with sufficient experience in their handling that do not have a Nuclear Medicine service and for which access to a support Nuclear Medicine Service is impossible.

- **Axillary conservation.**

  Percentage of patients clinically NOT undergoing SSLNB. This is a parameter for measuring overtreatment.

- **Oncoplasty.**

  Percentage of patients undergoing conservative surgery in whom oncoplastic techniques have been applied.

  The cavity must be marked after conservative surgery with clips that allow a precise location of the tumour bed for the application of radiotherapy. This recommendation is absolutely essential when oncoplastic techniques have been performed, since the surgical bed may be far from the scar made and covered by glandular flaps.

- **Immediate reconstruction[11,19].**

  Percentage of mastectomy patients who have undergone immediate oncological surgery reconstruction. In cases where this has not been done, the reason why it is not considered appropriate must be stated and the patient must always be informed of this possibility, as she is ultimately the person that can decide on the reconstruction, unless it is contraindicated for technical or oncological reasons.

  All patients should be provided with the possibility of immediate reconstruction, carried out by the surgeons at their hospital or by external specialists who have moved to that hospital. If this cannot be done and the patient wishes to be reconstructed, she must have a reference centre to which she can be referred.

- **Effectiveness of surgery[88].**

  Percentage of patients in whom surgical treatment has been completed in a single act. The percentage of 25% re-intervention for margin widening is considered a reasonable figure.

  The **British Association of Surgical Oncology (BASO)**[88] states that more than 95% of patients will have a maximum of 3 interventions, with the goal of 100% of patients having 3 or less than 3 interventions.

  The time between surgery and the full pathology report should be less than 3 weeks.

- **Recurrences[88].**

  In infiltrating ductal carcinoma, the recurrence rate should be less than 1% per year and should not exceed 10% in total. The **British Association of Surgical Oncology (BASO)**[88], based on the results of the START study, recommends a maximum of 5% in 5 years with a target of less than 3% at 5 years.

  In intraductal carcinoma, less than 10% should have a local recurrence after conservative surgery at 5 years.

  Axillary recurrence at 5 years should always be less than 5%, with the goal being less than 3%.

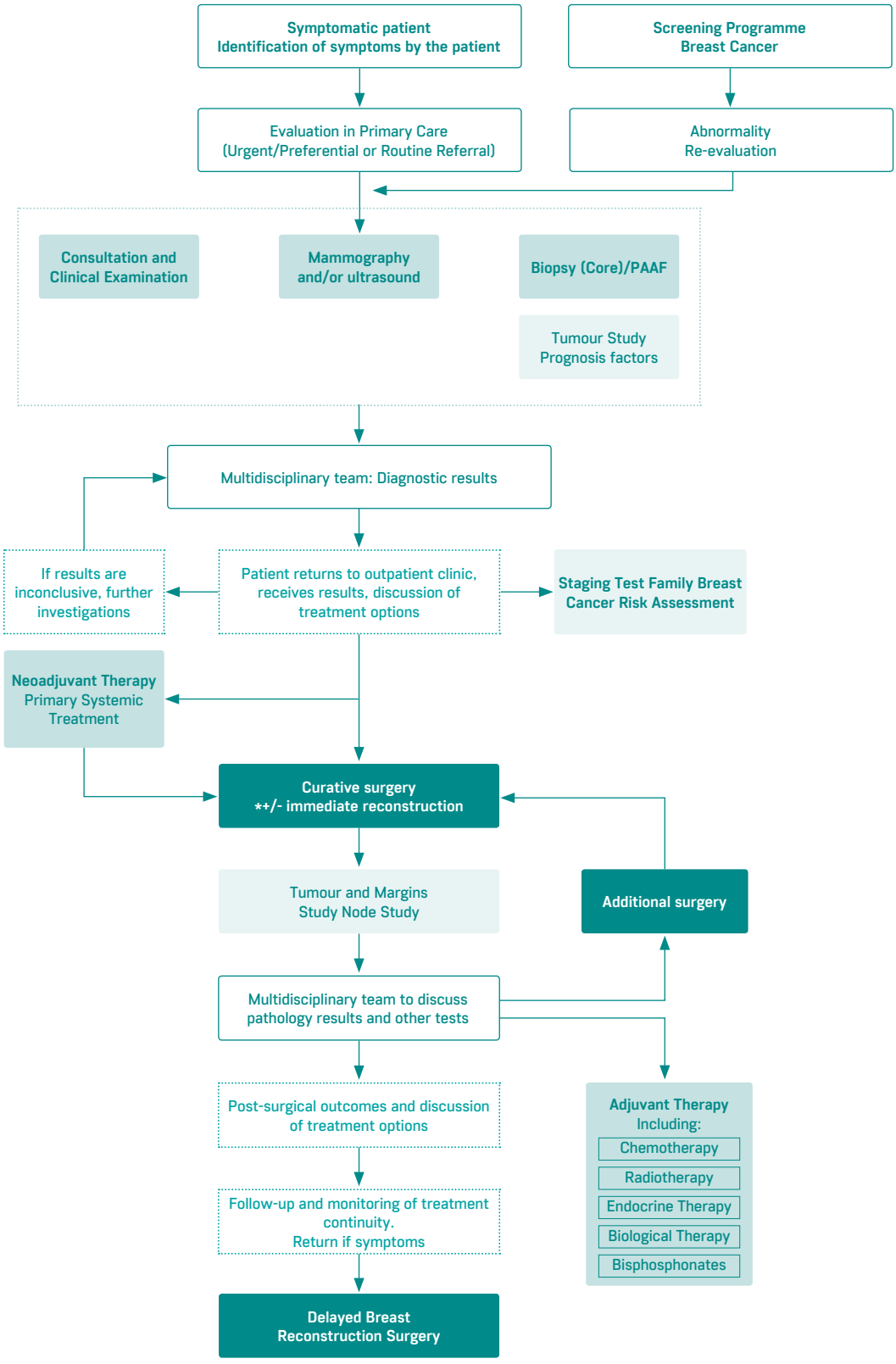


Figure 2.4. Surgical treatment.

2.2. RECOMMENDATIONS ON THE SURGICAL APPROACH TO BREAST CANCER.

	Level of Evidence/ Strength of Recommendation
• An axillary lymph node status assessment should be performed for ALL early invasive breast cancers to stage the disease, to minimize the risk of loco-regional disease recurrence, and to assist in planning adjuvant therapy. Cases where they are not performed must be justified in the Breast Committee.	I/A
In the presence of clinically positive nodes, an evaluation should always be performed by Radiology and FNAP or CNB if appropriate. • In case of positivity, a level I/II lymphadenectomy will be performed. In the absence of a cytological or histological diagnosis of malignancy, a sentinel lymph node biopsy will be performed[101-102]. **If the SLN is negative (*) no additional axillary surgery is required[103] .** • If the patient has micrometastasis or isolated tumour cells, no additional axillary surgery is required[104] . **If she meets ALL of the following criteria she will not need additional axillary surgery.** • T1 - T2. • Only 1 or 2 positive lymph nodes (**). • Conservative Surgery. • RT of the intended breast. • No previous neoadjuvant treatment. **If the sentinel lymph node is not identified, a level I/II lymphadenectomy should be performed.** **Level III in axillary lymphadenectomy should only be removed if there is significant involvement of levels I/II.**	I/A
• Patients should be informed about the side effects of axillary node dissection, including seroma formation, altered sensation in the arm, lymphedema, and possible long-term reduction in shoulder movement.	I/A
• Due to lack of evidence, there are no recommendations on the effectiveness of removing the supraclavicular and internal mammary chain nodes versus no excision.	
(*) Negative sentinel lymph node: • Tumour Burden: Definition: Sum of the number of copies of mRNA-CK19/uL from each of the nodes. • Diagnostic limit (12,000-25,000 copies). **(**) Positive Sentinel Lymph Node: (>25,000 copies)**	
Strength of recommendation: › A: The recommendation is supported by quality scientific evidence (based on well-designed, valid, consistent, applicable and clinically relevant studies). › B: There is moderate quality evidence to support the recommendation. › C: The recommendation is based on the opinion of an international panel of experts. › I: No or insufficient and poor quality evidence available.	

Source:
- New Zealand Guidelines Group (NZZG). Evidence-Based Best Practice Guideline. Management of Early Breast Cancer New Zealand Guidelines Group (2009). Current Review date (2014).
- Lyman GH, Temin S, SB Edge, Newman LA, Turner RR, Weaver DL, Benson AB, Bosserman LD, Burstein HJ, Sentinel Lymph Node Biopsy for patient with early-Stage Breast Cancer: American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update. J Clin Oncol 2014; 32:1365-1383.

Table 2.6. Recommendations on surgical treatment.

	Strength of recommendation
• The patient should be informed of the procedure, benefits and potential risks of the sentinel lymph node biopsy technique.	C
• The patient should be informed of the possibility of an unsuccessful sentinel lymph node biopsy or a false negative result.	C
• The team performing the sentinel lymph node biopsy should include a surgeon, a nuclear medicine physician (where available), a pathologist, an anesthesiologist, and appropriate nursing support.	C
• The surgeon who performs the sentinel lymph node biopsy must be properly trained and experienced in the technique.	B
• Whenever possible, preoperative lymph mapping with lymphoscintigraphy should be used in combination with intraoperative use of the gamma probe and blue dye or iron particles with sentinel lymph node location probe.	B
• When a combination technique for the sentinel lymph node biopsy procedure is not available, the use of blue dye or radioisotopes, or the use of iron particles, is appropriate.	B
• If a negative sentinel lymph node is identified, clinical monitoring of the axilla is recommended.	B
• In neoadjuvant therapy, the selective sentinel lymph node biopsy (SSLNB) can be performed either pre- or post-neoadjuvancy.	B

Strength of recommendation:

› A: The recommendation is supported by quality scientific evidence (based on well-designed, valid, consistent, applicable and clinically relevant studies).
› B: There is moderate quality evidence to support the recommendation.
› C: The recommendation is based on the opinion of an international panel of experts.
› I: No or insufficient and poor quality evidence available.

Source:
- New Zealand Guidelines Group (NZZG). Evidence-Based Best Practice Guideline. Management of Early Breast Cancer New Zealand Guidelines Group (2009). Current Review date (2014).
- Lyman GH, Temin S, SB Edge, Newman LA, Turner RR, Weaver DL, Benson AB, Bosserman LD, Burstein HJ, Sentinel Lymph Node Biopsy for patient with early-Stage Breast Cancer: American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update. J Clin Oncol 2014; 32:1365-1383.

If neoadjuvant treatment is performed[100]:

- If Sentinel Lymph Node (SLN) is negative, post-neoadjuvancy SSLNB and axillary lymphadenectomy are not indicated.
- If Sentinel Lymph Node (SLN) is positive, the post-neoadjuvancy Sentinel Lymph Node Biopsy (SSLNB) can be repeated. In case of positivity for isolated tumour cells, micrometastasis or macrometastasis, Axillary Lymphadenectomy (AL) should be performed.

Consensus from International Expert Panel

Source: Kaufmann M, Morrow M, von Minckwitz G, Harris JR. Locoregional treatment of primary breast cancer: Consensus recommendations from an International Expert Panel. Cancer 2010;116(5):1184-91.

Table 2.7. Recommendations related to selective sentinel lymph node biopsy.

	Strength of recommendation
• Only for invasive breast cancer. Breast conservative surgery requires complete removal of the tumour with margins and an acceptable cosmetic result after excision and radiation therapy.	C
• Detailed pathological evaluation of the distance of the invasive carcinoma from all margins should be done. • For an infiltrating carcinoma it is estimated that an adequate margin is one in which the tumor is not stained by the marking ink regardless of the distance to the edge. • For intraductal tumors, margins of 2 mm or greater should be achieved. • In the case of intraductal carcinoma associated with infiltrating ductal carcinoma, the criteria for infiltrating ductal carcinoma apply.	C

Strength of recommendation:
- A: The recommendation is supported by quality scientific evidence (based on well-designed, valid, consistent, applicable and clinically relevant studies).
- B: There is moderate quality evidence to support the recommendation.
- C: The recommendation is based on the opinion of an international panel of experts.
- I: No or insufficient and poor quality evidence available.

Source: New Zealand Guidelines Group (NZZG). Evidence-Based Best Practice Guideline. Management of Early Breast Cancer New Zealand Guidelines Group (2009). Current Review date (2014).

Table 2.8. Recommendations on excision/resection margins.

	Strength of recommendation
• A woman being prepared for a mastectomy should be informed of the option of breast reconstruction and discuss it with a surgeon trained in reconstructive techniques prior to surgery.	C
• The use of immediate or delayed breast reconstruction is an important means of improving body image and self-confidence after mastectomy, and both options should be available to women.	C

Strength of recommendation:
- A: The recommendation is supported by quality scientific evidence (based on well-designed, valid, consistent, applicable and clinically relevant studies).
- B: There is moderate quality evidence to support the recommendation.
- C: The recommendation is based on the opinion of an international panel of experts.
- I: No or insufficient and poor quality evidence available.

Source: New Zealand Guidelines Group (NZZG). Evidence-Based Best Practice Guideline. Management of Early Breast Cancer New Zealand Guidelines Group (2009). Current Review date (2014).

Table 2.9. Recommendations related to reconstructive surgery.

3. SYSTEMIC TREATMENT FOR BREAST CANCER.

3.1. RISK ASSESSMENT AND ADJUVANT TREATMENT DECISION.

To adapt the complementary treatment in certain situations, there are gene platforms for predicting the risk of recurrence as described in Table 2.10 [105-107].

In an attempt to optimize its use with efficiency criteria, integrating the information provided with validated immunohistochemical tools, a series of criteria could be established for their application:

"Patients with early stage breast cancer with expression of estrogenic receptors and absence of Her2 expression, without nodal involvement and with an intermediate risk of recurrence according to conventional clinical-pathological variables, in which the stage is less than or equal to T2 and meets at least one of the following criteria: G2-3, Ki-67 > 20% (Luminal Profile B), RP < 20, postmenopausal woman with Nmic, N1 and Luminal Profile A with no other risk factors or lymphovascular infiltration".

GENE PLATFORM	PAM 50/ PROSIGNA	MAMMAPRINT	ONCOTYPE DX	ENDOPREDICT
Technology	DNA microarray/ qRT-PCR	DNAmicroarray/ qRT-PCR	qRT-PCR	qRT-PCR
Number de Genes	50	70	21	11
Inclusion criteria	RH + N – or N1 Her2–	N – or N1	RH + N –	RH + Her2 –
Results	Molecular Subtypes Risk of Relapse	Risk of Relapse	Risk of Relapse	Risk of Relapse
Level of Evidence	**2A** RE+, Her2-, N1-3	**AIs** RE+, Her2-, N1-3	**2A** RE+, Her2-, N1-3	**2A** RE+, Her2-, N1-3
FDA approval	Yes	Yes	No	No
Clinical Guidelines	Yes	Yes	Yes	No
Evaluation in Prospective Studies	No	MINDACT	TAILORx RXPONDER	No

Tabla. Most Used Gene Expression Profiles
modified from Sebatier et al.
Source: Sebatier R, Gonçalves A and Bertucci F. Personalized medicine: Present and future of breast cancer management. Crit Rev Onc 2014; 91: 223-233

Table 2.10. Most Widely Used Gene Expression Profiles.

3.2. ADJUVANT BREAST CANCER THERAPY.

Complementary therapy for Breast Cancer according to tumor phenotype includes chemotherapy, hormone therapy and biological agents[53,63,108,109].

The **National Cancer Comprehensive Network (NCCN)** guidelines recommend adding chemotherapy (CT) if the lymph node involvement is greater than Nmic. They recognize the use of gene platforms to predict the risk of recurrence and the utility of CT if there is N1 lymph node involvement (1-3 nodes) and in the absence of it, when the tumor size (T) is > 0.5 cm, in luminal BC[110].

TUMOR SUBTYPE	RECOMMENDED THERAPY	REMARKS
⁖ Luminal A-like	Hormone therapy	Consider CT in case of high tumor burden (N2, T3 or G3)
⁖ Luminal B- like	Hormone therapy + CT	If her2 positive, add anti-her2 therapy
⁖ Her2 positive	CT + anti-Her2	
⁖ Triple-Negative (ductal histology)	CT	

Recommendations for adjunctive treatment of early BC (Modified from Coates et al.)
Source: Coates AS, Winer EP, Goldhirsch A et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. GPC ESMO (2015). Ann Oncol 2015; 26:1533-1546.
Senkus E, Kyriakides S, Ohno S et al. ESMO Clinical Practice Guidelines for diagnosis. Treatment and follow-up. Annals of Oncology 2015;26(Supplement 5): v8-v30.

Table 2.11. Recommendations for complementary treatment of early Breast Cancer.

HORMONE THERAPY.

Pre-menopausal women	High-risk relapse factors *	GUIDELINES/ Therapeutic options	Level of Evidence/ Strength of Recommendation
	Presence	OFS*** Exemestane	II/B
		OFS*** Tamoxifen[111]	II/B
	Absence	1-Tamoxifen 5 years[112]	I/A
		2-Tamoxifen 10 years	I/B
		3-OFS in monotherapy. *** It may be used in cases where other treatments are not tolerated[113-114]	

* High-risk relapse factors: Define them: lymph node involvement, tumor size (T2 or larger), grade of differentiation (G3).
** Ovarian Function Suppression (by oophorectomy, radiotherapy or with LHRH agonists (A-LHRH).
*** May be used in cases where other treatments are not tolerated.

Postmenopausal women	GUIDELINES/ Therapeutic options	Level of Evidence/ Strength of Recommendation
	1st option[115]: **Aromatase Inhibitors** 5 years[1].	I/A
	2nd option[115] **Tamoxifen** 2-3 years and change to Aromatase Inhibitors completing 5 years of endocrine treatment.	I/A
	3rd option[116,117]: **Tamoxifen** (2-3 years) and change to **Aromatase Inhibitors keeping it (5 years).**	I/A
	3rd option[118,119]: Tamoxifen (5 years). Complete hormone therapy for another 5 years.	I/B
	4th option: Initial **Aromatase inhibitors** and change to Tamoxifen at 2-3 years .	II/A

Quality of evidence:
- I: Evidence from ≥ 1 correctly randomized controlled trial.
- II: Evidence from ≥1 well-designed, non-randomized clinical trial; from cohort or case-control analytical studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments.
- III: Evidence of opinions from respected authorities, based on clinical experience, descriptive studies or expert committee reports.

Strength of recommendation:
- A: Good evidence to support a recommendation for use.
- B: Moderate evidence to support a recommendation for use.
- C: Bad evidence to support a recommendation.
- D: Moderate evidence to support a recommendation against use.
- E: Good evidence to support a recommendation against use.

Source: Ayala de la Peña F, Andreés R, García-Sáenz JA, Manso L, Margeli M, Dalmau E, Pernas S, Prat A, Servitja S, Ciruelos E. SEOM clinical guidelines in early stage breast cancer (2018). Clin Transl Oncol 2019;21(1):18-30.

Table 2.12. HORMONE THERAPY in the treatment of EARLY breast cancer.

1] No AIs has been shown to be better in the context of adjuvancy than another.

CHEMOTHERAPY: PRIMARY SYSTEMIC TREATMENT.

Recommendation	Level of Evidence/ Strength of Recommendation
CT is recommended in: Patients with Luminal B profile that are not low-risk. Triple Negative (TN) > 1 cm (between 0.5-1 cm III, C) excluding medullary carcinoma, cystic adenoid and apocrine. Breast cancer expressing Her2: (Her2 Phenotype and Luminal B)> 1 cm.	I/A
Women with Luminal B profile and Her2 expression who reject CT or have contraindications may receive hormone therapy (HT) and Trastuzumab.	III/C
Most A Luminals do not require complementary CT.	I/A
The concomitant use of complementary CT and HT is not recommended.	II/D
The addition of taxanes (Paclitaxel or Docetaxel) to anthracyclines has shown greater efficacy independent of age, size and tumour grade, lymph node involvement, expression of hormone receptors.	I/A
Regimens without anthracyclines, but with taxanes and cyclophosphamide are considered in women at risk or with cardiological complications, in selected patients.	I/A
Dense-dose CT requires granulocyte-stimulating factor (G-CSF) support and individualized use in patients with highly proliferative BC.	I/B
The use of high doses of CT supported by Stem-cells is not recommended.	I/E

Quality of evidence:

- I: Evidence from ≥ 1 correctly randomized controlled trial.
- II: Evidence from ≥1 well-designed, non-randomized clinical trial; from cohort or case-control analytical studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments.
- III: Evidence of opinions from respected authorities, based on clinical experience, descriptive studies or expert committee reports.

Strength of recommendation:

- A: Good evidence to support a recommendation for use.
- B: Moderate evidence to support a recommendation for use.
- C: Bad evidence to support a recommendation.
- D: Moderate evidence to support a recommendation against use.
- E: Good evidence to support a recommendation against use.

Source: García-Saenz JA, Bermejo B, Estevez LG, Palomo AG, Gonzalez-Farre X, Margeli M, Pernas S, Servitja S, Rodriguez CA, Ciruelos E. SEOM Clinical Guidelines in Early stage Breast Cancer (2015) Clin Transl Oncol 2015;17(12):939-45.
Source: Ayala de la Peña F, Andreés R, García-Sáenz JA, Manso L, Margeli M, Dalmau E, Pernas S, Prat A, Servitja S, Ciruelos E. SEOM clinical guidelines in early stage breast cancer (2018). Clin Transl Oncol 2019;21(1):18-30.

Table 13. Chemotherapy recommendations: primary systemic treatment.

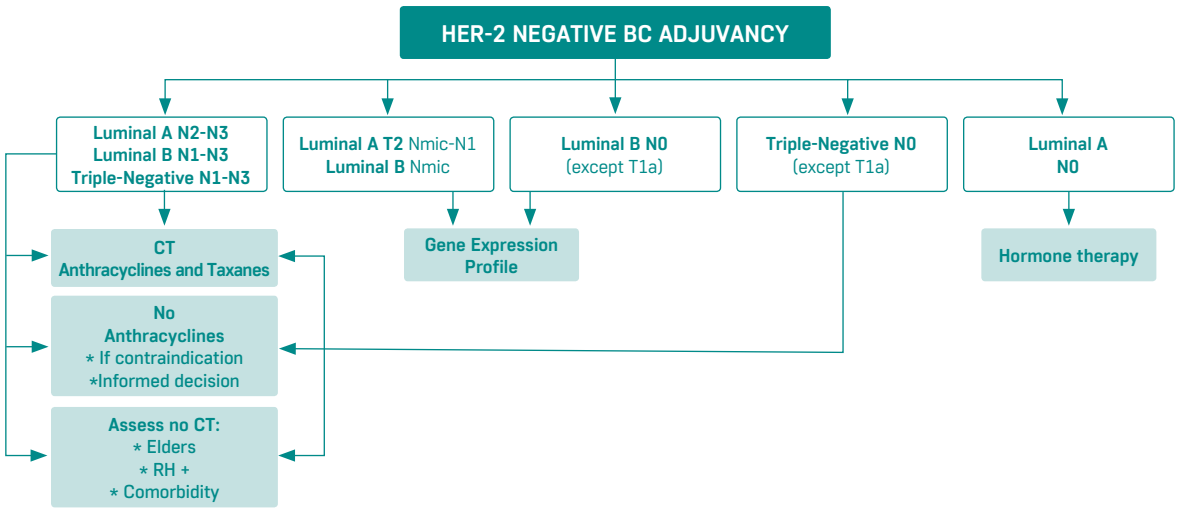


Figure 2.5. Complementary treatment algorithm for early breast cancer - HER2 Negative.

TREATMENT WITH BIOLOGICAL AGENTS: Therapy with Anti-Her2 Agents

Recommendation	Level of Evidence/ Strength of Recommendation
In Her2 T1c Breast Cancer, therapy with Trastuzumab and CT. It reduces the risk of relapse by half and increases overall survival.	I/A
In T1b its administration should be considered because of the high risk of relapse, especially if there is no expression of hormone receptors.	II/B
Most studies include one year of complementary therapy with Trastuzumab. There's no greater benefit in keeping it for two years.	I/A
In Luminal B-Her2 Breast Cancer without lymph node involvement and T1-2 it is feasible to use Trastuzumab concomitantly with Paclitaxel for 12 weeks, and then continue with Trastuzumab until completing one year of treatment (in selected patients).	II/B

Quality of evidence:

- I: Evidence from ≥ 1 correctly randomized controlled trial
- II: Evidence from ≥1 well-designed, non-randomized clinical trial; from cohort or case-control analytical studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments
- III: Evidence of opinions from respected authorities, based on clinical experience, descriptive studies or expert committee reports.

Strength of recommendation:

- A: Good evidence to support a recommendation for use
- B: Moderate evidence to support a recommendation for use
- C: Bad evidence to support a recommendation
- D: Moderate evidence to support a recommendation against use
- E: Good evidence to support a recommendation against use

Source: García-Saenz JA, Bermejo B, Estevez LG, Palomo AG, Gonzalez-Farre X, Margeli M, Pernas S, Servitja S, Rodriguez CA, Ciruelos E. SEOM Clinical Guidelines in Early stage Breast Cancer (2015) Clin Transl Oncol 2015;17(12):939-45

Table 2.14. Therapy with Anti-Her2 Agents

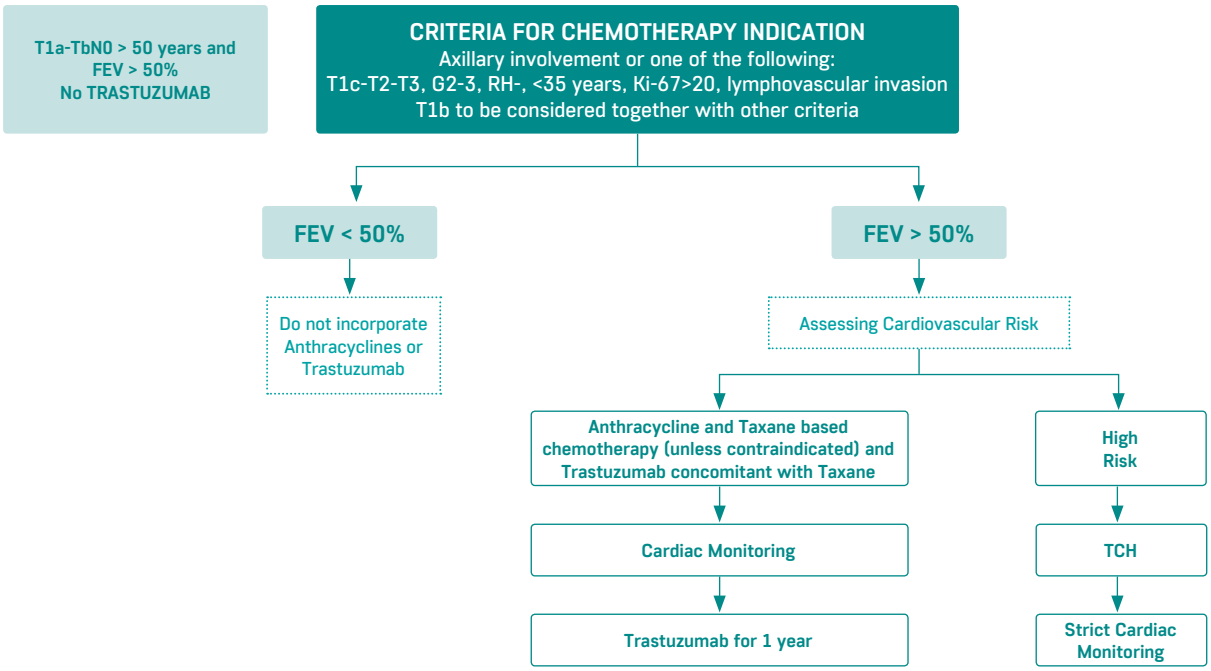


Figure 2.6. Complementary treatment algorithm for early Her2-positive breast cancer.

3.3. NEOADJUVANT BREAST CANCER THERAPY.

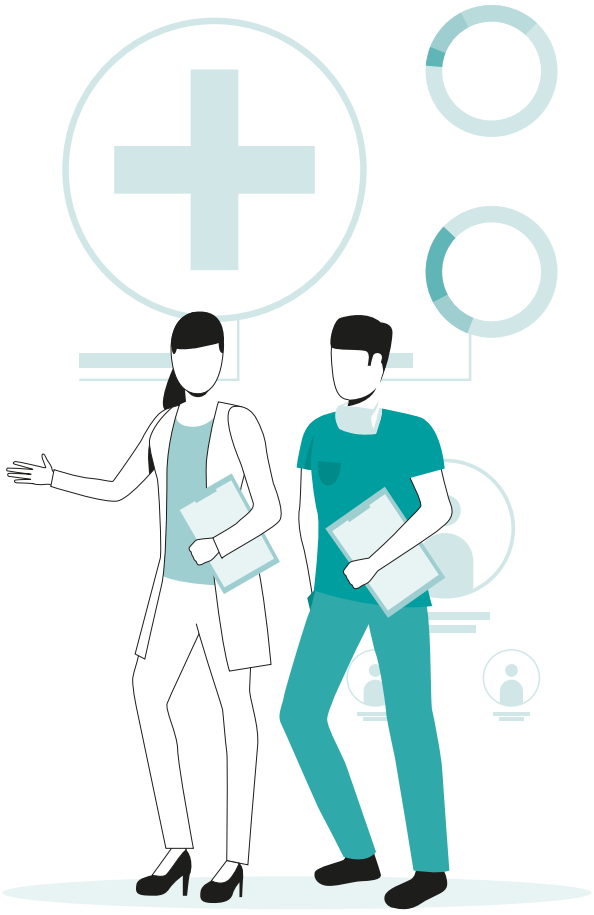
NEOADJUVANT THERAPY.

Neoadjuvancy (NA) is defined as a systemic treatment administered prior to surgery. Those breast cancer patients in whom adjuvant therapy is indicated would also have an indication for neoadjuvant therapy (I, A), providing the same benefits in disease-free survival (DFS) and overall survival (OS).

It allows to treat the disease early by testing in vivo the sensitivity to different therapies, which can be modified in case of poor response or progression. Reduces breast cancer staging and facilitates conservative surgeries with mastectomy indication to diagnosis[120-121].

Breast cancer with a high rate of proliferation (Ki67 >30%) or grade, RH-, Her2+ or TN is the one that benefits most (I, A).

The Pathological Complete Response (PCR) is strongly associated with improved disease-free survival (DFS) and overall survival (OS) in TN and HER2+ tumours. In luminal breast cancer the PCR rate is low and is not related to better long-term prognosis (II, B)[122-126].



NEOADJUVANT CHEMOTHERAPY SCHEMES (NA)[127].

- Same as in adjuvancy: a sequence of anthracyclines and taxanes (6-8 cycles), prior to surgery.
- It usually takes 3-4 weeks from the completion of CT to surgery to recover the haematological toxicity of CT regimens. II/B

Chemotherapy treatment Neo-adjuvant	Recommendation	Level of Evidence/ Strength of recommendation
⁖ Neoadjuvancy in HER2 Positive BC[126,128-130]	The combination of CT and anti-Her2 therapy (Pertuzumab + Trastuzumab) is recommended. *	I/A
	Classic anthracyclines with Trastuzumab are cardiotoxic so this association will not be used.	I/B
	Trastuzumab is combined with a taxane in NA and later completed for 1 year including the adjuvancy.	I/A
	Pertuzumab can be indicated with Trastuzumab and CT in NA for locally advanced, inflammatory BC or T>2 cm.	II/B
⁖ Neoadjuvancy in Triple-Negative BC[123]	They generally achieve high PCR rates after therapy with the Anthracycline and Taxane sequence.	I/A
	The use of Platinum is being studied, which contributes high rates of PCR, especially in patients with BRCA mutations.	II/B
⁖ Neoadjuvancy in Luminal BC[123,131]	There is very little scientific evidence to suggest that the use of HT in NA can be as effective as CT	
	For HT candidates in NA, AIs administration is suggested rather than Tamoxifen[132].	I/A
	The duration should be individualized according to the clinical characteristics of the patient and the response achieved.	

BC: Breast Cancer; HT: Hormone therapy; CT: Chemotherapy; AIs: Aromatase Inhibitors; PCR: Complete pathological response.
* The first antibody approved for this indication was Trastuzumab.

Quality of evidence:
- I: Evidence from ≥ 1 correctly randomized controlled trial.
- II: Evidence from ≥1 well-designed, non-randomized clinical trial; from cohort or case-control analytical studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments.
- III: Evidence of opinions from respected authorities, based on clinical experience, descriptive studies or expert committee reports.

Strength of recommendation:
- A: Good evidence to support a recommendation for use.
- B: Moderate evidence to support a recommendation for use.
- C: Bad evidence to support a recommendation.
- D: Moderate evidence to support a recommendation against use.
- E: Good evidence to support a recommendation against use.

Source: García-Saenz JA, Bermejo B, Estevez LG, Palomo AG, Gonzalez-Farre X, Margeli M, Pernas S, Servitja S, Rodriguez CA, Ciruelos E. SEOM Clinical Guidelines in Early stage Breast Cancer (2015) Clin Transl Oncol 2015;17(12):939-45.

Table 2.15. Neoadjuvant Chemotherapy Schemes (NA).

3.4. THERAPY OF METASTATIC DISEASE.

It aims to prolong life and optimize quality with good symptomatic control[133-134].

HORMONE TREATMENT.

The therapeutic strategy should be evaluated individually[135-139].

PREMENOPAUSAL WOMEN[138,141]

Guidelines/ Therapeutic options		Level of Evidence/ Strength of recommendation
⁖ FIRST LINE	1st option: Tamoxifen[c]	I/B
	2nd option: Tamoxifen + A-LHRH[d]	I/A
	3rd option: A-LHRH + 3rd generation AIs[e]	II/A
⁖ SECOND LINE	• It is suggested to evaluate some of the options not used in the first line. • Maintain OFS and treat as postmenopausal.	

Level of Evidence:

- Discharge (I): The available evidence generally includes consistent results from well-designed and well-conducted studies in representative populations. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
- Moderate (II): The available evidence is sufficient to determine the effects of interventions on health outcomes, but confidence in the estimation is limited by factors such as the number, size or quality of individual studies; inconsistency of findings in individual studies; limited generalisation of findings to routine practice; or inconsistency in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect may change, and this change may be large enough to alter the conclusion.
- Low (III): The available evidence is insufficient to assess the effects on health outcomes. The evidence is insufficient due to the limited number or size of studies, major shortcomings in study design; inconsistencies of findings among individual studies; findings not generalisable to practice; or lack of information on important health outcomes. More information may allow an estimate of the effects on health outcomes.

Strength of recommendation:

- A: It is recommended. There is a high certainty that the net benefit is substantial.
- B: It is recommended. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
- C: It is recommended not to provide routinely. There may be considerations that support intervention in an individual patient. There is moderate to high certainty that the net benefit is small.
- D: Not recommended. There is moderate to high certainty that the intervention has no net benefit or that the harms outweigh the benefits.
- E: The current evidence is insufficient to assess the balance of benefits and harms. Evidence is missing, of poor quality, or the balance cannot be determined.

[c] Tamoxifen compared to Ovarian Function Suppression (OFS) improves overall survival and PFS.
[d] Tamoxifen + A-LHRH compared to A-LHRH in monotherapy improves OS, PFS, and response rate to treatment.
[e] Analogues -LHRH (A-LHRH) + 3rd generation AROMATASE INHIBITORS shows a 2-year survival rate of 82%, a median time to progression (TTP) of 9.5 months and a clinical benefit of 74%.

Source: Gavilá J, Lopez-Tarruella S, Saura C, Muñoz M, Oliveira M, De la Cruz-Merino L, Morales S, Alvarez I, Virizuela JA, Martín M. SEOM Clinical Guidelines in metastatic breast cancer 2015. Clin Transl Oncol 2015,17(12):946-55.

Table 2.16. HORMONAL THERAPY in the treatment of METASTATIC breast cancer[47,140].

POSTMENOPAUSAL WOMEN

- It is recommended to take into account the adjuvant treatment received and the relapse-free interval.
- If no Aromatase Inhibitor has been prescribed, the use of 3rd generation Aromatase Inhibitor is recommended. (AIs)
- There is no evidence that one 3rd generation aromatase inhibitor is better than another.

Guidelines/ Therapeutic options		Level of Evidence/ Strength of Recommendation
⁖ FIRST LINE[136]	1st option:	
	Fulvestrant at doses of 500 mg[a]	I/B
	Palbociclib + Letrozol[b] Individualise this option according to patient characteristics. Ribociclib + Letrozol[c]	II/B
⁖ SECOND LINE* Therapeutic options dependent on the treatment received in 1st L and the ILP	1st option: Fulvestrant 500mg[d] [142]	
	2nd option: Exemestane+Everolimus[e] [143-144]	I/B
	3rd option: Fulvestrant +Palbociclib[f]	
	Ribociclib is not approved for this indication)	
⁖ If metastatic bone involvement	Add: Denosumab, Zoledronic acid or Pamidronate[145-147]	I/A
⁖ If Her2 + breast cancer	It is recommended to add anti-Her2 therapy[148]	I/A

› Quality of evidence and strength of recommendation (see description of Table 2.16 see page 54).

[a] **Fulvestrant** (dose 500 mg) versus Anastrozole, shows a greater clinical benefit with a significant increase in TTP and increased OS in a Phase III EC FALCON STUDY*
[b] **Palbociclib with Letrozol**: shows a greater increase in PFS, TTP and in toxicity including neutropenia and fatigue. This option should be individualised according to the patient's characteristics.
[c] **Ribociclib with Letrozol**: shows a greater increase in PFS, TTP and in toxicity including neutropenia and fatigue. This option should be individualised according to the patient's characteristics. Ribociclib prolongs the CT space on the electrocardiogram (ECG). A basal ECG should be performed prior to the start of treatment.
In the Palbociclib + Letrozol study all the subgroups pre-specified in the study benefit from it. For Ribociclib + Letrozol there is no clear benefit in the subgroup with only metastatic bone involvement. When we refer to individualization of treatment we mean "taking into account the patient's comorbidities, ECOG and potential toxicities of the treatment".
[d] Fulvestrant 500 mg dose is more effective than 250 mg (EC CONFIRM) in OS and PFS
[e] Exemestane combined with Everolimus shows higher PFS versus Exemestane in monotherapy, although with higher toxicity and no difference in Overall Survival (OS).
[f] Fulvestrant with Palbociclib has shown greater PFS versus Fulvestrant-Placebo in a phase III EC.

Source: Gavilá J, Lopez-Tarruella S, Saura C, Muñoz M, Oliveira M, De la Cruz-Merino L, Morales S, Alvarez I, Virizuela JA, Martín M. SEOM Clinical Guidelines in metastatic breast cancer 2015. Clin Transl Oncol 2015,17(12):946-55
Source: Chacón López-Muñiz JI, de la Cruz Merino L, Gavilá Gregori J, Martínez Dueñas E, Oliveira M, Seguí-Palmer MA, Álvarez-López I, Antolin Novoa S, Bellet Ezquerra M, López-Tarruella Cobo S. SEOM clinical guidelines in advanced and recurrent breast cancer (2018). Clin Transl Oncol 2019;21(1):31-4

Table 2.17. HORMONAL THERAPY in the treatment of METASTATIC breast cancer.

CYTOTOXIC TREATMENT.

Sequential monotherapy is preferred over combination therapy, except in cases of need for accelerated response due to rapidly progressive disease, evidence of visceral crisis or need for rapid symptomatic control (I, A)[148].

The use of anthracyclines or taxanes (in monotherapy or combination) is recommended in the first line, particularly in cases that have not received them in adjuvancy or in late relapses (I, A)[133-134].

The combination of Bevacizumab and taxanes has shown benefit in objective responses (OR) and progression-free survival (PFS) but not in overall survival (OS). It could be considered as a first-line option in selected patients such as those with high tumour burden, early recurrence or during adjuvancy and tumour phenotype TN (II, C)[149].

In patients already treated with anthracyclines and taxanes, Vinorelbine and Capecitabine are other therapeutic options in the first line (II, B)[150-151].

Multiple agents have been tested in second and subsequent lines in metastatic breast cancer: Capecitabine, Vinorelbine, Eribulin, Liposomal Doxorubicin, Nab-Paclitaxel and Gemcitabine (I, A)[150-151].

In women treated with anthracyclines and taxanes, Eribulin has not shown superiority over Capecitabine, but in the TN subgroup, an OS benefit was observed in favour of Eribulin. In addition, it has shown a modest overall survival benefit in women pre-treated with anthracyclines and taxanes (I, A)[152].

In metastatic TN breast cancer the role of platinum and its derivatives remains to be confirmed against standard chemotherapy recommendations. EMA and FDA consider the combination of Carboplatin and Gemcitabine as a control arm in randomized clinical trials (RCTs) in TN metastatic breast cancer (MBC) as it has shown activity in women resistant to anthracyclines and taxanes (III, B).

In TN-MBC patients with BRCA mutation, Carboplatin showed superiority over Docetaxel in OR and PFS and should be considered as an option in this subgroup of patients (II, B).

TREATMENT IN Her2-positive METASTIC BREAST CANCER : AntiHer2 THERAPY.

Specific anti-Her2 therapy should be initiated in the face of evidence of Her2-positive metastatic breast cancer. It has demonstrated a benefit in OR, PFS and OS in combination with taxanes and other drugs such as Vinorelbine, Capecitabine (I, A)[153].

Trastuzumab with CT in 1st line of MBC (whether or not they have previously received Trastuzumab in adjuvancy) is higher than the combination of Lapatinib and CT (I, A).

Pertuzumab in combination with Trastuzumab and Docetaxel has shown benefit in OR, PFS and OS compared to Trastuzumab and Docetaxel (I, A).

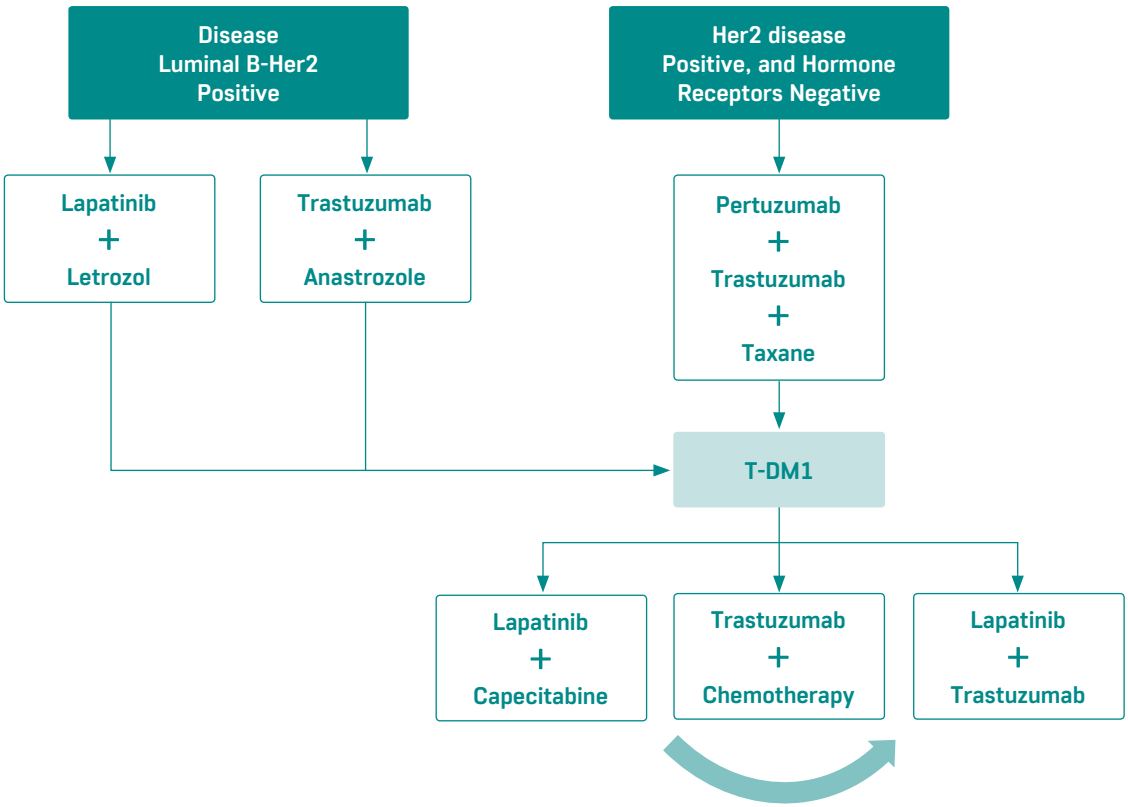
In patients who have received Trastuzumab as an adjuvancy there is limited evidence to establish the best first-line treatment regimen for relapse. If the relapse is later than one year after the completion of adjuvant Trastuzumab, the combination of Pertuzumab, Trastuzumab and Docetaxel could be considered. In relapses between 6-12 months there seems to be more evidence in favour of T-DM1 (II, B). There are also no data on the continuation of Trastuzumab with Pertuzumab to the progression of the 1st line combined with another drug other than Docetaxel. However, the use of Pertuzumab beyond the 1st line could be assessed if it has not been previously received (II, C).

T-DM1 has shown benefit in 2nd line after progression during or after 1st line with Trastuzumab and CT (I, A) and better results against the combination of Lapatinib and Capecitabine, in OR, PFS and OS in patients who have received Trastuzumab in 1st line and in those in early progression after adjuvancy (I, A)[154].

Lapatinib and Capecitabine could be used in 2nd line if there is contraindication for T-DM1 (I, B). It may be beneficial to maintain Her2 therapy in successive lines, beyond the 2nd (I, A). T-DM1 may be considered the standard therapy in patients who have already received several antiHer2 agents (including Trastuzumab, Lapatinib and Pertuzumab) with or without CT (I, A). The combination of **Lapatinib and Trastuzumab** in progression to Trastuzumab provides benefits in PFS and OS versus Lapatinib in monotherapy, especially in the absence of hormone receptor expression (II, B).

The **optimal number of antiHer2 therapy lines is unknown**. The available data suggest that there is still benefit in 3rd line and beyond (II, B).

In hormone-sensitive tumors, the combination of **aromatase inhibitors** (AIs) and anti-Her2 agent (Trastuzumab or Lapatinib) produces benefit in OR and PFS, not in OS. This is less than that achieved with the combination of antiHer2 and CT, so this strategy should be limited to low risk patients or as a maintenance therapy for toxicity or poor tolerance to CT (II, B).



Source: Gavilá J, López-Tarruella S, Saura C, Muñoz M, Oliveira M, De la Cruz-Merino et al. SEOM clinical guidelines in metastatic breast cancer 2015. Clin Transl Oncol 2015; 17:946-955.

Figure 2.7. Treatment algorithm for Her2-positive metastatic breast cancer (modified from Gavilá et al).

3.5. GENETIC PREDISPOSITION TO BREAST CANCER.

EPIDEMIOLOGY.

Between 7-10% of breast cancer cases are hereditary[155].

BC susceptibility genes have been identified which, depending on their frequency in the population and the risk they confer, can be grouped into high, moderate or low penetrance genes. About 3-5% of BC and 10% of ovarian cancers (OC) are associated with germline mutations in the genes BRCA1 and BRCA2, which are responsible for the hereditary breast and ovarian cancer syndrome (HBOC).

The cumulative risk of BC and OC at 70 years of age for BRCA1 mutation carriers is estimated at 57% and 40%, respectively. For BRCA2 mutation carriers, penetrance estimates are 49% for BC and 18% for OC[155-157].

RISK ASSESSMENT OR GENETIC PREDISPOSITION TO BREAST CANCER. SELECTION CRITERIA FOR THE STUDY of BRCA1 and BRCA2 genes.

The selection criteria to indicate the study of BRCA1 and BRCA2 genes should be reviewed and modified periodically based on the scientific evidence and knowledge gained[155-158].

Royal Decree 1030/2006 of 15 September, which establishes the portfolio of common services of the National Health System and the procedure for updating it with regard to specialised care, only provides for the assessment of individual risk.[3]

In Spain, the Spanish Society of Medical Oncology (SEOM) proposes the selection criteria described at Table 2.18 see page 58.

3] Royal Decree 1030/2006 of 15 September establishing the portfolio of common services of the National Health System and the procedure for updating it.

Regardless of family history, if:

- Woman with synchronous or metachronous BC and OC.
- BC <30 years.
- Bilateral BC <40 years.
- High-grade epithelial OC (or fallopian tube or primary peritoneal cancer).

Existence of family history of breast cancer:

2 or more immediate family members with a combination of any of the following high-risk characteristics:

- Bilateral BC + another BC <50 years.
- BC in the male.
- BC + OC or cancer of the fallopian tube or primary peritoneum.
- ≥2 OC at any age.
- Both cases diagnosed before the age of 50.

3 or more immediate family members with BC and/or OC:

- ≥ 3 BC + OC.
- ≥ 3 BC.

Triple-Negative BC:

- Diagnosed <50 years.
- Regardless of age at diagnosis:
  - If BC/OC family history and/or
  - If medullary cancer histology

Quality of evidence:

› I: Evidence from ≥ 1 correctly randomized controlled trial.
› II: Evidence from ≥1 well-designed, non-randomized clinical trial; from cohort or case-control analytical studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments.
› III: Evidence of opinions from respected authorities, based on clinical experience, descriptive studies or expert committee reports.

Strength of recommendation:

› A: Good evidence to support a recommendation for use.
› B: Moderate evidence to support a recommendation for use.
› C: Bad evidence to support a recommendation.
› D: Moderate evidence to support a recommendation against use.
› E: Good evidence to support a recommendation against use.

Source: Llort G, Chirivella I, Morales R, Serrano R, Sanchez AB, Teulé A, Lastra E, Brunet J, Balmaña J, Graña B; SEOM Hereditary Cancer Working Group. SEOM clinical guidelines in Hereditary Breast and ovarian cancer. Clin Transl Oncol. 2015;17(12):956-61.

Table 2.18. Risk assessment. Selection criteria for the study of BRCA1 and BRCA2 genes.

RISK-REDUCING STRATEGIES IN BRCA1 and BRCA2 GENES MUTATION CARRIERS.

Risk-reducing strategies in BRCA1 and BRCA2 gene mutation carriers[159-160].

Preventive strategies in BRCA1 or BRCA2 mutation carriers include both primary prevention (mainly through risk-reducing surgeries) and secondary prevention strategies aimed at early detection of BC and OC with the aim of improving the prognosis[161-163].

1 EARLY DETECTION OF BREAST CANCER.

It is recommended to start early detection of BC by means of an annual MRI from the age of 25. From the age of 30 onwards, it is advisable to add annual mammography to avoid the risk of irradiation at a young age. Prospective studies and a meta-analysis have demonstrated a higher sensitivity of MRI compared to mammography (93.4% v 39.6%; p<.001) in detecting BC in mutation carriers[164].

2 PROPHYLACTIC BILATERAL SALPINGO-OOPHORECTOMY (PBSO).

OC screening is not effective for the early diagnosis of this neoplasm. PBSO is recommended for women who are mutation carriers after completing their gestational desires, after demonstrating an 80% reduction in the risk of OC after performing a PBSO and a 50% reduction in the risk of BC[161].

3 BILATERAL RISK-REDUCING MASTECTOMY (BRRM).

BRRM reduces the risk of BC by 90% in BRCA1 or BRCA2 mutation carriers, although there is no evidence that this translates into a survival benefit. In a recent prospective analysis, BRRM is associated with improved overall survival in BRCA1 or BRCA2 carriers with breast cancer. The benefit is demonstrated especially in young patients (<40 years), with grade I/II breast cancer with or without TN phenotype and not treated with adjuvant chemotherapy[163].

WOMEN	AGE	Level of Evidence and Degree of Recommendation
⁙ Breast self-examination	Start at age 18	III, B
⁙ Clinical breast examination every 6-12 months	Start at 25 years old	III, B
⁙ Annual breast MRI	Start at 25 years old	II, A
⁙ Annual mammography	Start at age 30-35	II, A
⁙ Transvaginal ultrasound and annual Ca12.5	If done, start at age 30	II, C
⁙ Prophylactic Bilateral Salpingo-Oophorectomy (PBSO)	From the age of 35-40 and after completing genetic wishes	II, A
⁙ Bilateral Risk-Reducing Mastectomy (BRRM)	There is no established age of recommendation	II, B
⁙ Tamoxifen as primary chemo-prevention	No benefit demonstrated in BRCA1/BRCA2	II, C
⁙ Oral contraceptives as primary chemo-prevention	Conflicting results regarding breast cancer risk	II, C

Quality of evidence:
- I: Evidence from ≥ 1 correctly randomized controlled trial
- II: Evidence from ≥1 well-designed, non-randomized clinical trial; from cohort or case-control analytical studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments
- III: Evidence of opinions from respected authorities, based on clinical experience, descriptive studies or expert committee reports.

Strength of recommendation:
- A: Good evidence to support a recommendation for use.
- B: Moderate evidence to support a recommendation for use.
- C: Bad evidence to support a recommendation.
- D: Moderate evidence to support a recommendation against use.
- E: Good evidence to support a recommendation against use.

Source: Llort G, Chirivella I, Morales R, Serrano R, Sánchez AB, Teulé A, Lastra E, Brunet J, Balmaña J, Graña B; SEOM Hereditary Cancer Working Group. SEOM clinical guidelines in Hereditary Breast and ovarian cancer. Clin Transl Oncol. 2015;17(12):956-61.

Table 2.19. Recommendations for the management of women who are BRCA1 and BRCA2 mutation carriers

4. RADIOTHERAPY TREATMENT OF BREAST CANCER.

4.1. VOLUMES, DOSES AND TREATMENT SCHEMES[165-180].

TREATMENT VOLUMES.

Treatment volumes vary depending on the tumor stage and the surgery performed. Thus, it can be distinguished:

- **Full breast:** always indicated after conservative surgery for both in-situ and infiltrating tumors[168,181].
- **Lumpectomy bed (boost or overlapping):** indicated on many occasions, especially if there is margin involvement[182-183].
- **Nodal areas:** irradiation of nodal areas has shown benefit in the presence of nodal tumor involvement: that of supraclavicular and axillary levels 3 whenever nodes are involved; and that of nodal levels 1-2 when nodal involvement exists without lymphadenectomy. The irradiation of the internal mammary chain is recommended in young patients with large tumors, located in central-internal quadrants or with N2-N3 node involvement in the axilla, and whenever it is pathologically affected.
- **Partial breast irradiation or lumpectomy bed with wide margin:** it can be a treatment option in patients with good prognosis criteria (T1 not multicentric, not lobular, well and moderately differentiated, with free margins, positive hormonal receptors), with age equal or above 60 years, without intraductal component, nor lymphovascular invasion.
- **Chest wall:** indicated in tumors larger than 5 cm or T4, and may be indicated in those T1-2 with bad prognosis factors. Silicone expanders or prostheses are not contraindicated for irradiation, so it can be administered regardless of whether reconstruction has been or will be performed.

DOSES AND TREATMENT SCHEMES.

The total dose to be administered will depend on the dose per fraction used, i.e. the treatment scheme. The scheme proposed by the NSABP and other cooperative groups (Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC)) is traditionally used in their trials. This consists of 50 Gy in 25 fractions of 2 Gy/day, 5 days per week for a total of 35 days. However, other schemes have been shown to be biologically equivalent and to achieve the same degree of effectiveness.

This classic scheme of irradiation of breast volume, chest wall or nodal areas is being replaced by hypofractionated schemes obtaining the same results, both in terms of healing and morbidity, but in three weeks.

On many occasions it is necessary to administer a dose complement in the tumour bed or scar. This can be done, as mentioned above, concomitantly with intensity modulated radiotherapy techniques (IMRT) by increasing the dose per fraction in the problem area, adding a few irradiation sessions on the problem area, with brachytherapy or even previously with intra-operative radiation therapy (IORT).

The most commonly used schemes are described on Table 2.20.

Scheme	Fractionation Radiotherapy (Gy/No. fractions)	Overlapping fractionation (Gy/No. fractions)	Total treatment days	Indications
⁖ Classic	2 x 25 1.8 x 28	2 x 8-10	43-48	Post-mastectomy; post-conservative surgery
⁖ Accelerated hypofractionation	2.67 x 15 2.66 x 16	5 x 2.67	22-31	Post-mastectomy; post-conservative surgery
⁖ Weekly hypofractionation	5-6.5 x 5	6.5 x 2	42	Fragile, inoperable patients, or patients refusing surgery
⁖ Hypofractionation in partial irradiation	4 x 8 3.85 x 10 3.75 x 10	-	5	Partial breast irradiation
⁖ Extreme hypofractionation	20-22 x 1	-	1	Partial breast irradiation*
⁖ Hyperfractionation	1,5 (b.i.d.) x 40-44	1,5(b.i.d.) x 10	33-37	Inflammatory cancer; unresectable tumors

* Intraoperative radiation.
Source: Fisher C, Ravinovich R. Frontiers in Radiotherapy for early-stage invasive breast cancer. J Clin Oncol 2014;32(26):2894-901

Table 2.20. Summary of the most commonly used treatment schemes in radiotherapy.

DOSE IN RISK ORGANS

The maximum tolerable doses in the risk organs will depend on the treatment scheme. Various parameters for dose assessment in risk organs are available on Table 2.21.

Organ	Parameter	Hypofractionation	Classic fractionation
⁙ Bilateral lung	Average dosage	Less than 6.5 Gy	10 Gy (7-13 Gy)
	V20	Less than 20%	Less than 25-30%
	V10	Less than 40%	
	V5	Less than 55%	
⁙ Ipsilateral lung	Average dosage	Less than 17 Gy	
	V30 V20	Less than 200 cc	
⁙ Contralateral lung	Average Dose	6.5	Less than 5 Gy
	V10	14.0	Less than 10%
⁙ Pericardium	Average Dose	20.0	26 Gy
	V30	23.5	46%
⁙ Heart	Average dosage	Less than 20 Gy	
	V25		Less than 10%
	V30	Less than 30 cc	
	V40	Less than 25%	
	V50	Less than 5 cc	
⁙ Esophagus	Average Dose	27.0	34 Gy
	V35	28.0	Less than 50%
⁙ Contralateral breast	Maximum dose		Less than 5 Gy
	V10		Less than 12%
⁙ Liver	V30		Less than 30%
⁙ Brachial Plexus	Maximum dose	47.5	60
⁙ Rib	Maximum dose	45.5	50
⁙ Skin	Maximum dose	115% to 1.8 cc	
	V110	Less than 50 cc	
	100 cm2	39.0	50
	30 cm2	47.0	60
	10 cm2	55.0	70

Source: https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/RTOG

Table 2.21. Dose in risk organs.

VERIFICATION AND CONTROL

Verification is a very important part of the radiotherapy process, it has three parts: technical verification, clinical control and interruption control.

Technical verification.

It is necessary to establish guidelines for the approval of the planned technique and to allow control over the time that the radiotherapy lasts. The guided image in its different modalities should be the standard of verification and control of the treatment. There are two main systems:

- The beam imaging system (Portal Vision) is the most common in our environment. It distinguishes metallic, bone and aerial structures and allows the isocentre of the treatment volume to be located by acquiring 2 orthogonal images, informing about the displacements in the three spatial axes;
- The second system, called volumetric (cone-beam), allows the acquisition of volumetric images of the patient and an adjustment of the rotations in addition to the 3 spatial axes, just like the PV. In breast irradiation, it is recommended that the verification of the treatment isocentre be carried out by acquiring orthogonal images, and performing fusion available in the different computer applications with digitally reconstructed images (RDR) from the planning CT in these projections.

The frequency with which a check image must be performed significantly influences the quality of the treatment. A minimum number of verification images of about 10% of all treatment fractions is recommended.

Clinical control.

During the course of breast irradiation, clinical controls should be carried out, mainly focused on acute skin alterations and side effects on the upper aerodigestive tract.

Skin damage usually occurs from session 10 - 15 of the standard treatment of 25 fractions of 2 Gy, and at 6-7 fractions in hypofractionated regimens, and usually lasts until 7-10 days after the end of treatment. It is advisable to establish a revision 3-5 weeks after the end of the treatment and propose the following revisions depending on the existing clinic. It is important that they are graded according to international scales.

With the new treatment techniques available, toxicity in the upper aerodigestive tract is becoming less frequent. However, in the case of irradiation of some regional nodal areas, the possibility of dysphagia secondary to oesophagitis should be controlled. In these cases, an analgesic/anti-inflammatory treatment should be introduced. As in the case of skin, it is important to grade it according to internationally recognized scales.

To a lesser extent, the appearance of symptoms such as fever, asthenia or dyspnea, that could indicate secondary alterations to the treatments applied, shall be taken into account.

Interruption control.

Radiotherapy is administered with highly sophisticated treatment units that require exhaustive mechanical and dosimetric controls, and which undergo scheduled shutdowns for preventive maintenance, as well as unplanned breakdowns. To these must be added those derived from the patient's own evolution and care, due to health problems or any other non-medical cause. As a result, on many occasions, depending on the series, between 25-60% of the treatments are interrupted. For this reason, various action protocols have been established to deal with pauses and the start of treatment, which take into account the type of tumour, the purpose of the treatment and the cause of the interruption.

Breast cancer falls into the category of tumours where there is no level of evidence about the negative effect that interruptions in breast treatment can have. Nevertheless, it seems advisable to establish a compensation plan for loss of treatment days, as is advisable for any other tumor. In this group, breast tumours that show a more accelerated growth kinetics with a higher percentage of local and regional relapses after treatment should be considered. This recommendation will be of special interest in inflammatory breast cancer, and in general in young patients, in high grade (G3) tumors and in those with a high proliferation rate. "Triple negative" tumors tend to have a higher rate of local relapse after radiotherapy and should therefore be considered in this regard.

4.2. CLINICAL DOCUMENTATION: RADIOTHERAPY ONCOLOGY REPORT[184-186].

The report proposed in this guide is comprehensible for the rest of the specialities involved in the treatment of breast cancer and, therefore, does not replace the dosimetric report regulated by Royal Decree 1566/1998 of 17 July, nor does it aim to be as exhaustive as the report carried out when a radiotherapy oncology service refers a patient to another service to complete the treatment. Therefore, the radiation oncology report must reflect clinical and technical data.

The latter will be different for external radiotherapy and brachytherapy.

CLINICAL DATA.

Clinical data.

To define the clinical data, it is proposed to follow the recommendations of Royal Decree 1093/2010 of 3 September, which provides for the minimum data set of clinical reports in the National Health System. In particular, it is proposed to be based on the clinical report from outpatient consultations.

- **Administrative data of issuer:** date of consultation and date of document signature. Name of the person in charge, category, service and unit.
- **Data of issuing institution:** name of the Health Service, data of the centre with postal address and e-mail.
- **Patient's identification data:** administrative, etc.
- **Data about the care process:** it must include a summary of the medical history, with special mention of the oncological treatments and any radiotherapies carried out previously.
- **Reason for consultation:** CIE 9 or 10, SNOMED, etc.
- **Personal history:** hereditary diseases, allergies, toxic habits, medication received, functional status, etc.
- Current history, physical examination, summary of relevant complementary explorations in the process, evolution and comments, main and secondary diagnosis, procedures, treatments, recommendations and drugs.

TECHNICAL DATA.

Technical data of external radiotherapy.

The technical section must include:

- The intention of the treatment (radical/palliative), the treatment volumes defined in an understandable way (not with acronyms), the treatment position and immobilisation systems, the simulation system, the prescribed dose and fractionation, the number of fractions administered, the day of treatment start and the final day, the energy used, the dose compensation systems, the verification system employed, interruptions and their compensation if any, the toxicity that occurred and the planned monitoring plan.
- It is recommended that this report be given to the patient at the end of treatment or at the follow-up visit after treatment is completed.
- It is also recommended that, in cases where the tolerance doses of the critical organs are above the usual ones, the report should reflect these and the reason for them.

Technical data of brachytherapy.

- The intention of the treatment (radical/palliative), the system used to define the treatment volume, the simulation and calculation system, the prescribed dose and fractionation, the number of fractions administered, the day of treatment initiation and the final day, the technique and energy used, interruptions and their compensations if any, the toxicity that occurred and the planned follow-up plan should also be reflected.
- It is recommended that this report be given to the patient at the end of treatment or at the follow-up visit after treatment is completed.
- It is also recommended that, in those cases where the tolerance doses of the critical organs are above the usual ones, the report should reflect these and the reason for them.

Chapter 3

Evaluation of breast cancer clinical pathway.

1. EVALUATION INDICATORS.

1.1. LISTING: EVALUATION INDICATORS.

› STAGE: DIAGNOSTIC CONFIRMATION.

PATHOLOGY

PH-01: Percentage of quality pathology reports, i.e. use of reports following the criteria of the standardised pathology report.

PH-02: Proportion of cases with determination of prognosis and predictive factors in infiltrating carcinoma.

PH-03: Proportion of patients with the immunohistological diagnosis within 9 days.

RADIOLOGY

RX-04: Proportion of breast cancer patients who underwent preoperative imaging tests of both breasts and axillas.

RX-05: Proportion of patients who have undergone breast cancer surgery, with previous CNB and diagnosis of malignancy.

RX-06: Proportion of patients treated with primary systemic therapy who have undergone MRI.

NUCLEAR MEDICINE

NM-07: Proportion of patients with invasive cancer and negative axilla both clinically and by imaging test, who underwent sentinel lymph node biopsy.

NM-08: Proper identification of the sentinel lymph node: Proportion of patients in whom at least one sentinel node was identified (detection rate) in the following subgroups:

- (A) Patients who have received previous neoadjuvant treatment.
- (B) Patients who have not received previous neoadjuvant treatment.

NM-09: Proportion of patients undergoing SSLNB by means of isotope marker in whom lymphogammagraphy has been previously performed.

› STAGE: THERAPEUTIC APPROACH.

SURGERY

Sur-10: Ratio between mastectomy and conservative treatment in stage I or II infiltrating carcinoma.

Sur-11: Breast cancer patients evaluated by a multidisciplinary committee.

Sur-12: Proportion of re-interventions in conservative surgery.

- A Proportion of patients with conservative surgery reoperated due to affected margins.
- B Percentage of re-interventions for affected margins where the piece does not show residual tumour.

Sur-13: Proportion of patients who receive immediate reconstruction at the same time as their mastectomy.

MEDICAL ONCOLOGY

MedOnco-14: Percentage of patients with interval between surgical removal of the tumor and administration of adjuvant chemotherapy less than 8 weeks.

MedOnco-15: Proportion of patients with HER2-positive invasive carcinoma treated with monoclonal anti-HER2 therapy.

MedOnco-16: Proportion of patients receiving Primary Systemic Therapy (PST) as treatment in the following subgroups:

- A Inflammatory breast cancer.
- B Unresectable, locally advanced, estrogen receptor positive carcinoma.

RADIATION THERAPY ONCOLOGY

Rta-Onco-17: Proportion of patients with invasive breast cancer (M0) who received postoperative radiotherapy (RT) after conservative surgical resection of the primary tumour and appropriate axillary staging.

Rta-Onco-18: Proportion of patients with axillary lymph node involvement (pN2a) who received radiation therapy to all unresected regional lymph nodes.

Rta-Onco-19: Proportion of patients with involvement of up to three axillary lymph nodes (pN1) who received radiation therapy, after surgery, to unresected regional lymph nodes.

1.2. INDICATOR SHEETS.

EVALUATION INDICATORS: PATHOLOGY

PH-01: Percentage of quality pathology reports, i.e. use of reports following the criteria of the standardised pathology report.

PH-02: Proportion of cases with determination of prognosis and predictive factors in infiltrating carcinoma.

PH-03: Proportion of patients with immunohistological diagnosis within 9 days.

PH-01 INDICATOR	
SPECIALTY AREA	PATHOLOGY
DESCRIPTION	**PH-01:** Percentage of quality pathology reports, i.e. use of reports following the criteria of the standardised pathology report.
NUMERATOR	Number of reports with a diagnosis of infiltrating cancer following the quality criteria contemplated in the Pathology report, specified in the Clinical Pathway.
DENOMINATOR	Number of reports with a diagnosis of infiltrating cancer.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Compliance with quality criteria: Standard: ≥90%
INCLUSION CRITERIA	• Infiltrating breast cancer. • Lesions treated surgically with excisional purposes.
EXCLUSION CRITERIA	• Carcinoma in situ/Paget's disease. • Recurrences. • Metastasis. • Lymphoproliferative and hematopoietic tumours.
Source:	Medical history

REMARKS:

- The indicator should measure that the pathology report follows both its description and compliance with the required criteria related to the pathological study, including its macroscopic description, microscopic description, the results of immunohistochemical techniques, diagnosis and results of the genetic profile study.
- Compliance will be considered when the fulfilment of these criteria is greater than 90%, provable in the content and description in the report.

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PH-02 INDICATOR	
SPECIALTY AREA	**PATHOLOGY**
DESCRIPTION	**PH-02:** Proportion of cases with determination of prognosis and predictive factors in infiltrating carcinoma.
NUMERATOR	Number of cases of infiltrating breast cancer with immunohistochemical determination of prognosis and predictive factors.
DENOMINATOR	Number of cases of infiltrating breast cancer.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: 100%
INCLUSION CRITERIA	• Infiltrating carcinomas of the breast. • In multifocal carcinoma, each focus will be considered a case.
EXCLUSION CRITERIA	• Ductal Carcinoma in situ • Infiltrating carcinoma of the breast in which there is already a determination of prognosis and predictive factors in previous biopsy of the same lesion. • Determination in lymph node or metastasis.
Source:	Medical history

REMARKS:

› The prognosis or predictive factors considered in the definition of the indicator include the determination of: Estrogen receptors, progesterone receptor, HER2, IHC, FISH.

› *The determination of Ki67 (Recommended).

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PH-03 INDICATOR	
SPECIALTY AREA	**PATHOLOGY**
DESCRIPTION	**PH-03:** Proportion of patients with immunohistological diagnosis within 9 days.
NUMERATOR	• Number of patients with a diagnosis of breast cancer issued in less than 9 days from receiving biopsy in Pathology. • Numerator: Number of patients whose interval between the reception of the biopsy in Pathology and the result of immunohistological tests (diagnosis) is equal to or less than 9 calendar days.
DENOMINATOR	Total number of patients with reports issued with a diagnosis of breast cancer.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: ≥95%
INCLUSION CRITERIA	• Needle biopsy (CNB, VAB...) • Infiltrating carcinoma of the breast.
EXCLUSION CRITERIA	• Carcinoma in situ. • Metastasis.
Source:	Medical History; Pathology Reports

REMARKS:

› Considering the frequency of meetings of the Tumours Committee in the centres, the period is defined and established as less than 9 days.

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EVALUATION INDICATORS: RADIOLOGY

RX-04: Proportion of breast cancer patients who underwent preoperative imaging tests of both breasts and axillas.

RX-05: Proportion of patients who have undergone breast cancer surgery, with previous CNB and diagnosis of malignancy.

RX-06: Proportion of patients treated with primary systemic therapy who have undergone MRI.

INDICATOR RX-04	
SPECIALTY AREA	RADIOLOGY
DESCRIPTION	**RX-04:** Proportion of breast cancer patients who underwent preoperative imaging tests of both breasts and axillas.
NUMERATOR	Proportion of breast cancer patients who underwent preoperative imaging tests of both breasts and axillas.
DENOMINATOR	Number of patients with surgically indicated breast cancer.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Threshold: 85%
EXCLUSION CRITERIA	• Patients with a positive diagnosis for breast cancer who are not surgical candidates by clinical condition (comorbidity, surgical risk ...), clinical or patient decision.
Source:	Medical History, Tumor Registry

REMARKS:

- Axillary study by ultrasound +/-FNAP or CNB (fine needle aspiration puncture or core needle biopsy) are considered.
- Axillary ultrasound is taken into account as the gold standard of imaging, although there are other tests (MRI, CT) that study the nodal territories.

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RX-05 INDICATOR	
SPECIALTY AREA	**RADIOLOGY**
DESCRIPTION	**RX-05:** Proportion of patients who have undergone breast cancer surgery, with previous CNB and diagnosis of malignancy.
NUMERATOR	Number of patients surgically intervened with breast cancer (Surgical biopsy (+) and previous CNB with a diagnosis of malignancy [CNB (+)].
DENOMINATOR	Number of patients surgically intervened.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: 85% Desirable >90%
Source:	For example: Medical history, discharge report; prescriptions.

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RX-06 INDICATOR	
SPECIALTY AREA	**RADIOLOGY**
DESCRIPTION	**RX-06:** Proportion of patients treated with primary systemic therapy who have undergone MRI.
NUMERATOR	Number of patients treated with primary systemic therapy who receive an MRI (at least before and at the end).
DENOMINATOR	Number of patients treated with primary systemic therapy.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Threshold: 60%
EXCLUSION CRITERIA	Contraindication to MRI: Claustrophobia, significant obesity or physical condition that does not allow MRI, pacemaker or other device not compatible with magnetic field, allergy to gadolinium.
Source:	Medical history, discharge report; prescriptions.

REMARKS:

› In the case of gadolinium allergy, non-contrast breast MRI can be performed (DWI-diffusion and T2 sequences). At the time of drafting this clinical pathway, these sequences are considered complementary, although there are numerous studies underway to validate it as an isolated technique.

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EVALUATION INDICATORS: NUCLEAR MEDICINE

NM-07: Proportion of patients with invasive cancer and negative axilla both clinically and by imaging test, who underwent sentinel lymph node biopsy.

NM-08: Proper identification of the sentinel lymph node: Proportion of patients in whom at least one sentinel lymph node was identified (detection rate) in the following subgroups:

- A Patients who have received previous neoadjuvant treatment.
- B Patients who have not received previous neoadjuvant treatment.

NM-09: Proportion of patients undergoing SSLNB by means of isotope marker in whom lymphogammagraphy has been previously performed.

INDICATOR NM-07	
SPECIALTY AREA	NUCLEAR MEDICINE
DESCRIPTION	**NM-07:** Proportion of patients with invasive cancer and negative axilla both clinically and by imaging test, who underwent sentinel lymph node biopsy.
NUMERATOR	Number of patients with invasive and axillary cancer clinically and by negative imaging test who have sentinel lymph node biopsies performed.
DENOMINATOR	Number of patients with invasive cancer and axilla clinically and by negative imaging test.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: 95%
EXCLUSION CRITERIA	• Patients who received systemic primary treatment.
Source:	For example: Medical history, discharge report; prescriptions.

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INDICATOR NM-08	
SPECIALTY AREA	**NUCLEAR MEDICINE**
DESCRIPTION	**NM-08:** Proper identification of the sentinel lymph node: Proportion of patients in whom at least one sentinel lymph node was identified (detection rate) in the following subgroups: Patients who have received previous neoadjuvant treatment. Patients who have not received previous neoadjuvant treatment.
Sub-group 1	**Patients who have received previous neoadjuvant treatment.**
NUMERATOR	Ⓐ Number of patients who have received previous neoadjuvant treatment in whom at least one sentinel lymph node is identified.
DENOMINATOR	Ⓑ Number of patients who have received previous neoadjuvant treatment and who underwent intraoperative lymphogammagraphy and sentinel lymph node isotope detection.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Ⓐ Detection rate in sub-group a: ≥80%
Sub-group 2	**Patients who have not received previous neoadjuvant treatment.**
NUMERATOR	Ⓐ Number of patients who have not received previous neoadjuvant treatment in whom at least one sentinel lymph node is identified
DENOMINATOR	Ⓑ Number of patients who have not received neoadjuvant treatment and who underwent intraoperative lymphogammagraphy and sentinel lymph node isotopic detection.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Ⓑ Detection rate in subgroup b: ≥95%
INCLUSION CRITERIA	• All breast cancer patients in whom sentinel lymph node identification is performed.
Source:	For example: Medical history, discharge report; prescriptions.

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NM-09 INDICATOR	
SPECIALTY AREA	**NUCLEAR MEDICINE**
DESCRIPTION	**NM-09:** Proportion of patients undergoing SSLNB by means of isotope marker in whom lymphogammagraphy has been previously performed.
NUMERATOR	Number of patients undergoing sentinel lymph node biopsy (use of isotopic marker) who have previously undergone lymphogammagraphy.
DENOMINATOR	Number of patients undergoing sentinel lymph node biopsy using an isotope marker.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: 100%
INCLUSION CRITERIA	• All breast cancer patients in whom the isotope tracer is used in the identification of the sentinel lymph node.
Source:	For example: Medical history, discharge report; prescriptions.

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EVALUATION INDICATORS: SURGERY

Sur-10: Ratio between mastectomy and conservative treatment in stage I or II infiltrating carcinoma.

Sur-11: Breast cancer patients evaluated by a multidisciplinary committee.

Sur-12: Proportion of re-interventions in conservative surgery.

- A Proportion of patients with conservative surgery reoperated due to affected margins.
- B Percentage of re-interventions for affected margins where the piece does not show residual tumour.

Sur-13: Proportion of patients who receive immediate reconstruction at the same time as their mastectomy.

Sur-10 INDICATOR	
SPECIALTY AREA	SURGERY
DESCRIPTION	**Sur-10:** Ratio between mastectomy and conservative treatment in stage I or II infiltrating carcinoma.
Sub-group 1	**Invasive carcinoma no larger than 3 cm.**
NUMERATOR	Number of patients with infiltrating carcinoma susceptible to conservative treatment who undergo mastectomy in the following cases: A Invasive carcinoma no larger than 3 cm.
DENOMINATOR	Number of patients with infiltrating carcinoma susceptible to conservative treatment in the following cases: A For invasive carcinoma no larger than 3 cm.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Indicative standard (85-90%) * – STANDARD I-II A STANDARD: Invasive carcinoma no larger than 3 cm: Percentage of conservative surgery should be 85%
Sub-group 2	**Non-invasive carcinoma less than 2 cm.**
NUMERATOR	Number of patients with infiltrating carcinoma susceptible to conservative treatment who undergo mastectomy in non-invasive carcinoma smaller than 2 cm.
DENOMINATOR	Number of patients with infiltrating carcinoma susceptible to conservative treatment in non-invasive carcinoma smaller than 2 cm.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Indicative standard (85-90%) * – STANDARD I-II B STANDARD: Non-invasive carcinoma less than 2 cm: Percentage of conservative surgery should be 90%
INCLUSION CRITERIA	• Stage 0 • Stage I -II Infiltrating Carcinoma
Source:	For example: Medical history, discharge report; prescriptions.

REMARKS:

› (*) The standard has been proposed by the developers of the Clinical Pathway.

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Sur-11 INDICATOR	
SPECIALTY AREA	**SURGERY**
DESCRIPTION	**Sur-11:** Cancer patients evaluated by a multidisciplinary committee.
NUMERATOR	Number of patients evaluated by a multidisciplinary committee.
DENOMINATOR	Number of breast cancer patients evaluated.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: 100%
INCLUSION CRITERIA	All breast cancer patients in whom the isotope tracer is used in the identification of the sentinel lymph node.
Source:	For example: Medical history, discharge report; prescriptions.

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Sur-12 INDICATOR	
SPECIALTY AREA	**SURGERY**
DESCRIPTION	**Sur-12:** Proportion of re-interventions in conservative surgery.
Sub-group 1	**Proportion of patients with conservative surgery reoperated due to affected margins.**
NUMERATOR	(A) Number of patients with previous conservative surgery requiring re-intervention due to affected margins.
DENOMINATOR	(B) Number of patients treated with conservative surgery.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: Sub-group 1 Reinterventions of the tumor due to affected margins: Standard: <20%
Sub-group 2	**Percentage of re-interventions for affected margins where the piece does not show residual tumour.**
NUMERATOR	(A) Percentage of re-interventions due to affected margins where the piece does not show residual tumour.
DENOMINATOR	(B) Total number of re-interventions due to affected margins.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: Sub-group 2 First re-intervention due to affected margins where the piece does not show residual tumour*: Standard less than 80%
INCLUSION CRITERIA	• First re-intervention (indicator section B)
Source:	For example: Medical history, discharge report; prescriptions.

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Sur-13 INDICATOR	
SPECIALTY AREA	**SURGERY**
DESCRIPTION	**Sur-13:** Proportion of patients who receive immediate reconstruction at the same time as their mastectomy.
NUMERATOR	Number of patients receiving immediate reconstruction at the same time as the mastectomy with indication for possible reconstruction.
DENOMINATOR	Number of patients undergoing a mastectomy.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: >85%
EXCLUSION CRITERIA	• Over 70 years old. • No desire for reconstruction by the patient.
Source:	For example: Medical history, discharge report; prescriptions.

REMARKS:

› Unless contraindicated for technical or oncological reasons.

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EVALUATION INDICATORS: MEDICAL ONCOLOGY

MedOnco-14: Percentage of patients with interval between surgical removal of the tumor and administration of adjuvant chemotherapy below 8 weeks.

MedOnco-15: Proportion of patients with HER2-positive invasive carcinoma treated with monoclonal anti-HER2 therapy.

MedOnco-16: Proportion of patients receiving Primary Systemic Therapy (PST) as treatment in the following subgroups:

- A Inflammatory breast cancer.
- B Unresectable, locally advanced, estrogen receptor positive carcinoma.

MedOnco-14 INDICATOR

SPECIALTY AREA	MEDICAL ONCOLOGY
:: DESCRIPTION	• MedOnco-14: Percentage of patients with interval between surgical removal of the tumor and administration of adjuvant chemotherapy below 8 weeks.
:: NUMERATOR	Number of patients who start chemotherapy treatment within 8 weeks from the date of tumour surgery. Numerator: Number of patients whose interval between surgery and the start of the adjuvant treatment regimen is equal to or below 8 weeks.
:: DENOMINATOR	• Number of patients receiving surgical treatment of the tumor. • Total number of patients diagnosed with breast cancer and treated surgically.
:: STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: 99%
:: Source:	For example: Medical history, discharge report; prescriptions.

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MedOnco-15 INDICATOR	
SPECIALTY AREA	**MEDICAL ONCOLOGY**
DESCRIPTION	• **MedOnco-15:** Proportion of patients with HER2-positive invasive carcinoma treated with monoclonal anti-HER2 therapy.
NUMERATOR	Proportion of patients with HER2-positive invasive carcinoma treated with monoclonal anti-HER2 therapy.
DENOMINATOR	Number of patients with HER2-positive invasive carcinoma.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: 95%
Source:	For example: Medical history, discharge report; prescriptions.

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MedOnco-16 INDICATOR	
SPECIALTY AREA	**MEDICAL ONCOLOGY**
DESCRIPTION	• **MedOnco-16:** Proportion of patients receiving Primary Systemic Therapy (PST) as a treatment in the following subgroups: Inflammatory breast cancer. Unresectable, locally advanced, estrogen receptor positive carcinoma.
Sub-group 1	**Inflammatory breast cancer.**
NUMERATOR	Ⓐ Number of patients with inflammatory breast cancer receiving neoadjuvant chemotherapy.
DENOMINATOR	Ⓑ Number of patients with inflammatory breast cancer
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: Sub-group 1 Patients with inflammatory breast cancer: Standard: 100%
Sub-group 2	**Unresectable, locally advanced, estrogen receptor positive carcinoma.**
NUMERATOR	Ⓐ Number of patients with locally advanced unresectable estrogen receptor positive carcinoma receiving neoadjuvant chemotherapy.
DENOMINATOR	Ⓑ Number of patients with locally advanced unresectable estrogen receptor positive carcinoma.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard: Sub-group 2 Unresectable, locally advanced, estrogen receptor positive carcinoma: Standard: 90%
INCLUSION CRITERIA	• Applied to cases where chemotherapy treatment is indicated.
Source:	For example: Medical history, discharge report; prescriptions.

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EVALUATION INDICATORS: RADIATION THERAPY ONCOLOGY

Rta-Onco-17: Proportion of patients with invasive breast cancer (M0) who received postoperative radiotherapy (RT) after conservative surgical resection of the primary tumour and appropriate axillary staging.

Rta-Onco-18: Proportion of patients with axillary lymph node involvement (pN2a) who received radiation therapy to all unresected regional lymph nodes.

Rta-Onco-19: Proportion of patients with involvement of up to three axillary lymph nodes (pN1) who received radiation therapy, after surgery, to unresected regional lymph nodes.

OncoRta-17 INDICATOR

SPECIALTY AREA	RADIATION THERAPY ONCOLOGY
DESCRIPTION	• OncoRta-17: Proportion of patients with invasive breast cancer (M0) who received postoperative radiotherapy (RT) after conservative surgical resection of the primary tumour and appropriate axillary staging.
NUMERATOR	Number of patients with invasive breast cancer undergoing conservative surgery and appropriate axillary staging (M0) receiving postoperative radiotherapy (RT).
DENOMINATOR	Number of patients with invasive breast cancer (M0) treated with conservative surgery of the primary tumor and appropriate axillary staging.
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard 95%
INCLUSION CRITERIA	• Stage I, II, III invasive breast carcinoma. • Conservative surgery or mastectomy and axillary study (lymphadenectomy/sentinel lymph node biopsy). • Breast RT and/or partial irradiation techniques.
EXCLUSION CRITERIA	• Presence of distant metastasis (stage IV). • Impossibility to understand the treatment. • Preliminary chest irradiation.
Source:	EHR, Discharge Report, Radiation Oncology Report, Surgery Report.

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OncoRta-18 INDICATOR

SPECIALTY AREA	RADIATION THERAPY ONCOLOGY
DESCRIPTION	• **OncoRta-18:** Proportion of patients with axillary lymph node involvement (pN2a) who received radiation therapy to all unresected regional lymph nodes.
NUMERATOR	Proportion of patients with axillary lymph node involvement (pN2a) who received radiation therapy to all unresected regional lymph nodes.
DENOMINATOR	Number of patients with axillary lymph node involvement (pN2a).
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard 95%
INCLUSION CRITERIA	• Staged breast carcinoma with pN2 lymph node involvement.
EXCLUSION CRITERIA	• Presence of distant metastasis (stage IV). • Impossibility to understand the treatment. • Preliminary chest irradiation.
Source:	EHR, Discharge Report, Radiation Oncology Report, Surgery Report.

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OncoRta-19 INDICATOR

SPECIALTY AREA	RADIATION THERAPY ONCOLOGY
DESCRIPTION	• **OncoRta-19:** Proportion of patients with involvement of up to three axillary lymph nodes (pN1) who received radiation therapy, after surgery, to unresected regional lymph nodes.
NUMERATOR	Number of patients with up to three axillary lymph node involvement (pN1) treated with post-surgical radiation therapy to unresected regional lymph nodes.
DENOMINATOR	Number of patients with axillary lymph node involvement (pN1).
STANDARD	(Definition of acceptable threshold in the absence of a standard) Standard 95%
INCLUSION CRITERIA	• Breast carcinoma with pN1 lymph node involvement.
EXCLUSION CRITERIA	• Presence of distant metastasis (stage IV). • Impossibility to understand the treatment. • Preliminary chest irradiation.
Source:	EHR, Discharge Report, Radiation Oncology Report, Surgery Report.

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Annex I

EVALUATION OF BREAST CANCER CLINICAL PRACTICE GUIDELINES (CPG). AGREE-II DOMAINS: OBJECTIVES/SCOPE AND METHODOLOGICAL RIGOUR.

No. CPG	Title of CPG	Processing body Publication date Update	Scope of CPG	Domain Objective/Scope Methodological rigour
1	**Early and Locally advanced breast cancer: diagnosis and management (NG101).** CPG update: Early and locally advanced breast cancer: diagnosis and treatment (CG80). National Institute for Health and Care Excellence (NICE); 2018 (Clinical Guideline No. 101) NICE 2018	• National Institute Clinical Excellence • 2009/ • Update 2018	In this CPG, interventions during the performance are contemplated.It provides the best available evidence and recommendations for the diagnosis and management of non-advanced breast cancer. It includes RECOMMENDATIONS related to: Referral, diagnosis and preoperative evaluation. Breast and axillary surgery. Breast reconstruction. To establish a diagnostic and therapeutic planning. Hormone treatment. Adjuvant chemotherapy for infiltrating cancer. Treatment with bisphosphonates. Radiotherapy. Primary systemic therapy. Lymphoedema. Complications of local treatment and menopausal symptoms. Monitoring.	Domain: Methodological rigour: ‣ Points: 43.5 77.7% Domain: Scope/Objective: ‣ Points: 21 100%
2	**Advanced breast cancer: diagnosis and treatment NICE (CG81)** National Institute for Health and Care Excellence (NICE); 2017 Clinical Guideline (No. 81) NICE 2017	• National Institute Clinical Excellence • 2009/ • Update August 2017	In this CPG, interventions during the performance are contemplated.It provides the best available evidence and recommendations for the diagnosis and management of advanced breast cancer. It includes RECOMMENDATIONS related to: Diagnosis and evaluation. Providing information and support for decision making. Treatment for systemic disease. Supportive care. Management of complications.	Domain: Methodological rigour: ‣ Points: 48 85.7% Domain: Scope/Objective: ‣ Points: 21 100%

No. CPG	Title of CPG	Processing body Publication date Update	Scope of CPG	Domain Objective/Scope Methodological rigour
3	Familial Breast Cancer: Classification, care, and managing breast cancer and related risks in people with a family history of Breast Cancer (CG164) Clinical Guideline (Nº 164) NICE 2017	• National Institute Clinical Excellence • Junio 2013/ • Update March 2017	In this CPG, interventions during the performance are contemplated. It provides the best available evidence and recommendations for the diagnosis and management of breast cancer and its risk assessment. It includes RECOMMENDATIONS related to: - Clinical significance of breast cancer with family history. - Information and support. - Primary care and people care. - Secondary care and clinical genetics specialists. - Genetic tests. - Surveillance and strategies for the early detection of breast cancer. - Risk reduction and therapeutic strategies.	Domain: Methodological rigour: ‣ Points: 46.5 83% Domain: Scope/Objective: ‣ Points: 21 100%
4	Primary Breast Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.	• European Society Medical Oncology • (ESMO); 2015	Published in: Senkus E, Kyriadkides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S and Cardoso F. Primary Breast Cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2015 (supp 5): v8-v30 The ESMO CPG refers to primary breast cancer and includes information on staging, diagnosis, treatment and follow-up. - Breast cancer screening. - Diagnosis and pathology/molecular biology. - Staging and risk assessment - Disease management. Loco-regional. - Monitoring and long-term implications.	Domain: Methodological rigour: ‣ Points: 37 66% Domain: Scope/Objective: ‣ Points: 15 71.4%

No. CPG	Title of CPG	Processing body Publication date Update	Scope of CPG	Domain Objective/Scope Methodological rigour
5	**Advanced Breast Cancer ESMO Clinical Practice Guidelines** 4th ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)	• European Society Medical Oncology (ESMO) • 2018/	Published in: Cardoso D, Senkus E, Costa A et al. 4th ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol 2018; 29:1634-1657 https://www.esmo.org/Guidelines/Breast-Cancer It describes recommendations on evaluations and interventions. This CPG includes recommendations on: Organization of care The ESO-ESMO 4th international consensus guidelines for advanced breast cancer (ABC 4) focus on methodology, assessment guidelines and treatment recommendations for specific breast cancer subtypes, including ER positive / HER2 negative (luminal) ABC, HER2 positive ABC, triple negative ABC and male mestastatic breast cancer, as well as patients with specific metastases. Palliative and supportive care recommendations are also included. It incorporates a new section that addresses integrative medicine.	Domain: Methodological rigour: ‣ Points: 41.5 74.1% Domain: Scope/Objective: ‣ Items: 17 81%

No. CPG	Title of CPG	Processing body Publication date Update	Scope of CPG	Domain Objective/Scope Methodological rigour
6	Prevention and Screening in BRCA Mutation Carriers and other Breast/ Ovarian Hereditary Cancer Syndromes	• European Society Medical Oncology (ESMO) • 2016/	Published: Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, Senkus E. Prevention and Screening in BRCA Mutation Carriers and other Breast/Ovarian Hereditary Cancer Syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol 2016,27(suppl 5): v103-v110. Available at: https://www.esmo.org/Guidelines/Hereditary-Syndromes/Prevention-and-Screening-in-BRCA-Mutation-Carriers-and-Other-Breast-Ovarian-Hereditary-Cancer-Syndromes These guidelines focus on cancer prevention and detection in people known to harbor a pathogenic BRCA1/2 mutation. The presence of a BRCA1 or BRCA2 mutation represents the majority of hereditary breast and ovarian cancer syndromes. Genetic susceptibility to breast or ovarian cancer may also be associated with mutations in other genes, some of which are associated with known hereditary cancer syndromes. The association of cancer risk with other genes is still under investigation or clinical validation. For the initial risk assessment and decision on when to perform genetic counseling and testing, the reader is referred to the recently updated National Comprehensive Cancer Network (NCCNG) guidelines on high genetic/family risk assessment and the National Institute of Health and Clinical Excellence (NICE) guidelines. - Breast cancer risk reduction: lifestyle modifications, screening tests, surgery to reduce risk. - Screening recommendations after the diagnosis of breast and ovarian cancer. - Reproductive considerations in BRCA mutation carriers. - Prevention and detection of other cancers associated with BRCA and addressing male carriers. - Prevention and detection of cancer in the presence of other syndromes, of moderate to high risk genetic mutation.	Domain: Methodological rigour: ‣ Points: 39.5 70.5% Domain: Scope/Objective: ‣ Items: 18 85.7%

No. CPG	Title of CPG	Processing body Publication date Update	Scope of CPG	Domain Objective/Scope Methodological rigour
7	SEOM Clinical Guidelines in Early stage Breast Cancer (2015)/ (2018)	• Sociedad Española Oncología Médica (SEOM) • 2015/ • 2018 Update	Published: García-Saenz JA, Bermejo B, Estevez LG, Palomo AG, Gonzalez-Farre X, Margeli M, Pernas S, Servitja S, Rodriguez CA, Ciruelos E. Clin Transl Oncol 2015;17(12):939-45 This CPG includes aspects on: - Diagnosis and initial treatment. - Principles of surgery in early stage breast cancer. - Principles of adjuvant systemic treatment. Genomic profiles in the decision-making for systemic adjuvant therapy: systemic treatment for early luminal breast cancer, systemic treatment for early HER2-positive breast cancer; systemic therapy for early triple-negative breast cancer. Published: Ayala de la Peña F, Andreés R, García-Sáenz JA, Manso L, Margeli M, Dalmau E, Pernas S, Prat A, Servitja S, Ciruelos E. SEOM clinical guidelines in early stage breast cancer (2018). Clin Transl Oncol 2019;21(1):18-30. The following aspects are included in this CPG: - Diagnosis and initial treatment. - Principles of surgery. - Recommendations for adjuvant radiotherapy. - Principles of adjuvant systemic therapy. Genomic profiles in the decision-making for systemic adjuvant therapy: systemic treatment for early luminal breast cancer, systemic treatment for early HER2-positive breast cancer; systemic therapy for early triple-negative breast cancer.	Domain: Methodological rigour: ‣ Points: 34 60.7% Domain: Scope/Objective: ‣ Points: 15 71.4%

No. CPG	Title of CPG	Processing body Publication date Update	Scope of CPG	Domain Objective/Scope Methodological rigour
8	**SEOM Clinical Guidelines in Metastatic Breast Cancer** SEOM 2015/ Update 2018	• Spanish Society of Medical Oncology (SEOM); • 2015/ • Update 2018	Published: Gavilá J, Lopez-Tarruella S, Saura C, Muñoz M, Oliveira M, De la Cruz-Merino L, Morales S, Alvarez I, Virizuela JA, Martín M. SEOM Clinical Guidelines in metastatic breast cancer 2015. Clin Transl Oncol 2015,17(12):946-55 The objective of the SEOM guide is to make evidence-based recommendations on how to treat patients with metastatic breast cancer to achieve the best outcomes for patients based on the rational use of currently available therapies. - Objective of treatment. - Determination of metastatic spread and re-evaluation of biomarkers in recurrent disease. - Evaluation of the response to treatment in advanced breast cancer. - Treatment of HER2-positive metastatic breast cancer: first-line treatment, second-line treatment, third-line treatment, and additional treatment. - Treatment of hormone-sensitive HER2-negative metastatic breast cancer. - Treatment of triple-negative metastatic breast cancer. Published: Chacón López-Muñiz JI, de la Cruz Merino L, Gavilá Gregori J, Martínez Dueñas E, Oliveira M, Seguí-Palmer MA, Álvarez-López I, Antolin Novoa S, Bellet Ezquerra M, López-Tarruella Cobo S. SEOM clinical guidelines in advanced and recurrent breast cancer (2018). Clin Transl Oncol 2019;21(1):31-45. The SEOM guidelines (2018) aim to make evidence-based recommendations on how to treat patients with advanced and recurrent breast cancer to achieve the best outcomes for patients based on the rational use of currently available therapies. - Overview of advanced breast cancer: Objective of Treatment, Diagnosis of Relapse and Metastatic Disease, Staging - Loco-regional management of relapse. - Endocrine therapy in advanced HR/ HER2 negative breast cancer. - Targeted therapy in advanced breast cancer. - Treatment of advanced HER2-positive breast cancer. - Treatment of advanced triple-negative breast cancer. - Chemotherapy in luminal-advanced breast cancer.	Domain: Methodological rigour: ‣ Points: 34 60.7% Domain: Scope/Objective: ‣ Points: 15 71.4%

No. CPG	Title of CPG	Processing body Publication date Update	Scope of CPG	Domain Objective/Scope Methodological rigour
9	Hereditary cancer SEOM Clinical Guidelines in Hereditary Breast and Ovarian Cancer. (2015)	• Spanish Society of Medical Oncology (SEOM); 2015	Published: Llort G, Chirivella I, Morales R, Serrano R, Sanchez AB, Teulé A, Lastra E, Brunet J, Balmaña J, Graña B. SEOM clinical guidelines in Hereditary Breast and ovarian cancer. Clin Transl Oncol 2015; 17:956-961. - Risk-reducing surgery: bilateral salpingo-oophorectomy, prophylactic mastectomy, chemo-prevention. - Treatment strategies in BRCA carriers. - Management of women without identified BRCA mutations. - Other hereditary breast cancer syndromes.	Domain: Methodological rigour: ‣ Points: 32.5 58% Domain: Scope/Objective: ‣ Items: 13 61.9%
10	Treatment of primary Breast Cancer. SIGN (CG134).	• Scottish Intercollegiate Guidelines Network (SIGN). • 2003/ • Update 2013	Scottish Intercollegiate Guidelines Network (SIGN). Treatment of primary Breast Cancer. Edimburgh; SIGN; 2013. (SIGN publication no. 134) [September 2013]. https://www.sign.ac.uk/assets/sign134.pdf It includes RECOMMENDATIONS related to: - Treatment: surgery, radiotherapy, adjuvant systemic therapy, adjuvant endocrine therapy, systemic therapy and neoadjuvant endocrine therapy.	Domain: Methodological rigour: ‣ Points: 49.5 88.3% Domain: Scope/Objective: ‣ Points: 21 100%
11	New Zealand Guidelines Group (NZZG). Evidence-Based Best Practice Guideline. Management of Early Breast Cancer	• New Zealand Guidelines Group (2009). Current Review date (2014)	New Zealand Guidelines Group (NZZG). Evidence-Based Best Practice Guideline. Management of Early Breast Cancer https://www.health.govt.nz/system/files/documents/publications/mgmt-of-early-breast-cancer-aug09.pdf - General principles of care. - Staging. - Surgery for early invasive breast cancer. - Radiotherapy. - Systemic therapy: endocrine therapies. - Ductal carcinoma in situ. - Monitoring.	Domain: Methodological rigour: ‣ Points: 45.5 81.2% Domain: Scope/Objective: ‣ Points: 21 100%

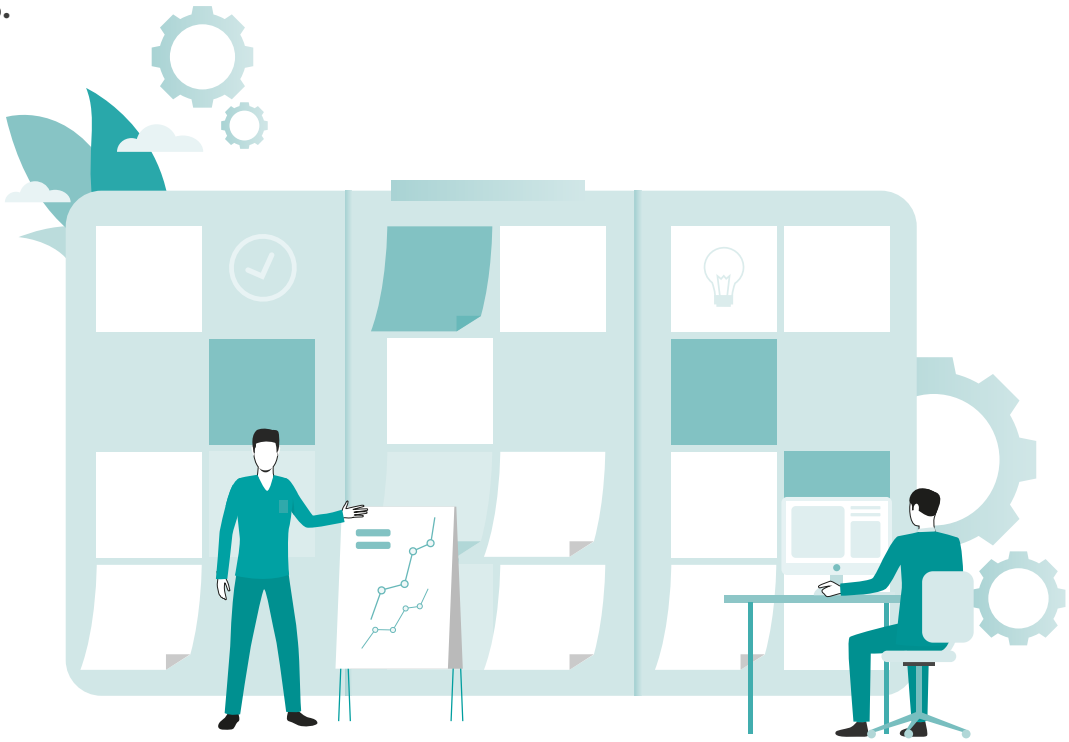
No. CPG	Title of CPG	Processing body Publication date Update	Scope of CPG	Domain Objective/Scope Methodological rigour
12	**National Comprehensive Cancer Network (NCCN) Guidelines. Breast Cancer** Version 1.2015 Version 2.2016	• National Comprehensive Cancer Network (NCCN) • 2015/	National Comprehensive Cancer Network (NCCN) Guidelines. Version 1.2015 Version 2.2016 Version 3.2017 Version 4.2018 National Comprehensive Cancer Network (NCCN) 2007/2016 Update Feb 8, 2019	Domain: Methodological rigour: ‣ Points: 44.5 81.2% Domain: Scope/Objective: ‣ Points: 21 100%
13	**Surgical guidelines for the management of breast cancer Eur J Surg Oncol 2009;35 Suppl 1:1-22**	• British Association Surgical Oncology (BASO) • 2009/	Published: Surgical guidelines for the management of breast cancer Eur J Surg Oncol 2009;35 Suppl 1:1-22 Section 1 Multidisciplinary care S2. Section 2 Diagnostics S4 Section 3 Treatment planning and patient communication S5. Section 4 Organization of breast cancer surgical services S7. Section 5 Surgery for invasive breast cancer S8 Section 6 Management of the axillary lymph node in invasive breast cancer S10 Section 7 Surgical management of ductal carcinoma in situ S12 Section 8 Surgery for lobular neoplasia in situ S14 Section 9 Breast reconstruction S15 Section 10 Post-operative and peri-operative care S16 Section 11 Adjuvant treatments S17 Section 12 Clinical monitoring S19	Domain: Methodological rigour: ‣ Points: 28.5 50.9% Domain: Scope/Objective: ‣ Points: 15 71.4%

No. CPG	Title of CPG	Processing body Publication date Update	Scope of CPG	Domain Objective/Scope Methodological rigour
14	**Sentinel Lymph Node Biopsy for patient with early stage Breast Cancer. ASCO Clinical Practice Guideline (2014);** Update 2014	• American Society of Clinical Oncology (ASCO) • ASCO 2014/ ASCO 2017 Sentinel biopsy • ASCO 2014/ ASCO 2017 Sentinel Lymph Node biopsy	Published: (*) Lyman GH, Temin S, SB Edge, Newman LA, Turner RR, Weaver DL, Benson AB, Bosserman LD, Burstein HJ. Sentinel Lymph Node Biopsy for patient with early-Stage Breast Cancer: American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update. J Clin Oncol 2014; 32:1365-1383 How should sentinel lymph node biopsy results be used in clinical practice and what are the potential benefits and harms associated with SSLNB? - Clinical question 1: Can Axillary Lymphadenectomy be avoided in patients with a negative SSLNB outcome? - Clinical question 2: Is Axillary Lymphadenectomy necessary for all patients with metastatic findings in SSLNB? a) For women with metastatic sentinel lymph nodes (SLN) who plan to undergo breast conserving surgery with full breast radiation therapy? b) For women with lymph node metastases who plan to have a mastectomy? - Clinical question 3: What is the role of the SSLNB in special circumstances in clinical practice? (**) Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE. Sentinel lymph node biopsy for patient with early-stage breast cancer: American Society for Clinical oncology Clinical practice guideline update. J Clin Oncol 2017; 35:561-4.	Domain: Methodological rigour: ‣ Points: 46 82.1% Domain: Scope/Objective: ‣ Points: 21 100%
15	**Selection of Optimal Adjuvant Chemotherapy and targeted therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update (2018)**	• American Society of Clinical Oncology (ASCO) • 2018/	Published in: Denduluri N, Chavez-MacGregor M, Telli ML, Eisen A, Graff SL, Hassett MJ, Holloway JN, Hurria A, King TA, Lyman GH, Partridge AH, Somerfield MR, Trudeau ME, Wolff AC, Giordano SH. Selection of optimal adjuvant Chemotherapy and targeted therapy for early breast cancer: ASCO Clinical Practice Guideline focused update. J Clin Oncol 2018;36(23):2433-2443. Update of ASCO guide recommendations. The Expert Panel reviewed phase III trials evaluating adjuvant capecitabine after completion of standard preoperative anthracycline-taxane-based combination chemotherapy in early stage HER2-negative breast cancer patients with residual invasive disease at surgery; the addition of 1 year of adjuvant pertuzumab to combination chemotherapy and trastuzumab for patients with early stage HER2 positive breast cancer; and the use of neratinib as extended adjuvant therapy for patients after combination chemotherapy and trastuzumab-based adjuvant therapy with early stage HER2 positive breast cancer.	Domain: Methodological rigour: ‣ Points: 48 85.7% Domain Scope/Objective: ‣ Points: 21 100%

No. CPG	Title of CPG	Processing body Publication date Update	Scope of CPG	Domain Objective/Scope Methodological rigour
16	**Adjuvant Endocrine Therapy for women with Hormone Receptor-Positive Breast Cancer** ASCO Clinical Practice Guideline Focused Update (2018)	• American Society of Clinical Oncology (ASCO); • 2018/	Published in: Harold J. Burstein, Christina Lacchetti, Holly Anderson, Thomas A. Buchholz, Nancy E. Davidson, Karen A. Gelmon, Sharon H. Giordano, Clifford A. Hudis, Alexander J. Solky, Vered Stearns, Eric P. Winer, and Jennifer J. Griggs N Adjuvant Endocrine Therapy for Women with Hormone Receptor–Positive Breast Cancer ASCO Clinical Practice Guideline Focused Update (2018) Update of the ASCO clinical practice guideline on adjuvant endocrine therapy based on emerging data on optimal duration of aromatase inhibitors (AIs) therapy. ASCO conducted a systematic review of randomised clinical trials from 2015 to 2018. The guide's recommendations were based on the Panel's review of evidence from six trials. Results: The six included studies on AIs treatment beyond 5 years of therapy showed that extension of AIs treatment was not associated with improved overall survival, but was significantly associated with lower risks of breast cancer recurrence and contralateral breast cancer compared to placebo. Bone related toxic effects were more common with prolonged AIs treatment.	Domain: Methodological rigour: ‣ Points: 48 85.7% Domain: Scope/Objective: ‣ Points: 21 100%
17	**GEICAM Clinical Practice Guidelines for the Diagnosis and Treatment of Metastatic Breast Cancer** GEICAM (2015)	• GEICAM Spanish Group for Breast Cancer Research; • 2015/	GEICAM Clinical Practice Guidelines for the Diagnosis and Treatment of Metastatic Breast Cancer GEICAM (2015) This guideline has the following objectives: - To provide updated data according to the most relevant scientific data in the different situations that may arise in patients with metastatic breast cancer. - To assist in making decisions regarding the diagnosis, management and treatment of patients with metastatic breast cancer. To help in the practical resolution of everyday questions among the professionals who treat these patients.	Domain: Methodological rigour: ‣ Points: 47 83.9% Domain: Scope/Objective: ‣ Points: 21 100%

Annex II

PATHOLOGICAL DIAGNOSIS. TECHNICAL NOTES.



- Note 1: Histological Type
- Note 2: Histological Grade
- Note 3: Carcinoma In Situ, Nuclear Grade
- Note 4: Margins
- Note 5: Nodal involvement
- Note 6: Response to neoadjuvant treatment
- Note 7: Other lesions
- Note 8: Hormone receptors
- Note 9: HER2
- Note 10: Ki67

Note 1:
Histological Type

The WHO, in its review from 2012[66], classifies breast tumors in:

A Epithelial tumors:

- **Micro-infiltrating carcinoma.**
- **Infiltrating carcinoma of non-special type (NOS):** In the 2003 WHO classification, carcinoma was called infiltrating ductal carcinoma NOS[64].
  - Pleomorphic carcinoma
  - Carcinoma with stromal osteoclastic giant cells
  - Carcinoma with choriocarcinomatous findings
  - Carcinoma with melanotic findings
- **Infiltrating lobular carcinoma**
  - Classic lobular carcinoma
  - Solid lobular carcinoma
  - Alveolar lobular carcinoma
  - Pleomorphic lobular carcinoma
  - Tubular-lobular carcinoma
  - Mixed lobular carcinoma
- **Tubular carcinoma**
- **Cribriform carcinoma**
- **Mucinous carcinoma**
- **Carcinoma with medullary findings**
  - Medullary carcinoma
  - Atypical medullary carcinoma
  - Infiltrating carcinoma of unspecified type with medullary findings
- **Carcinoma with apocrine differentiation**
- **Carcinoma with signet ring cell differentiation**
- **Infiltrating micro-papillary carcinoma**
- **Metaplastic carcinoma**
  - Low-grade adenosquamous carcinoma
  - Fibromatosis-type metaplastic carcinoma
  - Squamous carcinoma.
  - Spindle cell carcinoma
  - Metaplastic carcinoma with mesenchymal differentiation
    - Chondroid differentiation
    - Bone differentiation
    - Other types of mesenchymal differentiation
  - Mixed metaplastic carcinoma
  - Myoepithelial carcinoma
- **Carcinoma with neuroendocrine findings**
  - Well-differentiated neuroendocrine tumor
  - Poorly differentiated small cell neuroendocrine carcinoma
  - Carcinoma with neuroendocrine differentiation
- **Secretory carcinoma**
- **Infiltrating papillary carcinoma**
- **Acinar cell carcinoma**
- **Mucoepidermoid carcinoma**
- **Polymorphous carcinoma**
- **Oncocytic carcinoma**
- **Lipid-rich carcinoma**
- **Glycogen-rich clear cell carcinoma**
- **Sebaceous carcinoma**
- **Salivary gland/skin adnexal carcinoma**
- **Cystic adenoid carcinoma**

B Mesenchymal tumors:

- **Liposarcoma**
- **Angiosarcoma**
- **Rhabdomyosarcoma**
- **Osteosarcoma**
- **Leiomyosarcoma**

C Fibroepithelial tumors:

- **Borderline phyllodes tumor**
- **Malignant phyllodes tumor**
- **Low-grade periductal stromal tumor**

D Malignant lymphoma:

- **Large cell diffuse B lymphoma**
- **Burkitt's lymphoma**
- **T-cell lymphoma**
  - Anaplastic large cell lymphoma
  - ALK-negative lymphoma
- **Marginal extranodal B-cell lymphoma or MALT-type lymphoma**
- **Follicular Lymphoma**

E Metastatic Tumors

Note 2:
Histological Grade[64-65,67]

The most widely used histological grading system is the Elston-modified Scarff-Bloom Richardson system, which is applicable to any breast carcinoma. This is a score that considers three variables that are scored between 1 and 3 according to the following criteria[67]:

A Formation of tubules:

- **Score 1:** More than 75% of the tumor area forms glands or tubules.
- **Score 2:** Between 10 and 75% of the tumor area forms glands or tubules.
- **Score 3:** Less than 10% of the tumor area forms glands or tubules.

B Nuclear pleomorphism:

- **Score 1:** Small nuclei with little increase in size from the normal breast epithelial cell. Regular contour, uniform chromatin and little variation in size.
- **Score 2:** The cells are larger than normal with visible nucleolus and moderate variation in size and nuclear shape.
- **Score 3:** Vesicle nucleus with prominent nucleolus with marked variation in size and shape and occasionally with bizarre nuclei.

C Mitotic index: It varies according to the size of the microscopic field used and should therefore be established by means of equivalence tables.64,65 As an approximation it is established as follows:

- **Score 1:** 3 or less mitosis per mm2.
- **Score 2:** Between 4 and 7 mitosis per mm2.
- **Score 3:** 8 or more mitoses per mm2.

If the sum is 3, 4 or 5 it is assigned a grade I; if it is 6 or 7, a grade II; and if it is 8 or 9, a grade III.

Note 3:
Nuclear grade carcinoma in situ[69-71]

There are several ductal carcinoma in situ grading systems[69]. Among the most used are the Van Nuys[70] system, and the ductal carcinoma in situ[71] classification from the consensus conference:

A Van Nuys' Classification[70]:

Score	1	2	3
Tumour size (mm)	≤ 15	16 – 40	> 41
Margins (mm)	≥ 10	1 – 9	< 1
Pathological classification	Not high grade No necrosis	Not high grade Necrosis	High grade With/without necrosis
Age (years)	> 60	40 – 60	< 40

B Classification of ductal carcinoma in situ[71] by the consensus conference

Finding	Grade I (Low)	Grade II (Intermediate)	Grade III (High)
Pleomorphism	Monomorph	Intermediate	Markedly pleomorphic
Size	1.5 to 2 times the size of a nucleus of a normal ductal cell or hematy.	Intermediate	More than 2.5 times the size of a hematy or the nucleus of a normal ductal cell.
Chromatin	Diffuse	Intermediate	Vesicular and irregularly distributed
Nucleolus	Occasional	Intermediate	Prominent and sometimes multiple
Mitosis	Occasional	Intermediate	Common
Orientation	Polarization around the luminal space	Intermediate	No polarization

Note 4:
Margins[72]

The fresh surgical piece must be conveniently referenced, especially the lumpectomies, so that its orientation is clear. The surface will be painted with Indian ink in order to establish the distance between the tumor and the margin.

A positive margin is one that shows tumor cells in contact with the Indian ink.

Note 5:
Nodal involvement[73-74]

The definition of nodal involvement varies depending on the method used to determine the presence of tumor cells:

A Conventional Method of Hematoxylin-Eosin/Immunohistochemistry[73]:

- **Macrometastasis:** Size greater than 2mm.
- **Micrometastasis:** Size between 0.2 mm and 2 mm and/or more than 200 cells.
- **Isolated tumor cells:** Size 0.2 mm or less and/or 200 cells or less.

B OSNA Method[74]:

- **Positive:** CK19/uL mRNA copy number greater than 250/µl.
  - Micrometastasis: Number of copies equal to or greater than 250/µl and less than 5000/µl.
  - Macrometastasis (++): Number of copies equal to or greater than 5000/µl.
- **Negative (-):** Number of copies less than 250/µl.
  - Isolated tumor cells: Number of copies equal to or greater than 160/µl and less than 250/µl.
  - Negative: Number of copies less than 160/µl.

Note 6:
Response to neoadjuvant treatment[76,77]

There are several systems of grading the tumor response to neoadjuvant chemotherapy that generally consider the size of the lesion, the percentage of residual cellularity, and in many cases the node status. The most widely used are the Miller and Payne system and the Residual Cancer Burden (RCB) system:

A Miller and Payne's system[76]:

- **Grade 1:** Lack of response.
- **Grade 2:** Minor reduction (≤30%)
- **Grade 3:** Some reduction (30-90%).
- **Grade 4:** Marked reduction (>90%).
- **Grade 5:** Absence of residual infiltrating cancer, although carcinoma in situ may be present.

B Evaluation of the nodal response (A-D):

- **N-A:** True negative axilla.
- **N-B:** Positive axillary lymph nodes with no therapeutic response.
- **N-C:** Positive axillary lymph nodes, but with evidence of therapeutic response.
- **N-D Positive axillary nodes initially, but negativized after treatment.**

C RCB System[77]:

- **RCB index that considers in a formula (www.mdanderson.org/breastcancer_RCB) the following variables:**
  - Larger diameter of the tumor bed.
  - Smaller diameter of the tumor bed.
  - Percentage of infiltrating cancer.
  - Percentage of the tumour cellularity that corresponds to carcinoma in situ.
  - Number of positive lymph nodes.
  - Size of the major metastasis.
- **RCB class:** 0 complete response, I, II and III lack of response.

Note 7:
Other lesions[65]

Non-neoplastic injuries[65] will be included in this section.

A Benign lesions:

- **Complex sclerosing lesion/Radial scar**
- **Fibroadenoma**
- **Papilloma:** Includes ductal adenoma, nipple adenoma and retroareolar sclerosing ductal hyperplasia
- **Periductal mastitis/Ductal ectasia (plasma cell mastitis):**
- **Fibrocystic changes**
- **Sclerosing adenosis**
- **Solitary cyst**
- **Change of columnar cells**
- **Others**

B Proliferative epithelial lesions:

- **No atypia:** includes those lesions of non-typical ductal hyperplasia and some with cytological atypia that do not meet the criteria for atypical ductal hyperplasia.
- **Lesions classified as Risk:** such as columnar cell hyperplasia with atypia and atypia in flat epithelium.

Lesions classified as "of uncertain biological potential" or B3 constitute a heterogeneous group of lesions diagnosed in 5-10% of CNB. They are associated with malignancy in a percentage that varies from 9.8 to 35.1% of cases. Its importance derives from the possible underestimation of associated malignancy and the associated risk of cancer in any topography of the same breast or contralateral breast.

They are subdivided into:

- **B3a:** Non-precursor lesions
- **B3b:** Precursor lesions, i.e. Atypical Ductal Hyperplasia, Flat Epithelial Atypia, Lobular Neoplasia (Atypical Lobular Hyperplasia and Lobular Carcinoma in situ).

Note 8:
Hormone receptors[79-81]

The determination of estrogen and progesterone hormone receptors is done through immunohistochemical techniques.

The percentage of cells expressing the receptor through nuclear staining should be established. The entire tumor area must be evaluated. The method used can be manual or by means of image analysis.

The intensity of the staining must be indicated as weak, moderate or intense, and is usually estimated jointly for the whole tumour area.

Indicate an interpretation of the result so that they are considered positive hormone receptors when at least 1% of cells are stained, and consider these values negative when they are below, regardless of the staining intensity[79-81].

There are several standardized systems for reporting the status of hormone receptors. Among the most used are the H-SCORE and the Allred system.

A H-SCORE[81]:

Calculation of H-Score

Cellular signal	Percentage of Cells	Value
⁙ Unsignaled cells		% x 0 = 0
⁙ Cells with weak signal		% x 1 =
⁙ Cells with moderate signal		% x 2 =
⁙ Cells with strong signal		% x 3 =
⁙ Total Score =		

It is determined by multiplying the percentage of cells with any intensity of staining (with values between 0 and 3) and by adding the results. If the value is greater than 1 it is considered positive.

B Allred System[81]:

Score	Positive Cells (%)	Intensity	Intensity Score
⁙ 0	0	None	0
⁙ 1	Less than 1	Weak	1
⁙ 2	1 a 10	Moderate	2
⁙ 3	11 a 33	Intense	3
⁙ 3	34 a 66		
⁙ 5	67 or more		

The system combines the percentage of positive cells with the intensity of staining that predominates in the tumour area, except if the result is 3 with a percentage of positive cells below 1%. The two scores are summed up in another with 8 possible values. Values 0 and 2 are considered negative, values between 3 and 8 are considered positive.

Note 9:
HER2[82]

The determination of HER is carried out by immunohistochemistry and/or in-situ hybridization (fluorescent (FISH), chromogenic (CISH)...) in equivocal cases by immunohistochemistry, following standarised protocols[82].

The results shall be expressed, depending on the technique used, as follows:

A POSITIVE:

- **IHC (3+):** Circumferential membrane staining, complete and intense in more than 10% of the tumour cells (*).
- **ISH:**
  - Single probe with average HER2 copy ≥ 6.0 signals per cell (**)
  - Dual probe HER2/CEP17 ratio ≥ 2.0 with average HER2 copy < 4.0 signals per cell (further analysis required)
  - HER2 ≥ 2.0 with an average of HER2 copies ≥ 4.0 signals per cell.

B EQUIVOCAL:

- **IHC (2+):** Circumferential full-membrane staining with mild or moderate intensity on more than 10% of the tumor cells (*).
- **ISH:**
  - Single probe with average HER2 copies ³ 4.0 and < 6.0 signals per cell.
  - Dual probe HER2/CEP17 ratio < 2.0
  - HER2 ³ 6.0 signals per cell (further analysis required).
  - with an average of HER2 copies ³ 4.0 and < 6.0 signals per cell (further analysis required).

C NEGATIVE:

- **IHC (1+):** Incomplete membrane staining is practically unnoticeable in more than 10% of the tumour cells (*).
- **IHC (0):** Incomplete membrane staining or staining is virtually unnoticeable in 10% or less of the tumor cells.
- **ISH:**
  - Dual probe HER2/CEP17 ratio ≥ 2.0 with average HER2 copy < 4.0 signals per cell (further analysis required). If same result by second observer, consider negative).
  - Single probe with average HER2 copy ≥ 4.0 signals per cell.
  - Dual probe HER2/CEP17 ratio<2.0 with average HER2 copies <4.0 signals per cell in a homogeneous and continuous population.

(*) Appreciable staining with a low increase target in a homogeneous and continuous infiltrating cell population.

(**) Concomitant IHC recommended.

D UNDETERMINATE:

When there has been some technical problem, artifact or with difficulties of interpretation. In this case the analysis should be repeated on another sample.

If the result is equivocal in IHC, the determination has to be repeated in the same sample using ISH or in another specimen using IHC or ISH.

If the equivocal result is with single probe ISH the test must be repeated using dual probe ISH or IHC on the same specimen or on another specimen using IHC or ISH.

Note 10:
Ki67[84]

It is a nuclear staining that is determined by immunohistochemistry. The result is expressed through the percentage of cells that are stained among the total number of evaluated malignant cells[84].

The evaluation should be made on the basis of the homogeneity of staining:

- **If the staining is homogeneous in the tumor area:** it is recommended to count at least the positive cells in three fields of highest magnification.
- **If the staining is heterogeneous in the tumor area:**
  - In case of a gradient that increases between the periphery and the center: it is recommended to count three fields in the periphery of the tumor because the periphery is considered the most active area of the tumor.
  - In case of hot spots: their interpretation is controversial. It is recommended, pending further studies, to establish an approximation to the average of the entire tumor.

In conclusion, the pathology report must integrate all the morphological, immunohistochemical, molecular and genetic determinations that have been determined in the tumour, the method by which they have been carried out and the results obtained in a clear, easily interpretable and extrapolable manner, in order to facilitate understanding and to adopt the necessary therapeutic measures according to the characteristics and biology of the lesion.

Annex III

RADIOTHERAPY PROCEDURES AND TECHNIQUES[186-190].

TECHNOLOGY.

Definition of volumes.

CT (Computed Tomography) is the most widely used equipment to obtain the image data of the tumor volume in the case of the breast. Currently there are 4D CT scans that are able to relate the images to the time of the respiratory cycle. CT data are sent via the network to the planning workstation where the contours are manually defined by the radiation oncologist.

The Radiation Therapy Oncology Group (RTOG) and the European Society for Radiation Oncology (ESTRO) have developed consensus guidelines for defining volumes. Some of the risk organs such as the skin and the lung can be automatically contoured. Modern planning systems generate libraries or files from clinical cases, from which the programme will be able to "learn" and delimit the critical organs in an automated way.

Immobilization and positioning of the patient.

The treatment position must be reproducible and comfortable to reduce movements in order to administer the prescribed dose. In general, patients are treated in a supine position and immobilizers are used to secure the position by keeping the arms in abduction above the head, the chest straight on a flat board and the arms resting on supports. Sometimes it is necessary to use inclined planes of 10 to 20 degrees to decrease the lung volume included in the irradiation field. To achieve alignment, lasers are used in the longitudinal and transverse plane, and reference points are marked or tattooed in different planes and locations.

Treatment.

The standard technique of irradiation in breast cancer is the so-called 3D conformal radiotherapy using a field segmentation technique and, in some cases, intensity modulated dose radiation therapy (IMRT) to achieve homogeneous doses in the breast tissue. In general, photon beams from linear accelerators with energies from 4 to 6MV are used, especially 6 MV. A linear accelerator with multi-layer collimation system should be available. External radiotherapy and brachytherapy are useful for overlapping. If external radiotherapy is used, it is essential to have photons and electrons to be able to adapt to the anatomy and size of the tumour cavity. The multi-catheter, high-dose rate (HDR) technique is the most commonly used when doing brachytherapy.

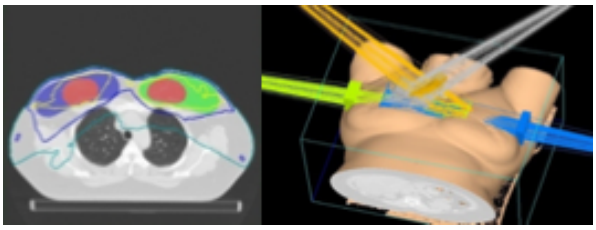


Figure 1. Treatment planning and beams in a patient with bilateral breast cancer and integrated boost.

The emergence of miniaturised accelerators and kilovoltage devices available in operating rooms has led to a resurgence of intra-operative radiation therapy.

Techniques.

Classic technique.

The classic technique is that of two oblique fields tangential and isocentric to the breast volume or the mastectomy bed. To homogenize the prescribed dose, wedge filters, different energies and segmented fields can be used. Dosimetry must be based on CT images and requires a three-dimensional dose calculation with dose-volume histograms.

Intensity-modulated technique.

IMRT is a radiotherapy technique that allows for more precise irradiation, using incidence from fields with non-uniform dose intensity in the white volume. When IMRT is used, immobilization of the patient and daily reproduction becomes more important. IMRT improves dose homogeneity in the volume to be treated and reduces the dose to healthy tissues, including the ipsilateral lung and the heart in left breast tumors, as different published studies have shown. This technique also allows for the integrated "boost", with which a superior dose can be administered in the tumoral bed, in those patients who need this complement; with the advantage of diminishing the total number of sessions and duration of treatment. Figure 1 shows the irradiation of a bilateral breast cancer with an integrated "boost" performed by IMRT.

4D technique.

It is also known as radiation therapy guided by respiratory movement. CT images of the different phases of the respiratory cycle are acquired and monitored, and breathing is also monitored during treatment, thus synchronizing radiation with respiratory movement.

Depending on the patient's anatomy, it is decided at what point in the breathing cycle it is best to treat the patient to lower the dose to healthy organs, especially the heart.

Volumetric technique.

VMAT (Volumetric Modulated Arc Therapy) is a sophisticated IMRT technique that achieves greater dose conformance in the target volume, with a reduction in dose in the risk organs. With VMAT, the radiation beam rotates around the patient in one or more arcs.

Interstitial breast brachytherapy.

It is a technique that consists of inserting a certain number of catheters into the lumpectomy cavity, covering the lumpectomy bed with a safety margin. It is used as a boost or in partial radiation treatments. Figure 2

Intra-Operative Radiation Therapy (IORT).

The appearance in 1998 of miniaturized and "portable" linear accelerators that can be used within the operating room has increased their use. IORT allows the administration of complementary or adjuvant irradiation in the same surgical act, directly on the tumour bed, minimally affecting the surrounding tissues in a single dose, with the aim of obtaining results similar to repeated postoperative doses, which means time and cost savings for the patient and for the health system.

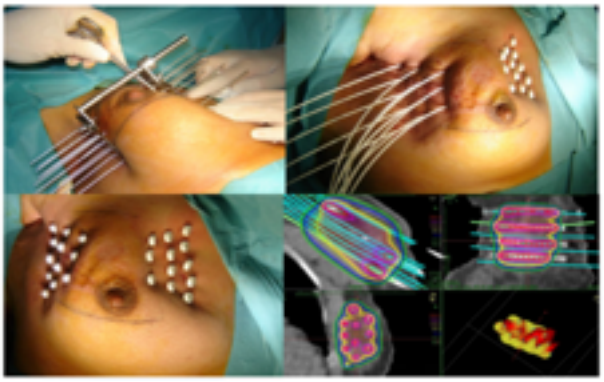


Figure 2. Plastic vector brachytherapy in an accelerated partial breast irradiation.

Abbreviations

ACR: American College of Radiology

ASCO: American Society of Clinical Oncology

CNB: Core needle biopsy

VAB: Vacuum-assisted biopsy

BASO: British Association of Surgery Oncology

BI-RADS: Breast Imaging and Data System

SSLNB: Selective Sentinel Lymph Node Biopsy

CISH: Chromogenic In Situ Hybridization

BC: Breast Cancer

MBC: Metastatic Breast Cancer

HBOC: Hereditary Breast and Ovarian Cancer

OC: Ovarian Cancer

EORTC: European Organisation for Research and Treatment of Cancer

ESMO: European Society of Medical Oncology

EUSOMA: European Society of Specialist of Breast Cancer Specialists

ECIBC: European Commission Inniative on Breast Cancer

FISH: Fluorescent In-Situ Hybridization

GEICAM: Grupo de Investigación del Cáncer de Mama

ISH: In Situ Hybridization

AIs: Aromatase Inhibitors

IHC: Immunohistochemistry

IMRT: Intensity-Modulated Radiation Therapy

FDG PET CT: Tomography ‹Positron emission with Fluorodeoxyglucose

BRRM (Bilateral Risk-Reducing Mastectomy)

NA: Neoadjuvancy

NAPBC: National Accreditation Program for Breast Cancer

NCCN: National Comprehensive Cancer Network

NICCQ: National Initiative for Cancer Care Quality

NICE: National Institute Clinical Excellence

NZZG: New Zealand Guidelines Group

OSNA: One-Step Nucleic Acid Amplification

FNAP: Fine Needle Aspiration Puncture

CT: Chemotherapy

RCB: Residual Cancer Burden

IORT: Intra-Operative Radiation Therapy

IQR: Interquartile Range

MRI: Magnetic Resonance Imaging

OR: Objective Response

RTOG: Radiation Therapy Oncology Group

RT: Radiotherapy

SEOM: Sociedad Española de Oncología Médica

OFS: Ovarian Function Suppression

OS: Overall survival

SIGN Scottish Intercollegiate Guidelines Network

DFS: Disease Free Survival

PFS: Progression-Free Survival

PBSO: Prophylactic Bilateral Salpingo-Oophorectomy

CT: Computed Tomography

TN: Triple-Negative

PST: Primary Systemic Therapy

VMAT: Volumetric Modulated Arc Therapy

Index of figures

Index of tables

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