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CONSENSUS

Breast cancer Mexican consensus 2025. Early breast cancer management

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Abstract

Breast cancer, in early stages, has specific surgical, RT, and systemic management. This type of cancer includes ductal carcinoma in situ and breast cancers in stages I, IIA, IIB, and IIIA. This eleventh update of the Mexican Breast Cancer Consensus addressed the management of early stages. The dissemination of this consensus contributes to the updating and homogeneity of breast cancer management criteria. This article aims to present the update in the multidisciplinary management of breast cancer.

Keywords: *Breast cancer. Early stage. Consensus.*

Consenso mexicano de cáncer mamario 2025. Manejo del cáncer de mama temprano

Resumen

El cáncer mamario en estadios tempranos tiene un manejo local (quirúrgico y radioterapia) y sistémico específico. Este tipo de cáncer incluye el carcinoma ductal in situ y los cánceres de mama en estadios I, IIA, IIB y IIIA. Esta undécima actualización del Consenso Mexicano de Cáncer Mamario abordó el manejo de los estadios tempranos. La difusión de este consenso contribuye a la actualización y la homogeneidad de criterios de manejo del cáncer mamario, y el objetivo de este artículo es presentar la actualización en el manejo multidisciplinario del cáncer de mama.

Palabras clave: *Cáncer de mama. Estadios tempranos. Consenso.*

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Surgical management of early-stage breast cancer

Surgery is the cornerstone of breast cancer treatment and aims to achieve tumor resection with negative pathologic margins and nodal assessment, either selectively (sentinel lymph node biopsy) or with lymphadenectomy, for staging or as part of radical local control.

Surgical treatment may be performed after diagnosis (primary or upfront surgery) or following neoadjuvant therapy. Clinical and radiologic responses may modify the extent of surgery (mastectomy vs breast-conserving surgery; axillary lymph node dissection vs sentinel lymph node biopsy).

Primary or upfront surgical management is indicated in patients with early-stage breast cancer and favorable molecular subtypes in which no benefit from neoadjuvant therapy is expected. The decision depends on multiple factors, including lesion size and its relationship to breast volume, molecular subtype, lymphovascular invasion, tumor grade, and the patient's preference for breast preservation. For this reason, the strategy of performing excisional biopsy with intraoperative pathology assessment of a clinically and radiologically suspicious breast lesion, followed by modified radical mastectomy if malignancy is confirmed, should be abandoned.

Each case should be evaluated by a multidisciplinary team to determine the optimal treatment strategy. Surgical management of the breast is independent of axillary management. Surgical options for primary management of breast cancer include:

- Breast-conserving surgery with or without oncoplastic techniques.
- Simple mastectomy.
- Skin-sparing mastectomy.
- Skin- and nipple-areola complex-sparing mastectomy.

In patients with hormone receptor-positive tumors, primary surgical management is indicated for T1 or T2 tumors (≤ 5 cm) with clinically node-negative disease (N0). Neoadjuvant systemic therapy may be considered to reduce surgical extent[1]. In the N1 setting, the approach should focus on de-escalating axillary surgery. Therefore, all patients with positive lymph nodes should be considered for neoadjuvant systemic therapy.

In patients with HER2-positive or triple-negative tumors, primary surgical management is recommended for tumors up to T1c. For tumors > 2 cm, neoadjuvant therapy is recommended to achieve a pathologic complete response, providing prognostic and predictive information. However, this recommendation is not categorical; neoadjuvant therapy may also be considered in selected T1c tumors, particularly triple-negative cases, although this does not apply to HER2-positive tumors in which weekly paclitaxel with trastuzumab (APT regimen) is intended (see "adjuvant systemic therapy")[2,3].

Perioperative pain management and chronic postoperative pain

Currently, implementation of ultrasound-guided regional chest wall blocks is essential as part of multimodal postoperative pain management[1]. Knowledge of these techniques, as well as thoracic anatomy, is crucial for anesthesiologists. Level A evidence supports the use of regional techniques in breast surgery as an adjunct to general anesthesia and, in some cases, as the primary anesthetic technique combined with sedation[1,2]. This approach improves acute postoperative pain control, reduces the rate of chronic pain, enhances postoperative rehabilitation, decreases pulmonary complications, and – although not yet conclusively proven – may be associated with lower recurrence rates in oncologic surgery[2,3].

When planning analgesia, the expected postoperative pain according to the surgical procedure (primary tumor resection site and type of axillary procedure), patient-specific factors (preexisting pain, catastrophizing, age, medications, comorbidities), and prior cancer treatments (systemic and regional) must be considered to individualize multimodal analgesia strategies[1-3].

For breast surgery involving the pectoral muscles, the pectoral (PEC) I block is indicated. When the axillary region is involved, satisfactory evidence supports the use of PEC II[4,5]. For surgery in the outer quadrants, the serratus-intercostal block is recommended. For the inner quadrants, the pectointercostal block is most appropriate[6,7]. If the surgical approach includes the nipple-areola complex, with or without sentinel lymph node biopsy, the blockade of intercostal branches in the midaxillary line (BRILMA block) may be performed[8,9]. These techniques, as adjuncts to general anesthesia, reduce opioid use and intraoperative anesthetic requirements. Paravertebral and intercostal nerve blocks are the only techniques considered suitable as primary anesthetic approaches with sedation. The paravertebral block remains the reference method in radical mastectomy, either as the sole anesthetic technique or combined with general anesthesia[10,11].

Most of the abovementioned blocks are interfascial, ultrasound-guided, and relatively easy to learn; however, detailed anatomic knowledge is essential to identify

Table 1. Perioperative strategies for the prevention of postmastectomy pain syndrome

Preoperative	Intraoperative	Postoperative
Psychotherapy[13-15] Sleep[17] Adequate rest prior to surgery Pharmacotherapy[13-15]: Acetaminophen* 1 g PO Gabapentin* 300-600 mg PO Pregabalin* 75-150 mg PO Duloxetine* 60 mg PO Dexamethasone 8 mg IV, single dose, 1 hour before the start of surgery or during anesthetic induction	Adjuvant drugs[14,15]: Acetaminophen 1 g IV every 6-8 hours NSAID/COX-2 inhibitor IV before incision Lidocaine 3 mg/kg + Mg sulfate 50 mg/kg IV Dexmedetomidine 0.5-1 µg/kg/h IV or ketamine 0.25-0.5 mg/kg/h IV Regional blocks[14,17]: Thoracic epidural in bilateral mastectomy Thoracic paravertebral block in unilateral radical mastectomy Interfascial blocks in mastectomy or quadrantectomy Combined with general anesthesia (preferably TIVA) or sedation, as appropriate Avoid nerve injury[13]: careful positioning and retraction, meticulous surgical techniques	Physical therapy[13-16] Psychotherapy[13-15] Pharmacotherapy[2-4,7,8]: Acetaminophen 1 g PO every 6-8 hours NSAID/COX-2 inhibitor PO, scheduled according to patient conditions Gabapentin† 600-1200 mg/day PO Pregabalin† 150-300 mg/day PO Duloxetine† 60 mg/day PO blocks[15,17]: use of catheters for analgesia for 24 to 48 hours[13] Avoid nerve injury and timely treatment of seromas and hematomas

*Initiate the night before surgery or at least 2 hours prior to surgery.
†For 2 weeks.
NSAID/COX-2: nonsteroidal anti-inflammatory drugs/cyclooxygenase-2; IV: intravenous; TIVA: total intravenous anesthesia; PO: oral.

structures by ultrasonography and to master needle-transducer coordination to ensure proper needle visualization and local anesthetic spread at all times[9,12].

Potential complications associated with ultrasound-guided blocks for breast surgery are classified into 2 categories: those common to peripheral nerve blocks and those specific to the thoracic region. Among the former, local anesthetic systemic toxicity should be emphasized due to the rich vascularization of the area, including arterial vessels such as the thoracoacromial artery at the infraclavicular level, the internal mammary arteries at the parasternal level, and the intercostal vessels. Among thoracic-specific complications, pneumothorax must be considered due to proximity to the pleura[12].

After breast cancer-related surgical procedures, it is estimated that 25 to 60% of patients develop chronic pain, often referred to as postmastectomy pain syndrome (Tables 1 and 2). The current definition used by the International Association for the Study of Pain is "chronic pain in the anterior chest wall, axilla, or upper half of the arm that begins after mastectomy or quadrantectomy and persists for more than 3 months after surgery"[13,14].

Treatment options include oral and topical analgesics, physical therapy, psychotherapy, fat grafting, among others. However, the effectiveness of these treatments varies, and many patients continue to experience chronic pain; therefore, prevention remains the optimal strategy[15-17].

It is essential that the breast surgical oncologist, plastic surgeon (when applicable), and anesthesiologist coordinate a multimodal analgesic plan for the acute and long-term postoperative management of patients with breast cancer. With the increasing number of breast cancer-related surgeries and improved patient survival, efforts must focus on preventing chronic pain and improving quality of life after surgery.

Table 2. Management of patients with established postmastectomy pain syndrome

Management	Description
Physical therapy	Scar massage, silicone patches, compression garments with sleeves and gloves, manual lymphatic drainage, and exercises[13,14]
Pharmacologic	Amitriptyline 25-150 mg/day, Duloxetine 60-90 mg/day, Gabapentin 600-1200 mg/day, Pregabalin 150-300 mg/day[14,16]
Topical	Capsaicin cream 0.075% 4 times daily or 8% cutaneous patch for 30-60 minutes[14] Lidocaine 5%[14-16]
Psychotherapy	Cognitive-behavioral therapy, group therapy, relaxation techniques, and hypnotherapy[14,16]
Interventional	Myofascial trigger point injections, nerve blocks (intercostobrachial, intercostal, stellate ganglion), cryoablation, and pulsed radiofrequency[16]
Surgical	Autologous fat grafting in scars, targeted muscle reinnervation, regenerative peripheral nerve interfaces, and nerve allograft[13,14]

Breast-conserving surgery

Breast-conserving surgery (partial mastectomy), formerly referred to as quadrantectomy, tumorectomy, or

lumpectomy, consists of complete excision of the primary tumor with negative pathologic margins. Oncoplastic techniques are included within this approach and allow mobilization of a larger proportion of breast tissue (and therefore resection of larger lesions) without compromising cosmetic outcomes[18-20].

Although all cases should be complemented with adjuvant radiation therapy (RT), which remains the standard treatment in early-stage disease[21], criteria for omission have been expanded (patients > 65 years, early-stage lesions, hormone receptor-positive disease receiving 5 years of endocrine therapy). This expansion allows more patients without access to RT to be considered candidates for breast-conserving surgery.

The literature demonstrates that long-term survival rates are not only equivalent to those of mastectomy but may even be superior[22-27]. In addition, patients undergoing breast-conserving surgery report better quality of life and lower complication rates vs those treated with mastectomy[28].

Selection criteria and indications:
- Favorable breast-to-tumor ratio, allowing an acceptable cosmetic outcome.
- Patient preference.

Absolute contraindications:
- Extensive and diffuse microcalcifications or distribution precluding adequate gland preservation.
- Diffusely positive margins.
- Inability to obtain negative margins in the presence of a single or multicentric lesion.
- Unfavorable breast-to-tumor ratio, even with oncoplastic techniques.
- Inability to receive adjuvant RT (lack of access, pregnancy).

Relative contraindications:
- Active collagen vascular disease involving the skin (eg, scleroderma, lupus).
- Prior RT to the chest wall or breast.
- Li-Fraumeni syndrome.
- Known *BRCA1*/*BRCA2* pathogenic variant[29].

Although multicentricity was previously considered a contraindication to breast-conserving surgery, the use of oncoplastic techniques allows excision of lesions in different quadrants, and recent evidence supports oncologic safety with respect to local recurrence[30]. Therefore, gland preservation may be reasonable in selected multicentric cases, provided that complete excision with negative margins and acceptable cosmetic results can be achieved. Preoperative breast magnetic resonance imaging is recommended.

Candidates for this approach include patients undergoing primary surgical management with a maximum of 3 tumor foci in the same breast separated by ≤ 2 cm, aged ≥ 40 years, and with cN0 or cN1 disease. Histopathologic and immunohistochemical evaluation of all tumors is mandatory. Radio-opaque marking of the surgical bed for all excised lesions is required. In the ACOSOG Z11102 (Alliance) trial, breast irradiation with boost to more than 1 surgical bed was well tolerated[31].

The objective is to obtain negative pathologic margins with satisfactory cosmetic results, achieved either through simple resections or oncoplastic techniques. The surgical specimen must always be oriented and marked for pathologic evaluation. Margins may be inked with different colors[32] or marked with clips or sutures. It is recommended that the surgeon perform this marking and that institutions standardize surgical specimen handling. A negative margin in invasive cancer is defined as no ink on tumor[33]. In the case of positive margins, re-excision is indicated (re-excision may be omitted when focal positivity is < 2 mm). Persistent positive margins or positivity throughout the specimen constitutes an indication for mastectomy.

The surgical bed should be marked with radio-opaque clips for future localization (RT and surveillance).

Various strategies may reduce the rate of positive margins, including specimen orientation and marking, intraoperative radiologic assessment, intraoperative pathologic assessment, systematic cavity shaving, or margin extension. None has demonstrated superiority over others in achieving negative margins; therefore, selection depends on institutional experience and resource availability.

Modern oncoplastic techniques enable mobilization of larger volumes of breast tissue, improving cosmetic outcomes without increasing conversion to mastectomy when re-excision is required[34,35].

In retroareolar lesions, skin retraction of the nipple-areola complex may indicate direct involvement and warrant resection of the complex. However, when no direct infiltration is present, preservation may be considered, with removal of a retroareolar tissue cuff for intraoperative pathologic assessment to ensure negative margins.

Mastectomy

Mastectomy, defined as complete removal of breast tissue, is recommended for patients who are not candidates for breast-conserving surgery because of tumor

size, multicentricity, or contraindications to RT. It is also an option for patients who prefer this procedure.

Types of mastectomy:

– Simple (total): resection of all breast tissue, including skin and nipple-areola complex, without axillary lymph node dissection.
– Skin-sparing mastectomy.
– Nipple-areola complex-sparing mastectomy.
– Modified radical mastectomy: resection of all breast tissue, including skin and nipple-areola complex, with axillary lymph node dissection.
– Radical mastectomy: resection of all breast tissue, including skin and nipple-areola complex, with axillary lymph node dissection and resection of the pectoralis major, minor, or both muscles.

The first 3 approaches allow immediate reconstruction. The type of reconstruction (implant-based, autologous tissue, or combined techniques) depends on patient anatomy, comorbidities, need for adjuvant RT, and patient preference. Patients should be evaluated by plastic surgery and informed of reconstructive options before surgery. The last 2 techniques are rarely performed today and are reserved for advanced lesions with pectoral muscle invasion.

Patients must be informed about surgical techniques and reconstruction options, including timing. Whenever feasible, preservation of the skin and nipple-areola complex should be considered to facilitate immediate reconstruction.

Indications for mastectomy:

– Patient preference.
– Multicentric disease without possibility of negative margins.
– Inability to achieve negative margins.
– Unfavorable breast-to-tumor ratio for acceptable cosmetic outcome.
– Difficulty ensuring appropriate follow-up[36-39].

Oncoplastic surgery

Risk factors for aesthetic deterioration in breast-conserving surgery include[18-20]:

– Resection of > 20% of breast volume in lateral or central quadrants.
– Resection of > 10% in inferior or medial quadrants.
– Effects of postoperative RT.

These factors may result in deformities (Table 3).

When negative margins with satisfactory cosmetic results cannot be achieved through simple resection, oncoplastic techniques should be used.

Table 3. Types of deformities after breast-conserving surgery[21]

Type	Description
I	There is asymmetry in volume or appearance vs the contralateral breast
II	Deformity that can be corrected by partial reconstruction using the patient's own tissue
III	Significant deformity or diffuse painful fibrosis that must be corrected by mastectomy

Planning is the most critical component of these procedures. It requires thorough technical and aesthetic knowledge of breast anatomy, familiarity with oncoplastic patterns, and the ability to manage potential complications. It involves a learning curve and experience with high patient volumes[19-27].

Selection and design of the oncoplastic pattern must be performed preoperatively, with the patient seated or standing, after careful review of breast imaging studies and consideration of patient preferences (Fig. 1).

Oncoplastic procedures are classified according to the volume of resection[20]:

– Level I: < 20% of breast volume excised. These procedures may be performed by breast oncologic surgeons without formal oncoplastic training.
– Level II: 20-50% of breast volume excised. In these cases, excision of excess skin is often required to remodel the breast. These procedures are based on reduction mammoplasty techniques and require specific training in oncoplastic surgery.

Because the breast is not a homogeneous organ and each region responds differently to tissue resection, 8 anatomical segments have been proposed (Fig. 2)[28-38], along with different oncoplastic patterns according to complexity (Figs. 3 and 4, and Table 4)[34,39,40].

As in all breast-conserving procedures, the surgical specimen must always be oriented and marked for pathologic assessment. Institutional standardization of specimen handling is recommended.

In the case of positive margins, re-excision is indicated. In some centers, systematic cavity shaving is performed to reduce the need for reoperation due to margin involvement.

The surgical bed should be marked with radiopaque clips after tumor excision and before tissue repositioning to allow future localization (RT and surveillance).

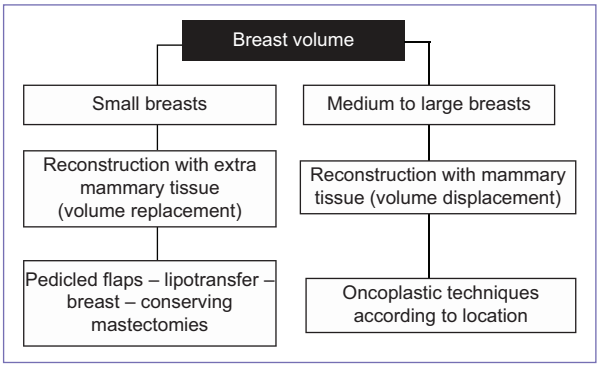


Figure 1. Surgical options according to breast volume.

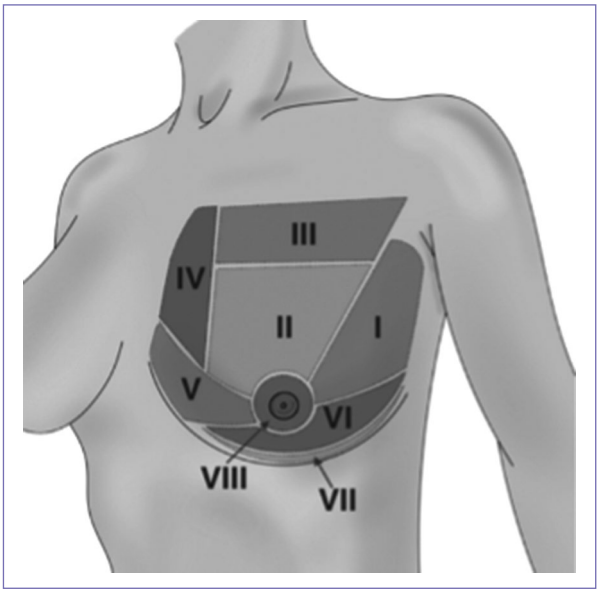


Figure 2. Breast segmentation. Segment I: lateral; segment II: superior; segment III: infraclavicular; segment IV: superomedial; segment V: inferomedial; segment VI: inferior pole; segment VII: inframammary fold; segment VIII: central.

Skin-sparing mastectomy

Scientific evidence supports the oncologic safety of skin-sparing mastectomy vs conventional mastectomy, as it does not increase local recurrence rates and follows the same criteria for postmastectomy RT indication[33-37]. Its principal advantage is facilitation of immediate breast reconstruction.

Types of skin-sparing mastectomy include:

– Skin-sparing mastectomy.
– Skin- and nipple-sparing mastectomy (total skin-sparing mastectomy).
– Skin-reducing mastectomy.

Indications:

– Contraindication to breast-conserving treatment.
– Indication for risk-reducing mastectomy.
– Patient preference.

Absolute contraindications:

– Inflammatory carcinoma.
– Extensive skin involvement.

Complications associated with both oncoplastic procedures and skin-sparing mastectomies include partial or total necrosis of skin flaps or the nipple-areola complex, as well as loss of nipple sensation. Patients must be informed of these risks preoperatively. Complication rates are higher in patients with large breast volume, breast ptosis, obesity, advanced age, comorbidities, smoking history, and in those undergoing mastectomy with concomitant RT[41].

Patients undergoing oncoplastic surgery must understand that it is not cosmetic surgery but oncologic surgery aimed at achieving optimal aesthetic outcomes. The treating team must inform patients about expected results and potential complications. In cases involving large-volume resections, asymmetry with the contralateral breast may occur. Patients should be counseled

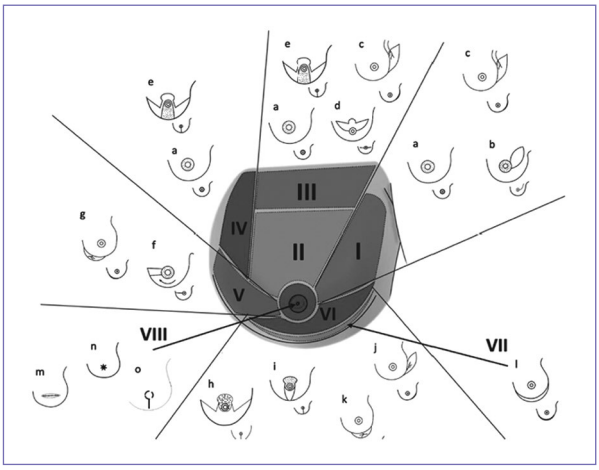


Figure 3. Oncoplastic patterns. a: circular mammoplasty (round block); b: lateral mammoplasty; c: pedicled flaps LTAP (lateral thoracic artery perforator) and TDAP (thoracodorsal artery perforator); d: horizontal mammoplasty (batwing); e: vertical mammoplasty with inferior pedicle, double-branch (Wise); f: rotation mammoplasty; g: pedicled MICAP flap (medial or internal intercostal artery perforator); h: vertical mammoplasty with superior pedicle, double-branch (Wise); i: vertical mammoplasty with superior pedicle, single-branch; j: pedicled LICAP flap (lateral intercostal artery perforator); k: pedicled AICAP flap (anterior intercostal artery perforator); l: inframammary fold; m: fusiform excision; n: concentric excision; o: Grisotti technique.

Table 4. Oncoplastic patterns according to complexity[34,39,40]

Low complexity	Intermediate complexity	High complexity
Circular mammoplasty (round block)	Vertical mammoplasty with superior pedicle	Vertical mammoplasty in central tumors
Horizontal mammoplasty (batwing)	Vertical mammoplasty with inferior pedicle	Re-excision for positive margins
Lateral mammoplasty	Low-visibility incisions	Borderline breast/tumor ratio in inner quadrants
	Single-port access	After neoadjuvant therapy with poor response
	Tunneling	Extreme oncoplastic surgery
		Pedicled flaps Skin-sparing mastectomies

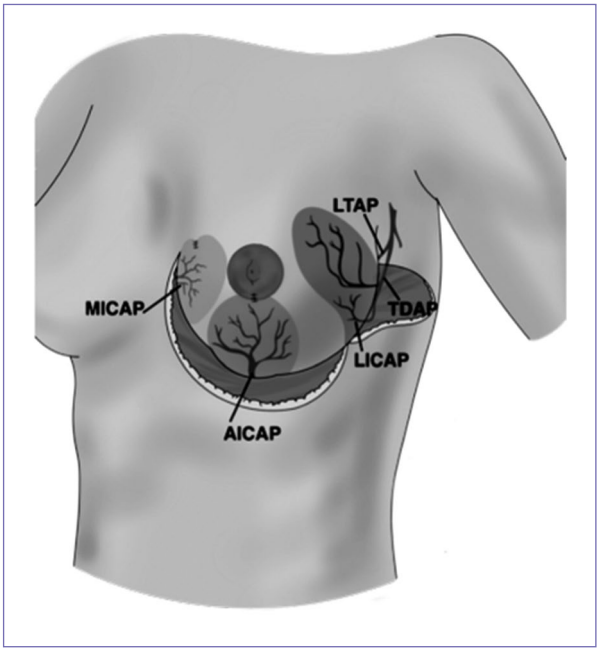


Figure 4. Pedicled flaps based on thoracic perforator arteries. AICAP: anterior intercostal artery perforator; LICAP: lateral intercostal artery perforator; LTAP: lateral thoracic artery perforator; MICAP: medial or internal intercostal artery perforator; TDAP: thoracodorsal artery perforator.

regarding the feasibility of symmetrization either during the same procedure or in a staged approach.

Surgical management of the axilla

Nodal involvement in breast cancer is a key prognostic factor that significantly influences treatment and outcomes. Over time, axillary surgery has evolved from a fundamental therapeutic procedure to primarily a staging and prognostic tool. In the 20th century, axillary dissection was standard; in the 21st century, its role has shifted substantially, allowing omission in selected patients without clinical evidence of axillary disease[42-46].

Currently, nodal evaluation is mainly prognostic and guides adjuvant treatment strategies. After neoadjuvant systemic therapy, pathologic nodal response (ypN) together with pathologic tumor response (ypT) helps identify patients who may benefit from additional adjuvant treatment to improve disease-free or overall survival in cases of residual disease (yp+)[47].

Axillary evaluation begins with careful physical examination. In the presence of a palpable lymph node, size, consistency (soft vs hard), mobility (mobile vs fixed), and the presence of nodal conglomeration (cN2) should be assessed. Imaging evaluation follows, and when available, core needle biopsy or fine-needle aspiration biopsy is recommended[48].

The following sections summarize axillary staging recommendations in invasive breast cancer.

Sentinel lymph node biopsy in ductal carcinoma in situ (DCIS)

Indications for sentinel lymph node biopsy (SLNB) in DCIS are increasingly limited. A meta-analysis of 16 prospective studies found nodal involvement in only 5% of patients; among these, 58% were micrometastases. The probability of a positive node was < 1%. Factors associated with nodal metastases included necrosis and mastectomy; thus, these remain the primary indications for SLNB in DCIS[49].

Sentinel lymph node biopsy in microinvasive DCIS

Because nodal metastases occur in 4.9-7.7% of patients with 1 or 2 microinvasive foci, SLNB is not

routinely recommended in this subgroup[50]. In cases with ≥ 3 microinvasive foci, additional risk factors associated with nodal metastases in DCIS–such as necrosis or planned mastectomy–should be considered[49].

Sentinel lymph node biopsy in invasive breast cancer cN0

There is currently no indication for routine axillary lymph node dissection in patients presenting with cN0 disease. SLNB is the standard of care, supported by trials such as NSABP-32, ACOSOG Z0011, AMAROS, and ALMANAC[43,45,51,52] (Fig. 5).

In 2022, the phase III noninferiority SINODAR-ONE trial included patients with cT1c-cT2, cN0 tumors and ≤ 2 macrometastatic nodes randomized to axillary dissection (≥ 10 nodes) vs SLNB (median of 2 nodes). After a median follow-up of 34 months, no significant differences in overall survival or recurrence were observed. Notably, 24% underwent mastectomy; therefore, intraoperative SLNB assessment during mastectomy in cN0 patients is no longer indicated[53].

These findings were corroborated by the SENOMAC trial and another phase III noninferiority study published in 2024, which included 34% mastectomy patients and allowed extracapsular extension and T3 tumors[54]. Because adjuvant RT differed across studies, regional nodal RT is recommended when extracapsular extension or T3 disease is reported. Close coordination with radiation oncology is essential.

In cases with > 3 positive nodes, axillary dissection is generally recommended. However, in hormone receptor–positive, HER2-negative disease, the probability of high nodal burden (pN2-pN3) is approximately 13%[55]. Therefore, molecular subtype, adjuvant RT, and systemic therapy availability should be considered when determining whether additional axillary dissection is necessary.

Omission of sentinel lymph node biopsy in cN0 invasive breast cancer

Currently, it is possible to consider the omission of sentinel lymph node biopsy in two highly selected groups of patients. In the INSEMA study, a prospective noninferiority clinical trial, invasive disease-free survival was evaluated in patients who underwent sentinel lymph node biopsy vs observation, and no differences were found in this outcome between the two groups. Of note, 100% of the patients underwent breast-conserving surgery, only 10% were < 50 years (median age, 62 years), 90% of tumors were ≤ 2 cm on preoperative assessment, 95% had hormone receptor-positive and HER2-negative tumors, only 8.7% had high-grade tumors, and 87% had Ki67 ≤ 20%. It was also mandatory that any patient with suspected nodal disease on imaging (iN+), defined as cortical thickening > 2.5 mm, undergo fine-needle aspiration or core needle biopsy[56]. The SOUND study, published by Gentilini et al.[46] in 2023, had a very similar design and results. Unlike INSEMA, there was a higher proportion of patients with high-grade tumors (18%), 64% had Ki67 ≤ 20%, and 21% were premenopausal.

It is important to consider these aspects (Table 5) whenever omission of sentinel lymph node biopsy is contemplated, particularly in iN+ disease. Therefore, if cortical thickening is present at or above this cutoff and no biopsy has been performed, sentinel lymph node biopsy is recommended given the false-negative rate that may occur with ultrasonographic evaluation. A decision should always be made by a multidisciplinary team considering the previously mentioned factors.

Sentinel lymph node in patients with invasive breast cancer cN1

It is highly relevant to clarify that every patient with cN1 disease should receive neoadjuvant systemic therapy followed by sentinel lymph node biopsy (Fig. 6). Sentinel lymph node biopsy after neoadjuvant therapy has been performed with oncologic safety since its inception, as demonstrated in the most recent studies. The NEOSENTITURK MF18-02/18-03 trial sought to identify the axillary recurrence rate, along with invasive disease-free survival, of the sentinel lymph node procedure in patients with cT1-cT4 and cN1-cN3 tumors who converted to cN-after neoadjuvant therapy (physical examination plus another modality, such as ultrasound, positron emission tomography, or magnetic resonance imaging). A total of 67% of sentinel lymph node procedures were performed using blue dye alone, and the median number of nodes retrieved was 4 (interquartile range, 3-5). Locoregional recurrence was 0.79%, and ipsilateral axillary recurrence was 0.37%, regardless of ypN+ status. All patients received RT with extended fields. In the prospective cohort of that study, in which these outcomes were vs women who underwent axillary lymph node dissection, no statistically significant differences were observed. There are also at least two retrospective precedents[57].

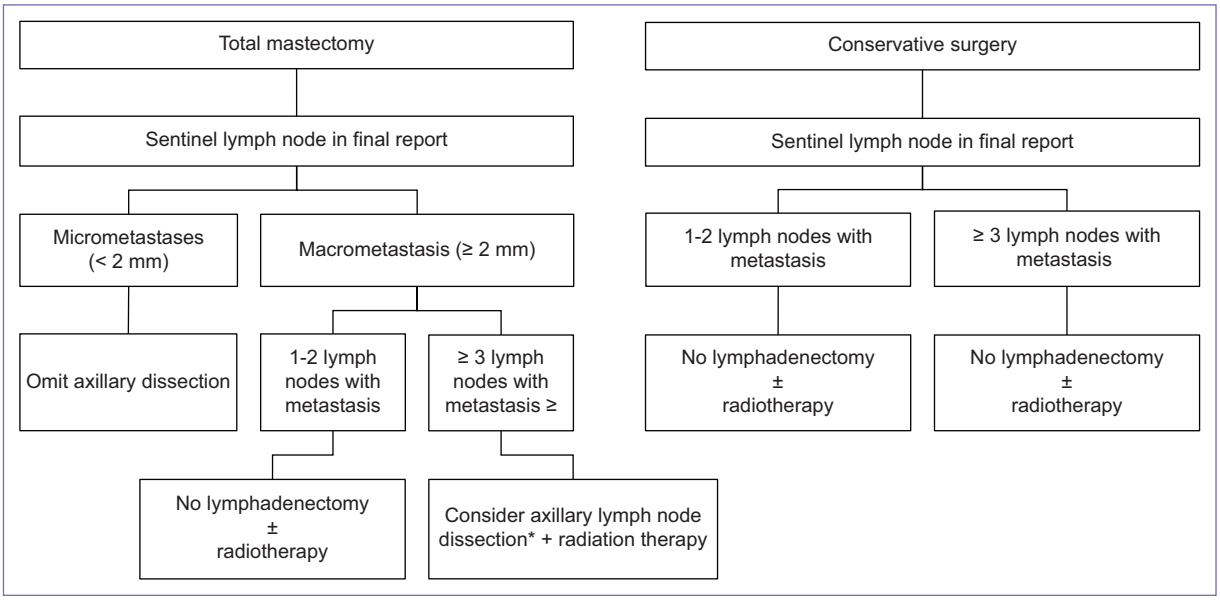


Figure 5. Nodal staging in cN0. *Consider whether it is necessary by weighing morbidity and benefit (eg, whether obtaining a greater number of nodes will guide the adjuvant treatment decision).

In a South Korean cohort of 676 patients with ypN1 disease, axillary lymph node dissection was vs sentinel lymph node biopsy to determine whether it offered any survival advantage or lower local recurrence, and no differences were found between procedures[58].

Therefore, the utility of sentinel lymph node biopsy appears more than sufficient in terms of oncologic safety; however, it is also used to guide adjuvant systemic therapy[47,59-62] in patients who received initial chemotherapy (CT).

In the cN1 setting, a false-negative rate < 10% is required for the procedure to be effective. Although dual tracer and clip placement yield a false-negative rate < 10%, the number of nodes retrieved *per se* is also associated with a false-negative rate < 10% provided that at least three nodes are removed, as indicated in the literature[44,63-65]. It is also known that adjuvant systemic therapy is not compromised, given that the overall pathologic complete response (ypT ypN), across all subtypes, ranges from 19-22%. Lack of response (which determines whether adjuvant treatment is beneficial) is primarily driven by residual primary tumor (ypT)[66].

There is a scenario in which complementary axillary lymph node dissection could be considered to identify patients who will benefit from adjuvant therapy in high-risk luminal-like breast cancer. Abemaciclib, a cyclin-dependent kinase 4 and 6 inhibitor, demonstrated benefit in invasive disease-free survival in the adjuvant setting in patients with four or more positive nodes, raising the reasonable question of whether completion axillary lymph node dissection should be performed in this group to prevent recurrences[60]. This issue was addressed in a post hoc analysis of the SENOMAC study, which measured the number needed to treat and the number needed to harm (severe or very severe deterioration in quality of life among patients undergoing axillary lymph node dissection) to prevent one recurrence using abemaciclib. It was found that 108 axillary dissections are required to prevent one recurrence, and that for every 11 dissections, one patient experiences severe or very severe morbidity[67].

Similarly, in 2023 the NATALEE clinical trial was published, in which ribociclib was used in patients with stage II and III luminal-like tumors. It was determined whether this adjuvant therapy improved invasive disease-free survival vs endocrine therapy alone.

Benefit was observed starting at stage IIB and without the requirement of a specific number of positive nodes[59]. Therefore, the need to perform complementary axillary lymph node dissection in this group of patients must be weighed considering resources, risks, and the true benefit of a second surgery, all within a multidisciplinary framework.

Based on this evidence, sentinel lymph node biopsy is recommended in all cN1 patients who are clinically

Table 5. Considerations for omission of sentinel lymph node biopsy in invasive carcinoma (all criteria must be met)

Age > 60 years
Positive hormone receptors, HER2-negative tumor
cN0 or cN0(i+)[42]
cT1a-cT1c
Low or intermediate histologic grade
Ki-67 < 20%

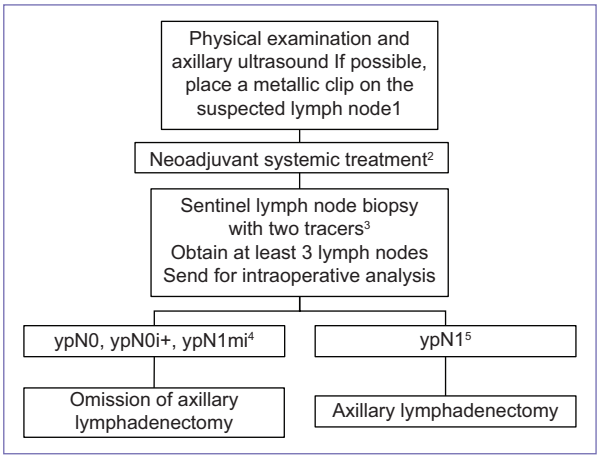


Figure 6. Nodal staging in cN1/cN1(f).
[1]Use of a metallic clip is not mandatory. If used and not retrieved, this is not an indication for axillary lymph node dissection, provided that at least three lymph nodes are removed.
[2]The only group of patients with clinically or pathologically confirmed cN1 nodal disease who may undergo upfront surgery are luminal-like patients in whom systemic therapy de-escalation using a genomic test is planned; this must be discussed by the multidisciplinary team.
[3]Sentinel lymph node biopsy may be performed with a single tracer if, and only if, three lymph nodes are obtained. For this reason, it is recommended to request the number of nodes identified in the intraoperative study.
[4]ypN0i+ and ypN1mi are usually reported in the final pathology report; therefore, in the presence of these findings, complementary axillary lymph node dissection is not necessary.
[5]From the presence of a nodal macrometastasis (≥ 2 mm) in the intraoperative study.

node-negative on preoperative evaluation after neoadjuvant CT. It is very important to clarify that the procedure may be performed with a single tracer if, and only if, at least three lymph nodes are removed and the resources are available to ensure that the patient receives complete adjuvant therapy.

Axillary lymph node dissection in patients with invasive breast cancer cN2–cN3

All patients with locally advanced disease should initially receive neoadjuvant CT, and currently the standard axillary surgery is axillary lymph node dissection, regardless of pathologic nodal response. However, this is based on studies conducted several decades ago, when local control was highly relevant due to the lack of highly effective systemic treatments and when adjuvant RT was not fully standardized[68,69].

Currently, various systemic therapies achieve ypN0 in a much higher proportion of patients, and the true utility of performing a classic extended axillary dissection, as well as retrieving a minimum of 10 lymph nodes, is beginning to be questioned[70-74], given the exceptional axillary response rates[75], regardless of initial stage in some subtypes, and the fact that this response is often not decisive in determining the type of adjuvant therapy[20,76,77]. Furthermore, all patients with locally advanced disease will receive RT with extended fields, providing a second local control strategy that, since the early days of de-escalation in breast cancer, has demonstrated excellent results[74,76,78].

Despite the above, the standard in patients with invasive breast cancer cN2-cN3 remains axillary lymph node dissection with retrieval of at least 10 lymph nodes. Recommendations to reduce morbidity in this procedure are presented below.

Anatomic considerations for axillary surgery

The surgeon is fundamental for adequate axillary staging and a low false-negative rate[79]. Anatomic knowledge is indispensable to perform optimal surgery. Lymphatic drainage of the breast has its first nodal relay in a region initially described by Clough et al[80] in 2010. In their study, they demonstrated that 98% of the tracer localizes in lymph nodes adjacent to the medial border of the lateral thoracic vein, from the inferior border of the axilla to above the second intercostobrachial nerve (Fig. 7). Ten years later, an attempt was made to identify sentinel nodes of the arm using reverse mapping with a radioisotope, and it was found that 97% of the nodes draining the upper extremity were located lateral to the lateral thoracic vein[81]. This means that axillary staging, whether by sentinel lymph node biopsy or axillary lymph node dissection, should not extend

lateral to the lateral thoracic vein if the goal is to prevent lymphedema. Similarly, all nonnodal structures should be preserved to reduce the likelihood of postoperative sequelae.

Another option to decrease the probability of lymphedema is the use of reverse mapping, in which 2 mL of dye are injected into the medial bicipital groove to subsequently avoid transection of lymphatic channels or excision of stained nodes, and to perform dissection only of the breast lymph nodes (Fig. 7)[82].

Considering whether axillary lymph node dissection is necessary – by weighing potential morbidity against benefit (eg, whether obtaining a greater number of nodes will guide the adjuvant treatment decision) – should be based on the following points:

- The use of a metallic clip is not mandatory. If used and not retrieved, this is not an indication for axillary lymph node dissection, provided that at least three lymph nodes are removed.
- The only group of patients with cN1 nodal disease, clinically or pathologically confirmed, who may undergo upfront surgery are luminal-like patients in whom systemic therapy de-escalation using a genomic test is planned; this must be discussed by the multidisciplinary team.
- Sentinel lymph node biopsy may be performed with a single tracer only if three lymph nodes are obtained. For this reason, it is recommended to request the number of nodes identified in the intraoperative study.
- ypN0i+ and ypN1mi are usually reported in the final pathology report; in the presence of these findings, complementary axillary lymph node dissection is not necessary.
- It may be necessary in the presence of a nodal macrometastasis (≥ 2 mm) in the intraoperative study.
- cN0i is defined as the absence of suspicious features of nodal disease (loss of fatty hilum, cortical thickening). In the presence of cortical thickening, this should be emphasized with the radiology team if it is focal and > 2 mm.

This consensus recommends medial dissection to the lateral thoracic vein and in relation to the second intercostobrachial nerve.

Breast reconstruction

Breast reconstruction options include oncoplastic techniques, alloplastic materials (expanders and implants), and autologous tissue flaps (pedicled or free). Adjuvants such as acellular dermal matrices and fat grafting are also used.

The choice of method depends on patient characteristics, disease factors, cancer treatment, reconstructive goals, and available resources. Preoperative planning by the oncologic-reconstructive team is essential to optimize aesthetic outcomes and ensure oncologic safety[83]. Reconstruction is approached according to the type of mastectomy: partial or total, with or without skin and nipple preservation[84]. Tools such as indocyanine green and thermography optimize reconstruction after mastectomy by assessing flap viability and improving outcomes[84,85].

Reconstructive approach after total mastectomy

Modern reconstruction techniques have few contraindications, generally related to comorbidities, age, or advanced tumor stages. Usually, two surgical procedures are required, even with immediate reconstruction, and minor surgeries may be necessary to optimize results[86,87].

Breast reconstruction after mastectomy improves quality of life without interfering with oncologic management. Staged reconstruction and multiple surgical procedures are frequently required.

Immediate prepectoral reconstruction with direct implant

This is performed in skin-sparing or skin- and nipple-sparing mastectomies, as well as in risk-reducing mastectomies. If the skin flaps are at least 2 cm thick and the volume to be reconstructed is small or moderate, a direct prepectoral implant may be placed. If this thickness is not achieved, an intermediate tissue layer is required, and acellular dermal matrices are an excellent option. These provide an integrating interface, either completely wrapping the implant in the prepectoral position or serving as a caudal extension of the pectoralis muscle in partial reconstructions, thereby reducing animation deformity[86-92].

Immediate retropectoral reconstruction with expander or implant, or both

The retropectoral technique in breast reconstruction involves creating a pocket behind the pectoralis major, pectoralis minor, and serratus muscles, releasing the rectus sheath to define the inframammary fold. An acellular dermal matrix may be used as a caudal extension to enlarge the pocket. If a tissue expander is used, after expansion a second procedure is performed to replace the expander with a definitive implant and adjust symmetry[93].

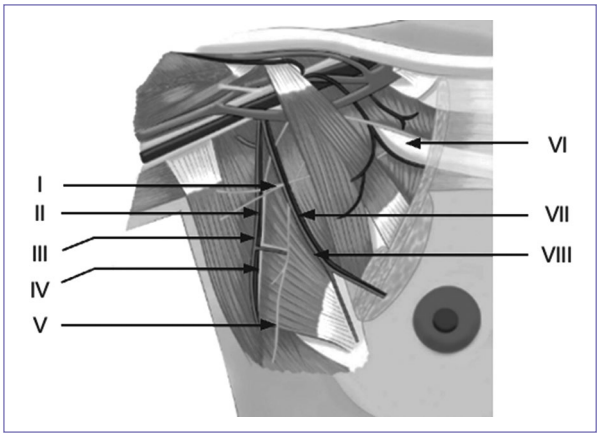


Figure 7. Diagram of anatomic landmarks for locating the main zone of traced or involved nodes according to the Clough and Li classification. I: second arch, intercostobrachial nerve; II: thoracodorsal artery; III: thoracodorsal vein; IV: thoracodorsal nerve; V: long thoracic nerve; VI: second costal arch; VII: lateral thoracic artery; VIII: lateral thoracic vein.

Fat transfer as an adjunct to reconstruction

In recent years, autologous fat transfer (lipotransfer) has proven to be a useful, effective, and safe tool for breast reconstruction[11]. It is used to increase volume and shape the breast, alone or combined with flaps. Its richness in growth factors and stem cells enhances regeneration, especially in patients with chronic radiodermatitis; furthermore, it improves skin quality and elasticity. It is useful in delayed reconstructions after RT, optimizing aesthetic and functional outcomes[94-96].

Reconstruction with autologous tissue (flaps)

Immediate or delayed autologous tissue reconstruction is ideal for patients who will receive RT, especially in advanced tumors with skin loss. RT is not a contraindication to immediate reconstruction, and no differences have been reported in satisfaction, texture, or fat necrosis of the flap. Delayed reconstructions, recommended 12 months after RT, improve the quality of irradiated tissue by transferring healthy tissue. Although autologous flaps are an excellent option, they require personnel trained in microsurgery and appropriate infrastructure, which is not always available in all hospitals in the country[97].

Pedicled flaps

The latissimus dorsi muscle and thoracodorsal artery perforator flaps continue to play an important role in postmastectomy reconstruction. These flaps are good options for overweight or obese patients, in whom implant-based reconstruction is not always safe, particularly when large volumes are not required[98-100].

Free abdominal flap

Breast reconstruction with a free abdominal tissue flap is ideal for patients with or without preserved skin. It allows immediate and delayed reconstruction, adding skin as needed. The pedicled transverse rectus abdominis muscle flap is obsolete due to its greater morbidity and inferior outcomes,and is used only in centers without access to microsurgery[97-101].

Nonabdominal free flap

For patients with nonviable abdominal tissue, options include free gracilis muscle flaps (oblique, transverse, vertical), superior or inferior gluteal artery perforator flaps, profunda femoris perforator flaps, and lumbar perforator flaps. The choice depends on patient characteristics and the availability of recipient vessels; appropriate selection and planning are key factors for success[102,103].

Reconstruction and RT

RT reduces breast cancer recurrence and improves survival but affects wound healing due to fibrosis. It is safe after reconstruction with expanders or implants, although it presents technical challenges, such as partially deflating expanders to avoid irradiating critical tissues. Infection rates after RT range from 0 to 27%, capsular contracture rates from 2 to 57.8%, and reconstructive failure rates from 4.8 to 40%, more commonly with irradiated expanders. It is recommended to wait 4 to 6 months after RT before placing the definitive implant to reduce complications. Studies show good results with 2-stage reconstructions, with greater satisfaction and well-being in nonirradiated patients according to BREAST-Q[104-107].

Bilateral risk-reducing mastectomy

It is an intervention option in women at high risk of developing breast cancer, as it has been shown to be

the most effective method to reduce risk in patients who carry BRCA1 and BRCA2 mutations and other high-risk pathogenic variants such as PALB2, and moderate-risk variants such as ATM and CHEK2[108]. The decision to undergo risk-reducing mastectomy is influenced by a variety of factors, including the patient's perceived breast cancer risk, anxiety generated by screening and diagnostic procedures, and expectations regarding the cosmetic outcomes of surgery[109].

The multidisciplinary team can assist in the decision-making process by providing an accurate estimate of an individual's breast cancer risk, taking into account genetic and nongenetic factors within a biopsychosocial approach (Table 6).

Tools are available to calculate 5-year and lifetime risk, based on different mathematical models. Among the most widely used are the Claus, Gail, and Tyrer-Cuzick models, although currently none includes all risk factors[110].

Genetic testing to identify individuals who carry pathogenic mutations provides information about the mutation type and the lifetime risk of developing breast cancer.

There is no single risk threshold above which risk-reducing mastectomy is clearly indicated. It is important that the surgeon and the multidisciplinary team explain to the patient not only the risk assessment, but also all available intervention strategies, to facilitate shared decision-making. Counseling should include discussion of the degree of protection, reconstruction options, and risks. In addition, counseling should consider family history and the residual risk of breast cancer with age and life expectancy[108].

Risk-reducing mastectomy is the most effective way to decrease the rate of breast cancer. It has been shown to reduce risk by up to 90% in women who carry *BRCA1* and *BRCA2* gene mutations, and by 95% if accompanied by bilateral risk-reducing salpingo-oophorectomy[109].

Studies have demonstrated protection close to 95% when meticulous surgical technique is used to remove as much breast tissue as possible. The incidence of cancer after risk-reducing mastectomy is attributed to residual breast tissue[111].

Moreover, available data indicate a survival advantage for women at highest risk who undergo the procedure at a relatively early age. Large studies with long-term follow-up are needed to demonstrate a true overall survival benefit; therefore, patients should understand that evidence supports the greatest benefit of risk-reducing mastectomy in *BRCA1* and *BRCA2* mutation carriers at an early age (younger than 40 years), and especially when accompanied by bilateral risk-reducing salpingo-oophorectomy (from age 35 years onwards).

A concrete consideration for selecting candidates for risk-reducing mastectomy is that they be women with a high-risk genetic mutation, for whom there are 3 surgical options: total (simple) mastectomy, skin-sparing mastectomy, or nipple-sparing mastectomy. All must

Table 6. Risk factors and their relative risk[3]

Genetic risk factors	
Female sex	114
Age	4-158
High-penetrance gene mutation (*BRCA1, BRCA2, p53, STK11*)	26-36
Moderate-penetrance gene mutation (*PTEN, p16, PALB2, CDH1, NF1, CHEK2, ATM, BRIP1*)	2.0-2.7
History of breast cancer in mother, sister, or daughter	1.55-1.8
Nongenetic factors	
Mantle radiation (lymphoma treatment)	5.6
Histologic/genetic tissue-related factors	
Number of alveoli per lobule in benign breast tissue 11-20 (involutive breast)	2.8
21-40	3.23
≥ 41	1.85
Mammographic density	
25-50% (scattered densities)	2.4
50-75% (heterogeneously dense)	3.4
51-75% (dense)	5.3
Lobular carcinoma *in situ* on breast biopsy	5.4
Atypical hyperplasia on breast biopsy	5
Increased bone mineral density	2.0-2.5
Age at first childbirth (35 years)	1.31-1.93
Obesity (body mass index 30 kg/m^2)	1.2-1.8
Any benign breast disease	1.47
High circulating insulin level	1.46
Five years of combined hormone replacement therapy (eg, estrogen and progestin)	1.26-1.76
Nulliparity (no live births)	1.26-1.55
Alcohol consumption: more than one drink per day	1.31
Menarche before age 12 years	1.21

include removal of the axillary tail (tail of Spence) and the pectoralis muscle fascia. Based on current evidence, the reference method appears to be nipple-sparing mastectomy, which, by preserving the skin envelope and the nipple-areola complex, allows optimization of oncologic surgery and aesthetic outcomes. This technique does not appear to compromise preventive oncologic efficacy vs other mastectomy types; however, nipple-sparing mastectomy must be performed with technical skill to avoid leaving macroscopic residual breast gland tissue, particularly in the axillary tail, the lateral and medial regions of the gland, and the nipple-areola complex. Careful dissection and meticulous preparation of the skin flaps and the nipple-areola complex are required; these should be reasonably thin without compromising viability[112].

In no scenario is sentinel lymph node biopsy indicated[113,114].

A precise preoperative radiologic assessment with mammography, ultrasound, and occasionally magnetic resonance imaging should always be performed to rule out suspicious breast lesions and minimize the risk of occult carcinomas, followed by definitive histologic examination.

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

Breast reconstruction should be performed by plastic surgeons using permanent prostheses or autologous tissues. The most appropriate reconstructive technique depends on several factors, such as the patient's physical and anatomic structure, breast morphology and degree of ptosis, comorbidities, and the patient's desires and preferences[115,116].

In nipple-sparing mastectomy, complications may occur, such as partial or total necrosis of the skin flaps and nipple, or loss of nipple sensation; therefore, the patient must be informed of these risks before surgery. The complication rate is higher in women with large breast volume, breast ptosis, older age, and smokers.

Contralateral risk-reducing mastectomy

This is defined as mastectomy of the healthy side in a woman with unilateral breast cancer. The prognostic impact of contralateral risk-reducing mastectomy is difficult to assess because available data largely come from retrospective studies. A Cochrane review on the efficacy of this procedure concluded that it reduces the risk of contralateral breast cancer by 90 to 100%; however, it does not appear to impact overall survival[110]. It is clear that endocrine therapy and systemic CT affect the reduction in contralateral breast cancer incidence, and these factors must be fully considered in the decision-making process regarding contralateral risk-reducing mastectomy and its true utility[117].

The use of this procedure is increasing, often at the patients' request, because they frequently perceive contralateral cancer risk to be higher than it truly is and believe that contralateral risk-reducing mastectomy is associated with improved survival.

In patients without elevated risk of contralateral breast cancer, discussion of the risks associated with the procedure and the lack of survival benefit, along with a surgeon recommendation against the procedure (when it provides no benefit), are effective in reducing unnecessary use[110].

Contralateral risk-reducing mastectomy is an option for BRCA1 and BRCA2 mutation carriers with early-stage breast cancer who will undergo total mastectomy[118].

Anxiety associated with cancer phobia may drive procedures without clinical benefit; therefore, efforts in education and appropriate counseling should be extensive[115]. Another factor to consider is contralateral mastectomy as a symmetrization procedure in certain patients, which may lead the patient or the plastic surgery team to request it.

As care moves toward an increasingly personalized, patient-centered approach, careful consideration should be given to respecting patient preferences and autonomy[108,119,120].

In this scenario, we recommend using an additional tool such as CBCRisk (https://cbc-predictor-utd.shinyapps.io/CBCRisk/) for risk assessment to corroborate that there is an individual clinical risk that can be modified through an effective intervention.

Vascular venous access for the administration of systemic therapy

Since the description of the circulatory system in 1616, veins have been used for the administration of various drugs[120]. Currently, more than 75% of patients with breast cancer will require some form of intravenous systemic therapy (CT, immunotherapy, bisphosphonates)[121].

For this purpose, there is a wide variety of catheters available, with little prospective evidence demonstrating the superiority of one over another[121-123].

It should be considered that cancer patients have additional risk factors (malnutrition, neutropenia) that

make them more susceptible to catheter-related complications (thrombosis, infection); therefore, their indication must be carefully analyzed[120,124,125].

Types of catheters

The choice of catheter generally depends on the physician's recommendation, based mainly on the expected duration of use and the type of medication administered[122]. However, a balance should be sought among safety, patient preference, and costs derived from placement, maintenance, and removal[121,122].

Peripheral venous catheter

Although it is easy to place and does not require special equipment or training, a new catheter must be inserted for each use, which implies multiple punctures for a single treatment[120,125,126].

It is associated with serious complications, such as psychological trauma, pain, bleeding, extravasation, necrosis of surrounding tissues, and vascular endothelial injury[122,123,126,127]; therefore, administration of chemotherapeutic agents via the peripheral route should be limited to fewer than three occasions[126].

Short central venous catheter

It is placed in the jugular or subclavian vein, ideally by ultrasound-guided puncture. Femoral access is not recommended for the administration of cancer treatment.

It has a limited duration (< 30 days) and is associated with the highest infection rate compared with the other options[124].

Peripherally inserted central venous catheter

It is inserted into the basilic, brachial, or cephalic vein by puncture. Special training is required for proper placement, although not necessarily a surgical team[4]. It has a lifespan of several months but carries higher risks of deep venous thrombosis, occlusion, and infection[121-123].

Although the cost of placement is lower than that of an implanted port, maintenance and associated complications make it more expensive in the long term[121,124,128,129].

Implantable port catheter

Placement requires an operating room or interventional suite and must be performed by a surgeon or interventional radiologist[123]. It may be inserted through the jugular, subclavian, or cephalic vein at the deltopectoral groove, by puncture or venous cutdown under local anesthesia, although sedation is ideal to minimize patient discomfort[126].

It carries a lower risk of infection, causes minimal discomfort during medication administration, and does not interfere with activities of daily living; therefore, patient satisfaction is high[122,126,128].

In terms of cost, it has the best cost-benefit ratio when considering placement and maintenance[123,128-130].

Heparinization every 2 to 4 months is suggested if the device is not in use, although there is no evidence to recommend maintaining the catheter beyond the duration of treatment. Timely removal positively impacts the patient's psychological status and reduces the risk of infection and thrombosis[126].

These characteristics are summarized in table 7.

Insertion techniques

After selecting the appropriate catheter, the best insertion technique should be determined. The ideal patient should have a platelet count > 50,000 and a prothrombin time > 18 seconds. Antiangiogenic agents should be discontinued 2 weeks before and after port placement. Prophylactic antibiotics prior to placement are debatable and not strictly necessary[131].

Although there is no strict contraindication to placing the catheter ipsilateral to the primary tumor, since there is no increased risk of lymphedema, a higher risk of thrombosis has been observed[122,131].

Placement should be performed in a sterile area with intraoperative fluoroscopy, or at least chest radiography, to promptly detect placement-related complications[124,130]. Associated complications are summarized in table 8.

The desired catheter tip position is at the junction of the right atrium and the superior vena cava[124].

The described insertion techniques are:

- Puncture (Seldinger technique).
- Anatomic: access to the subclavian or internal jugular vein is obtained using only anatomic landmarks. It is associated with a higher rate of immediate complications (pneumothorax, hemothorax, arterial injury)[125].
- Ultrasound-guided: increases success of placement and reduces the likelihood of complications, but is not easy without adequate training[121,132].
- Venous cutdown: a surgical procedure that involves control of the vein – external jugular or cephalic – through the deltopectoral groove; the latter is

preferred due to the lower probability of arterial injury and because the port reservoir can be placed through the same incision[132,133]. This technique is associated with < 0.5% immediate complications[132]. When its reproducibility was evaluated in nonexpert hands, it proved to be a safer technique compared with ultrasound-guided puncture, although at the expense of longer operative time[133].

If a port is chosen, the reservoir should be secured to the pectoral fascia with sutures to prevent rotation[131].

Although IV administration of cancer treatment is not a new concept, increasing efforts are being made to standardize venous access placement for this purpose. It is therefore mandatory for the oncology team to understand and communicate to the patient the advantages and disadvantages of each catheter type, as well as the differences among insertion techniques.

Adjuvant systemic therapy

To determine the optimal adjuvant systemic therapy, the medical oncologist must have complete information regarding the tumor's biologic characteristics. In particular, hormone receptor and HER2/neu expression (potential therapeutic targets), Ki-67, and, when indicated and available, genomic signature testing are of paramount importance in designing the best individualized treatment[134,135].

Definition, objectives, and indications

Adjuvant therapy refers to any antineoplastic treatment administered after surgical management, with the objectives of prolonging disease-free survival, reducing local and systemic recurrences, and increasing overall survival[134,136,137]. Adjuvant systemic therapy (hormone therapy [HT] ± CT ± biologic therapy ± immunotherapy) should be evaluated and administered by a medical oncologist due to the level of expertise required and the potential complications and toxicities associated with treatment.

All patients with positive lymph nodes, due to their high risk of relapse, should receive some modality of adjuvant systemic therapy (CT ± HT ± trastuzumab), regardless of the number of affected nodes (see section "Genomic profiles and systemic therapy").

In patients with negative lymph nodes, adjuvant systemic therapy (CT ± HT ± trastuzumab) is recommended when any of the following conditions are present[138,139]:

- Tumor > 1 cm (> 3 cm for favorable histology, such as tubular and mucinous carcinoma), hormone receptor–positive and HER2-negative (HT ± CT).
- Triple-negative tumor > 5 mm (CT).
- Tumor > 5 mm with HER2/neu overexpression (CT + trastuzumab ± HT).
- Genomic signature testing when indicated and available (CT + HT).

Systemic therapy (CT ± HT ± trastuzumab) should also be considered if any of the following features are present:

- High-grade tumor.
- Presence of lymphovascular invasion.
- Oncotype DX score > 25, or age < 50 years with a score of 16 to 25.6.
- Age < 35 years.

Selection of adjuvant systemic therapy

Systemic therapy should be initiated as soon as possible, preferably within 6 weeks after surgery. Concurrent use of RT and CT is not recommended due to increased toxicity; when both are indicated, CT should be initiated first, followed by RT upon completion. CT and HT should not be administered concomitantly; HT should begin only after completion of CT.

Optimal timing to initiate adjuvant CT

In recent years, the impact of early treatment initiation on reducing time to recurrence has been described. Several studies have shown that the time to initiate adjuvant CT after definitive surgery should be less than 60 days; the longer the delay in starting treatment, the greater the probability of recurrence and death (hazard ratio [HR], 1.20 and 1.36, respectively)[140].

Of note, in various studies, delays in the administration of adjuvant CT are more frequent in older patients, those with greater comorbidity, and those with sociodemographic disadvantages[140]. Furthermore, triple-negative and HER2-positive tumors are the subtypes in which delay in initiating adjuvant treatment has the greatest impact (HR, 1.54 and 3.09, respectively)[140].

Recently, results from a cohort study of patients with triple-negative tumors showed that adjuvant CT should be initiated within 30 days, as this is associated with improved disease-free survival and overall survival. Conversely, initiating CT after this period is associated with a 10% lower 10-year overall survival[141].

Table 7. Characteristics of the main types of catheters for administration of systemic cancer treatment

	PIVC	Short CVC	Peripherally inserted CVC	Port
Duration	7 days	< 30 days	6-9 months	5 years
Mechanical occlusion	-	10-14%	3.8-14.4%	0.9-7.9%
Catheter-associated thrombosis	3.9%	12-21%	3.6-11.5%	0.8-8.2%
Infection	2%	10-15%	7.6%	2.1%

CVC: central venous catheter; PIVC: peripheral intravenous catheter.

Table 8. Complications associated with insertion technique

	Anatomic puncture	Ultrasound-guided puncture	Venous section
Operative time	-	33 (23-82) min	48 (28-68) min
Complications			
Pneumothorax	0-6.6%	1.5%	0%
Hemothorax	0.4-0.6%	0.1%	0%
Arterial injury	6.3-9.4%	0.1-0.6%	0%
Improper placement*	10%	0.3%-7%	1.7%

*Rotation, kinking, or tip outside the superior vena cava.

Adjuvant CT

CT should be indicated and properly supervised by a medical oncologist, in an appropriate setting (outpatient infusion unit or hospital) and with the support of nursing staff specialized in oncology and the administration of antineoplastic agents.

Appropriate antiemetics must be available to reduce gastrointestinal toxicity, as well as colony-stimulating factors to prevent or treat neutropenia.

Anthracycline-based regimens are recommended due to their modest benefit in disease-free and overall survival vs first-generation regimens such as CMF (cyclophosphamide, methotrexate, and fluorouracil)[134-136].

Similarly, the addition of taxanes has also demonstrated moderate clinical benefit, regardless of hormone receptor expression, number of affected axillary nodes, or ovarian function[137,142-146].

Recommendations for CT and targeted therapy depend on the biologic subtype. The recommended regimens are detailed in table 9[147].

Dose-dense CT regimens with doxorubicin plus cyclophosphamide (AC) every 2 weeks, followed by weekly or every-2-week paclitaxel with filgrastim support, achieve a 26% reduction in recurrence risk and a 31% reduction in mortality risk[147,148]. The PHANTER study, with 10.3 years of follow-up, also showed benefit with dose-dense EC followed by docetaxel every 2 weeks at 75 mg/m^2, improving recurrence-free survival and disease-free survival, without statistically significant improvement in overall survival[148,149]. Regarding the sequence of anthracyclines and taxanes, a meta-analysis supports the use of taxanes followed by anthracyclines as a reasonable option in daily clinical practice. Pathologic response results from some phase III clinical trials also support this suggestion.

Adjuvant capecitabine should be considered in patients with triple-negative disease who do not achieve a pathologic complete response after neoadjuvant therapy[150]. The addition of other agents such as gemcitabine or platinum salts to anthracycline- and taxane-based regimens is not routinely recommended, as studies to date have not demonstrated clinical benefit.

Currently, this consensus recommends discontinuing the use of 5-fluorouracil (FAC [fluorouracil, doxorubicin, and cyclophosphamide] and FEC [fluorouracil, epirubicin, and cyclophosphamide] regimens) as part of adjuvant treatment. When comparing 6 cycles of FAC or FEC100 with 4 cycles of AC, no benefit has been demonstrated in disease-free survival or overall survival[151].

Adjuvant HT

Adjuvant HT should be administered for at least 5 years in all hormone receptor-positive cases to prevent metastatic disease, locoregional recurrence, and contralateral tumors. This reduces recurrence rates by 10 to 30% in tumors with moderate expression and by 40 to 50% in tumors with high expression (table 10)[152].

Aromatase inhibitors (AIs) provide greater benefit in the adjuvant setting. Tamoxifen is an acceptable alternative in patients who do not tolerate aromatase inhibitors.

HT may be combined with cyclin inhibitors (abemaciclib or ribociclib) in cancers at high risk of recurrence, based on high grade, tumor size T3/T4, positive nodes N2/N3, hormone receptor expression < 10%, residual disease after treatment, a high-risk genomic platform category, or the Breast Cancer Index, which combines clinical prognostic factors and predictive risk measured by genomic profile testing[153].

Ductal carcinoma in situ

For ductal carcinoma *in situ*, tamoxifen (20 mg/day) for 5 years is recommended as risk-reducing therapy in patients with breast-conserving surgery and hormone receptor-positive disease[154]. In postmenopausal women, treatment with an aromatase inhibitor for 5 years may be considered[155,156].

Invasive carcinoma

Premenopausal patients at diagnosis

Patients are defined as postmenopausal if they have undergone bilateral oophorectomy, are aged ≥ 60 years, or are aged ≤ 60 years with amenorrhea for 12 or more months in the absence of CT, tamoxifen, or ovarian suppression, and have follicle-stimulating hormone and estradiol levels in the postmenopausal range. In patients receiving tamoxifen and aged ≤ 60 years, postmenopausal-range follicle-stimulating hormone and serum estradiol levels are required. In women who are premenopausal at the start of CT, amenorrhea is not a reliable indicator of menopausal status; therefore, serial hormone level measurements are recommended before indicating AIs.

Tamoxifen (20 mg/day), with or without gonadotropin-releasing hormone analogs, is recommended for 5 years in premenopausal or perimenopausal women with hormone receptor-positive or unknown status[157]. In high-risk patients, adjuvant therapy may be extended to 10 years[157,158].

In women who remain premenopausal after CT (or who recover ovarian function within the first 8 months after completing CT) and who have any high-risk feature, AIs plus ovarian ablation are recommended (SOFT and TEXT studies)[159,160].

The frequency of adverse events was higher in both groups receiving ovarian suppression vs tamoxifen alone[159,160]. Ovarian suppression plus AIs provides greater efficacy but also greater toxicity. It is recommended to initiate medical ovarian ablation to assess tolerance and adverse effects before recommending a permanent method such as surgery or RT[157-160].

Postmenopausal patients at diagnosis

An AI for 5 years is recommended, or sequential therapy with tamoxifen for 2 to 3 years followed by an aromatase inhibitor to complete 7 to 10 years of treatment[161].

Patients with early-stage, high-risk breast cancer

For pre- and postmenopausal patients with early-stage, HER2-negative breast cancer at high risk of relapse, abemaciclib for the first 2 years plus endocrine therapy is suggested according to the MonarchE study[162,163], or ribociclib for 3 years at 400 mg/day for 3 weeks on and 1 week off plus endocrine therapy, according to the results of the NATALEE study[59,164].

Extended adjuvant HT

Extended adjuvant HT is recommended in patients at high risk for late recurrence, after first considering patient comorbidity and adverse effects[165].

Findings from the ATLAS and aTTom tamoxifen studies[166,167], studies evaluating more than 5 years of adjuvant aromatase inhibitor therapy[167], and the most recent American Society of Clinical Oncology (ASCO) guideline[168] support extended adjuvant HT for 7 to 10 years in node-positive patients. In premenopausal patients, tamoxifen has increased overall survival; in postmenopausal patients, an aromatase inhibitor is associated with a lower risk of breast cancer recurrence and contralateral breast cancer vs placebo.

Adjuvant targeted therapies

In tumors with HER2/neu overexpression (3+ by immunohistochemistry) or positive fluorescence in situ hybridization, the use of the monoclonal antibody trastuzumab in combination with adjuvant CT has provided benefit in both relapse-free survival (hazard ratio [HR], 0.62) and overall survival (HR, 0.66)[169-171].

It is recommended to initiate adjuvant trastuzumab together with taxane-based CT after anthracyclines, because this sequence has been shown to be useful and safe[172]. Concomitant administration of trastuzumab with anthracyclines is not advised because it increases cardiotoxicity.

The TCH regimen (docetaxel, carboplatin, and trastuzumab) for 6 cycles, without anthracyclines, should be considered in patients at high risk of cardiovascular disease (history of cardiac dysfunction, older age, hypertension, obesity, or prior anthracycline exposure)[173,174].

Currently, a 1-year duration of adjuvant trastuzumab is advised, because shorter or longer durations have not, to date, demonstrated better outcomes[175-177].

In selected cases with node-negative disease and small tumors (< 3 cm), weekly paclitaxel plus

Table 9. Adjuvant systemic therapy regimens in early breast cancer

Regimens in HER2-negative disease	
Dose-dense AC followed by paclitaxel every 2 weeks Dose-dense AC followed by weekly paclitaxel Dose-dense EC followed by docetaxel every 2 weeks, 75 mg/m^2 TC Olaparib in cases of germline *BRCA1* or *BRCA2* mutations Capecitabine in triple-negative subtype with residual disease after neoadjuvant therapy	
Regimens in special circumstances	**Other regimens**
Dose-dense AC Dose-dense EC AC every 3 weeks AC followed by weekly paclitaxel CMF	AC followed by docetaxel every 3 weeks EC TAC
Regimens in HER2-positive disease	
Paclitaxel + trastuzumab Dose-dense AC followed by weekly paclitaxel Dose-dense EC followed by docetaxel every 2 weeks, 75 mg/m^2 TCH Trastuzumab ± pertuzumab for 1 year if no residual disease after neoadjuvant therapy, or if no neoadjuvant therapy was received T-DM1 if residual disease after neoadjuvant therapy, or trastuzumab ± pertuzumab if T-DM1 is not tolerated due to toxicity Trastuzumab + pertuzumab if positive nodes at initial staging	
Regimens in special circumstances	**Other regimens**
TC + trastuzumab AC followed by (paclitaxel) + trastuzumab AC followed by (paclitaxel) + trastuzumab + pertuzumab Paclitaxel + trastuzumab + pertuzumab T-DM1 Neratinib as extended therapy	AC followed by docetaxel + trastuzumab AC followed by docetaxel + trastuzumab + pertuzumab

AC: doxorubicin + cyclophosphamide; EC: epirubicin + cyclophosphamide; TC: docetaxel + cyclophosphamide; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; TAC: docetaxel, doxorubicin, cyclophosphamide; TCH: docetaxel, carboplatin, and trastuzumab; T-DM1: trastuzumab emtansine.

trastuzumab for 12 weeks, followed by trastuzumab every 3 weeks to complete 1 year, may be an option[178].

Patients receiving trastuzumab or any anti-HER2 therapy should be carefully assessed because of the risk of cardiotoxicity, especially if there is a personal history of cardiac disease or high risk. Left ventricular ejection fraction should be evaluated before starting this agent, every 12 weeks, and at the end of treatment. All patients receiving this drug should be monitored by echocardiography or nuclear imaging to detect early decreases in ventricular function (Table 11).

Given improved recurrence-free survival in node-positive patients, the use of dual anti-HER2 adjuvant blockade (trastuzumab plus pertuzumab) is currently recommended[177-181].

In selected high-risk cases among HER2-positive and estrogen receptor-positive patients, extended therapy with oral neratinib for 1 year after completion of adjuvant trastuzumab may be used (patients may have received pertuzumab in the neoadjuvant setting). This strategy provides benefit in recurrence-free survival and overall survival[182-184].

Because of improved recurrence-free and overall survival in high-risk patients with a germline BRCA mutation (pathogenic variant) and HER2-negative disease, based on the OlympiA study, oral olaparib for 1 year after conventional treatment may be used[158].

Genomic profiles and systemic therapy

Genomic profiling tests can be used as support for prognostication and decision-making regarding systemic therapy in patients with early breast cancer that is estrogen receptor/progesterone receptor-positive and HER2-negative. They should not be used in patients with triple-negative tumors or HER2-positive tumors. Recommendations for the use of the 4 molecular signatures available in Mexico (Oncotype DX, MammaPrint, EndoPredict, and PAM50) are presented below.

Table 10. Adjuvant hormonal therapy in breast cancer

Tamoxifen 5 to 10 years Premenopausal at diagnosis	AI plus ovarian suppression 5 to 10 years*
AI 4.5 to 6 years followed by tamoxifen to complete 10 years	Postmenopausal at diagnosis Tamoxifen 2 to 3 years followed by AI to complete 10 years Tamoxifen 5 to 10 years in case of AI intolerance

*Analyze the case and risk factors to select candidates for this treatment.
AI: aromatase inhibitor.

Oncotype DX

This is a 21-gene assay with prognostic and predictive value and broad validation, generating a recurrence score based on the expression of each gene. It is recommended in postmenopausal women with T1b/c or T2, N0 tumors, or T1-3, N1 tumors (1 to 3 nodes)[185,186], and in premenopausal women with T1b/c or T2, N0, hormone receptor-positive, HER2-negative tumors[185,186].

MammaPrint

This is a 70-gene assay with prognostic utility that generates a low- or high-genomic-risk result. It is recommended in postmenopausal patients with N0 tumors and high clinical risk (> 3 cm; > 2 cm moderately or poorly differentiated; or > 1 cm poorly differentiated), or with 1 to 3 positive nodes and high clinical risk (> 2 cm or moderately or poorly differentiated)[187].

EndoPredict

This is a 12-gene assay that can be used in patients with T1-2 tumors and node-negative disease. Cases with a low-risk score (< 3.3287) have a prognosis similar to T1a-T1b N0 M0 disease, with a 10-year distant recurrence rate of 4%. Patients with 1 or 2 positive nodes and a low-risk score have a 10-year distant recurrence risk of 5.6%[188-190].

PAM50 (Prosigna)

This test can be used in patients with T1 or T2 tumors with node-negative disease. Patients with a low recurrence score (0-40) have a prognosis similar to T1a-T1b N0 M0 disease. Patients with 1 to 3 positive nodes and a low recurrence score have a less than 3.5% risk of distant recurrence at 10 years if treated with endocrine therapy alone[186,190,191].

Postoperative RT in early breast cancer

Breast-conserving surgery and RT

Breast-conserving surgery with postoperative RT is superior to mastectomy in terms of local control and overall survival. Even though newer systemic treatments allow an effective reduction in local and distant recurrences, postoperative RT should be offered as soon as wound healing permits (Table 12)[192].

In the setting of breast-conserving surgery, the procedure is irradiation of the entire breast, preferably using moderate hypofractionation, which involves fewer sessions with doses > 2 Gy. Ultrahypofractionation with 26 Gy in 5 fractions is also an option, provided that at least 3D RT is used with strict adherence to dosimetry and daily image verification. Priority should be given to coverage of the surgical bed and to dosimetric constraints of surrounding organs. Relative contraindications include active connective tissue diseases and high-penetrance pathogenic variants (see section “RT in patients with pathogenic variants”) (Table 13)[193-197].

Accelerated partial breast irradiation

This consists of irradiating only the surgical bed site and immediately adjacent tissues, with oncologic outcomes similar to whole-breast irradiation[195]. Partial irradiation techniques include intraoperative RT, brachytherapy, and external conformal or intensity-modulated RT (Table 14)[196].

Genomic signatures and RT

Genetic panels influence systemic and local treatment decisions in breast cancer patients. In Mexico, DCISionRT is available[197].

Boost to the surgical bed

This consists of an additional radiation dose to the site of breast-conserving surgery. This dose improves local control in patients at high risk of recurrence, although modern series have not reported an overall survival benefit. Therefore, a boost – either concomitant or sequential – is imperative in the following scenarios: age < 50 years, extensive intraductal component, triple-negative or HER2-positive subtype, histologic grade 3, and positive or inked surgical margins, after neoadjuvant CT regardless of pathologic response[198]. In breast-conserving surgery with multiple resections

(up to 3 tumors), each surgical bed should be irradiated[199].

Nodal irradiation after axillary lymph node dissection in breast-conserving surgery

Patients who underwent axillary lymph node dissection, and those whose pathology report shows 3 or more positive nodes, should be offered regional nodal irradiation (axilla, supra- and infraclavicular regions, considering the internal mammary chain)[200].

Regardless of response to neoadjuvant CT, T1-3 N2 tumors should receive regional nodal irradiation. Patients with T1-3 N1 tumors after surgery, without neoadjuvant CT, and with risk factors such as age < 45 years, high-grade tumors, aggressive histologies, lymphovascular invasion, estrogen receptor-negative status, or triple-negative subtype should receive regional nodal irradiation[201]. T1-3 N1 tumors with pathologic complete response after neoadjuvant CT may receive breast irradiation without regional nodal irradiation, as shown in the NSABP B-51/RTOG 1304 study[202].

Nodal irradiation in patients undergoing breast-conserving surgery with a positive sentinel node

In patients with a positive sentinel lymph node with micro- or macrometastases, complementary axillary lymph node dissection is not recommended; instead, regional nodal irradiation is offered, with the same local control and a lower incidence of lymphedema, based on evidence from the AMAROS and SENOMAC studies[54,203]. However, in individuals with more than 3 positive sentinel nodes, axillary lymph node dissection should be considered[204].

RT after mastectomy in early-stage disease

The BIG 2-04 MRC SUPREMO study evaluated RT after mastectomy in patients with pN0 tumors and found no improvement in 10-year survival, local control, disease-free survival, or metastasis-free survival; therefore, RT should be performed based on multidisciplinary discussion[205,206].

RT in young patients with breast cancer

In patients younger than 40 years, RT with moderate hypofractionation or ultrahypofractionation is an option, in addition to delivering a concomitant or sequential boost. Because younger patients have a higher risk of local recurrence, accelerated partial breast irradiation is not recommended in this group[207].

Table 11. Dose restrictions for healthy organs

Characteristic	Absolute decrease in LVEF		
	< 10%	10-15%	> 15%
Normal LVEF	Continue	Continue	Discontinue
1-5% below the LLN of LVEF	Continue	Continue	Discontinue
> 5% below the LLN of LVEF	Discontinue	Discontinue	Discontinue

LVEF: left ventricular ejection fraction; LLN: lower limit of normal.

RT in patients with pathogenic variants

Genetic screening of individuals with cancer has made it possible to consider the potential implications of RT on local control. Discussion of potential risks and benefits is recommended for carriers of any of the mutations mentioned in table 15[208].

Neoadjuvant management

Although neoadjuvant therapy was initially used to treat tumors in locally advanced stages, this therapeutic modality is currently also used in patients with tumors considered operable, > 2 cm, or with positive nodes. Therefore, this section includes treatment of stage III breast carcinomas and certain cases of stage IIA/IIB tumors or T2-3 N0 M0, and T1-2 N1 M0[209], especially the HER2-positive and triple-negative subtypes[210].

The initial evaluation of these patients should include:

- Clinical evaluation.
- Bilateral mammography and breast and axillary ultrasound, or magnetic resonance imaging in indicated cases.
- Core needle biopsy of the primary tumor and fine-needle aspiration biopsy of axillary lymph nodes.
- Complete histologic evaluation, including determination of hormone receptors, HER2/neu, and Ki67.
- Imaging modalities of potential metastatic sites with chest computed tomography, abdominal ultrasound or computed tomography, or bone scan (for patients with stage III tumors). Positron emission tomography with 18-fluorodeoxyglucose is an alternative for staging.

In addition, it is suggested to:

– Place a radiopaque clip in the tumor bed or the axillary nodes, or both, in patients who are candidates for breast-conserving surgery or sentinel lymph node biopsy[211]. In multicentric disease (up to 3 lesions separated by ≥ 2 cm), placement of a clip in all tumors is recommended.
– Determine a monogenic (BRCA) or multigene panel in patients with HER2-negative tumors or suspicion of hereditary cancer[212].
– In premenopausal women, offer gonadotropin-releasing hormone analogs to preserve fertility or ovarian function, and timely referral to reproductive medicine if pregnancy is desired[213].

The therapeutic proposal should be defined by the multidisciplinary medical group and will be based on the characteristics of each patient (age, menstrual status, concomitant diseases, preferences, presence of pathogenic variants in susceptibility genes, etc), the clinical status of the disease, and the histologic and immunohistochemical variables of the primary tumor.

Even if the patient has a clinically locally advanced tumor, upfront surgery may be recommended when the following circumstances are present: technically resectable cancer; tumors with favorable histologies (eg, well differentiated; mucinous, neuroendocrine, metaplastic, or tubular histology; high-titer hormone receptor positivity associated with Ki67 expression < 10% and HER2-negative status); or a low probability of response to CT with high toxicity risk[209]; or when breast-conserving surgery is not desired by the patient.

Benefits of neoadjuvant CT

– Allows de-escalation of locoregional surgical management of the breast and axilla[214].
– Allows *in vivo* assessment of chemosensitivity.
– Allows evaluation of new regimens (de-escalation) or incorporation of new medications.
– Allows determination of pathologic response.

Pathologic complete response is defined as ypT0/is, ypN0. This outcome is associated with a better prognosis (hazard ratio [HR] for disease-free survival, 0.48; 95% CI, 0.43-0.54; HR for overall survival, 0.36; 95% CI, 0.30-0.44)[215-217].

The presence of residual disease after neoadjuvant CT requires individualization of adjuvant treatment.

Disadvantages of neoadjuvant CT

– Loss of initial staging information.

Table 12. Ideal timing for adjuvant RT

Event	Ideal timing*
Surgery without adjuvant CT	Up to 8 weeks
Neoadjuvant CT and surgery	30 days to 8 weeks
Surgery and adjuvant CT	Within the first 30 days after completion of CT and < 7 months from surgery

*The benefit of RT is maintained over time; therefore, it should always be offered when available, even if the time frame mentioned in the table has elapsed[192].

Table 13. Whole-breast RT regimens after breast-conserving surgery[194]

Regimen	Fractionation
50 Gy in 25 fractions	Conventional
42.5 Gy in 16 fractions	Moderate hypofractionation
40 Gy in 15 fractions	Moderate hypofractionation
26 Gy in 5 fractions	Ultrahypofractionation

– Possibility of overtreatment if the decision is based on incomplete information (eg, lesion size may be overestimated due to the association of carcinoma in situ seen on imaging).
– Disease progression, which may occur in < 2% of cases.

It is important to emphasize that, before neoadjuvant treatment, the number of lesions, their location, distance to the skin and chest wall, and extension toward the nipple must be documented and recorded.

Neoadjuvant CT and targeted therapies

Recommended neoadjuvant treatment is based on 6 to 8 cycles of CT, as it is associated with a greater likelihood of pathologic complete response[215,218]. The main recommended regimens are specified in table 16 and should be adjusted to the tumor phenotype[219-222].

Breast cancer hormone receptor-positive and HER2-negative

Standard management is described in figure 8. The decision to indicate adjuvant treatment should be individualized based on menopausal status, initial clinical stage, and response to treatment.

Table 14. Indications and contraindications for accelerated partial breast irradiation

Indications	Contraindications
> 40 years at the time of diagnosis	Age < 40 years at the time of diagnosis
Unifocal disease	Positive margins
Tumor < 2 cm	Multifocal tumor
Estrogen receptor positive and Her2 negative	Tumor > 3 cm
Grade 1 or 2	≥ 1 positive lymph node
Absence of lymphovascular invasion	Extensive lymphovascular invasion (25%)
Negative margins	*BRCA* 1/2 mutation
	HER2-positive

Neoadjuvant HT

Currently, there are no clinically useful biomarkers for the clinical benefit of neoadjuvant HT, which leads to heterogeneous use in clinical practice[223]. It may be appropriate in older postmenopausal women or those with multiple comorbidities who have breast cancer with high hormone receptor expression and require tumor size reduction[224].

The goal is to increase the likelihood of tumor resection or breast-conserving surgery[225]. After initiating HT, if a response is achieved, continuation for at least 6 to 8 months is recommended, with subsequent assessment for timely local surgical treatment[226]. Continuation with adjuvant HT or CT will be considered according to the pathologic response and the patient's clinical conditions[227].

There are no efficacy data in premenopausal women; therefore, this intervention is not recommended unless there is a contraindication to adjuvant CT[214]. CDK4/6 inhibitors in combination with AIs in the neoadjuvant setting are not indicated[228].

A genomic signature – specifically the Recurrence Score – may be used to omit CT[229].

Breast cancer HER2-positive

The current recommendation for management of early or locally advanced HER2-positive breast cancer (Figs. 9 and 10) is neoadjuvant systemic therapy for tumors T2N0 and T1-4 N1-3. Table 16 illustrates the standard of care in this context consists of dual anti-HER2 blockade with trastuzumab and pertuzumab + CT, as this strategy has been associated with pathologic complete response rates of up to 68%. Dual HER2 blockade therapy based on combinations with lapatinib, neratinib, or T-DM1 (ado-trastuzumab emtansine) is not recommended.

In patients with residual invasive disease after neoadjuvant treatment combined with anti-HER2 agents, adjuvant T-DM1 for 14 cycles is recommended, as this strategy improves disease-free survival and overall survival[230].

Triple-negative breast cancer

The addition of pembrolizumab to neoadjuvant CT has improved 5-year overall survival and disease-free survival (86.6 vs 81.7%; $p < 0.002$), and is therefore the standard of care[231].

In the absence of immunotherapy, regimens including carboplatin are recommended.

Inflammatory breast cancer

Inflammatory breast cancer should be treated with neoadjuvant CT (+ trastuzumab/pertuzumab in tumors with HER2/neu overexpression). Depending on response to systemic therapy, locoregional management with modified radical mastectomy and postoperative RT should be evaluated. If response to neoadjuvant CT is poor and the tumor is not resectable, RT may be considered and then radical surgery performed[232].

Response assessment during neoadjuvant treatment

After each CT cycle, clinical response should be assessed. In cases of stable disease or progression, radiologic correlation is suggested; recommended methods are breast ultrasound and mammography with or without tomosynthesis[233]. If disease progression is confirmed, changing the systemic treatment regimen and considering local control with surgery or RT, or both, is recommended. If there is a partial or complete clinical response, neoadjuvant treatment should be continued until completion.

Although magnetic resonance imaging and 18-fluorodeoxyglucose positron emission tomography have been shown to help evaluate clinical response and its correlation with pathologic response, they are not mandatory to date[234,235].

Fragmented response is particularly challenging, because only 65% of cases show a > 50% reduction

Table 15. Pathogenic variants and their implications in RT

High-penetrance genes		
Gene	**Frequency**	**Implication in RT**
TP53	0.005%	Minimize exposure to ionizing radiation Radical mastectomy is preferred to avoid RT When the risk of tumor progression or recurrence warrants RT, conventional (non-hypofractionated) regimens should be used, employing 3D RT and avoiding intensity-modulated or stereotactic techniques Reirradiation and partial breast irradiation are not recommended High risk of second primary neoplasms
BRCA1/2 PTEN, STK11, CDH1	0.2-0.3% (Ashkenazi up to 3%)	No contraindication to RT Partial breast irradiation is not recommended
Moderate-penetrance genes		
ATM	0.4-1%	RT contraindicated in homozygotes Increased risk of toxicity More common variants have no contraindication to RT Partial breast irradiation is not recommended Possible increased risk of contralateral breast cancer
PALB2	0.12%	No contraindication to RT. Partial breast irradiation is not recommended
CHEK2	0.5-1% (Northern Europeans)	No contraindication to RT. Possible increased risk of contralateral breast cancer

in lesion size; this should be evaluated individually and likely warrants consideration of oncoplastic surgery to ensure a negative margin[236].

Management after neoadjuvant systemic therapy

Surgical treatment

The current surgical trend is to achieve a good oncologic outcome while reducing extent and morbidity; breast-conserving surgery and sentinel lymph node biopsy, rather than mastectomy and elective axillary dissections, are an example of this approach[237].

Neoadjuvant treatment increases the likelihood of breast-conserving surgery; however, this occurs only with adequate planning of the procedure. Patients considered for neoadjuvant therapy should be evaluated by the multidisciplinary team before initiating treatment.

The most important strategies in surgical planning are pre-neoadjuvant marking with radiopaque clips of the primary lesion and ideally of affected axillary nodes and deciding which study will be used to assess response to systemic therapy. Breast-conserving surgery after neoadjuvant therapy has shown the same outcomes as total mastectomy in terms of overall survival and disease-free survival[238].

The planning process is similar to that for primary surgical treatment. Nonpalpable lesions should be localized preoperatively, either with a wire or radioactive material.

After a complete clinical or radiologic response, the clipped area should be resected with a rim of surrounding tissue, without needing to expand the area where the lesion was initially located. Imaging of the resected specimen should be performed to confirm the presence of residual lesion or pretreatment marker (clip)[239].

Neoadjuvant treatment in breast cancer has been shown to increase the likelihood (up to 75% of patients) of eligibility for breast-conserving surgery in patients initially considered not candidates due to tumor size relative to breast volume. If criteria for breast-conserving surgery are not met, total mastectomy should be performed. Axillary management is independent of breast management[225].

Initial cancer management of locally advanced breast cancer is neoadjuvant systemic therapy; however, in histologies with null, very low, or uncertain response, upfront surgical treatment may be considered, provided the disease is resectable and an R0 resection can be achieved. This is the case in metaplastic carcinoma, lobular carcinoma, and less frequent histopathologic lineages such as mucinous, tubular, papillary, adenoid cystic, secretory, and neuroendocrine carcinomas.

Regarding the influence of progression on surgical treatment, it has not been reported that this condition generates significant changes in the type of surgery[240]. In settings where adequate systemic therapy is not available, local control of the primary tumor should be considered,

provided tumor-free margins can be guaranteed. The recommended surgery is modified radical mastectomy.

RT

Preoperative RT

Preoperative RT is used in patients with aggressive molecular subtypes, such as HER2-positive or triple-negative disease, and in combination with CT in cases of local progression or when resectability is unlikely[241]. Conventional fractionation or moderate hypofractionation is used. Modern series report oncologic benefits comparable to those of postoperative RT. The ideal sequence consists of neoadjuvant CT followed by preoperative RT and then surgery within the first 6 weeks after RT. However, it should be used with caution because of the risk of excessive tissue and vascular fibrosis[241].

Table 16. Recommended neoadjuvant CT regimens according to tumor subtype

Hormone-sensitive tumors
ddAC × 3-4 cycles followed by taxanes × 3-4 cycles[219-220]* AC × 3-4 cycles followed by taxanes × 3-4 cycles
HER2-positive tumors
TCHP × 6[221]* AC × 4 → taxane + trastuzumab + pertuzumab × 4 AC × 4 → paclitaxel + trastuzumab × 4
Triple-negative tumors
Paclitaxel/carboplatin × 12 + pembrolizumab followed by ddAC or AC × 4 + pembrolizumab[222]* ddAC × 4 → ddPaclitaxel × 4 ddAC × 4 → weekly paclitaxel × 12 + carboplatin AC × 3-4 → docetaxel × 3–4 + carboplatin

*Preferred regimens.
AC: doxorubicin and cyclophosphamide; ddAC, dose-dense doxorubicin and cyclophosphamide; TCHP: docetaxel, carboplatin, trastuzumab, and pertuzumab.

Indications for postoperative RT

RT to the breast or chest wall and nodal regions (axillary, supra- and infraclavicular, and internal mammary chain) is a standard in patients with locally advanced breast cancer. It should be offered considering clinical stage at diagnosis, using conventional RT or moderate hypofractionation. Currently, absolute indications for postoperative RT include patients at high risk of locoregional recurrence, such as those with ≥ 4 positive nodes (N2), T4N0 disease, 1 to 3 positive nodes with a medial tumor and unfavorable tumor biology, clinical stage III (tumor > 5 cm and ≥ 1 positive node), and positive margins[242]. According to results from the BIG 2-04 MRC SUPREMO study, chest wall RT in intermediate-risk patients (pT2N0 grade 3 or with lymphovascular invasion) does not provide benefit in overall survival or disease-free survival, local recurrence, or distant metastasis; therefore, in this setting RT should be offered based on multidisciplinary evaluation. Patients with pT2N1 and pT3N0 disease should receive local treatment according to their risk factors[206].

Elective irradiation of the internal mammary chain should be offered in the setting of a central primary tumor > 5 cm, pT4 disease, bulky nodal disease, age < 40 years, tumors in the inner quadrants, lymphovascular invasion, ≥ 6 positive level I axillary nodes, or positive nodes with an inadequate axillary dissection (< 10 nodes). Inclusion of the internal mammary chain in the irradiation field improves overall survival, distant metastasis-free survival, and breast cancer mortality[243]. RT is imperative in N2-N3 patients even when a pathologic complete response is achieved in the axilla[202,244].

RT in inflammatory breast cancer

It may be used as definitive treatment in combination with CT when, after neoadjuvant therapy, resectability with negative margins is not feasible[245]. After radical mastectomy, the irradiation field should include the chest wall with the use of a skin bolus, as well as the axillary nodal region, the supra- and infraclavicular regions, and the internal mammary chain[246]. After breast-conserving surgery, the irradiation field should include the breast with the use of a skin bolus, as well as the axilla, the supra- and infraclavicular regions, and the internal mammary chain, with a dose of 50 Gy in 25 fractions. The benefit of an additional boost to reach 60 Gy, or hyperfractionation to 66 Gy (1.5 Gy per fraction, twice daily), appears greater in patients who do not achieve a pathologic complete response after neoadjuvant therapy, those with close or positive margins, ≥ 4 positive nodes, and younger age[247].

Interactions between RT and systemic therapy

Multimodal therapy is essential to maintain locoregional control and survival in individuals with breast cancer; its interaction may be determinant for tumor response and acute or chronic toxicity (Table 17)[248-254].

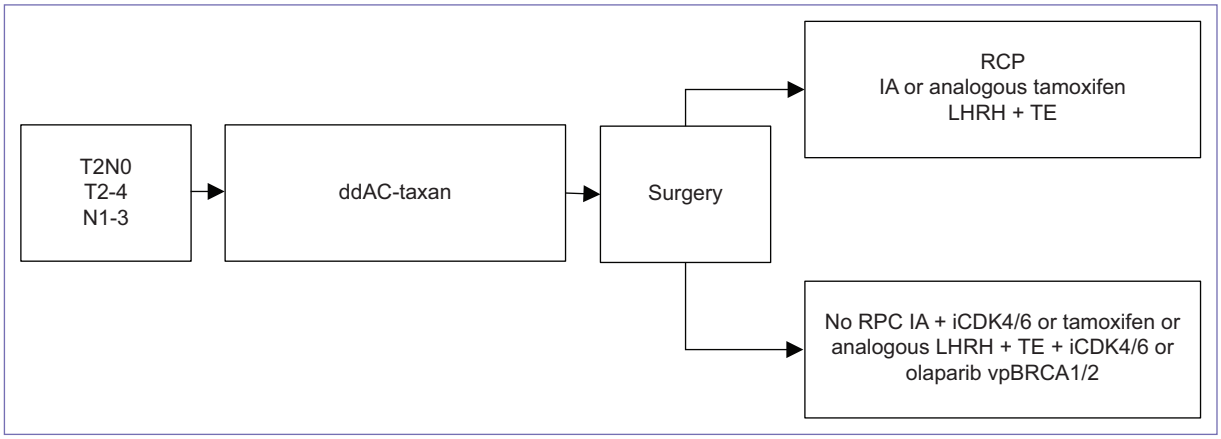


Figure 8. Neoadjuvant management algorithm for locally advanced hormone receptor-positive and HER2-negative breast cancer. ddAC, dose-dense doxorubicin and cyclophosphamide; AI: aromatase inhibitor; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; LHRH: luteinizing hormone-releasing hormone; pCR: pathologic complete response; ET: endocrine therapy.

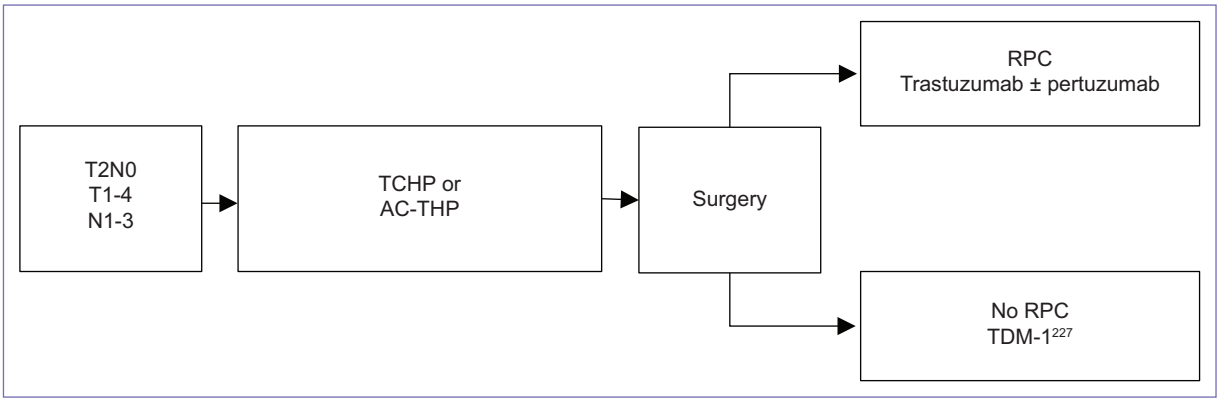


Figure 9. Neoadjuvant management algorithm for locally advanced HER2-positive breast cancer. AC-THP: doxorubicin and cyclophosphamide followed by paclitaxel, trastuzumab, and pertuzumab; pCR: pathologic complete response; TCHP: docetaxel, carboplatin, trastuzumab, and pertuzumab; T-DM1: ado-trastuzumab emtansine.

Reirradiation in patients with local recurrence as the only site of disease

Approximately 8% of breast cancer survivors develop an ipsilateral relapse. After breast-conserving surgery and RT, the probability of recurrence is 4 to 6 at 10 years and 10% to 15% at 20 years. The decision to offer reirradiation should be made by the multidisciplinary team considering disease extent and prior management of the area. Tolerance of prior treatment and patient preference are key pillars of the treatment decision. In these cases, evidence supports a second breast-conserving surgery when feasible.

Brachytherapy is the most studied technique, although other RT modalities may be used, such as 3D conformal RT, intensity-modulated RT, proton therapy to the whole breast, or partial irradiation combined with hyperthermia[255-257]. In mastectomized patients with local recurrence, reirradiation is a therapeutic option considering dosimetry, irradiation technique, and the interval to recurrence[258].

RT and pregnancy

RT is contraindicated at any stage of pregnancy. In the puerperium, breastfeeding is feasible from the contralateral breast[259].

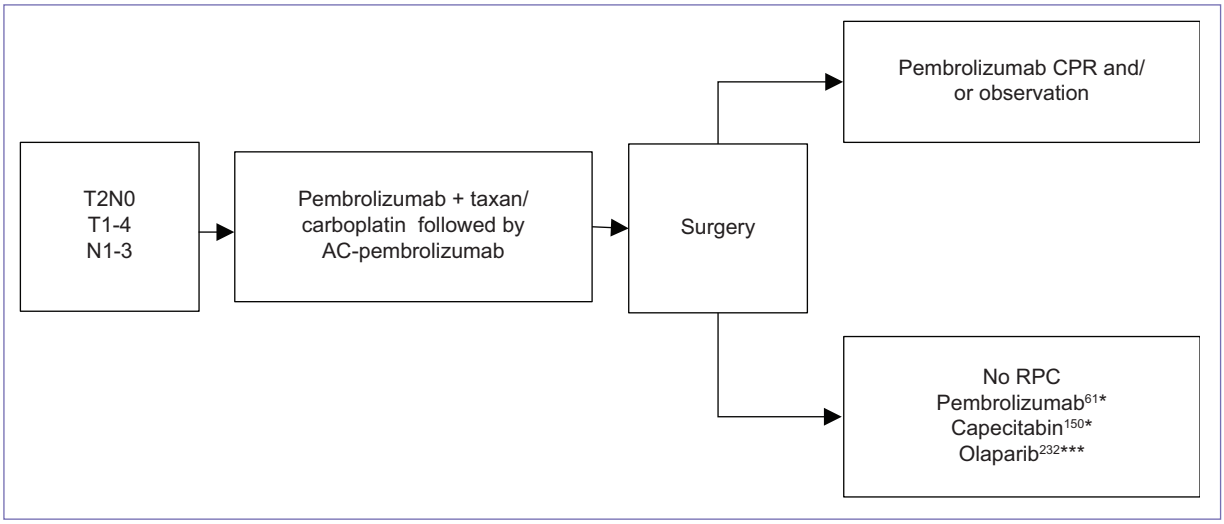


Figure 10. Neoadjuvant management algorithm for locally advanced triple-negative breast cancer. AC: doxorubicin and cyclophosphamide; pCR: pathologic complete response.
*Indicated only in patients on pembrolizumab with neoadjuvant CT.
**Indicated in patients with residual disease; concomitant use with olaparib is not recommended.
***Indicated only in patients who carry BRCA pathogenic variants. There is no evidence of clinical benefit for the combination of olaparib with pembrolizumab; however, there is evidence that the combination is safe to administer.

Table 17. Drug-RT interactions

Drugs	Considerations
Selective estrogen receptor modulators	Concomitant administration of tamoxifen with RT is possible and does not increase toxicity. Usual practice is to prescribe it after RT to facilitate adherence to both treatments
Aromatase inhibitors	Concomitant administration with RT is possible
Selective estrogen receptor degraders	There is no information supporting concomitant use of fulvestrant with RT; it is not recommended
Anthracyclines	Increased acute skin toxicity and risk of cardiac toxicity when RT is administered concomitantly to the left breast
Taxanes	Increased acute skin and pulmonary toxicity with concomitant RT
Platinum agents and capecitabine	Concomitant administration with RT is possible. Close monitoring is required due to a significant radiosensitizing effect
Anti-HER2 therapies	Trastuzumab and pertuzumab may be administered concomitantly with RT. Several trials have validated the concomitant use of T-DM1 with RT, reporting acceptable toxicities such as radiation-induced pneumonitis and interstitial lung disease
CDK4/6 inhibitors	Concomitant treatment is considered safe but requires closer hematologic monitoring, especially at treatment initiation
Tyrosine kinase inhibitors	Concomitant administration of lapatinib with RT is possible
Vascular endothelial growth factor inhibitors	Concomitant administration of bevacizumab with RT is possible
Anti-CTLA-4 antibodies and anti-PD-1/PD-L1 agents	Concomitant administration with RT is possible; however, a greater immunogenic effect has been observed with stereotactic RT and improved responses when administered 3-5 weeks before immunotherapy
Poly (ADP-ribose) polymerase inhibitors	The phase I RADIOPARP study, which evaluated the safety and tolerability of olaparib combined with RT in patients with breast cancer, reported no grade 3 or higher toxicity
PI3K/AKT/mTOR inhibitors	Contraindicated with any RT technique due to severe toxicity

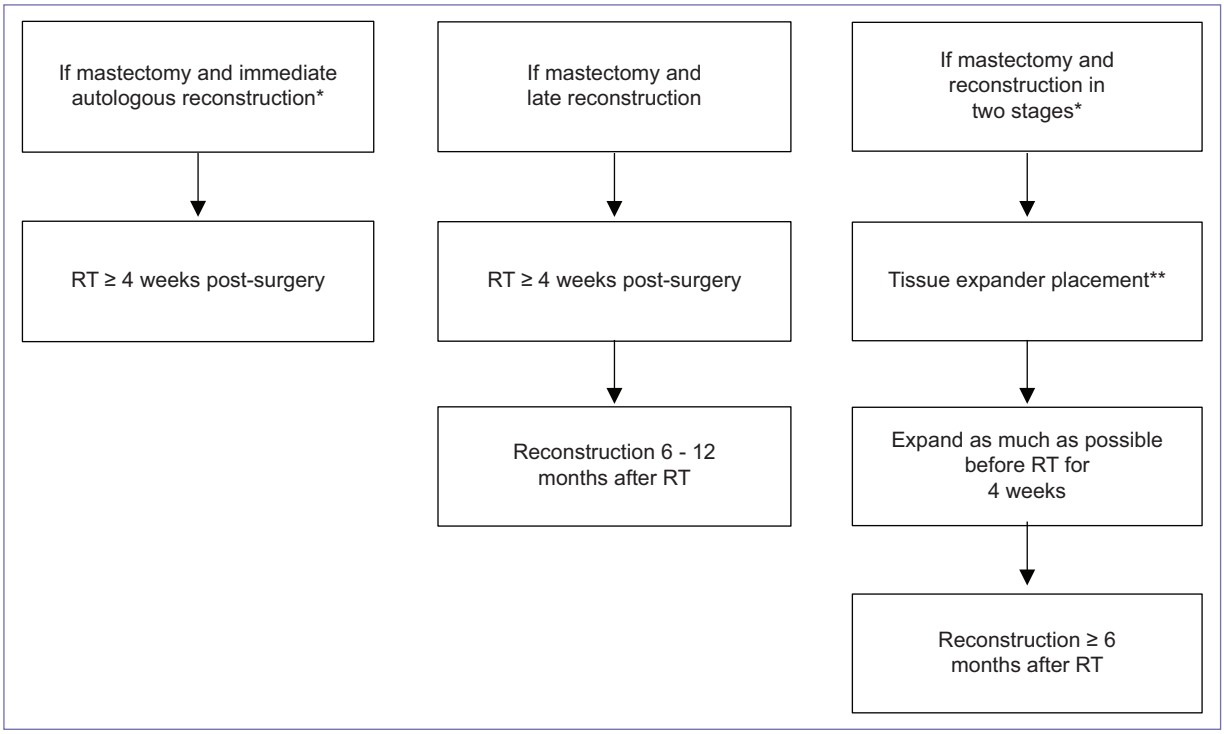


Figure 11. Timing of reconstruction and RT.
*Requires constant communication among surgery, RT, and medical oncology for an optimal outcome.
**Do not modify expander volume during RT.

Table 18. Modern RT techniques in locally advanced breast cancer

Technique	Specifications
Deep inspiration breath hold	In left-sided breast cancer, it reduces the following parameters: Maximum and mean heart dose Cardiac V30 Gy, V10 Gy, and V5 Gy (conventional fractionation) Maximum and mean dose to the left anterior descending artery Mean dose to the ipsilateral lung Pulmonary V20 Gy, V10 Gy, and V5 Gy
Intensity-modulated techniques	Justified in the following situations: Large breast volume with heterogeneity ≥ 110% Pectus excavatum or carinatum, barrel chest Contralateral breast cancer Inadequate coverage of clinical target volume or planning target volume (CTV/PTV) with 3D technique Unmet organ-at-risk constraints Thin chest wall after mastectomy
Hybrid techniques (3D and VMAT/IMRT) (combination of intensity-modulated RT [IMRT] with volumetric modulated arc therapy [VMAT])	Less scattered radiation to healthy organs Superior dose distribution and homogeneity Reduced cardiac doses
Surface-guided RT	Improves positioning of volumes close to the surface Real-time monitoring of patient movement Allows intrafraction tracking in high-precision techniques, such as deep inspiration breath hold
Bolus	Should be used only in: Postmastectomy tumors with skin involvement (T4b, c, d, or any ypT4) Inoperable masses close to the skin or fungating lesions Superficial margins involved by ductal carcinoma *in situ* or invasive cancer Local skin recurrences

RT in patients with breast reconstruction

Immediate autologous reconstruction or two-stage reconstruction with a temporary expander followed by definitive autologous reconstruction is recommended. Patients who received preoperative RT should undergo mastectomy with definitive breast reconstruction at least 6 months after RT[260]. Conversely, in the setting of postmastectomy RT, a tissue expander should be inserted immediately after surgery and maximally inflated with saline solution. The tissue expander should be maintained during RT without modifying its volume, and 6 months later a definitive reconstructive technique should be performed[261]. It should be noted that, according to recent results, moderate hypofractionation is equivalent to conventional fractionation in patients undergoing breast reconstruction[262] (Fig. 11).

Indications for modern RT techniques

Currently, the different irradiation techniques allow optimization of the dose to the target volume and reduction of radiation exposure to healthy tissues (Table 18)[263].

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Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of persons and animals. The authors declare that no experiments in humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal data, medical records, or human biological samples; therefore, it does not require ethical approval. The SAGER guidelines do not apply.

Statement on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used for writing or content creation in this manuscript.

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