Mexican Journal of Oncology
Gaceta Mexicana de Oncología

CONSENSUS

Mexican breast cancer consensus. Management of early breast cancer

*Juan E. Bargalló-Rocha[1], Sergio Aguilar-Villanueva[1], Carolina Ahumada-Pámanes[2], Claudia Arce-Salinas[1], Alethia Álvarez-Cano[2], Isaac Baley-Spindel[3], Verónica Bautista-Piña[4], Guadalupe Cervantes-Sánchez[5], Mariana Chávez-MacGregor[6], Nereida Esparza-Arias[1], Jonathán Figueroa-Padilla[1], Christian H. Flores-Balcázar[7], Sonia Ma. Flores-Moreno[8], Antonio Maffuz-Aziz[3], Federico Maldonado-Magos[1], Ma. del Carmen Lara-Tamburrino[9], Ana Lluch-Hernández[10], Sarina Navarro-Santiesteban[11], Víctor M. Pérez-Sánchez1, Adela Poitevín-Chacón[12], Eva Ruvalcaba-Limón[4], Efraín Salas-González[13], Amelia Sarricolea-Puch[14], Enrique Soto-Pérez-de Celis[7], Laura Torrecillas-Torres[5], Vicente Valero-Castillo[6], Yolanda Villaseñor Navarro[1], Yanin Chávarri-Guerra[15], and Jesús Cárdenas-Sánchez[16]**

[1]Department of Breast Tumors, Instituto Nacional de Cancerología, Secretaría de Salud, Mexico City, Mexico; [2]Department of Radio-Oncology, Hospital Universitario Dr. José Eleuterio González, Monterrey, N.L., Mexico; [3]Department of Plastic Surgery, Centro Médico ABC, Mexico City, Mexico; [4]Pathology Department, Institute of Breast Diseases (FUCAM), Mexico City, Mexico; [5]Department of Medical Oncology, Centro Médico Nacional 20 de Noviembre, ISSSTE, Mexico City, Mexico; [6]Department of Health Services Research/Department of Breast Medical Oncology, The University of Texas, Anderson Cancer Center, Houston, Texas, USA; [7]Department of Medical Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Secretaría de Salud, Mexico City, Mexico; [8]Department of Surgical Oncology, Hospital Regional de Alta Especialidad Materno Infantil, Monterrey, N.L., Mexico; [9]Grupo CT Scanner de México, Mexico City, Mexico; [10]Department of Medical Oncology, Hospital Clínico, Valencia, Spain; [11]Department of Surgical Oncology, Hospital General Agustín O'Horan, Mérida, Yuc., Mexico; [12]Radiotherapy Department, Médica Sur, Mexico City, Mexico; [13]Department of Oncology, Centro Médico de Occidente, IMSS, Guadalajara, Jal., Mexico; [14]Department of Radiotherapy, High Specialty Medical Unit Ignacio García Téllez, Mérida, Yuc., Mexico; [15]Hemato-Oncology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [16]Department of Medical Oncology, Centro Médico de Colima, Col., Mexico

Abstract

Breast cancer, in early stages, has specific surgical, radiotherapy, and systemic management. This type of cancer includes ductal carcinoma in situ and breast cancers in stages I, IIA, IIB, and IIIA. This tenth 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. 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 décima actualización del Consenso Mexicano de Cáncer Mamario abordó el manejo de los estadios tempranos. La difusión de este consenso contribuye a la actualización y 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.*

***Correspondence:**
Jesús Cárdenas-Sánchez
E-mail: jesuscardenass@gmail.com

Date of reception: 22-12-2023
Date of acceptance: 03-01-2024
DOI: 10.24875/j.gamo.M24000265
Available online: 25-03-2024
Gac Mex Oncol. 2024;23(1):17-47
www.gamo-smeo.com

Primary surgical management of breast cancer

Primary surgical management is indicated for those patients with early breast cancer. It can be carried out with breast-conserving surgery (BCS) or total mastectomy, regardless of axillary surgical management. It should be followed by adjuvant therapies, as indicated. As in other clinical scenarios, evaluation of each case by multidisciplinary teams is recommended. The strategy of performing excisional biopsies with intraoperative study of a breast lesion suspicious by clinical and imaging findings and, in case of malignancy, the strategy of performing a modified radical mastectomy should be abandoned. Currently, a histopathological study with tumor immunohistochemistry must be obtained before the treatment.

Perioperative pain management with analgesia and regional anesthesia

Currently, implementation of ultrasound-guided regional chest wall blocks is necessary as part of postoperative pain multimodal management[1]. Knowledge of these techniques, as well as of regional anatomy, is crucial for anesthesiologists, since there is level-A scientific evidence that recommends the use of regional techniques for breast surgery, as a complement of general anesthesia and, in some cases, as anesthetic technique plus sedation. For multiple reasons, among which acute postoperative pain treatment improvement, lower incidence of chronic pain, post-surgical rehabilitation improvement, and a decrease in pulmonary complications stand out and, with special relevance, although still with no conclusive studies on their association with a lower incidence of relapse/recurrence, regional analgesic techniques are being increasingly used in oncological surgery[2,3].

For their application, the fact that it is essential to know the expected postoperative pain should be taken into account, according to the scheduled intervention (primary tumor resection region, as well as the type of procedure in the axillary region), in addition to patient inherent factors (pre-existing pain, pain catastrophizing, age, medication, and concomitant diseases), as well as previous cancer treatment (systemic and regional), to individualize the best multimodal analgesic strategy.

In case of a breast surgical intervention that involves pectoral muscles, performing a PEC I block is indicated. When the axillary region is involved, there is satisfactory evidence with the use of PEC II[4,5]. For external quadrants surgery, there is the serratus intercostal plane block. For internal quadrants, the most appropriate option is the pecto-intercostal fascial block[6,7]. In case the surgical approach includes the nipple-areola complex (NAC) with or without sentinel lymph node (SLN), we could perform a block of the lateral branches of the intercostal nerves in the middle axillary line (BRILMA)[8,9]. The latter, as a complementary part of regional anesthesia, which reduces opioid consumption and intraoperative anesthetic requirements. Paravertebral block and intercostal nerve block are the only procedures regarded as anesthetic techniques plus sedation. Paravertebral block continues to be the reference method in the case of radical mastectomies, either as a single anesthetic technique or in combination with general anesthesia[10,11].

Most of the above-mentioned techniques are interfascial, ultrasound-guided, and easy to learn; however, anatomical knowledge should not be obviated to achieve identification of the structures by ultrasonography, as well as acquisition of skills for the management of the needle-transducer binomial, for correct visualization of the needle and the local anesthetic at all times[9,12].

The possible complications resulting from ultrasound-guided blocks for breast surgery are divided into two groups: those common to the performance of a nerve block and those specific to the thoracic location. Within the first group, toxicity due to local anesthetics should be highlighted due to an important vascularization of the area, with arterial vessels, such as the thoracoacromial artery at the infraclavicular level, the internal mammary arteries at the parasternal level or the intercostal vessels, and within the latter, pneumothorax should be taken into account, due to proximity to the pleura[12].

BCS

BCS is the complete excision of the primary tumor with a negative pathological margin. Most cases must be complemented with adjuvant radiotherapy (RT), and it is the standard treatment at early stages[13].

At these stages, BCS and adjuvant RT have demonstrated similar results in terms of locoregional recurrence and overall survival (OS) in comparison with mastectomy[14-17].

Although multicentricity was considered a contraindication to the performance of BCS, the use of oncoplastic techniques allows the excision of lesions at different quadrants, with evidence of their safety in terms of local recurrence having recently been published[18]; in

consequence, it is reasonable to try to preserve the gland even in cases of multicentricity, as long as the surgeon guarantees excision of the lesions without compromising the margins and/or the esthetic result. Using magnetic resonance imaging (MRI) is recommended as preoperative imaging modality. Patients who are candidates for this type of management are those who meet certain characteristics: primary surgical management, a maximum of three foci in the same breast and separation of ≥ 2 cm between them, 40 or more years of age, and cN0 or cN1 disease. It is essential to have histopathological examination and immunohistochemistry of all tumors. Radiopaque marking of the surgical bed of all excised lesions will be necessary; of note, in the ACOSOG Z11102 project (Alliance), good tolerance of the gland was documented when more than one surgical bed was irradiated with RT boost[19].

The objective is to obtain negative margins in the pathology examination with a satisfactory esthetic result, which can be accomplished by simple resections or using oncoplastic techniques. The surgical specimen should always be oriented and marked for recognition by the pathologist. The margins can be stained with different colors of Indian ink[20] or each margin be marked with staples or sutures. It is recommended for the surgeon to be the one to carry out this marking procedure and for hospital centers to standardize the handling of the surgical specimen. A negative margin for invasive cancer involves the absence of neoplastic cells at inked margin[21]. In case of positive margins, they should be widened. The surgical bed should be marked with radiopaque clips for future localization (RT and surveillance).

The current oncoplastic techniques allow mobilization of a larger proportion of breast tissue, thus obtaining a better esthetic result, without conferring a higher risk of conversion to mastectomy in case of requiring re-excisions[22,23].

Mastectomy

Types of mastectomies

- Simple or total.
- Skin sparing.
- NAC sparing.
- Modified radical.
- Radical.

It is important for patients to be informed about the techniques and possibilities of reconstruction, as well as the times they can be carried out at.

Indications for mastectomy

- Patient preference.
- Multicentric disease with no possibility of free margins.
- Impossibility to obtain free margins.
- Unfavorable breast-tumor ratio for a good esthetic result.
- Difficulty for appropriate follow-up[24-27].

Oncoplastic surgery

BCS followed by RT has shown similar results in terms of locoregional control and OS in comparison with radical surgery[13-17,28] and is the treatment of choice at early stages[28,29].

As in other clinical scenarios, evaluation of each individual case by multidisciplinary teams is recommended.

BCS pursues two purposes: local control of the disease and a satisfactory esthetic result[30].

There are risk factors that increase esthetic deterioration in BCS[31-33]:

- Resection of more than 20% of breast volume in the lateral or central quadrants.
- Resection larger than 10% in the lower and medial quadrants.
- Postoperative RT effects.
- Deformities do occur (Table 1)[33].

When the goal to obtain negative surgical margins with a satisfactory esthetic result cannot be achieved by simple resections, oncoplastic techniques are resorted to.

Oncoplastic surgery has emerged as a new approach to enable BCS and optimize subsequent irradiation. It is based on integrating plastic surgery techniques for remodeling after extensive excision for breast cancer. It allows large volumes to be resected and a larger proportion of breast tissue to be mobilized, and thereby obtain a better esthetic result, without the risk of conversion to mastectomy being increased if re-excisions are required, with breast remodeling and symmetry in relation to the contralateral breast being increased[30].

Oncoplastic procedures in BCS comprise various techniques. From simple remodeling with intramammary glandular-adipose flaps to more advanced mammoplasty techniques that allow resection of large volumes using reductive patterns according to the breast and tumor size and location[31].

Planning these procedures is the most important part of surgery. It requires from the surgeon to have

Table 1. Deformities after breast-conserving surgery

Type I	The treated breast has a normal appearance with no deformity to treat, but there is an asymmetry in volume or appearance in comparison with the contralateral breast
Type II	The treated breast exhibits a deformity that can be corrected by a partial reconstruction of the breast using its own tissue
Type III	The treated breast exhibits an important deformity or painful diffuse fibrosis that must be corrected by mastectomy

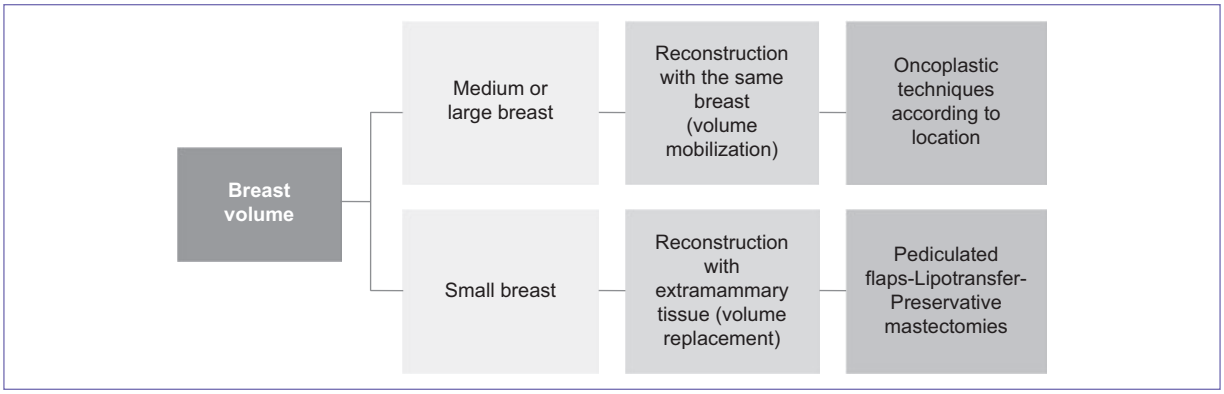

Figure 1. Surgical options according to breast volume.

technical and cosmetic knowledge of the anatomical foundations of the breast, to be familiar with oncoplastic patterns, as well as with the resolution of possible complications. It entails a learning curve and management of high volumes of patients[32-39].

Planning the type of technique and the choice and design of the pattern should be carried out preoperatively, with the patient sitting or standing and with careful examination of previous breast imaging studies and taking patient preferences into account (Fig. 1).

It depends on three elements[40,41]:

- The volume to be resected: It is the predictive factor of surgical results and possible postoperative deformity. The tumor volume/breast size ratio is essential. It is possible to resect large volumes in medium-to-large breasts without significant cosmetic compromise.
- Tumor location: There are areas that are at high risk of deformity such as the lower pole or the upper-inner quadrant.
- Breast density: Evaluation is carried out clinically and with mammography. In cases of adipose composition in most part of the breast, the risk of necrosis is higher in the event of large volume excision and closure mobilizations.

Classification of oncoplastic procedures by resection size[33]:

- Level I: < 20% of breast volume is removed. These procedures can be carried out by surgical oncologists without oncoplastic training.
- Level II: 20-50% of breast volume is removed. In these cases, excess skin excision is usually necessary for breast remodeling. The procedures are based on reductive techniques and require specific training in oncoplastic surgery.

The breast is not a homogeneous organ, and each area of it reacts differently to the resection of the tissue that composes it; different areas or segments offer different resources for remodeling and reducing the impact of the scar. Eight segments have been proposed (Table 2)[41-50] and different oncoplastic patterns according to their complexity (Table 3)[51].

As in any BCS, the surgical specimen should always be oriented and marked for recognition by the pathologist. Standardization at hospital centers is recommended for surgical specimen referral.

In case of positive margins, they should be widened; in some centers, the approach is to systematically widen margins (shaving of the surgical cavity) to avoid reintervention due to compromised margins.

The surgical bed should be marked with radiopaque clips after resection and before tissue repositioning for future localization (RT and surveillance).

Table 2. Breast segmentation according to tumor location

Segment	Location	Deformity	Patterns
I	Lateral	Lateral contour deformity, NAC lateral deviation	Periareolar pattern or circular mammoplasty Lateral mammoplasty, lateral resection+NAC medialization pedicled perforator flaps
II	Upper	Upper pole depletion, NAC upper deviation, fibrous bands	Periareolar pattern or circular mammoplasty Horizontal mammoplasty Lower pedicle vertical mammoplasty Pedicled perforator flaps
III	Infraclavicular ("social breast")	Visible scar, "step" effect	Periareolar pattern or circular mammoplasty Axillary approach Lower pedicle vertical mammoplasty
IV	Upper medial ("social breast")	Visible scar, visible deformity	Periareolar pattern or circular mammoplasty Inframammary access Lower pedicle vertical mammoplasty
V	Lower medial ("social breast")	Visible scar, visible deformity	Rotation mammoplasty Adipofascial flap Pedicled perforator flaps
VI	Lower pole	Lower pole rectification, NAC distortion ("parrot beak"), "axe blow" sign	Upper pedicle vertical mammoplasty Circular mammoplasty Pedicled perforator flaps
Segment	**Location**	**Deformity**	**Patterns**
VII	Inframammary fold	Deformity when there is scarce breast volume	Adipofascial flap Pedicled perforator flaps
VIII	Central	"Axe blow" sign	Lower pedicle vertical mammoplasty Grisotti's technique Pedicled perforator flaps

NAC: nipple-areola complex. Adapted from Weber et al., 2018[50].

Table 3. Oncoplastic patterns according to their complexity

Low complexity	Intermediate complexity	High complexity
Circular mammoplasty (round block)	Upper pedicle vertical mammoplasty	Vertical mammoplasty for central tumors
Horizontal mammoplasty (batwing)	Lower pedicle vertical mammoplasty	Re-excision due to compromised margins
Lateral mammoplasty	Low visibility incisions	Limiting B/T ratio at inner quadrants
	Access to single port – Tunnelization	After neoadjuvant treatment with poor response
		Extreme oncoplasty
		Pediculated flaps – Conservative mastectomies

Conservative mastectomies (CM)

Scientific evidence supports the oncological safety of CM, compared to conventional mastectomy, since they do not increase local recurrence and the same criteria are used to indicate post-mastectomy RT (Table 4)[46-50].

CMs have the advantage of facilitating immediate breast reconstruction. Indications:

- When there is contraindication to conservative treatment.
- When risk-reducing mastectomy (RRM) is indicated.
- Patient preference.

Table 4. Conservative mastectomies

SSM	SNSM and TSSM	SSM
Attempts to preserve as much as possible of the outer covering skin	Also known as total skin-sparing mastectomy	Skin-sparing mastectomy type IV
Respects the inframammary fold, the middle line and upper pole: "breast footprint"	Preservation of the entire skin cover, including the NAC	Large and ptotic breasts that require skin cover reduction or contralateral mastopexy
Includes the NAC, mammary gland and any previous scar	Proximal galactophore ducts excision, with only NAC dermis and epidermis being preserved	NAC can be preserved or not according to its compromise or viability
Minimal changes in skin color and symmetry	Indications regardless of tumor size or NAC distance: negative nipple base biopsy	Immediate breast reconstruction indicated
Axillary approach through the same incision	Immediate breast reconstruction indicated	
Facilitates reconstruction with a more natural shape	Contraindicated in case of NAC clinical or pathological compromise	
Allows filling of the glandular opening with autologous tissue or breast implants	Contraindicated in case of Paget's disease or in the presence of pathological thelorrhagia	
Immediate breast reconstruction indicated		

NAC: nipple-areola complex; SNSM: skin and nipple-sparing mastectomy; SRM: skin-reducing mastectomy; SSM: skin-sparing mastectomy; TSSM: total skin-sparing mastectomy.

Types of CM

- Skin-sparing mastectomy (SSM).
- Skin and nipple-sparing mastectomy (SNSM) or total skin-sparing mastectomy.
- Skin-reducing mastectomy.

Absolute contraindications to CM

- Inflammatory carcinoma.
- Extensive skin involvement.

Both in oncoplastic patterns and CM, complications such as partial or total necrosis of the skin flaps and/or nipple and loss of nipple sensitivity may occur, which is why the patient must be informed about this before the surgical procedure. The complication rate is higher in patients with large breast volume, breast ptosis, obesity, senile patients, with comorbidities and smokers and in mastectomies with concomitant RT.

When undergoing oncoplastic surgery, the patient must be aware that the procedure is not an esthetic surgery, but rather an oncological surgery that seeks to achieve the best esthetic result; in addition, it is the duty of the treating team to inform her of the true results and possible complications associated with the intervention. In cases of surgeries with resection of large volumes, it is possible that this may lead to asymmetry in relation to the contralateral breast. In this case, it is necessary to inform the patient about the feasibility of symmetrization in the same surgical act or at another stage (Figs. 2-4).

Follow-up after oncoplastic surgery should be carried out by clinical examination and imaging studies that include mammography and breast ultrasound and, when indicated, MRI of the breast.

Surgical treatment of the axilla

Axillary evaluation in the management of invasive breast cancer is essential for obtaining prognostic information about the disease, guiding adjuvant treatment, and for obtaining OS and regional relapse estimates[51,52].

Initial evaluation should include a thorough clinical examination and define the necessary studies. If there is clinical/radiological suspicion, it must be confirmed with lymph node tissue or cytology (lymph node core needle biopsy/fine needle aspiration biopsy). This step is necessary for definitive axillary management to be planned[51,52]. Although axillary dissection has classically been accepted if there is no other high-sensitivity and specificity diagnostic method, its use has been declining to give way to SLN evaluation in cN0, and/or negativization in cases of low burden (cN1) after neoadjuvant treatment[53,54]. The considerations are shown in table 5.

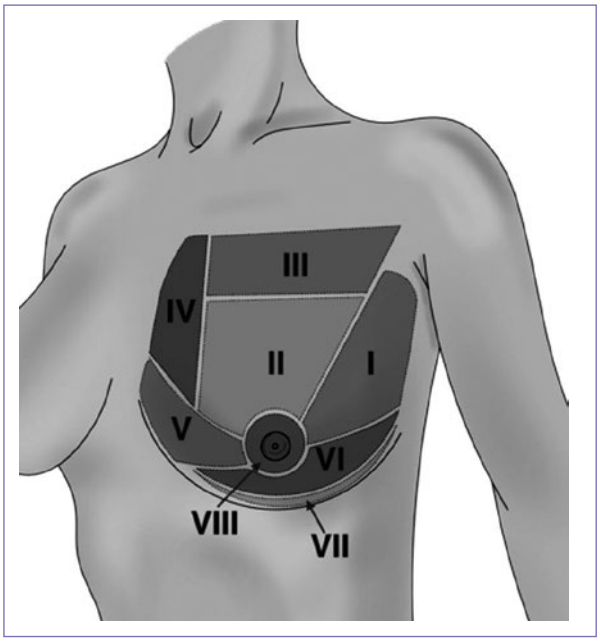

Figure 2. Breast segmentation. Segment I or lateral, segment II or upper, segment III or infraclavicular, segment IV or medial, segment V or lower medial, segment VI or lower pole, segment VII or intramammary fold, segment VIII or central segment.

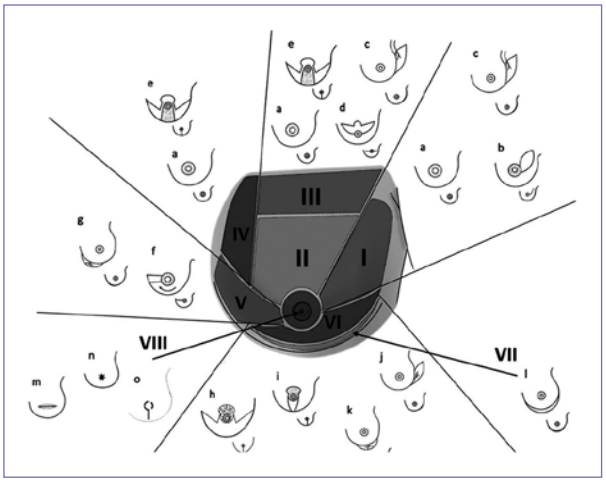

Figure 3. Oncoplastic patterns: a) circular mammoplasty (round block); b) lateral mammoplasty; c) lateral thoracic artery perforator, thoracodorsal artery perforator pedicled flaps; d) horizontal mammoplasty (batwing); e) double branch vertical mammoplasty with lower pedicle (Wise); f) rotation mammoplasty; g) medial or internal intercostal artery perforating pedicled flap; h) double branch vertical mammoplasty with upper pedicle (Wise); i) single branch vertical mammoplasty with upper pedicle; j) lateral intercostal artery perforator pedicled flap; k) anterior intercostal artery perforator pedicled flap; l) inframammary fold; m) spindle cleavage; n) concentric excision; and o) Grisotti's technique.

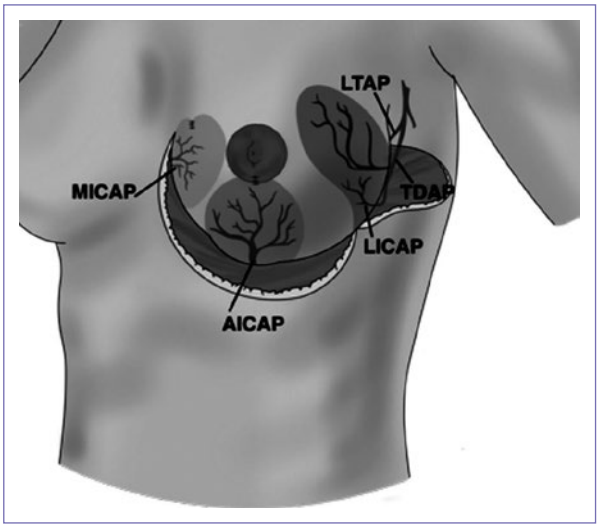

Figure 4. Thoracic arteries pedicled perforator flaps. LTAP: lateral thoracic artery perforator flap; TDAP: thoracodorsal artery perforator flap; LICAP: lateral intercostal artery perforator flap; AICAP: anterior intercostal artery perforator flap; MICAP: medial or internal intercostal artery perforator flap.

Omission of surgical axillary evaluation

The scenarios where surgical axillary staging can be omitted are the following:

- When surgical axillary evaluation will not affect the recommendation for adjuvant management (old age, significant comorbidity).
- Pure ductal carcinoma *in situ* (DCIS), which will be treated with BCS and without clinical suspicion of invasion.
- Patients aged 70 years or older with cT1-2N0, positive hormone receptors (HR).
- RRM.
- Primary breast sarcoma or phyllodes tumor.

SLN

In clinically negative axilla (cN0), SLN biopsy is the standard for surgical staging, and its purpose is to know the histopathological status. Several randomized clinical trials, such as NSABP32 and ACOSOG Z011, have demonstrated the oncological safety of the procedure and lower morbidity (lymphedema, pain, and upper extremity and shoulder sensory alterations), in comparison with the effects of axillary dissection[55-57].

The recommendation of the SLN procedure primarily includes the surgeon's experience, who must demonstrate mastery of the mapping technique. As for SLN identification, we recommend functional dissection as

Table 5. Considerations to be taken into account at the time of axillary evaluation

Disease-related	Surgery-related	Related to the information provided by surgical extent
Positive lymph nodes	Post-neoadjuvant treatment surgery	Axillary dissection
	Availability of tracers/ markers	
	Primary tumor surgery extent: partial vs. total mastectomy	

the first option, given that it is relevant for SLN accurate localization, with the least morbidity. The SLN localization is independent of the dye-radioisotope-tracer application site (peritumoral vs. periareolar)[58,59].

Although high localization rates have been demonstrated with a single technique (and regardless of which one is used), we suggest performing it with a double tracer in combination: dyes (patent blue, indocyanine green), radioisotope (when there is a nuclear medicine department available), or magnetic tracer if this technology is accessible. If the necessary conditions are not available (mastery of the technique, surgical devices, tracers or pathology team familiar with the management of lymph nodes), referral of patients to centers specialized in the procedure should be considered (currently, performing an axillary dissection in case of cN0 and primary surgery is considered incorrect from the oncological point of view)[60,61].

Omission of axillary dissection in case of positive SLN

Prospective studies such as NSABP-32, IBCSG 23-01, ACOSOG Z0011, and AMAROS have been established as pivotal studies in the advancement of SLN consolidation as a single procedure for axillary evaluation in cases of cN0 and/or low pathological lymph node burden (micrometastasis and macrometastasis), in addition to supporting the use of RT for appropriate regional control in some cases with positive lymph nodes, and always with lower rates of morbidity in comparison with axillary dissection per se, all of this in the primary surgery scenario[56,58,60-64].

In case of negativization (ycN0) with no or low initial lymph node disease burden, the acceptable scenario for de-escalation to axillary surgery would be the technique that achieves false-negative rates < 10%, although a certain arbitrariness is suggested for this figure[65]. It should be noted that, globally, the pathological response is higher in the axilla than in the primary lesion (37 vs. 49%), but in high-risk biological subtypes, it can be substantially higher. For this scenario, we used the results of classic studies such as ACOSOG Z1071, SENTINA, and TAD (targeted axillary dissection), to retrieve information supporting the recommendations on the axillary approach[66-72].

Axillary dissection

The NSABP B-04 trial clarifies the impact of the lymph node area itself as an independent factor; however, this is limited to a single procedure, which cannot be entirely compensated by non-invasive studies. This translates into the recommendation to offer axillary dissection only to patients with high lymph node burden; N2-N3, whether at initial clinical staging or after neoadjuvant treatment. This recommendation clarifies that the use of the information is for staging purposes, i.e., in these clinical presentations, today, it will be in few cases (if not zero) that we will recommend primary surgery and regardless of the subtype (Table 6)[62,70].

It is recommended to complete axillary dissection in patients undergoing total mastectomy with SLN, who on pathological (definitive) examination turn out to have macrometastatic disease and will not undergo adjuvant RT, in addition to those patients undergoing primary surgery with three or more positive SLNs, and in whom post-neoadjuvant treatment pathological study shows disease persistence and require a larger number of positive lymph nodes for adjuvant treatment to be considered (e.g., RT extent, cyclin inhibitor ck4,6 application)[71-77].

Morbidity decrease at axillary evaluation: reverse mapping and risk-reducing functional axillary lymphadenectomy

Currently, one of the most relevant situations during axillary evaluation according to morbidity decrease is related to the extent, but we could strongly emphasize that the handling of tissues during the procedure is essential. In fact, over the last decade, different study groups (Li from China and Clough from France) have tried to characterize anatomical points that are relevant to the main location of lymph nodes of the mammary gland main drainage and thus have managed to identify, by quadrants, the structures that are related to each other (lateral thoracic vein and 2nd intercostobrachial

Table 6. Criteria for omission at surgery

Criteria for axillary dissection omission at primary surgery	Criteria for axillary dissection omission at surgery after neoadjuvant treatment
– Patients with T1-T2, with SLN positive for micrometastases, who will undergo adjuvant treatment – Patients with T1-T2 tumors, treated with conservative and SLN surgery; if the result is one or two SLNs positive for micrometastases and will undergo adjuvant treatment with RT and systemic treatment	– Double mapping technique – Dissection of at least three lymph nodes – Marked lymph node dissection

SLN: sentinel lymph node; RT: radiotherapy.

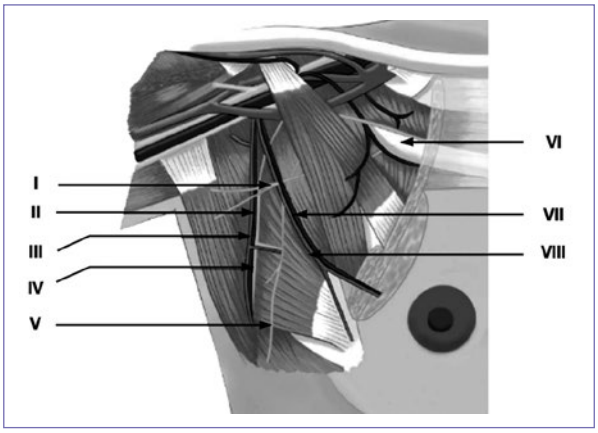

Figure 5. Scheme of anatomical points for localization of the largest area of lymph nodes and/or condition based on Clough and Li's classification. I: 2nd arch, intercostobrachial nerve; II: thoracodorsal artery; III: thoracodorsal vein; IV: thoracodorsal nerve; V: long thoracic nerve; VI: second costal arch; VII: lateral thoracic artery; VIII: lateral thoracic vein.

Figure 6. Double drainage tracing for reverse mapping and upper extremity drainage preservation.

arch), with these structures being regarded as relevant to a functional dissection of the area. Not less relevant, and with higher diffusion, is the use of reverse mapping (arm and breast drainage marking with different tracers), which enables to significantly reduce axillary management inherent morbidity, specifically lymphedema, by between 37 and 43% of expected rates. The anatomical references are identified in figures 5 and 6, and schematizes the relationship between different types of staining of the breast/upper extremity drainage tracing[78-80].

The possible scenarios are summarized and depicted in figures 7 and 8. However, management individualization cannot be fully captured by them.

Breast reconstruction

Breast reconstruction is an integral part of the treatment of the patient with breast cancer. Different studies have demonstrated the importance of breast reconstruction after mastectomy, whether partial or total, and the long-term impact it has on patient quality of life regardless of the oncological status[76].

In general terms, the reconstructive armamentarium the breast surgeon has includes: oncoplastic techniques for rearranging breast tissue, alloplastic materials (expanders/implants), and autologous tissue flaps, whether pedicled or free. There are also reconstruction adjuvants such as acellular dermal matrices and autologous fatty tissue transfer (lipotransfer). The choice of the reconstructive method must be individualized according to patient characteristics, the oncological disease and its treatment, the desire for reconstruction, and the feasibility of performing a particular procedure (availability of expanders, implants, matrices, microscopes, etc.).

To determine the best reconstruction method, collaboration between the oncology team and the reconstructive surgeon is essential, since when the case is preoperatively jointly evaluated, it is possible to trace a plan that optimizes the esthetic result according to patient wishes, without oncological safety of the treatment being compromised.

When reconstructive methods are analyzed, it is useful to divide the cases between partial mastectomies and total mastectomies (whether or not they are skin and nipple-sparing).

Reconstructive approach for partial defects

Partial defects immediate reconstruction

When there is sufficient breast tissue after tumor resection, oncoplastic surgery techniques (see

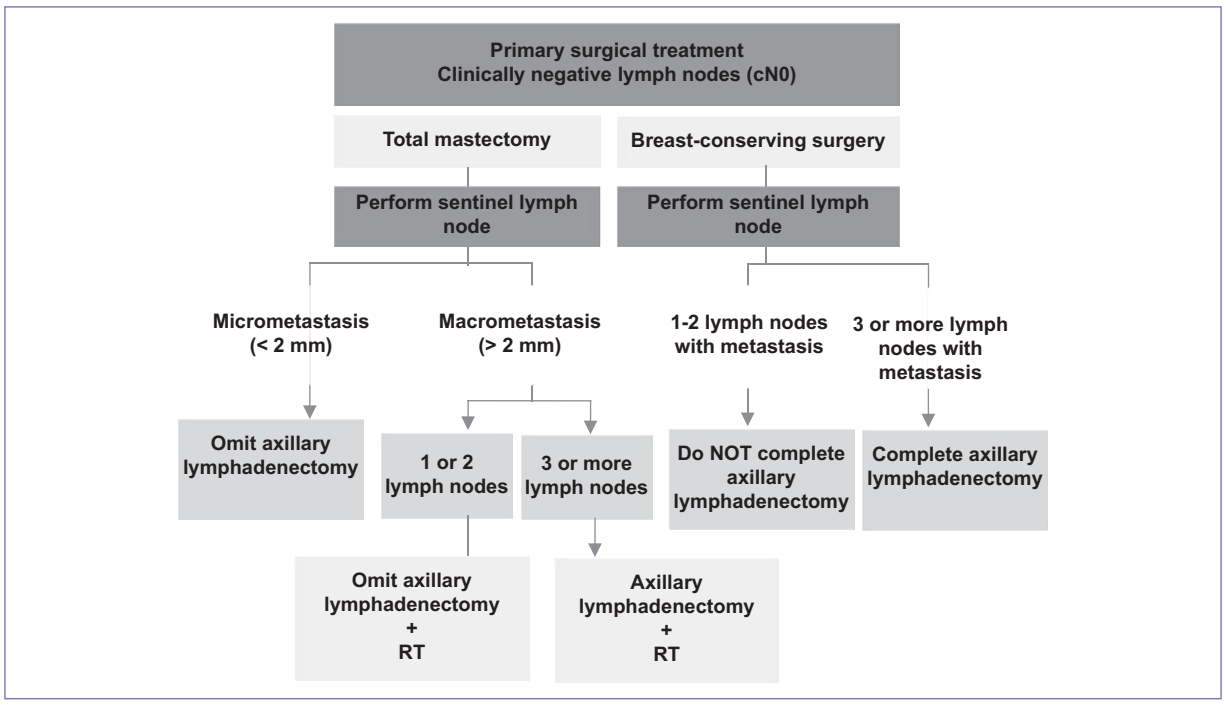

Figure 7. Clinically negative lymph nodes and primary surgery.

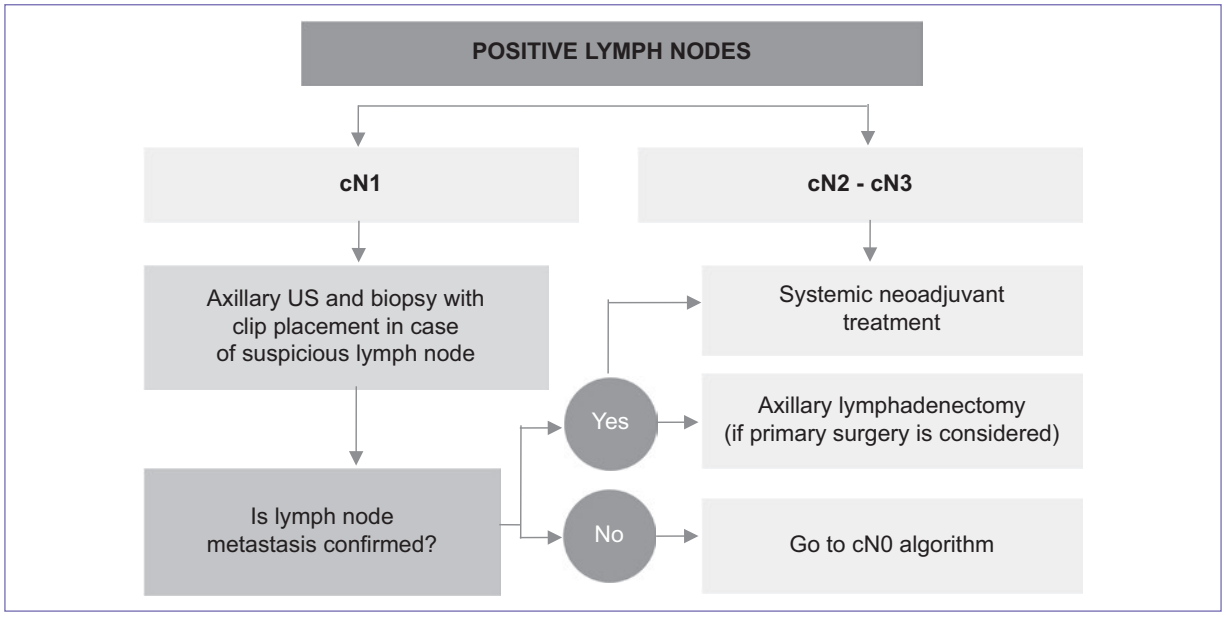

Figure 8. Approach to lymph node disease present at initial evaluation.

oncoplastic surgery section) allow the reorganization of the remaining breast tissue to rearrange it in such a way that the resection defect is less perceptible[81-86].

Occasionally, partial mastectomy defects exceed the dimensions that can be repaired with tissue mobilization oncoplastic techniques and require tissue

replacement reconstructive techniques, i.e., autologous flaps and/or fat transfer (see oncoplastic surgery section)[85,87,88].

Late reconstruction of partial defects

The technique to be chosen for the reconstruction of partial defects largely depends on the moment when it is performed. Late reconstructions of partial mastectomies in patients who have already received RT represent a major reconstructive challenge. In these cases (especially when only part of the breast has been irradiated), it is possible to apply the same oncoplastic techniques using the tissue that has not been irradiated. On the other hand, sometimes the tissue damage caused by RT requires using other reconstructive techniques such as tissue expansions, autologous fat tissue transfers (lipotransfer) or even using muscle or musculocutaneous flaps[89].

Lower and outer quadrant defects often require tissue replacement with pedicled artery perforator flaps, such as the thoracodorsal artery flap, or myocutaneous flaps such as latissimus dorsi flap. It is important to consider the symmetry of the contralateral breast at the same surgical time whenever possible.

Reconstructive approach after total mastectomy

Modern reconstruction techniques, whether with alloplastic materials (expander/implant), dermal matrices, or autologous tissues, allow contraindications to the performance of immediate breast reconstruction to actually be very few, and generally are more related to patient performance status, age and comorbidities, or to very advanced tumor stages, where treatment is palliative[90,91].

In general terms, it should be considered that any breast reconstruction may require two surgical procedures, even when an immediate reconstruction is carried out with an implant or definitive flap. Sometimes, minor touch-up procedures may also be required for improving the reconstruction final result.

Reconstruction with alloplastic materials

It refers to the use of tissue expanders and/or silicone implants for breast reconstruction. These materials can be placed immediately after mastectomy or belatedly. One of the necessary conditions for enabling their use is to have viable and well-vascularized skin flaps, which should be sufficiently thick to avoid exposure of the materials.

Immediate prepectoral reconstruction with direct implant

When the skin flaps are of good quality and there is no ptosis or excess skin, and the volume to be reconstructed allows for it, a direct implant can be placed at the prepectoral position, i.e., under the skin and above the pectoralis major muscle. It is the procedure of choice in cases of SSM or SNSM both in RRM scenarios and in patients with early-stage breast cancer[90-94].

In most cases, it is necessary to interpose some types of tissue between the alloplastic material and the skin flaps. Acellular dermal matrices are an excellent option for providing an interface that ultimately becomes integrated and vascularized. Unfortunately, its high cost can make its use prohibitive. The matrix can be used as the only coverage, completely wrapping the implant at the prepectoral position, or as a caudal extension of the pectoralis muscle when retropectoral reconstructions are performed. Recent studies have demonstrated the oncological and reconstructive safety of the use of polyurethane-coated implants for immediate prepectoral reconstructions, with overall complication rates similar to those reported for acellular dermal matrices, meshes, or subpectoral series, except for a higher implant exposure rate, with the technique being safe and economically advantageous, since it is a single-stage procedure without meshes or acellular dermal matrices. These are preliminary data, and further larger-scale and comparative studies are needed[95].

Immediate retropectoral reconstruction with expander and/or implant

One of the most common techniques that most reconstructive surgeons are familiar with is expander or implant retropectoral placement. In this procedure, a pocket is dissected behind the pectoralis major muscle, in continuity with fibers of the anterior serratus and oblique major and rectus abdominis anterior fasciae. This pocket allows the placement of either a silicone gel implant (up to a certain volume) or a tissue expander. It is possible to disinsert the pectoral muscle at its lower edge and use a dermal matrix as a caudal extension of the muscle, and thereby have a pocket of larger dimensions. In these cases, the upper pole of the implant is covered by the muscle and the lower pole by the matrix.

Tissue expanders are similar devices to a silicone implant, but they are placed empty and have a port through which they are gradually filled with solution via a percutaneous puncture within the first postoperative months. They are indicated in cases where the pectoralis muscle is thin, small, or highly inserted, or when it has been compromised during the mastectomy procedure and does not tolerate the tension generated by the definitive implant. They are also used when a significant portion of skin has been resected and prevents closure above an implant, and in cases of late breast reconstruction when the skin is adhered to the muscle. Once the expansion phase is over and the desired volume has been reached, a second procedure is performed (usually 4-6 months later) to exchange the expander for a definitive implant; in this second reconstruction stage, it is possible to make adjustments to the reconstructed breast or symmetrizations at the contralateral breast[96].

Reconstruction with alloplastic material + flap

Another option for reconstruction with alloplastic materials is to concomitantly use a muscle or myocutaneous flap to provide coverage and/or replace resected skin. The most commonly used is the latissimus dorsi flap, with or without a skin island. It is commonly used for late reconstructions or when the skin resection prevents direct closure of the mastectomy flaps[86,92].

Fat transfer as an adjuvant to reconstruction

In recent years, autologous fat tissue transfer or lipotransfer has been shown to be a useful, effective and safe tool for breast reconstruction[97]. This procedure consists of obtaining fat grafts using a liposuction cannula, and the fat is processed in the operating room and subsequently infiltrated, with integration of the fat grafts into a new anatomical site being thus achieved.

Fat transfer can be carried out at different planes and tissues and for different purposes. When injected at the level of the muscle and skin flap, it allows to thicken it in a generalized manner or to correct contour irregularities resulting from mastectomy. It can also be used to increase reconstructed breast overall volume[98,99].

Moreover, transferred fat is rich in growth factors and stem cells that have been shown to have a powerful regenerative action, especially in patients with trophic changes due to radiodermatitis. It improves the quality and elasticity of the skin and is especially useful for improving the skin in late reconstructions of patients who have been irradiated.

Immediate reconstruction with alloplastic materials is a reconstructive method with few contraindications. Especially in patients undergoing SSM, it has a very high satisfaction rate without compromising the result or oncological follow-up[98,99].

Reconstruction with flaps

Pedicled flaps

The latissimus dorsi muscle and the thoracodorsal artery perforator flap continue to play important roles in postmastectomy reconstruction. These flaps are good options for overweight or obese patients, for whom it is not always safe to perform reconstruction with implants, especially when large volumes are not required.

Abdominal-based free flap

It consists of performing breast reconstruction with a lower abdominal tissue free flap, better known as deep inferior epigastric perforator (DIEP) flap. For patients who received RT and in whom the skin was not preserved, this flap is used for late reconstruction, adding and/or replacing the necessary skin. The DIEP flap can also be implanted simultaneously with the mastectomy procedure, which allows immediate reconstructions to be carried out, even in patients who are to receive RT.

The reconstruction pedicled variant with abdominal tissue, better known as TRAM flap, is considered obsolete and should be avoided due to its donor site morbidity and less lasting results. However, this reconstructive option is reserved for centers where infrastructure and microsurgery-qualified personnel are not available.

Abdominal-based free flap

In this regard, the options are multiple. The decision on the tissue donor site will depend on the physical characteristics of each patient, as well as on recipient blood vessels availability. Some options for this alternative include the gracilis (oblique, transverse, and vertical) free flap, superior or inferior gluteal artery perforator flap, deep femoral artery perforator free flap, and lumbar artery perforator flap, among others. The technique and success of these options is also linked to proper selection and planning[100-102].

Reconstruction and RT

Perhaps one of the main obstacles faced by the reconstructive surgeon is treatment with RT, since the changes generated by it can compromise the esthetic result or even end up in reconstructive method loss[103].

Autologous tissue flaps

When due to tumor characteristics, it is anticipated that the patient will require treatment with RT, higher success has been demonstrated when reconstruction is carried out with autologous tissue, either immediate or belated, especially in advanced tumors with extensive skin loss.

The need for adjuvant treatment with RT is not a contraindication to immediate autologous reconstruction, even if postmastectomy RT is required. So far, no differences have been demonstrated that impact patient satisfaction in terms of flap shape and texture or differences in the percentage of fat necrosis in the flap.

Late reconstructions are recommended 12 months after RT completion. These flaps are also suitable for patients who have undergone RT and who have partial defects, since the additional blood supply provided to the reconstructed breast can help improve tissue quality by transferring healthy tissue to the irradiated site.

Autologous flaps are an excellent reconstructive option; however, the procedure requires doctors and personnel with special training in microsurgery, as well as hospital infrastructure, which, unfortunately, is not always available on a regular basis in our country.

Tissue expander and/or implant

The presence of a tissue expander has been shown not interfere with RT effectiveness[104,105]. In cases where a tissue expander has been placed before RT, it is recommended to fill the expander to a certain volume before RT. If the skin is regarded as being in poor condition or as having significant hypotrophy, it is advisable to reduce the volume of the expander before RT. The important thing is to maintain a constant and defined volume during RT planning and administration in order for not to modify the position of tissues. Subsequently, the second stage of reconstruction can be carried out with a change to a definitive implant 6-12 months later. As previously mentioned, fat transfer is especially useful in this subgroup of patients for improving skin quality.

The presence of a direct implant is not a contraindication to treatment with RT; however, the rates of periprosthetic capsular contracture significantly increase, and are reported in up to 21%, and to cause pain or asymmetry[105-107]. Therefore, in cases where the need for RT is preoperatively anticipated, it may be advisable to use an expander or another reconstructive method[104,105].

Other RT effects

Surgical wound complications are more common in irradiated patients. Changes due to acute or chronic radiodermatitis are also common. Treatment with fat can be useful in these cases, sometimes requiring damaged skin replacement with skin obtained by a myocutaneous flap.

Risk-reducing bilateral mastectomy

Risk-reducing bilateral mastectomy is an intervention option for women at high risk of developing breast cancer, since it has been shown to be the most effective method for reducing it in patients who are carriers of *BRCA* 1 and 2 mutations and other high-risk pathological variants such as *PALB2* and of moderate risk such as *ATM* and *CHEK2*[108]. The decision to perform a RRM is influenced by a variety of factors, including patient perceived risk of breast cancer, anxiety generated by screening, diagnostic procedures, and expectations the patient has about the cosmetic results of surgery[109].

The multidisciplinary team can help in the decision-making process, providing an accurate estimate of the individual risk for breast cancer, taking genetic and non-genetic factors into account, in a bio-psycho-social approach (Table 7).

There are tools available for calculating 5-year and lifetime risk. These are based on various mathematical models for calculating it. Among the most widely used are the Claus model, the Gail model, and the TyrerCuzik model, among others, although currently, there is no model that includes all risk factors[110].

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

There is not a unique risk value above which RRM is clearly indicated, and it is important that the surgeon and multidisciplinary team explain the patient not only the risk assessment but also all available intervention strategies to facilitate a shared decision-making

Table 7. Risk factors and their relative risk

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

process. Counseling should include a discussion about the degree of protection, reconstruction options, and risks. In addition, family history and residual risk of breast cancer with age and life expectancy should be considered during counseling[108].

RRM is the most effective way to reduce the incidence of breast cancer. It has been shown to reduce the risk by up to 90% in women who are carriers of mutations in the *BRCA* 1 and 2 genes and by 95% if accompanied by a risk-reducing bilateral salpingo-oophorectomy (RRSO)[108].

Studies have shown this protection to be close to 95% when a meticulous surgical technique is used to remove the largest amount of breast tissue. The incidence of cancer after RRM is attributed to residual breast tissue[111].

Available data also confer a survival advantage to higher-risk women who undergo the procedure at a relatively young age. Large-scale studies with long-term follow-up are necessary for demonstrating the real benefit in OS, and patients should be aware that the evidence confers the highest benefit of RRM in carriers of mutations in the *BRCA* 1 and 2 genes, at an early age (under 40 years of age) and especially when accompanied by RRSO (from age 35 onward).

Some considerations for selecting patients for RRM include:

- Women with a high-risk genetic mutation.
- History of family breast cancer.
- History of chest RT at young age (< 30 years of age).
- Lobular carcinoma *in situ* (lobular neoplasm *in situ*).

There are these surgical options:

- Total mastectomy (simple).
- SSM.
- SNSM.

All these procedures must include the axillary process (tail of Spence) and the pectoral muscle fascia. According to current evidence, the reference method appears to be SNSM, which, thanks to the preservation of the skin outer cover and the NAC, enables to optimize oncological surgery and esthetic results. This technique does not appear to compromise oncological/preventive efficacy in comparison with other types of mastectomy; however, SSM must be performed with technical skill to avoid leaving macroscopic residues of the mammary gland, particularly in the axillary process,

the lateral and medial regions of the gland, and the NAC; it is necessary to carry out a careful dissection and meticulous preparation of the skin flaps and the NAC, which should be reasonably thin, without this compromising its vitality[112].

In no procedure is SLN biopsy indicated[113,114].

A detailed preoperative radiological study with mammography, ultrasound, and sometimes MRI should always be carried out to rule out the presence of suspicious breast lesions and minimize the risk of occult carcinomas by definitive histological examination.

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

Breast reconstruction must be carried out by plastic surgeons, with permanent prostheses or autologous tissues; the choice of the most appropriate reconstructive technique depends on several factors such as patient physical-anatomical structure, morphology and degree of breast ptosis, comorbidities, as well as patient wishes and preferences[115,116].

Complications such as partial or total necrosis of the skin flaps and nipple, and nipple sensitivity loss may occur in SSM, and the patient should therefore be informed about this before the surgical procedure. The complication rate is higher in patients with large breast volume, breast ptosis, and in senile patients and smokers.

Contralateral RRM

It is defined as mastectomy on the healthy side in a woman with unilateral breast cancer. The prognostic impact of contralateral risk-reducing mastectomy (CRRM) is difficult to evaluate, since available data are largely from retrospective studies. A Cochrane review on the efficacy of this procedure concludes that CRRM reduces the risk of contralateral breast cancer by 90-100%; however, it does not appear to have an impact on OS[109]. It is clear that the use of endocrine therapy and systemic CT decrease the incidence of contralateral breast cancer development, and these factors should be fully considered in the decision-making process around CRRM and its actual usefulness[117].

The practice of this procedure is on the rise, often at the request of patients themselves, given that they tend to perceive that the risk of developing contralateral cancer is higher than it really is, and that CRRM is associated with higher survival rates.

In patients who are not at high risk for contralateral breast cancer, a discussion on the risk associated with the procedure and the lack of survival benefit with CRRM, as well as a recommendation against the procedure (when it confers no benefit) by the surgeon, are effective for reducing unnecessary use[110].

CRRM is an option for women who are carriers of *BRCA* 1 and 2 mutations, with early-stage breast cancer and who will undergo total mastectomy[118].

The anxiety associated with carcinophobia in breast cancer patients can lead to the performance of procedures without clinical benefit, and therefore, the efforts on education and proper advice should be broad[115]. Another factor to consider is the performance of contralateral mastectomy as symmetrization process in a particular group of patients, which may drive the patient or the plastic surgery team to request the procedure.

As we move toward an increasingly personalized and patient-centered approach to care, we must carefully consider respecting patient preferences and autonomy[119-121].

Adjuvant systemic treatment

To determine the optimal adjuvant therapy, the clinical oncologist must have complete information on the biological characteristics of the tumor. In particular, the expression or not of HR, HER2 neu (potential therapeutic targets), Ki67, and when indicated and available, a genomic signature study, given that these data are of substantial importance for designing the best individualized treatment[122,123].

Definition, objectives, and indications

Any antineoplastic treatment administered after surgical management is called adjuvant treatment; its goals are to prolong the disease-free period, reduce local and systemic recurrences, and increase OS[122,124,125]. Adjuvant systemic treatment (hormone therapy [HT] ± chemotherapy [CT] ± trastuzumab) should be evaluated and administered by a medical oncologist, due to the degree of updating required, as well as the complications and toxicities that may be related to it.

In patients with positive lymph nodes, given the high risk of relapse in this group, all patients should receive some form of adjuvant systemic treatment (CT ± HT ± trastuzumab), regardless of the number of compromised lymph nodes (see genomic profiles).

In patients with negative lymph nodes, administration of systemic adjuvant treatment (CT ± HT ± trastuzumab) is recommended when any of the following conditions is present[126,127]:

- Tumor > 1 cm (> 3 cm for favorable histological types) such as tubular and mucinous cancer, with positive HR and negative HER2 (HT ± CT).
- > 5 mm triple-negative tumor (CT).
- > 5 mm tumor with *HER2* neu oncogene overexpression (CT + trastuzumab ± HT).
- Genomic signature in cases where it is indicated and available (CT + HT).

Systemic treatment (CT ± HT ± trastuzumab) should also be considered if any of the following characteristics is present:

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

Selection of adjuvant systemic treatment

Systemic therapy should be started as soon as possible, preferably within 6 weeks after surgical treatment. RT and CT simultaneous use is not recommended, due to toxicity increase. When both are indicated, treatment should start with CT, with RT being applied at the conclusion of it. CT and HT concomitant administration is also not suggested; the latter should not be started until completion of the former.

Optimal timing for starting adjuvant CT

In recent years, the impact of treatment early start has been described in terms of time-to-recurrence reduction. Different studies have demonstrated that the time to start adjuvant CT after definitive surgery should be < 60 days; the longer the time to start treatment, the higher the probability of recurrence and death (hazard ratio [HR]: 1.20 and 1.36, respectively)[128]. It should be noted that, in various studies, delays in adjuvant CT administration are more frequent in older patients, with more comorbidities and with sociodemographic disadvantages[128].

On the other hand, triple-negative and HER2-positive tumors have been shown to be the subtypes in which delays in the start of adjuvant treatment acquire more relevance (HR: 1.54 and 3.09, respectively)[128].

Recently, the results of a cohort analysis of patients with triple-negative tumors were released, which describe that the start of adjuvant CT should be within < 30 days, since it is associated with better disease-free survival (DFS) and OS, and that, contrarily, starting CT after this time has elapsed is associated with 10% lower 10-year OS[129].

Adjuvant treatment with CT

CT should be indicated and duly monitored by a medical oncologist, in an appropriate area (outpatient or hospital infusion unit) and with the help of nursing staff specialized in oncology and antineoplastic drugs administration. It is important to have the necessary antiemetic drugs to reduce digestive toxicity, as well as colony-stimulating factors to prevent or treat neutropenia.

The use of anthracycline-based regimens is recommended, due to the modest DFS and OS benefits, when compared with first-generation regimens such as CMF (cyclophosphamide + methotrexate + fluorouracil)[122-124]. In addition, the administration of taxanes has shown moderate clinical benefit, regardless of HR expression, of the number of compromised axillary lymph nodes or ovarian function[125,130-134].

The recommendations for indicating CT and targeted therapy depend on the biological subtype. The recommended regimens are shown in table 8[135].

Dose-dense CT regimens with biweekly AC (doxorubicin + cyclophosphamide), followed by weekly or biweekly paclitaxel plus filgrastim, achieve a 26% reduction in the risk of recurrence and a 31% reduction in the likelihood of death[135].

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

Adjuvant capecitabine should be considered in patients with triple-negative disease who do not achieve a pathological complete response (pCR) to neoadjuvant treatment[136]. Adjuvant inclusion of other medications such as gemcitabine or platinum salts to regimens with anthracyclines and taxanes is not systematically recommended, since studies have so far not demonstrated clinical benefit.

Currently, this consensus recommends suppressing the use of 5-fluorouracil (FAC or FEC regimens) as part of adjuvant treatment. When comparing the FAC or FEC100 regimens for six cycles against AC for four

Table 8. Adjuvant systemic therapy regimens for early breast cancer

Regimens for negative HER2	
Dose-dense AC (doxorubicin+cyclophosphamide) followed by paclitaxel every 2 weeks Dose-dense AC followed by weekly paclitaxel TC (docetaxel, cyclophosphamide) Olaparib in case of *BRCA1* or *BRCA2* germline mutations Capecitabine for triple-negative subtype with residual disease after neoadjuvant treatment	
Regimens in special circumstances: Dose-dense AC AC every 3 weeks AC followed by weekly paclitaxel CMF	Other regimens: AC followed by triweekly docetaxel EC TAC
Regimens for positive HER2	
Paclitaxel+trastuzumab Dose-dense AC followed by weekly paclitaxel TCH (docetaxel, carboplatin, trastuzumab) Trastuzumab±pertuzumab for 1 year, if there is no residual disease after neoadjuvant therapy, or if neoadjuvant therapy was not administered TDM1 (trastuzumab+emtansine) if there is residual disease after neoadjuvant therapy or trastuzumab±pertuzumab if there is intolerance due to TDM1 toxicity Trastuzumab+pertuzumab if there are positive lymph nodes at initial staging	
Regimens in special circumstances: TC+trastuzumab AC followed by T (paclitaxel) + trastuzumab AC followed by T (paclitaxel) + trastuzumab+pertuzumab Paclitaxel+trastuzumab+pertuzumab TDM1 (trastuzumab+emtansine) Neratinib as extended therapy	Other regimens: AC followed by docetaxel+trastuzumab AC followed by docetaxel+trastuzumab+pertuzumab

CMF: cyclophosphamide+methotrexate+fluorouracil.

cycles, they do not demonstrate benefit in terms of disease-free period or OS[137].

Adjuvant treatment with HT

Adjuvant HT should be indicated for at least 5 years in all patients with positive HR to prevent metastatic disease, locoregional recurrence, and contralateral tumors. Recurrence rates show reductions from 10 to 30% in tumors with moderate expression and from 40 to 50% in tumors with high expression (Table 9)[138].

The superiority of aromatase inhibitors (AIs) in the adjuvant modality over tamoxifen is: 3% reduction in recurrence and 2% reduction in 10-year mortality. Using tamoxifen in patients who do not tolerate AI is acceptable.

The benefit of AIs is of higher value in the treatment of high-risk cancer (considering as high-risk factors: advanced clinical stage, tumor size larger than 5 cm, 4 or more positive lymph nodes, Grade 3, Ki67 higher than 20%), and in the treatment of lobular tumors[139,140].

Table 9. Adjuvant hormone therapy for breast cancer

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

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

Carcinoma *in situ*

For DCIS, tamoxifen (20 mg/day) is recommended for 5 years, as a therapy for reducing the risk of relapse, in patients with BCS and positive HRs[141-143]. For

postmenopausal women, treatment with AIs can be considered for 5 years[144] (see Primary prevention).

Invasive carcinoma

Premenopausal at diagnosis

Tamoxifen (20 mg/day) is recommended for a duration of 5 years in premenopausal or perimenopausal women with positive or unknown HR[145]. In high-risk patients, adjuvant treatment can be extended to 10 years[146].

In women who remain premenopausal after having received CT (or who have recovered ovarian function within the first 8 months after CT conclusion) and with any high risk factor, AI plus ovarian ablation is recommended (SOFT and TEXT trials)[147,148].

The frequency of adverse events was higher in the two groups that received ovarian suppression than in the tamoxifen alone group. Ovarian suppression plus AI results in higher efficacy and also higher toxicity. Starting with medical ablation to assess tolerance and adverse effects is recommended before suggesting a permanent method with surgery or RT[147-149].

Postmenopausal at diagnosis

AIs for 5 years or sequential therapy are recommended: tamoxifen for 2-3 years and continuing with an AI to complete 7-10 years[148].

Patients with early breast cancer and high risk

For premenopausal and postmenopausal patients with HER2-negative early breast cancer at high risk of relapse: four or more positive lymph nodes or one to three compromised lymph nodes, with grade 3 disease, or a tumor measuring 5 cm or more or KI67 higher than 20%, abemaciclib is recommended for the first 2 years plus endocrine therapy, which provides an absolute benefit in 4-year recurrence-free period of 6.4%, according to the MonarchE trial[150,151].

Extended adjuvant HT

Extended HT is recommended in patients at high risk of late recurrence. Before considering prescribing extended therapy, it is important to consider life expectancy, presence of high-risk clinicopathological factors, prior treatment tolerance, comorbidities of each patient, and side effects[152-154].

The results of the tamoxifen trials ATLAS[9], aTTom[151] and more than 5 years of adjuvant treatment with AI[147-151] and the latest ASCO guidelines[147-151] justify extended adjuvant HT for 7-10 years in patients with positive lymph nodes. In the case of premenopausal patients, tamoxifen has increased the OS rate, and in postmenopausal patients, an AI is associated with a lower risk of breast cancer recurrence and contralateral breast cancer, in comparison with placebo[155-158].

It should be mentioned that menopausal patients are defined as those with bilateral oophorectomy, ≥ 60 years of age, or ≤ 60 years of age with amenorrhea for 12 months or more in the absence of CT, tamoxifen or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol levels within postmenopausal ranges. In case of being under treatment with tamoxifen and being ≤ 60 years of age, FSH and estradiol serum levels within postmenopausal values are necessary. In women who are premenopausal at the start of CT, amenorrhea is not an indicator of menopausal status, which is why it is advisable to perform serial measurements of these hormonal levels before indicating an AI[154-157].

AIs are associated with a lower risk of breast cancer recurrence and contralateral breast cancer in comparison with placebo[154-157].

Adjuvant treatment with targeted therapies

In patients with tumors that exhibit HER2 neu overexpression +++ by immunohistochemistry or + by fluorescence *in situ* hybridization, the use of the monoclonal antibody trastuzumab, in combination with adjuvant CT, has allowed obtaining a benefit in both relapse-free survival (RFS) (HR: 0.62) and OS (HR: 0.66)[158-160].

Starting adjuvant trastuzumab together with taxane-based CT after the use of anthracyclines is recommended, given that this sequence has been shown to be useful and safe[161].

Simultaneous administration of trastuzumab with anthracyclines is not recommended, given that it increases cardiotoxicity.

The TCH regimen (docetaxel, carboplatin and trastuzumab) for six cycles, without the use of anthracyclines, should be considered in patients at high risk of cardiovascular disease (history of heart failure, older age, hypertension, obesity or previous use of anthracyclines)[162,163].

Currently, the duration of adjuvant treatment with trastuzumab is recommended to be 1 year, since administration for less or more time has so far not demonstrated better results[164-166].

In selected cases with negative lymph nodes and small tumors (< 3 cm), the weekly paclitaxel + trastuzumab regimen for 12 weeks, followed by trastuzumab every three weeks, until completing 1 year, may be an option[167].

Patients receiving trastuzumab or any anti-HER2 therapy should be carefully evaluated due to the risk of cardiotoxicity, especially those with 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 treatment completion. All patients receiving this drug should be monitored by echocardiography to early detect ventricular function decrease (Table 10).

Due to a RFS increase in patients with positive lymph nodes, the use of adjuvant dual anti-HER2 blockade (trastuzumab + pertuzumab) is currently recommended[168-170].

In high-risk cases of HER2-positive and estrogen receptor (ER)-positive patients, extended therapy with oral neratinib can be used for 1 year at the completion of adjuvant trastuzumab (they may have received neoadjuvant pertuzumab). This strategy entails a RFS and OS benefit[171-173].

Due to higher rates of RFS and OS in patients with BRCA germline mutation (pathogenic variant) and negative HER2, considered at high risk according to the OlympiA trial, oral olaparib can be used for 1 year after conventional treatment[174,175].

Table 10. Restriction dose to healthy organs

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

LVEF: left ventricular ejection fraction; NL: normal limit.

Genomic profiles and systemic adjuvant therapy

Genomic profiling tests can be used to support prognosis and/or in decision-making for administering systemic adjuvant treatment in patients with ER/progesterone receptor (PR)-positive, HER2-negative tumors. They should not be used in patients with triple-negative or HER2-positive tumors. The recommendations for the use of the four molecular signatures available in Mexico (Oncotype DX®, MammaPrint®, EndoPredict® and PAM50®) are outlined below.

Oncotype DX®

Test involving 21 genes with prognostic and predictive value, with broad validation and in which a recurrence score is generated according to the expression of each one of the genes. It is recommended in the following cases:

- Postmenopausal women with T1b/c or T2, N0, HR-positive, HER2-negative disease or T1-3, N1 (1-3 lymph nodes), HR-positive, HER2-negative disease. In case of a recurrence score < 26, only endocrine therapy is recommended, and with a score > 26, endocrine therapy + adjuvant CT is recommended.
- Premenopausal women with T1b/c or T2, N0, HR-positive, HER2-negative tumors. In case of a recurrence score < 16 there is no benefit from adding CT to endocrine therapy; from 16 to 25, consider adding adjuvant CT followed by endocrine therapy due to a small benefit in terms of distant recurrence (it cannot be ruled out that the CT effect is due to ovarian suppression) or, alternatively, ovarian suppression combined with tamoxifen or AI[176].

MammaPrint®

Seventy-gene test that has prognostic utility whereby a result regarded as low or high genomic risk is generated. It is recommended in postmenopausal patients with HR-positive, HER2-negative tumors, N0 and high clinical risk (> 3 cm; > 2 cm moderately or poorly differentiated; > 1 cm poorly differentiated). In patients with a low genomic risk result, endocrine therapy without CT is recommended. It can be used in patients with positive HR, one to three positive lymph nodes and high clinical risk (> 2 cm; or moderately/poorly differentiated). In patients with positive lymph nodes and low genomic risk, the benefit of adjuvant CT in terms of metastasis-free survival is limited[177].

EndoPredict®

Twelve-gene test that can be used in patients with HR-positive, HER2-negative T1-2, and lymph

node-negative tumors. Patients with a low risk score (< 3.3287) have a prognosis similar to T1a-T1b N0 M0, with a 10-year distant recurrence rate of 4%. Patients with 1-2 positive lymph nodes and a low risk score have a 5.6% likelihood of 10-year distant recurrence[178,179].

PAM50 Prosigna®

It can be used in patients with HR-positive, HER2-negative, T1 or T2, lymph node-negative disease. Patients with a low recurrence score (0-40) have a prognosis similar to T1a-T1b N0 M0. Patients with 1-3 positive lymph nodes and a low recurrence score have a risk of 10-year distant recurrence lower than 3.5% if treated with endocrine therapy alone[180].

Postoperative RT for early breast cancer

Invasive cancer

BCS with RT is superior to mastectomy in terms of local control and OS[181]. Timely access to this treatment should be a priority for doctors and authorities (Table 11)[182-184].

In case of BCS, the procedure consists of irradiating the entire gland. Moderate hypofractionation is standard regardless of age, tumor size and biology, surgical margin status, breast volume, use of systemic therapy or oncoplastic surgery[185]. It involves a smaller number of sessions with a dose higher than 2 Gy. The percentages of local and regional recurrence, DFS and OS, as well as cosmetic results and adverse effects are equivalent to those of the 50-Gy conventional fractionation in 25 fractions that is currently used at the discretion of the treating radiation oncologist. A dose of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions is prescribed. Priority will be given to surgical bed coverage and dosimetric restriction of organs at risk. There is no restriction for photon energy. Ultra-hypofractionation with 26 Gy in 5 fractions offers a local control that is equivalent to moderate hypofractionation, which is why it could be an option as long as at least 3D RT is used with strict adherence to dose restrictions, dosimetric quality control and daily imaging verification[185].

Accelerated partial breast irradiation

It consists of exclusive irradiation of the surgical bed during or after BCS. OS, specific cause, local control, freedom from distant metastasis, and percentage of conversion to mastectomy are similar to total breast irradiation with 3D conformal RT[186]. Partial irradiation techniques include intraoperative RT, brachytherapy, and external conformal or intensity-modulated RT; each one with its respective dosimetric specifications and prescription regimens[187]. Outside of a clinical trial, candidates for partial breast irradiation include those aged ≥ 50 years, luminal subtype, ≤ 3 cm, absence of lymphovascular invasion, grade 1-2 invasive carcinoma, low-intermediate grade DCIS (≤ 2.5 cm with ≥ 3-mm margins), unicentric or unifocal lesion, negative margins (> 2 mm), negative lymph nodes (including isolated tumor cells), with no use of systemic therapy or neoadjuvant CT. When taking this modality into account, internationally validated regimens are to be used[187]. It is not used in lobular carcinoma, lymphovascular invasion, in people aged < 45 years or in hereditary breast cancer[188].

Table 11. Ideal timing for adjuvant treatment with radiotherapy

Event	Timing
Surgery without chemotherapy	Before 8 weeks
Neoadjuvant chemotherapy and surgery	Before 30 days
Surgery and adjuvant chemotherapy	Within the first 30 days after chemotherapy conclusion and at<7 months from surgery

Genomic signatures and postoperative RT

Although genetic panels influence systemic treatment decisions in people with breast cancer, their use for guiding the RT decision is not yet recommended[185].

Surgical bed boost

It improves local control in patients at high risk of recurrence. The dose is 10-16 Gy. There is no uniform consensus on which patients should receive it. Usual indications are: people aged < 50 years with BCS and any tumor grade or molecular subtype. Patients aged 51-70 years with high-grade, triple negative or pure HER2 tumors or inked margins. Results from randomized clinical trials are awaited to define the indications for this procedure[189-191]. If BCS has been performed with multiple resection (up to three tumors), all tumors surgical beds should be irradiated.

Nodal irradiation in the setting of conservative surgery and axillary lymphadenectomy

It is offered in an individual context for N patients with risk factors: no neoadjuvant CT, high-grade tumors, aggressive histological types, ER (–), triple-negative, pT3, medial or central tumors. In N+ patients, lymph node RT is offered after an axillary lymphadenectomy, taking risk factors for recurrence into account, in addition to the number of lymph nodes[192-194].

Nodal irradiation in the setting of conservative surgery and positive SLN

In patients with positive SLN with micrometastasis or macrometastasis, complementary axillary dissection is not recommended if the ACOSOG Z0011 trial criteria are met (T1-2, cN0, M0, BCS, < 2 SLN+); instead, RT is offered. In cases of extracapsular extension or > 3 positive SLNs, axillary dissection plus RT is the ideal procedure[192-194].

Conservative surgery and RT omission

This decision is valid as long as postoperative endocrine therapy is offered and long-term risks of recurrence are informed. RT might be omitted in patients aged > 65 years, with axillary lymphadenectomy, lymph node sampling or SLN biopsy, T1-T2 N0, ER (+), HER2–, negative margins, G1-2, G3 or lymphovascular invasion (but not both). In patients with intolerance to medications or poor treatment adherence, postoperative RT must be strongly advised within a period of no more than 6 months[195].

RT in the setting of mastectomy and N0 early stages

RT to the chest wall should be individualized in people without lymph node invasion, but at high risk of locoregional recurrence.

Premenopausal women with > 2 risk factors or postmenopausal patients with > 3 risk factors such as lymphovascular invasion, medial location, tumor size > 2 cm, poorly differentiated tumors, positive margins, no systemic treatment and aggressive molecular subtypes such as pure HER2 or triple-negative tumors. After SSM or skin and NAC-sparing mastectomy, RT could be considered in patients aged < 50 years with positive margins or high-grade tumors[196].

RT in special situations

Young patients

In patients aged < 45 years, moderate hypofractionation RT to the breast and lymph node areas is an option. A concomitant or sequential boost should be administered. Although there is recent information that suggests that it is possible to omit the boost in case of complete response to neoadjuvant CT or HR+, it cannot yet be regarded as standard[197]. Accelerated partial breast irradiation is not recommended in this group[185,198].

Patients with pathogenic genetic variants

Cancer patients genetic screening has enabled to consider the possible implications of RT in local control, treatment toxicity and risk of second tumors in carriers of hereditary syndromes[18]. The radiation oncologist must be familiar with the possible radiosensitivity of patients with hereditary breast cancer. For patients with low penetrance genes and variants of uncertain significance, management with RT is offered as to the rest of people with breast cancer (Table 12)[199-205].

RT-systemic treatment interactions

The combination of new treatments with RT is complex due to the multiple factors involved. Both the technique and the dose and fractionation to be used can have a significant impact on clinical outcomes (Table 13)[206-209].

Preoperative RT

It is used in patients with aggressive molecular subtypes such as HER2-positive/triple negative or in case of local progression[210]. Conventional fractionation or moderate hypofractionation is used[211]. Modern series report no OS benefit when compared to patients who received postoperative RT, which is why it should be used with caution[211].

Locoregional recurrence and RT

In cases of single local recurrence with or without surgical management with or without a history of RT, local control with RT can be evaluated taking previous dose into account, as well as the site to be irradiated, and the radiation dose received by surrounding organs[212,213]. It can also be used for re-irradiation of

Table 12. Most frequent pathogenic variants and approach with radiotherapy

High penetrance genes	
BRCA1/BRCA2, PTEN, STK11, CDH1, PALB2	No contraindication for RT. Partial breast irradiation is not recommended
TP53	Minimize exposure to ionizing radiation whenever possible. Radical mastectomy is preferred to avoid RT. When the risk of tumor progression or recurrence warrants RT, conventional and non-hypofractionated schemes should be used, using 3D RT and not intensity modulated techniques or stereotaxy. Re-irradiation is not recommended.
Genes of moderate penetrance	
CHEK2	No contraindication for RT. Partial breast irradiation is not recommended.
ATM	Possible increased risk of acute and late toxicity from RT, ultrahypofractionation not offered. They merit close follow-up in consultation.

RT: radiotherapy.

unresectable disease for local control and palliation of symptoms such as bleeding or pain[214].

RT and pregnancy

Treatment with RT is contraindicated throughout pregnancy due to its teratogenicity, induction of malignant neoplasms and hematological alterations. Breastfeeding is feasible using the contralateral breast[215,216].

RT annexes

Neoadjuvant management

Although neoadjuvant modalities were initially used for the treatment of tumors at locally advanced stages, currently, this therapeutic modality is also used in patients with tumors regarded as operable, > 2 cm and/or with positive lymph nodes, which is why this chapter comprises the treatment of stage III breast carcinomas and, in certain cases, of tumors at IIA/IIB stages or T2-3 N0 M0, and T1-2, N1 M0[215], especially the HER2-positive or triple-negative subtypes[216].

Initial approach to these patients should include:

- Clinical evaluation.
- Bilateral mammography and breast and axillary ultrasound; MRI in indicated cases.
- Core needle biopsy of the primary tumor and fine needle aspiration biopsy of axillary lymph nodes.
- Complete histological study, which should include HR, HER2 neu and Ki67 determination.
- Imaging studies of potentially metastatic sites using chest computed tomography (CT), abdominal ultrasound or CT, bone scan (the latter for patients with stage III tumors). Positron-emission tomography (PET-CT) with 18-fluorodeoxyglucose (18-FDG) is an alternative for staging.

The following is also suggested:

- Placement of a radiopaque clip in the tumor and suspicious lymph nodes (less than three) in patients who are candidates for BCS and/or SLN procedures[3,217]. In case of multicentric disease (up to three lesions with ≥ 2-cm separation), placing a clip in all tumors is recommended.
- Determination of a monogenic (BRCA) or multigenic panel in patients with triple-negative tumors or suspicion of hereditary cancer[218].
- In premenopausal women, consider the possibility of using gonadotropin-releasing hormone analogues to preserve fertility and/or ovarian function and timely reference to the reproductive biology department[219].

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

In spite of the patient having a tumor at locally advanced clinical stage, initial surgery may be recommended when the following circumstances are met: the disease is technically resectable, in tumors with favorable histological types (e.g., well-differentiated tumors, mucinous, neuroendocrine, metaplastic or tubular histology, positive RH with high titers associated with Ki67 expression < 10% and negative HER2) or low probability of response to CT with high risk of toxicity[215], or when the BCS option is not desired by the patient.

Benefits of neoadjuvant CT

- Allows locoregional breast and axillary surgical management de-escalation[220].
- Allows evaluating chemosensitivity in vivo.

Table 13. Drugs and their interactions with radiotherapy

Selective estrogen receptor modulators	Concomitant administration of tamoxifen with RT is possible, there is no toxicity increase. Usual practice is prescription after radiotherapy to facilitate adherence to both treatments
Aromatase inhibitors	Concomitant administration with RT is possible
Selective estrogen receptor degraders	There is insufficient information to support concomitant use of fulvestrant with RT and it is not recommended
Anthracyclines	Caution: acute skin toxicity increase and risk of cardiac toxicity with concomitant RT use
Taxanes	Caution: acute skin and lung toxicity increase with concomitant RT use
Platinum salts and capecitabine	Concomitant administration with RT is possible. Caution with hypofractionation. Individualize cases
Anti-HER2 therapies	Trastuzumab and pertuzumab can be used together with RT. Caution with TDM-1
CDK4/6 inhibitors	Discontinue treatment 5-7 days before and after offering RT
Tyrosine kinase inhibitors	Lapatinib concomitant administration with RT is possible
VEGF inhibitors	Bevacizumab concomitant administration with RT is possible
Anti-CTLA-4 antibodies and anti-PD-1/PD-L1 agents	Concomitant administration with RT is possible. With SBRT, a greater effect has been observed if administered 3-5 weeks before immunotherapy
PARP inhibitors	There is insufficient data to support olaparib or talazoparib concomitant use with RT and it is not recommended.
PI3K/AKT/mTOR inhibitors	Contraindicated with any RT technique

RT: radiotherapy; TDM-1: trastuzumab+emtansine; SBRT: stereotactic body radiation therapy.

- Allows evaluating new treatment regimens (de-escalation) or incorporating new medications.
- Allows evaluating pathological response.
- Allows pCR to be evaluated, defined as ypT0/is, ypN0.
- This outcome is associated with a better prognosis (HR for DFS: 0.48, 95% confidence interval [CI]: 0.43-0.54 and for OS: 0.36, 95% CI: 0.30-0.44).
- It allows adjuvant treatment to be individualized based on initial response to CT[221,222].

Disadvantages of neoadjuvant CT

- Loss of initial staging information.
- Possibility of overtreatment, if the decision is based on incomplete information (e.g., the lesion size may be overestimated due to the association of carcinoma *in situ* observed by imaging).
- Disease progression, which can occur in 2% of cases.
- It is important to highlight that, before neoadjuvant treatment, the number of lesions, their location, distance from the skin and chest wall, as well as extension toward the nipple, should be documented and recorded.

Neoadjuvant CT and targeted therapies

The recommended neoadjuvant treatment is based on 6-8 cycles of CT, since they are associated with higher possibilities of pCR[221-223]. The main recommended regimens are specified in table 1[224] and must be adjusted to the tumor phenotype.

As for HER2-positive tumors, dual HER2 blockade therapy based on combinations with lapatinib, neratinib, or TDM-1 (trastuzumab + emtansine) is not recommended.

Inflammatory breast cancer

Inflammatory breast cancer should be treated with neoadjuvant CT (plus trastuzumab/pertuzumab in tumors with HER2 neu overexpression). Based on the response to systemic treatment, locoregional management with modified radical mastectomy and postoperative RT should be evaluated. If the response to neoadjuvant CT is poor and the tumor is not resectable, RT followed by radical surgery may be considered.

Neoadjuvant HT

Neoadjuvant HT is recommended for postmenopausal women with positive HR and negative HER2, without

a clear indication for CT, and in cases in which tumor size reduction is required, or in patients in whom CT toxicity is unacceptable or who have multiple comorbidities. The objective is to increase the possibility of tumor resection and/or BCS.

The use of neoadjuvant endocrine therapy has been associated with pCR rates of 14%, with a high probability for BCS to be performed[225-227].

The use of an AI is recommended. After starting HT, if an objective response is obtained, continuing it for at least 4-8 months is recommended, followed by local surgical treatment. Continuing with HT or adjuvant CT will be considered according to the pathological response and patient conditions[220,222].

The use of CDK4/6 inhibitors in combination with AI in the neoadjuvant setting is not indicated.

Response evaluation during neoadjuvant treatment

Clinical response should be evaluated after each CT cycle. In cases with stable disease and/or progression, radiological correlation is suggested; the recommended methods are breast ultrasound and/or mammography with or without tomosynthesis[228]. If disease progression is confirmed, changing the systemic treatment regimen and considering local control with surgery and/or RT is recommended.

If there is partial or complete clinical response, neoadjuvant treatment should be continued until its completion.

Although the use of MRI or ^{18}F-FDG PET-CT has been shown to help evaluate the clinical response and its correlation with pathological response, these procedures are, thus far, not mandatory[136,229].

Fragmented response is particularly difficult to deal with, since only in 65% of cases a reduction of more than 50% in lesion size is observed; this should be individually evaluated and probably consider the use of oncoplastic surgery to ensure a negative margin[230].

Treatment after neoadjuvant therapy

Surgical treatment

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

Neoadjuvant treatment allows the possibility of BCS to be increased; however, this only happens with proper planning of the procedure to be performed. Patients considered for neoadjuvant treatment should be evaluated by the multidisciplinary team before the start of treatment. Important strategies in surgery planning include marking of the primary lesion and, ideally, of compromised axillary lymph nodes with radiopaque clips before neoadjuvant treatment and the decision on the type of study to be performed for assessing the response to systemic treatment. BCS after neoadjuvant treatment has shown the same results in terms of OS and disease-free period in comparison with total mastectomy[216].

The process to be followed for surgery planning is similar to that for primary surgical treatment. Non-palpable lesions should be preoperatively located; this can be carried out with harpoon-shaped guided wires or with radioactive material. After a clinical or radiological complete response, the area with the clip should be resected with a portion of surrounding tissue, without the need to broaden the area where the lesion was initially located. An imaging study of the resected tissue should be performed to confirm the presence of residual lesion and/or pretreatment marking (clip)[231]. Considering all subtypes, the possibility of being eligible for BCS after neoadjuvant CT is 69-87%, and with neoadjuvant endocrine therapy, it has been of up to 77%[228,232].

In case the requirements for BCS are not met, total mastectomy should be performed. Management of the axilla is independent of breast management.

Initial oncological management in locally advanced breast cancer is with neoadjuvant systemic treatment; however, in those histological types where there is no response, or the response is very low or uncertain, starting with surgical treatment can be considered as long as the disease is resectable and an R0 surgery is obtained. Such is the case with metaplastic carcinoma, lobular carcinoma and rare histopathological lineages such as mucinous, tubular, papillary, adenoid cystic, secretory and neuroendocrine carcinomas.

As for the influence of progression on surgical treatment, this condition has not been reported to generate significant changes in the type of surgery[233]. However, given the conditions in our environment, if appropriate systemic treatment is not available, local control of the primary tumor will have to be considered as long as obtaining tumor-free margins is ensured. The recommended surgery is modified radical mastectomy.

Adjuvant systemic treatment

The type and duration of adjuvant treatment will be based on the pathological response achieved. For hormone-sensitive tumors, the therapeutic decision is independent of the pathological response obtained; however, for HER2 and triple-negative subtypes, the recommendations are described in the adjuvant treatment part of the early breast cancer section.

Table 2 describes in detail the management approaches, according to the response obtained with neoadjuvant systemic treatment.

RT

Postoperative RT

In patients undergoing BCS or radical mastectomy, RT is administered in those with a high risk of locoregional recurrence, namely: four or more positive lymph nodes (N2), T3-4, N0, patients at clinical stage III (tumor > 5 cm and > 1 positive lymph node), positive margins and mastectomized patients with 1-3 positive lymph nodes[137]. RT is administered to the breast/chest wall, lymph node regions (axillary, supraclavicular and infraclavicular, and internal mammary chain). Its indication is independent of the response to neoadjuvant CT and should be offered based on clinical stage at diagnosis. The standard dose to the chest wall and lymph node-bearing areas is 50 Gy. In the context of a mastectomy with one or two positive SLNs, axillary RT in addition to irradiation to the chest wall is offered as an alternative to lymphadenectomy. In case of a positive margin that is not amenable to resection, administering a RT boost to the costal wall is recommended[174].

Postmastectomy hypofractionated RT

Postmastectomy RT with moderate hypofractionation has similar efficacy and toxicity to conventional fractionation, which is why its use is increasingly common, as long as at least 3D conformal RT is administered with strict adherence to dose restrictions, dosimetric quality control, and daily imaging verification[234,235].

RT in patients with tissue expander or prosthetic implant reconstruction

At this moment, ultra-hypofractionated RT cannot be recommended in patients with immediate reconstruction. In case of expander or implant placement, RT can be started within the first 3-6 weeks if adjuvant CT is not administered and 6-8 weeks after autologous reconstruction. Changes in expander volume should be avoided during RT. The ideal timing for late autologous reconstruction or expander exchange for a permanent implant is between 6 and 12 months after post-mastectomy RT[236,237].

Inflammatory disease

Preoperatively, RT is used when resection with negative margins after neoadjuvant surgery is not feasible. The irradiation field should include the breast, supraclavicular and infraclavicular region, internal mammary chain and axillary region lymph nodes, bolus administration area and 50-60-Gy dose[238].

After radical mastectomy, the irradiation field should include the chest wall with the use of bolus to the skin, in addition to the axilla and supraclavicular and infraclavicular regions with a 50-Gy dose in 25 fractions. The benefit of a boost at 60-66 Gy appears to be greater in patients who do not achieve a complete pathological response with neoadjuvant therapy, with positive margins, > 4 positive lymph nodes, and in young patients[239].

Indications for the use of modern techniques

Current irradiation techniques optimize the dose to the target volume and decrease the amount of radiation to healthy tissues.

Conclusions

Neoadjuvant treatment and locoregional treatment, as well as axillary evaluation with RT and surgery in breast cancer, have undergone significant advances, driven by an increasingly deeper understanding of tumor biology, targeted therapies, biomarkers, genetics, and genomics. The following conclusions are derived from an exhaustive review of the medical literature and current clinical trends in this highly specialized field.

Treatment individualization

Based on clinical risk, as well as on the use of biomarkers, the work of the multidisciplinary group should be strengthened and stimulated; medical practice in the era of precision medicine has reached breast cancer. Patient stratification according to biomarkers such as ER,

PR, and HER2, together with the incorporation of genomic tests, allows the adaptation of specific neoadjuvant regimens, optimizing efficacy, and reducing toxicity.

pCR as a prognostic indicator

The achievement of a pCR, defined as an absence of viable tumor cells in the breast and axillary lymph nodes after neoadjuvant treatment, has become established as a crucial prognostic marker. Patients who achieve a pCR experience improved survival rates and reduced recurrence rates.

Focus on reducing treatments

The success of multimodal treatment and sequential changes, as it occurs in neoadjuvant therapy, has allowed a significant expansion of breast-conserving surgeries and to de-escalate the approach in axillary evaluation, with more functional dissections and less morbidity. In combination with an expansion in patient indications for RT, and increasingly promoting hypofractionation and different application modalities, it has allowed a reduction in locoregional treatment side effects with great impact on long-term quality of life of patients previously carefully selected and now with more evidence for including more patients.

Axillary de-escalation

Axillary de-escalation has gained relevance in the therapeutic strategy of breast cancer. Accurate identification of patients with axillary lymph node involvement and administration of selective therapies, as well as lymph node selection for obtaining prognostic information and axillary RT, reduces the morbidity associated with complete axillary dissection, with higher functionality being achieved without compromising oncological objectives.

Advanced surgical techniques and breast reconstruction

Oncoplastic surgery, along with immediate breast reconstruction, has considerably advanced, allowing the preservation of breast esthetics and faster recovery. NAC preservation techniques have been perfected.

Intraoperative margin evaluation

Incorporating intraoperative technologies, such as breast X-ray and ultrasound before and during surgery, improves accuracy in the assessment of surgical margins. Ensuring negative margins is essential for preventing local recurrence.

Personalized adjuvant therapy

After surgery, adjuvant therapy is based on a comprehensive evaluation of individual factors, including tumor subtype, pathological stage, and recurrence risk. HT, CT, and targeted therapies are an integral part of the treatment strategy.

In summary, the paradigm of neoadjuvant treatment and surgery in breast cancer has been transformed into a highly personalized and biomarker-based approach. Achievement of a pCR and quality of life preservation are essential objectives in this new era of breast oncology. As breast cancer molecular characterization advances, it is imperative that medical professionals adapt these conclusions to clinical practice to improve patient outcomes and quality of life.

Funding

This research has not received any specific grants from agencies of the public, commercial, or for-profit sectors.

Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments have been carried out on humans or animals for this research.

Confidentiality of data. The authors declare that no patient data appear in this article. In addition, the authors have recognized and followed the recommendations according to the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for text generation. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Temple-Oberle C, Shea-Budgell MA, Tan M, Semple JL, Schrag C, Barreto M, et al. Consensus review of optimal perioperative care in breast reconstruction: Enhanced Recovery after Surgery (ERAS) Society Recommendations. Plast Reconstr Surg. 2017;139(5):1056e-1071e.
2. Chiu C, Aleshi P, Esserman LJ, Inglis-Arkell C, Yap E, Whitlock EL, et al. Improved analgesia and reduced post-operative nausea and vomiting after implementation of an enhanced recovery after surgery (ERAS) pathway for total mastectomy. BMC Anesthesiol. 2018;18(1):41.
3. Jacobs A, Lemoine A, Joshi GP, Van de Velde M, Bonnet F; PROSPECT Working Group collaborators. PROSPECT guideline for oncological breast surgery: a systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia. 2020;75(5):664-73.
4. Bashandy GM, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Reg Anesth Pain Med. 2015;40(1):68-74.
5. Versyck B, van Geffen GJ, Chin KJ. Analgesic efficacy of the Pecs II block: a systematic review and meta-analysis. Anaesthesia. 2019;74(5): 663-73.
6. Fajardo Pérez M, García Miguel FJ, López Álvarez S, Diéguez García P, Alfaro de la Torre P. Bloqueo de las ramas laterales y anteriores de los nervios intercostales para analgesia de mama. Cir May Amb. 2012;17(3): 95-104.
7. Fajardo P, Alfaro A. Serratus-intercostal plane block. An encouraging approach for breast surgery. J Assoc Anesth AAGBI. 2013;2:1-3.
8. Diéguez García P, Fajardo Pérez M, García M, López Álvarez S, Alfaro de la Torre P, Pensado Castiñeiras AP. Abordaje guiado por ultrasonidos de los nervios intercostales en la línea media axilar para cirugía de mama no reconstructiva y de la axila. Rev Esp Anestesiol Reanim. 2013;60(7):365-70.
9. Diéguez P, Fajardo M, López S, Alfaro P. BRILMA methylene blue in cadavers. Anatomical dissection. Rev Esp Anestesiol Reanim. 2016;63(5):307-8.
10. Syal K, Chandel A. Comparison of the post-operative analgesic effect of paravertebral block, pectoral nerve block and local infiltration in patients undergoing modified radical mastectomy: A randomised double-blind trial. Indian J Anaesth. 2017;61(8):643-8.
11. de la Torre P. Will the new thoracic fascial blocks be as effective as paravertebral block? Rev Esp Anestesiol Reanim. 2016;63(10):553-5.
12. Diéguez P, Casasa P, López S, Fajardo M. Bloqueos guiados por ultrasonidos para cirugía mamaria. Rev Esp Anestesiol Reanim. 2016;63(3):159-67.
13. Veronesi U. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med. 1981;2:305(1):6-11.
14. Veronesi U. Conservative treatment of early breast cancer. Long-term results of 1232 cases treated with quadrantectomy, axillary dissection, and radiotherapy. Ann Surg. 1990;211(3):250-9.
15. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet. 2005;366(9503):2087-106.
16. Anderson SJ, Wapnir I, Dignam JJ, Fisher B, Mamounas EP, Jeong JH, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. J Clin Oncol. 2009;27(15):2466-73.
17. Houssami N, Macaskill P, Marinovich ML, Dixon JM, Irwig L, Brennan ME, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. Eur J Cancer. 2010;46(18):3219-32.
18. Almeida NR, Brenelli FP, Dos Santos CC, Torresan RZ, Shinzato JY, Cardoso-Filho C, et al. Comparative study of surgical and oncological outcomes in oncoplastic versus non oncoplastic breast-conserving surgery for breast cancer treatment. JPRAS Open. 2021;29:184-94.
19. Cuttino LW, McCall L, Kubicky C, Ballman KV, Le-Petross H, Hunt KK, et al. Feasibility of radiation therapy after breast-conserving surgery for multiple ipsilateral breast cancer: An initial report from ACOSOG Z11102 (Alliance) Trial. Int J Radiat Oncol Biol Phys. 2022;112(3):636-42.
20. Ruvalcaba Limón E, Espejo Fonseca R, Bautista Piña, Madero Preciado L, Capurso García M, Serratos Garduño JE, et al. Control radiológico intraoperatorio de una pieza quirúrgica en lesiones mamarias no palpables. Ginecol Obstet Mex. 2009;77(9):407-18.
21. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology; American Society for Radiation Oncology. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Int J Radiat Oncol Biol Phys. 2014;88(3):553-64.
22. Heeg E, Jensen MB, Hölmich LR, Bodilsen A, Tollenaar RAEM, Laenkholm AV, et al. Rates of re-excision and conversion to mastectomy after breast-conserving surgery with or without oncoplastic surgery: a nationwide population-based study. Br J Surg. 2020;107(13):1762-72.
23. Sherwell-Cabello S, Maffuz-Aziz A, Villegas-Carlos F, Domínguez-Reyes C, Labastida-Almendaro S, Rodríguez-Cuevas S. Factibilidad y resultado estético de la cirugía oncoplasica en el tratamiento de cáncer de mama. Cir Cir. 2015;83(3):199-205.
24. Halsted WS. The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. Ann Surg. 1894;20(5):497-555.
25. Fisher B, Montague E, Redmond C, Deutsch M, Brown GR, Zauber A, et al. Findings from NSABP Protocol No. B-04-comparison of radical mastectomy with alternative treatments for primary breast cancer. I. Radiation compliance and its relation to treatment outcome. Cancer. 1980;46(1):1-13.
26. Chiesa F, Sacchini VS. Risk-reducing mastectomy. Minerva Ginecol. 2016;68(5):544-7.
27. Gonzalez EG, Rancati AO. Skin-sparing mastectomy. Gland Surg. 2015;4(6):541-53.
28. Rosenkranz KM, Ballman K, McCall L, McCarthy C, Kubicky CD, Cuttino L, et al. Cosmetic outcomes following breast-conservation surgery and radiation for multiple ipsilateral breast cancer: Data from the alliance Z11102 study. Ann Surg Oncol. 2020; 4650-61.
29. de Boniface J, Szulkin R, Johansson ALV. Survival after breast conservation vs. mastectomy adjusted for comorbidity and socioeconomic status: A Swedish national 6-year follow-up of 48 986 women. JAMA Surg. 2021;156(7):628-37.
30. Mohamedahmed AYY, Zaman S, Zafar S, Laroiya I, Iqbal J, Tan MLH, et al. Comparison of surgical and oncological outcomes between oncoplastic breast-conserving surgery versus conventional breast-conserving surgery for treatment of breast cancer: A systematic review and meta-analysis of 31 studies. Surg Oncol. 2022;42:101779.
31. Cruz-Benítez L. Historia y estado actual sobre los tipos de procedimientos quirúrgicos realizados en cáncer de mama. Gac Mex Oncol. 2014;13(2):124-33.
32. Mariconde J. Manual de cirugía oncológica y oncoplástica de la mama. 1.ª ed. Córdoba, Argentina: Recfot, 2021.
33. Acea-Nebril B. Cirugía oncoplástica conservadora en el cáncer de mama. Indicaciones y límites en su aplicación quirúrgica. Cir Esp. 2005;78(1):12-8.
34. Clough KB, Cuminet J, Fitoussi A, Nos C, Mosseri V. Cosmetic sequelae after conservative treatment for breast cancer: classification and results of surgical correction. Ann Plast Surg. 1998;41:471-81.
35. Masetti R, Di Leone A, Franceschini G, Magno S, Terribile D, Fabbri MC, et al. Oncoplastic techniques in the conservative surgical treatment of breast cancer. Breast Cancer. 2000;7:276-80.
36. Acea Nebril B. Cirugía oncológica de la mama. Técnicas oncoplásticas y reconstructivas. Oncoplastia extrema, cirugía de precisión, puerto único. 4.ª edición. Elsevier España; 2019.
37. Asociación Española de Cirujanos. Máster en cirugía de mama. Módulo 3. Cirugía conservadora oncoplástica de la mama. Asociación Española de Cirujanos; 2021.
38. Salmon R. Paradigms for treating breast cancers have changed: The one-size-fits-all is no longer true. Arch Breast Cancer. 2019; 6(4):144-6.
39. Ho W, Stallard S, Doughty J, Mallon E, Romics L. Oncological outcomes and complications after volume replacement oncoplastic breast conservations - the Glasgow experience. Breast Cancer (Auckl). 2016;10:223-8.
40. Martellani L, Manara M, Renzi N, Papa G, Ramella V, Arnež Z. Use of LICAP and LTAP flaps for breast reconstruction. Acta Chir Plast. 2019;60(1):4-8.
41. Hamdi M, Van Landuyt K, de Frene B, Roche N, Blondeel P, Monstrey S. The versatility of the inter-costal artery perforator (ICAP) flaps. J Plast Reconstr Aesth Surg. 2006;59:644-52.
42. Quinn EM, Burrah R, O'Ceallaigh S, Highton L, Murphy J. Six-year experience of oncoplastic volume replacement using local perforator flaps. J Plast Reconstr Aesthet Surg. 2021;74(9):2184-93.
43. Holmstrom H, Lossing C. The lateral thoracodorsal flap in breast reconstruction. Plast Reconstr Surg. 1986;77:933-43.
44. Yang JD, Ryu DW, Lee JW, Choi KY, Chung HY, Cho BC. Usefulness of a lateral thoracodorsal flap after breast conserving surgery in laterally located breast cancer. Arch Plast Surg. 2013;40:367-73.
45. Mangialardi ML, Baldelli I, Salgarello M, Raposio E. Breast reconstruction using the lateral thoracic, thoracodorsal, and intercostal arteries perforator flaps. Plast Reconstr Surg Glob Open. 2021;9(1):e3334.
46. O'Connell R, Yildirim NG, Heeney A, St John E, Muktar S, Krupa K, et al. The use of pedicled perforator flaps in oncoplastic breast surgery. The Royal Marsden experience. En: Official Proceedings of the 2022 Annual Meeting; Vol. XXIII. Scientific Session Abstracts. 2022. p. 1143646.
47. Lanitis S, Tekkis PP, Sgourakis G, Dimopoulos N, Al Mufti R, Hadjiminas DJ. Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies. Ann Surg. 2010;251(4):632-9.
48. Li M, Chen K, Liu F, Su F, Li S, Zhu L. Nipple sparing mastectomy in breast cancer patients and long-term survival outcomes: An analysis of the SEER database. PLoS One. 2017;12(8):e0183448.
49. Fu M, Chen Q, Zeng L, Hong T, Zou Q, Yuan Y, et al. Prognosis comparison between nipple-sparing mastectomy and total mastectomy in breast cancer: a case-control study after propensity score matching. Ann Surg Oncol. 2022;29:2221-30.

50. Weber WP, Haug M, Kurzeder C, Bjelic-Radisic V, Koller R, Reitsamer R, et al. Oncoplastic Breast Consortium consensus conference on nipple-sparing mastectomy. Breast Cancer Res Treat. 2018;172(3):523-7.
51. Kaidar-Person O, Boersma LJ, Poortmans P, Sklair-Levy M, Offersen BV. Residual glandular breast tissue after mastectomy: a systematic review. Ann Surg Oncol. 2020;27(7):2288-96.
52. Bromham N, Schmidt-Hansen M, Astin M, Hasler E, Reed MW. Axillary treatment for operable primary breast cancer. Cochrane Database Syst Rev. 2017;1(1):CD004561.
53. Amin MB, Edge SB. AJCC cancer staging manual. New York: Springer; 2017.
54. Corso G, Galimberti V, Veronesi P. De-escalation treatment of axilla in breast cancer. Clin Transl Oncol. 2020;22(3):445-6.
55. Di Paola V, Mazzotta G, Pignatelli V, Bufi E, D'Angelo A, Conti M, et al. Beyond N staging in breast cancer: importance of MRI and ultrasound-based imaging. Cancers (Basel). 2022;14(17):4270.
56. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer N Engl J Med. 2003;349(6):546-53.
57. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABPB-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927-33.
58. Veronesi U, Viale G, Paganelli G, Zurrida S, Luini A, Galimberti V, et al. Sentinel lymph-node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg. 2010;251(4):595-600.
59. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(10):1385-93.
60. Solá M, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R, et al. Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multicenter clinical trial AATRM 048/13/2000. Ann Surg Oncol. 2023;20(1):120-7.
61. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of axillary dissection vs. no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. JAMA. 2017;318:918-26.
62. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial Lancet Oncol.2014;15:1303-10.
63. Sávolt Á, Péley G, Polgár C, Udvarhelyi N, Rubovszky G, Kovács E, et al. Eight-year follow up result of the OTOASOR trial: the optimal treatment of the axilla-surgery or radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: a randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol. 2017;43(4):672-9.
64. Simons JM, Koppert LB, Luiten EJT, van der Pol CC, Samiei S, de Wilt JHW, et al. De-escalation of axillary surgery in breast cancer patients treated in the neoadjuvant setting: a Dutch population-based study. Breast Cancer Res Treat. 2020;180:725-33.
65. Morrow M. Management of the node-positive axilla in breast cancer in 2017: selecting the right option. JAMA Oncol. 2018;4:250-1.
66. Boughey JC, Ballman KV, Le-Petross HT, McCall LM, Mittendorf EA, Ahrendt GM, et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0-T4, N1-N2) who receive neoadjuvant chemotherapy: results from ACOSOG Z1071 (Alliance). Ann Surg. 2016;263:802-7.
67. Lim M, Teo M, Gudi M, Ping N, Pang J, Seam T, et al. Initial results of a novel technique of clipped node localization in breast cancer patients postneoadjuvant chemotherapy: Skin Mark clipped Axillary nodes Removal Technique (SMART trial). Cancer Med. 2020;9:1978-85.
68. Tee SR, Devane LA, Evoy D, Rothwell J, Geraghty J, Prichard RS, et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. Br J Surg. 2018;105:15411552.
69. Classe JM, Loaec C, Gimbergues P, Alran S, de Lara CT, Dupre PF, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Res Treat. 2018;173:343-52.
70. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013;14(7):609-18.
71. Caudel AS. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. J Clin Oncol. 2016;34(10):1072-8.
72. Tinterri C. SINODAR-ONE Collaborative Group. Preservation of axillary lymph nodes compared with complete dissection in T1-2 breast cancer patients presenting one or two metastatic sentinel lymph nodes: The SINODAR-ONE multicenter randomized clinical trial. Ann Surg Oncol. 2022;29(9):5732-44.
73. Reimer T, Engel J, Schmidt M, Offersen BV, Smidt ML, Gentilini OD. Is axillary sentinel lymph node biopsy required in patients who undergo primary breast surgery? Breast Care (Basel). 2018;13(5):324-30.
74. Morigi C, Peradze N, Galimberti V, Leonardi MC, Radice D, Santomauro GI, et al. Feasibility and surgical impact of Z0011 trial criteria in a single-Institution practice. Breast J. 2020;26(7):1330-6.
75. Berg JW. The significance of axillary node levels in the study of breast carcinoma. Cancer. 1955;8(4):776-8.
76. Cirocchi R, Amabile MI, De Luca A, Frusone F, Tripodi D, Gentile P, et al. New classifications of axillary lymph nodes and their anatomical-clinical correlations in breast surgery. World J Surg Oncol. 2021;19(1):93.
77. Johnston SRD, Harbeck N, Hegg R, Toi M, Martin M, Shao ZM, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+ HER2-, node-positive, high-risk, early breast cancer (monarchE). J Clin Ocol. 2020;38(34):3987-98.
78. Caparica R, Lambertini M, Pondé N, Fumagalli D, de Azambuja E, Piccart M. Post-neoadjuvant treatment and the management of residual disease in breast cancer: state of the art and perspectives. Ther Adv Med Oncol. 2019;11:1758835919827714.
79. Wijaya WA. Clinical application of axillary reverse mapping in patients with breast cancer: A systematic review and meta-analysis. Breast. 2020;53:189-200.
80. Boneti C. Axillary reverse mapping: mapping and preserving arm lymphatics may be important in preventing lymphedema during sentinel lymph node biopsy. J Am Coll Surg. 2008;206(5):1038-42; discussion 1042-4.
81. Pusic AL, Klassen AF, Snell L, Cano SJ, McCarthy C, Scott A, et al. Measuring and managing patient expectations for breast reconstruction: impact on quality of life and patient satisfaction. Expert Rev Pharmacoecon Outcomes Res. 2012;12(2):149-58.
82. Kronowitz SJ, Kuerer HM, Buchholz TA, Valero V, Hunt KK. A management algorithm and practical oncoplastic surgical techniques for repairing partial mastectomy defects. Plast Reconstr Surg. 2008;122:1631-47.
83. Borm KJ, Schönknecht C, Nestler A, Oechsner M, Waschulzik B, Combs SE, et al. Outcomes of immediate oncoplastic surgery and adjuvant radiotherapy in breast cancer patients. BMC Cancer. 2019;19(1):907.
84. Losken A, Hamdi M. Partial breast reconstruction: Current perspectives. Plast Reconstr Surg. 2009;124:722-36.
85. Spear SL, Rottman SJ, Seiboth LA, Hannan CM. Breast reconstruction using a staged nipple sparing mastectomy following mastopexy or reduction. Plast Reconstr Surg. 2012;129:572-81.
86. Chu CK, Hanson SE, Hwang RF, Wu LC. Oncoplastic partial breast reconstruction: concepts and techniques. Gland Surg. 2021;10(1):398-410.
87. Gilmour A, Cutress R, Gandhi A, Harcourt D, Little K, Mansell J. Oncoplastic breast surgery: A guide to good practice. Eur J Surg Oncol. 2021;47(9):2272-85.
88. Losken A, Styblo TM, Carlson GW, Jones GE, Amerson BJ. Management algorithm and outcome evaluation of partial mastectomy defects treated using reduction or mastopexy techniques. Ann Plast Surg. 2007;59:235-42.
89. Akay CL, Meric-Bernstam F, Hunt KK, Grubbs EG, Bedrosian I, Tucker SL, et al. Evaluation of the MD Anderson Prognostic Index for localregional recurrence after breast conserving therapy in patients receiving neoadjuvant chemotherapy. Ann Surg Oncol. 2012;19:901-7.
90. Khouri RK, Eisenmann-Klein M, Cardoso E, Cooley BC, Kacher D, Gombos E, et al. Brava® and autologous fat transfer is a safe and effective breast augmentation alternative: Results of a 6-year, 81-patient, prospective multicenter study. Plast Reconstr Surg. 2012;129:1173-87.
91. Regan JP, Casaubon JT. Breast reconstruction [Internet]. Treasure Island (FL): StatPearls Publishing; ene 2023. Disponible en: https://pubmed.ncbi.nlm.nih.gov/29262104
92. Kronowitz SJ. Delayed-immediate breast reconstruction: Technical and timing considerations. Plast Reconstr Surg. 2010;125:463-74.
93. de Alcantara Filho P, Capko D, Barry JM, Morrow M, Pusic A, et al. Sacchini vs. nipple-sparing mastectomy for breast cancer and risk-reducing surgery: The Memorial SloanKettering Cancer Center experience. Ann Surg Oncol. 2011;18:311722.
94. Acea Nebril B, García Novoa A, García Jiménez L, Díaz Carballada C, Bouzón Alejandro A, Conde Iglesias C. Reconstrucción mamaria inmediata mediante implante prepectoral de poliuretano. Resultados preliminares del estudio prospectivo PreQ-20. Cir Esp. 2022;101(3):187-97.
95. Rancati A. Direct to implant reconstruction in nipple sparing mastectomy: patient selection by preoperative digital mammogram. Plast Reconstr Surg Glob Open. 2017;5(6):e1369.
96. Urban C, González E. Prepectoral direct-to-implant breast reconstruction without placement of acellular dermal matrix or mesh after nipple-sparing mastectomy. Plast Reconstr Surg. 2022;150(5):973983.
97. Cordeiro PG, Jazayeri L. Two-stage implant-based breast reconstruction: an evolution of the conceptual and technical approach over a two-decade period. Plast Reconstr Surg. 2016;138(1):1-11.
98. Hanson S, Kapur S, Garvey PB, et al. Oncologic safety and surveillance of autologous fat grafting following breast conservation therapy. Plast Reconstr Surg. 2020;146(2):215-25.
99. Chen Y, Li G. Safety and effectiveness of autologous fat grafting after breast radiotherapy: a systematic review and meta-analysis. Plast Reconstr Surg. 2021;147(1):1-10.

100. Shamoun F, Asaad M, Hanson SE. Oncologic safety of autologous fat grafting in breast reconstruction. Clin Breast Cancer. 2021;21(4):271-7.
101. Kronowitz SJ. Redesigned gluteal artery perforator flap for breast reconstruction. Plast Reconstr Surg. 2008;121:728-34.
102. Parra L, Marcelli S. Immediate breast reconstruction with abdominal free flap and adjuvant radiotherapy: Evaluation of quality of life and outcomes. Plast Reconstr Surg. 2017;140:681.
103. Ho AY, Hu ZI, Mehrara BJ, et al. Radiotherapy in the setting of breast reconstruction: types, techniques and timing. Lancet Oncol. 2017;18:e742-e753.
104. Jung SM, Jeon BJ, Woo J, et al. Does chemotherapy or radiotherapy affect the postoperative complication in breast cancer patients who underwent immediate breast reconstruction with tissue expander? BMC Cancer. 2021;21(1):88.
105. Woo KJ, Paik JM, Bang SI, et al. The impact of expander inflation/deflation status during adjuvant radiotherapy on the complications of immediate two-stage breast reconstruction. Aesthetic Plast Surg. 2017;41(3):551-9.
106. Shumway DA, Momoh AO, Sabel MS, et al. Integration of breast reconstruction and postmastectomy radiotherapy. J Clin Oncol. 2020;38(20):2329-40.
107. Kaidar-Person O, Vrou Offersen B, Hol S. ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer. Radiother Oncol. 2019;137:159-66.
108. Naoum GE, Salama L, Niemierko A, et al. Single stage direct-to-implant breast reconstruction has lower complication rates than tissue expander and implant and comparable rates to autologous reconstruction in patients receiving postmastectomy radiation. Int J Radiat Oncol Biol Phys. 2020;106(3):514-24.
109. Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: Breast and ovarian, 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):77-102.
110. The breast cancer risk assessment tool: online calculator (The Gail model) [Internet]. National Cancer Institute AQ1 [consultado el 2 de febrero de 2023]. Disponible en: https://bcrisktool.cancer.gov/
111. Hunt KK, Euhus DM, Boughey JC, et al. SSO Breast disease working group statement on prophylactic. Ann Surg Oncol. 2017;24:375-97.
112. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345(3):159-64.
113. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev. 2010;(11):CD002748.
114. Ramaswami R. Contralateral prophylactic mastectomy. N Engl J Med. 2017;377:13.
115. ESMO Clinical Practice Guidelines: Breast Cancer Guidelines [Internet]. European Society for Medical Oncology AQ2 [consultado el 2 de febrero de 2023]. Disponible en: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-breast-cancer
116. Amor Pan JR, Barón Duarte FJ, Regueiro García A, et al. Bioética y oncología. Una puerta abierta a la oportunidad. Sociedad Oncológica de Galicia; 2017.
117. Carbine N, Lostumbo L, Wallace J. Risk-reducing mastectomy for the prevention of primary breast cancer. Cochrane Database Syst Rev. 2018;4:CD002748.
118. Franceschini G, Di Leone A, Terribile D, et al. Bilateral prophylactic mastectomy in BRCA mutation carriers: what surgeons need to know. Ann Ital Chir. 2019;90:1-2.
119. Srethbhakdi A, Brennan ME, Hamid G, et al. Contralateral prophylactic mastectomy for unilateral breast cancer in women at average risk: Systematic review of patient reported outcomes. Psychooncology. 2020;29(6):960-73.
120. Lopez CD, Bluebond-Langner R, Houssock CA, et al. Plastic and reconstructive surgeons' knowledge and comfort of contralateral prophylactic mastectomy: A survey of the American Society of Plastic Surgeons. Front Oncol. 2019;8:647.
121. Nagaraja V, Edirimanne S, Eslick GD. Is sentinel lymph node biopsy necessary in patients undergoing prophylactic mastectomy? A systematic review and meta-analysis. Breast J. 2016;22(2):158-65.
122. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet. 2005;365:1687-717.
123. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant chemotherapy guided by a 21 gene expression assay in breast cancer. N Engl J Med. 2018;379(2):111-21.
124. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); R Peto, C Davies, J Godwin, R Gray, H C Pan, M Clarke, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomized trials. Lancet. 2012;379:432-44.
125. Gradishar WJ, Anderson BO, Balassanian R, et al. Breast cancer, version 4.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(3):310-20.
126. Aebi S, Davidson T, Gruber G, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22(suppl 6):vi12-24.
127. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011;22:1736-47.
128. Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, et al. Delayed initiation of adjuvant chemotherapy among patients with breast cancer. JAMA Oncol. 2016;2(3):322-9.
129. Morante Z, Ruiz R, Araujo JM, et al. Impact of the delayed initiation of adjuvant chemotherapy in the outcomes of triple negative breast cancer. Clin Breast Cancer. 2021;21(3):239-46.e4.
130. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak AK. Taxanes for adjuvant treatment of early breast cancer. Cochrane Database Syst Rev. 2007;4:CD004421.
131. Willson ML, Burke L, Ferguson T, Ghersi D, Nowak AK, Wilcken N. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. J Clin Oncol. 2008;26:44-53.
132. Sparano JA, Zhao F, Martino S, et al. Long-term follow-up of the E1199 phase III trial evaluating the role of taxane and schedule in operable breast cancer. J Clin Oncol. 2015;33(21):2353-60.
133. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008;358:1663-71.
134. von Minckwitz G, Raab G, Caputo A, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. J Clin Oncol. 2005;23(12):2676-85.
135. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 2.2023. National Comprehensive Cancer Network; February 7, 2023.
136. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376:2147-59.
137. Geyer CE Jr, Bandos H, Rastogi P, et al. Definitive results of a phase III adjuvant trial comparing six cycles of FEC-100 to four cycles of AC in women with operable node-negative breast cancer: the NSABP B-36 trial (NRG Oncology). Breast Cancer Res Treat. 2022;193(3):555-64.
138. Early Breast Cancer Trialists' Collaborative Group. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient level meta-analysis of randomised trials. Lancet. 2011;378:771-84.
139. Metzger Filho O, Giobbie-Hurder A, Mallon E, et al. Relative effectiveness of letrozole compared with tamoxifen for patients with lobular carcinoma in the BIG 1-98 trial. J Clin Oncol. 2015;33:2772-9.
140. Forbes JF, Sestak I, Howell A, et al. IBIS-II investigators. Anastrazole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet. 2016;387(10021):866-73.
141. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol. 2011;12:21-9.
142. Wapnir IL, Dignam JJ, Fisher B, et al. Long term-outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-27 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst. 2011;103:478-88.
143. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005;97:1652-62.
144. Margolese RG. Anastrazole versus tamoxifen in postmenopausal women in ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSAB B-35): a randomised, double-blind, phase 3 clinical trial. Lancet. 2016;387:845.
145. Sella T, Ruddy KJ, Carey LA, et al. Optimal endocrine therapy in premenopausal women: a pragmatic approach to unanswered questions. JCO Oncol Pract. 2022;18(3):211-6.
146. Davies C, Pan H, Godwin J, Gray, et al. Adjuvant tamoxifen: longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381(9869):805-16.
147. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med. 2018;379:122-37.
148. Pagani O, Francis PA, Fleming GF, et al. Absolute improvement in freedom from distant recurrence to tailor adjuvant endocrine therapies for premenopausal women: results from TEXT and SOFT. J Clin Oncol. 2020;38:1293-303.
149. Andre F, Ismaila N, Allison KH, et al. Biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer: ASCO Guideline Update. J Clin Oncol. 2022;40(16):1816-37.
150. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023;24(1):77-90.
151. Giordano SH, Freedman RA, Somerfield MR. Optimal Adjuvant Chemotherapy and Targeted Therapy Guideline Expert Panel. Abemaciclib with endocrine therapy in the treatment of high-risk early breast cancer: ASCO Optimal Adjuvant Chemotherapy and Targeted Therapy Guideline Rapid Recommendation Update. J Clin Oncol. 2022;40(3):307-9.
152. Burstein HJ, Somerfield MR, Barton DL, et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO Guideline update. J Clin Oncol. 2021;39(35):3959-77.

153. Bartlett JMS, Sgroi DC, Treuner K, et al. Breast cancer index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the adjuvant tamoxifen-to offer more? (aTTom) trial. Ann Oncol. 2019;30(11):1776-83.
154. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med. 2016;375:209-19.
155. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al. Optimal duration of extended adjuvant endocrine therapy for early breast cancer: Results of the IDEAL trial (BOOG 2006 05). J Natl Cancer Inst. 2018;110(1).
156. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): A randomised, phase 3 trial. Lancet Oncol. 2017;18:1502-11.
157. Colleoni M, Luo W, Karlsson P, et al. Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19:127-38.
158. Zardavas D, Tryfonidis K, Goulioti T M, et al. Targeted adjuvant therapy in breast cancer. Exp Rev Anticancer Ther. 2016;16(12):1263-75.
159. Dahabreh IJ, Linardou H, Siannis F, et al. Trastuzumab in the adjuvant treatment of early-stage breast cancer: a systematic review and metaanalysis of randomized controlled trials. Oncologist. 2008;13:620-30.
160. Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomized controlled trial. Lancet Oncol. 2011;12:236-44.
161. Pérez EA, Romond E, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival (OS) from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-52.
162. Lambertini M, Pondé NF, Solinas C, et al. Adjuvant trastuzumab: a 10 year overview of its benefit. Exp Rev Anticancer Ther. 2017;17(1):61-74.
163. Slamon DJ, Eiermann W, Robert NJ, et al. Ten year follow-up of the BCIRG-006 trial comparing doxorubicin plus cyclophosphamide followed by docetaxel (ACT) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer patients. Cancer Res. 2018;76(4 Suppl):abstr S5-04.
164. Perez EA, Suman VJ, Davidson NE, et al. Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. J Clin Oncol. 2011;29:4491-7.
165. Jackisch C, Piccart MJ, Gelber RD, et al. HERA trial: 10 years follow up of trastuzumab after adjuvant chemotherapy in HER2 positive early breast cancer Final analysis. Cancer Res. 2016;76(4 Suppl):abstr PD5-01.
166. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomized phase 3 trial. Lancet Oncol. 2013;14(8):741-8.
167. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for nodenegative, HER2-positive breast cancer. N Engl J Med. 2015;372(2):134-41.
168. Von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med. 2017;377(2):122-31.
169. Piccart M, Procter M, Fumagalli D, et al. Interim overall survival analysis of APHINITY (BIG 4-11): A randomized multicenter, double-blind, placebo controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. Cancer Res. 2020;80(4 Suppl):abstr GS1-04
170. Loibl S, German Breast Group (GBG). Updated results of APHINITY at 8.4 years median follow-up. ESMO Virtual Plenary, July 14, 2022. Abstract VP6-2022l.
171. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2016;17:367-77.
172. Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1688-700.
173. Chan A, Moy B, Mansi J, et al. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. Clin Breast Cancer. 2021;21(1):80-91.
174. Tutt A, Garber J, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1or BRCA2-mutated breast cancer. N Engl J Med. 2021;384:2394-405.
175. Geyer C, Garber J, Gelber J, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. Ann Oncol. 2022;33(12):1250-68.
176. Sparano JA, Gray RJ, Makower DF, et al. Trial Assigning Individualized Options for Treatment (TAILORx): An Update Including 12-year event rates. San Antonio Breast Cancer Symposium, Dec 6, 2022.
177. Piccart M, van't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021;22:476-88.
178. Sestak I, Martín M, Dubsky P, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res Treat. 2019;176:377-86.
179. Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res. 2011;17:6012-20.
180. Laenkholm AV, Jensen MB, Eriksen JO, et al. PAM50 risk of recurrence score predicts 10-year distant recurrence in a comprehensive Danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor-positive early breast cancer. J Clin Oncol. 2018;36:735-40.
181. De la Cruz K, Karamchandani M, Chambergo-Michilot D, et al. Does breast-conserving surgery with radiotherapy have a better survival than mastectomy? A meta-analysis of more than 1,500,000 patients. Ann Surg Oncol. 2022;29(19):6163-88.
182. Wang M, Huang J, Chagpar A. Factors associated with a delay in postmastectomy radiation therapy. Am Surg. 2021;87(9):1484-7.
183. Bleicher R, Moran M, Ruth K, et al. The impact of radiotherapy delay in breast conservation patients not receiving chemotherapy and the rationale for dichotomizing the radiation oncology time-dependent standard into two quality measures. Ann Surg Oncol. 2022;29(1):469-81.
184. Jobsen J, Struikmans H, van der Palen J, et al. Clinical relevance of the timing of radiotherapy after breast-conserving surgery: Results of a large, single-centre, population-based cohort study. Strahlenther Onkol. 2022;198(3):268-81.
185. Meattini I, Becherini C, Boersma L, et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol. 2022;23(1):e21-e31.
186. Hickey B, Lehman M. Partial breast irradiation versus whole breast radiotherapy for early breast cancer. Cochrane Database Syst Rev. 2021;8(8):CD007077.
187. Anderson B, Arthur D, Hannoun-Levi JM, et al. Partial breast irradiation: An updated consensus statement from the American brachytherapy society. Brachytherapy. 2022;21(6):726-47.
188. Burstein H, Curigliano G, Thürlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol. 2021;32(10):1216-35.
189. Hennequin C, Belkacémi Y, Bourgier C, et al. Radiotherapy of breast cancer. Cancer Radiother. 2022;26(1-2):221-30.
190. Beddok A, Kirova Y, Laki F, et al. The place of the boost in the breast cancer treatment: State of art. Radiother Oncol. 2022;170:55-63.
191. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 1.2023 [Internet]. National Comprehensive Cancer Network. Disponible en: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
192. Perera F, Baldassarre F, Eisen A, et al. A systematic review of axillary nodal irradiation for the management of the axilla in patients with early-stage breast cancer. Surg Oncol. 2022;42:101754.
193. Brackstone M, Baldassarre F, Perera F, et al. Management of the axilla in early-stage breast cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. J Clin Oncol. 2021;39(27):3056-82.
194. Allen S, Speers C, Jagsi R. Tailoring the omission of radiotherapy for early-stage breast cancer based on tumor biology. Semin Radiat Oncol. 2022;32(3):198-206.
195. Overgaard M, Nielsen H, Tramm T, et al. Postmastectomy radiotherapy in high-risk breast cancer patients given adjuvant systemic therapy. A 30-year long-term report from the Danish breast cancer cooperative group DBCG 82bc trial. Radiother Oncol. 2022;170:4-13.
196. Fodor A, Brombin C, Mangili P, et al. Impact of molecular subtype on 1325 early-stage breast cancer patients homogeneously treated with hypofractionated radiotherapy without boost: Should the indications for radiotherapy be more personalized? Breast. 2021;55:45-54.
197. Paluch-Shimon S, Cardoso F, Partridge A, et al. ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). Ann Oncol. 2022;33(11):1097-118.
198. Sibilio A, Curcio A, Toesca A, et al. Local treatment in patients with hereditary breast cancer: decision-making process in low-, moderate-, high-penetrance pathogenic germline mutation carriers. Curr Opin Oncol. 2022;34(6):614-22.
199. Chapman BV, Liu D, Shen Y, et al. Breast radiation therapy-related treatment outcomes in patients with or without germline mutations on multigene panel testing. Int J Radiat Oncol Biol Phys. 2022;112(2):437-44.
200. Lazzari G, Buono G, Zannino B, et al. Breast cancer adjuvant radiotherapy in BRCA1/2, TP53, ATM genes mutations: are there solved issues? Breast Cancer (Dove Medical Press). 2021;13:299-310.
201. Trombetta MG, Dragun A, Mayr NA, et al. ASTRO radiation therapy summary of the ASCO-ASTRO-SSO guideline on management of hereditary breast cancer. Pract Radiat Oncol. 2020;10(4):235-42.
202. Yip CH, Newman LA. American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline for Management of Hereditary Breast Cancer. JAMA Surg. 2021;156(3):284-5.

203. Goel V, Sharma D, Sharma A, et al. A systematic review exploring the role of modern radiation for the treatment of hereditary or familial breast cancer. Radiother Oncol. 2022;176:59-67.
204. Thariat J, Chevalier F, Orbach D, et al. Avoidance or adaptation of radiotherapy in patients with cancer with Li-Fraumeni and heritable TP53-related cancer syndromes. Lancet Oncol. 2021;22(12):e562-e574.
205. Beddok A, Cottu P, Fourquet A, et al. Combination of modern radiotherapy and new targeted treatments for breast cancer management. Cancers (Basel). 2021;13(24):6358.
206. Jungles KM, Holcomb EA, Pearson AN, et al. Updates in combined approaches of radiotherapy and immune checkpoint inhibitors for the treatment of breast cancer. Front Oncol. 2022;12:1022542.
207. Zhang Z, Liu X, Chen D, et al. Radiotherapy combined with immunotherapy: the dawn of cancer treatment. Signal Transduct Target Ther. 2022;7(1):258.
208. Santa-Maria CA, Dunn SA, Ho AY. Immunotherapy combined with radiation therapy in breast cancer: a rapidly evolving landscape. Semin Radiat Oncol. 2022;32(3):291-7.
209. Montero A, Ciérvide R. Preoperative radio(chemo)therapy in breast cancer: time to switch the perspective? Curr Oncol. 2022;29(12):9767-87.
210. Ciérvide R, Montero A, García-Rico E, et al. Primary chemoradiotherapy treatment (PCRT) for HER2+ and triple negative breast cancer patients: a feasible combination. Cancers (Basel). 2022;14(18):4531.
211. Pan Z, Yao Z, Huang M, et al. Long-term outcomes of preoperative radiotherapy in locally advanced breast cancer: Analysis of Surveillance, Epidemiology, and End Results (SEER) database. J Clin Oncol. 2020;38:15(suppl):e12600.
212. Pedersen R, Esen B, Mellemkjær L, et al. The incidence of breast cancer recurrence 10-32 years after primary diagnosis. J Natl Cancer Inst. 2022;114(3):391-9.
213. Hardy-Abeloos C, Xiao J, Oh C, et al. Early effectiveness and toxicity outcomes of reirradiation after breast conserving surgery for recurrent or new primary breast cancer. Breast Cancer Res Treat. 2023;198(1):43-51.
214. Michalet M, Dejean C, Schick U, et al. Radiotherapy and pregnancy. Cancer Radiother. 2022;26(1-2):417-23.
215. Loibl S, Denkert C, von Minckwitz G. Neoadjuvant treatment of breast cancer-Clinical and research perspective. Breast. 2015;24(Suppl 2):S73-7.
216. Kodali A, Gadi VK. Preoperative systemic therapy for breast cancer. Surg Clin North Am. 2023;103(1):201-17.
217. Caudle AS, Bedrosian I, Milton DR, et al. Use of sentinel lymph node dissection after neoadjuvant chemotherapy in patients with node-positive breast cancer at diagnosis: practice patterns of American Society of Breast Surgeons Members. Ann Surg Oncol. 2017;24(10):2925-34.
218. Chiba A, Hoskin TL, Hallberg EJ, et al. Impact that timing of genetic mutation diagnosis has on surgical decision making and outcome for BRCA1/BRCA2 mutation carriers with breast cancer. Ann Surg Oncol. 2016;23(10):3232-8.
219. Lambertini M, Moore HCF, Leonard RCF, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol. 2018;36(19):1981-90.
220. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO Guideline. J Clin Oncol. 2021;39(13):1485-505.
221. von Minckwitz G, Untch M, Nüesch E, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat. 2011;125(1):145-56.
222. Thompson J, Wright G. Contemporary approaches to the axilla in breast cancer. Am J Surg. 2023;225(3):583-7.
223. Cain H, Macpherson IR, Beresford M, et al. Neoadjuvant therapy in early breast cancer: treatment considerations and common debates in practice. Clin Oncol (R Coll Radiol). 2017;29(10):642-52.
224. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382(9):810-21.
225. Allevi G, Strina C, Andreis D, et al. Increased pathological complete response rate after a long-term neoadjuvant letrozole treatment in postmenopausal oestrogen and/or progesterone receptor-positive breast cancer. Br J Cancer. 2013;108(8):1587-92.
226. Montagna G, Sevilimedu V, Fornier M, et al. How effective is Neoadjuvant Endocrine Therapy (NET) in downstaging the axilla and achieving breast-conserving surgery? Ann Surg Oncol. 2020;27(12):4702-10.
227. Stafford A, Williams A, Edmiston K, et al. Axillary response in patients undergoing neoadjuvant endocrine treatment for node-positive breast cancer: systematic literature review and NCDB analysis. Ann Surg Oncol. 2020;27(12):4669-77.
228. Barchiesi G, Mazzotta M, Krasniqi E, et al. Neoadjuvant endocrine therapy in breast cancer: Current knowledge and future perspectives. Int J Mol Sci. 2020;21(10):3528.
229. Goorts B, Dreuning KMA, Houwers JB, et al. MRI-based response patterns during neoadjuvant chemotherapy can predict pathological (complete) response in patients with breast cancer. Breast Cancer Res. 2018; 20(1):34.
230. Scheel JR, Kim E, Partridge SC, et al. MRI, clinical examination, and mammography for preoperative assessment of residual disease and pathologic complete response after neoadjuvant chemotherapy for breast cancer: ACRIN 6657 trial. AJR Am J Roentgenol. 2018;210(6):13761385.
231. Law W, Cao X, Wright FC, et al. Adequacy of invasive and in situ breast carcinoma margins in radioactive seed and wire-guided localization lumpectomies. Breast J. 2021;27(2):134-40.
232. Petruolo O, Sevilimedu V, Montagna G, et al. How often does modern neoadjuvant chemotherapy downstage patients to breast-conserving surgery? Ann Surg Oncol. 2021;28(1):287-94.
233. Caudle A. Impact of progression during neoadjuvant chemotherapy on surgical management of breast cancer. Ann Surg Oncol. 2011;18(4):932-8.
234. Huang Z, Zhu L, Huang XB, Tang Y, Rong QL, Shi M, et al. Postmastectomy radiation therapy based on pathologic nodal status in clinical node-positive stage II to III breast cancer treated with neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys. 2020;108(4):1030-9.
235. Krug D, Lederer B, Seither F, et al. Post-mastectomy radiotherapy after neoadjuvant chemotherapy in breast cancer: a pooled retrospective analysis of three prospective randomized trials. Ann Surg Oncol. 2019;26(12):3892-901.
236. Marino L, Lancellotta V, Franco P, et al. Loco-regional adjuvant radiation therapy in breast cancer patients with positive axillary lymph-nodes at diagnosis (CN2) undergoing preoperative chemotherapy and with complete pathological lymph-nodes response. Development of GRADE (Grades of recommendation, assessment, Development and Evaluation) recommendation by the Italian Association of radiation therapy and Clinical Oncology (AIRO). Breast. 2021;55:119-27.
237. Belkacemi Y, Debbi K, Loganadane G, et al. Radiothérapie adjuvante et néoadjuvante des cancers du sein: mise au point sur les données de lalittérature disponibles en 2020. Cancer Radiother. 2020;24(67):482-92.
238. U.S. National Library of Medicine, Clinical-Trials.gov. National Cancer Institute, Radiation Therapy Oncology Group. Standard for comprehensive radiation therapy in treating patients with early-stage breast cancer previously treated with chemotherapy and surgery. Identifier NCT01872975 [Internet]. U.S. National Library of Medicine, Clinical-Trials.gov. Disponible en: https://www.clinicaltrials.gov/study/NCT01872975
239. U.S. National Library of Medicine, ClinicalTrials.gov. National Cancer Institute, Canadian Cancer Trials Group. Comparison of axillary lymph node dissection with axillary radiation for patients with node-positive breast cancer related with chemotherapy. Identifier: NCT01901094 [Internet]. U.S. National Library of Medicine, Clinical-Trials.gov. Disponible en: https://clinicaltrials.gov/ct2/show/NCT01901094