

Position Paper
EUSOMA Guidelines

Quality control in the locoregional treatment of breast cancer

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1. Introduction

This document provides guidelines for the control of the quality of locoregional treatment of invasive breast cancer.

This document does not provide specific treatment guidelines, but tries to set out the objectives which locoregional treatment in breast cancer should meet, and to determine the outcome measures to these objectives. This document is partly based on the guidelines for symptomatic breast disease of the British Association of Surgical Oncology (BASO) Breast Group [1], the European Society of Surgical Oncology (ESSO) principles and guidelines for surgeons in the management of symptomatic breast cancer [2], the European guidelines for quality assurance in the surgical management of mammographically-detected lesions [3]. As the measurement of outcome is an essential part of the quality control process, prospective registration of all relevant clinical, treatment-related and follow-up data on patients is mandatory [4]. The input criteria are mentioned in the text as operational procedures. Next, this document describes the most relevant outcome measures related to the quality of the locoregional treatment.

It should be stated here that breast cancer should be diagnosed and treated in a comprehensive environment as described in the EUSOMA document 'The requirements of a breast unit' [5].

2. Diagnosis of the primary lesion

Statement: The surgeon should aim to treat invasive breast cancer either:

1. if the triple diagnosis (including fine needle aspiration (FNA) result C-5) is concordant with invasive breast cancer, or
2. a core biopsy shows invasive breast cancer, or
3. an in- or excisional biopsy shows invasive breast cancer (note: this procedure is not recommended as an initial step in the diagnosis of breast cancer).

The diagnostic work-up of patients with breast abnormalities should be performed as described in the EUSOMA document 'Diagnosis of breast cancer' [6].

For locoregional treatment, the following diagnostic steps should be taken in every patient suspected to have invasive breast cancer. The diagnosis is based on the triple assessment:

- physical examination (by a surgeon)
- bilateral mammography in two projections
- ultrasound for symptomatic lesions and for clinical occult mammographically-detected densities.
- FNA cytology/core biopsy (depending on the expertise and availability).

Results of diagnostic tests must have been discussed in the multidisciplinary team [6,7]. After diagnosis of breast cancer, patients must have had a full explanation of the treatment options. In general, the surgeon can be considered as the coordinator of the patient with breast cancer during her diagnostic process, treatment and follow-up.

OUTCOME MEASURE: In over 95% of the patients with palpable breast cancer triple assessment is performed.

OUTCOME MEASURE: More than 90% of patients subsequently proven to have breast cancer should have a pre-operative FNA or core biopsy at the diagnosis of cancer.

OUTCOME MEASURE: More than 70% of patients subsequently proven to have clinically occult breast cancer should have had a pre-operative FNA/ core biopsy that is diagnostic for cancer.

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3. Diagnosis of distant disease

No evidence exists that any subset of tests is sufficiently accurate to exclude distant disease in primary operable breast cancer [8]. Therefore any tests will be performed on indication of symptoms and extent of local disease.

For patients with tumours suitable for primary surgery, with no clinical evidence of dissemination, a pre-operative screening test should be chest X-ray, full blood count and liver function tests. For patients with clinically involved axillary nodes or being considered for neo-adjuvant therapy by the size and extent of the primary tumour, further screening tests should be arranged. These include liver imaging (computed tomography (CT)-scan or ultra sound) and skeletal survey (bone scan); tumour markers are optional.

4. Surgery of the breast

Statement: Surgery for breast cancer must be carried out or directly supervised by a fully trained surgeon, specialised in breast surgery [1,2,7,9].

The aim of surgery in invasive breast cancer is to achieve tumour-free margins with the least possible mutilation, in accordance with the needs of the well informed patient. To reach this goal, the surgeons must be seen after an optimal pre-operative imaging process, depending on the clinical problem.

The results of imaging should be available in the operating theatre. The surgeon must have seen the patient before any surgery and have been completely informed about the clinical situation of the patient.

Patients where breast conserving therapy (BCT) seems feasible, must have been informed about the options: BCT, mastectomy and/or immediate reconstruction.

In cases of clinically-occult lesions or doubts of the location of the tumour, pre-operative localisation guided by ultrasound or stereotactic mammography equipment is mandatory.

The pre-operative histological or cytological diagnosis of malignant lesions improve the quality and completeness of therapeutical excisional biopsies (lumpectomies) [6,9]. Bracketing wires facilitate the completeness of excision of microcalcifications. Local excision in BCT aims at tumour-free margins and — as good as possible — cosmetic outcome. Consequently, the size of the lesion, i.e. the size of the excision, is limited and related to the size of the breast. No upper size limit for BCT for invasive cancer can be given.

The surgeon should aim to perform wide local excision in one complete specimen and mark the specimen for the pathologist. Margin assessment is preferably performed in one complete specimen. Margin assess-

ment by so-called touch prep-imprint-cytology or random shave biopsies from the cavity might be helpful, but has not proven to be superior over a complete careful assessment of the wide local excision specimen.

Incisions are placed to ensure best possible cosmetic result and the possibility of mastectomy should be taken into account. Closure of breast tissue, use of drains and closure of skin depends on local anatomy, width of excision and location of the tumour in the breast. Every measure should be taken to achieve the best possible cosmetic result [10].

OUTCOME MEASURE: Every patient with an invasive cancer considered to be suitable for breast conservation must have had information about the possibility of BCT.

OUTCOME MEASURE: Over 90% of women having conservation surgery should have 3 or less therapeutic operations.

5. Breast conserving treatment

BCT is a combination of a surgical excision aiming at microscopically-free margins and of radiotherapy of the breast. It generally applies to small (arbitrarily up to 4 cm) unifocal invasive breast cancer. The aims are:

1. to achieve local control,
2. to preserve breast cosmesis.

The requirements for breast surgery are described in the previous paragraph. In breast conservation, the surgeon aims at 1 cm free margins.

Requirements for breast radiotherapy are:

- high energy photons
- simulation and treatment planning
- use of appropriate beam modifiers to achieve homogeneity of dose distribution: dose should not exceed 110% and should not be under 95% of the prescribed dose
- avoidance of heart, lung and contralateral breast irradiation
- interval between surgery and initiation of radiotherapy should preferably not exceed 8 weeks.

Indications for BCT should take into account the risk factors for local recurrence and the determinants for cosmetic outcome [11,12].

The aim for BCT is to keep the breast relapse rate of invasive cancer less than 1–2% per annum follow-up (<15% at 10 years) [13,14]. If known risk factors indicate a higher risk for breast relapse (young age, incompletely excised infiltrating or *in situ* cancer, impossibility to deliver an adequate dose of radiation therapy), either a re-excision (when cosmetically feasible) or mastectomy has to be considered [15].

OUTCOME MEASURE: The breast relapse rate for invasive cancer after BCT should not exceed 15% at 10 years.

OUTCOME MEASURE: Excellent or good cosmetic result from a patient's point of view should be at least 80% at 3 years.

Recommendation: As radiation therapy substantially improves breast tumour control (by a factor of 2–3), every patient (>95%) with invasive cancer who have had breast conservation surgery must have had a consultation with a radiation oncologist to ensure sufficient information has been given on how to achieve the best tumour control with the least morbidity.

6. Mastectomy

A mastectomy is the *en bloc* removal of the complete breast parenchyma including parts of overlaying skin with the nipple areola complex.

Criteria for mastectomy are:

1. Patients who are not eligible for BCT
2. Patient's preference.

The aim of mastectomy is to achieve tumour-free margins.

Mastectomy remains a reasonable option to achieve local control in invasive breast cancer. The patient should be informed about this option, including the possibility of immediate breast reconstruction. Breast reconstruction can be offered, but may not delay or hamper locoregional treatment. In extensive disease (either clinically or after histological work-up of the excisional specimen) mastectomy may not result in sufficient local control. Factors associated with a high risk for local recurrence after mastectomy are:

1. invasive tumour > 5 cm (measured by pathologist)
2. vascular invasion
3. skin or muscle involvement
4. involved or close (< 1 mm) surgical margins
5. extensive nodal involvement (≥ 4 positive nodes).

In the presence of these risk factors, adjuvant chest wall radiation treatment must be discussed with the patient [16,17].

OUTCOME MEASURE: The chest wall relapse rate after mastectomy for invasive breast cancer should be less than 10% after 10 years.

Recommendation: In the presence of high risk factors for local relapse after mastectomy, more than 90% of the patients should have had a consultation with a radiation oncologist to inform them about the possibility of adjuvant radiation therapy of the chest wall and regional lymph node area.

Recommendation: Patients with primary operable breast cancer for whom mastectomy is advised or pre-

ferred by the patient should have been informed by the surgeon or plastic reconstructive surgeon about the possibilities of breast reconstruction.

7. Preoperative chemotherapy (for tumours too large for breast conserving treatment)

A number of studies have shown that different regimens of preoperative chemotherapy lead to a remission of primary invasive breast cancer in over 80% of the patients, with a pathological complete remission varying from 7 to 15% [18,19]. A number of trials show different rates (30–85%) of patients who could be treated with BCT for cancers initially considered too large for conservation treatment [19,21]. To date, after a limited follow-up, these trials showed equal survival rates in patients who had preoperative chemotherapy compared with postoperative chemotherapy [18–21]. In some studies, however, local failure rates are unacceptably high, so that the same surgical conditions apply for patients who are eligible for BCT without chemotherapy [21].

There is no role for preoperative chemotherapy in patients with invasive breast cancer who are already candidates for BCT. If tumours are too large for BCT, a core needle biopsy with histologically-confirmed invasive breast cancer is mandatory. Dispersed microcalcifications and multi-focal diseases appear contraindications for preoperative chemotherapy [22]. Since at this moment neither the optimal combination nor duration of chemotherapy have been clearly evaluated, preoperative chemotherapy to downstage the tumour in order to facilitate BCT should be applied with caution. In those patients in whom this treatment is considered, the patient should be informed only after histological confirmation of the diagnosis of breast cancer and optimal imaging by mammography at least. After completing chemotherapy, a second mammogram prior to the surgical treatment should be performed to evaluate the feasibility of BCT. After every course of chemotherapy, local tumour progression should be excluded by clinical examination [18,19].

OUTCOME MEASURE: Breast conservation therapy after preoperative chemotherapy for histologically-confirmed invasive breast cancer (more than 50% reduction) in tumours considered too large for BCT should result in a breast relapse rate of less than 15% after 10 years.

8. Locally advanced breast cancer (LABC)

Definition:

- Tumour > 5 cm (stage III) measured clinically, by ultrasound or mammography

- Proven skin involvement
- Chest wall muscle or chest wall skeletal involvement
- Fixed axillary lymph nodes
- Clinical signs of a mastitis carcinomatosa
- Tumour-positive apical (infraclavicular) node.

There is sufficient evidence that combined modality treatment is superior to ensure lasting locoregional control in locally advanced breast cancer. The influence on overall survival is uncertain [23,24].

The timing of each of the components of the multimodality treatment remains to be established. The advantage of upfront chemotherapy, in general accepted as the first step in LABC, is that the primary cancer functions as its own chemotherapy sensitivity test. For instance, in the situation of progressive disease after two courses of chemotherapy, one can decide to stop the applied chemotherapy. On the other hand, it has been convincingly shown that a partial or complete remission after upfront chemotherapy is an important favourable prognostic factor for local control and survival [24]. Overall, in the majority (>80%) of patients, a remission of tumour volume after upfront chemotherapy can be observed. Radiotherapy to the breast, chest wall and regional lymph nodes is an integral part of the treatment of LABC.

If, and to what extent, surgery should be applied is uncertain. For macroscopic invasive cancer, radiotherapy alone will provide a lasting local control in approximately 60–70% of the patients [25].

The situation of clinically-overt remaining invasive cancer, tumour reduction (debulking) by surgery will improve local control. In general, if upfront chemotherapy for LABC results in a partial remission, surgery (BCT, mastectomy or more extensive procedures depending on the extend of the remaining disease) is indicated to ensure a better local control in combination with adjuvant radiotherapy. However, the same holds true if upfront chemotherapy does not have any effect.

Adjuvant hormonal treatment should always be considered in patients with oestrogen receptor (ER)- and/or progesterone receptor (PgR)-positive tumors [26]. Tamoxifen is an equivalent to chemotherapy in elderly patients with receptor-sensitive tumours.

OUTCOME MEASURE: Over 80% of the patients with a locally advanced breast cancer should have had combined modality treatment including upfront chemotherapy, cytoreductive surgery for clinically overt disease and radiation therapy.

9. Lymphatic dissemination

Invasive cancer may lead to lymphatic dissemination. The most important primary tumour factors related to the risk of lymphatic dissemination are:

- Size of the tumour
- Grade
- Vascular invasion

Patients with micro-invasive (<2 mm) or tubular cancer up to 10 mm have a very low probability of lymph node metastasis. For these patients the search for lymph node metastasis or elective treatment of lymph nodes can be omitted [27–29].

The presence of lymph node metastasis is the most important prognostic factor for survival; the more involved the lymph nodes, the worse the prognosis [30]. Treatment of lymph node metastasis will result in a better lasting regional control of the disease [31]. Whether early treatment for clinically-occult lymph node metastasis has an impact on overall survival is not proven.

Indirect evidence strongly suggests a small, but significant, positive effect on survival [32–34].

In conclusion, the knowledge of lymph node dissemination will result in treatment adjustment to improve the outcome of the patient.

Measures to diagnose lymphatic dissemination are

1. FNA cytology of clinically-overt enlarged regional lymph nodes
2. Ultrasound-directed FNA cytology of suspicious lymph nodes
3. Non-selective lymph node sampling
4. Axillary lymph node dissection (ALND), level I-II
5. Full axillary lymph node dissection, level I-II-III
6. Lymphatic mapping by the sentinel node (SN) procedure.

Every method has its own accuracy depending on experience, the *a priori* chance of lymph node involvement, the applied techniques. ALND (at least level I-II) resulting in the examination of at least 10 lymph nodes by the pathologists, has proven to give an excellent prognostic information on nodal status and axillary tumour control at the expense of certain morbidity, which is particularly a price to pay for node-negative patients [35]. If ALND is used as a staging procedure, it is recommended to perform a complete axillary clearance which results in sufficient axillary tumour control in the majority of node-positive patients [33,34]. Non-selective lymph node sampling may result in a sampling error, but has proven to provide sufficient prognostic information with less morbidity [36].

Maturing data from many prospective studies indicate that lymphatic mapping by the sentinel node technique may be an equal staging procedure compared with ALND [37,38]. However, the sentinel node technique is laborious, demands expertise and a careful mapping of the sentinel nodes with tracers (lymphoscintigraphy, intraoperative use of the probe and dye). However,

anyone involved in this new technique should be subject to a certain learning phase, including a training course and the verification of the procedure by an ALND in at least 25 and preferably 50 patients [39].

Once lymphatic dissemination to the axilla is established, it is generally accepted that treatment of the axilla is indicated [31–34]. In clinically-overt disease, complete ALND (on indication followed by radiotherapy) provide the best axillary tumour control. If lymph node metastasis are found in the ALND specimen, in general the axilla is sufficiently treated except in extensive dissemination: arbitrarily more than four positive lymph nodes, a positive apical node, extra nodal growth are indications for adjuvant radiotherapy [32]. In these situations, the option of regional radiotherapy should be discussed with the patient. If, after non-selective lymph nodal sampling or after the sentinel node procedure, lymph node metastasis are found, there is a substantial risk that there are more tumour-positive nodes left behind in the axilla (after sentinel node procedures varying from 10 to 50%). These findings justify elective treatment of the axilla. The options for treatment of the axilla after lymph node sampling or sentinel node procedure are either complete ALND or radiation therapy of the axilla. What treatment leads to the best regional control with the least toxicity and long term morbidity remains to be established [34,40].

The elective treatment of internal mammary chain (IMC) nodes is heavily debated [41]. If lymphatic mapping locates sentinel nodes at the internal mammary chain, these nodes can be removed if they appear. If tumour-positive, the internal mammary chain area can be irradiated. When lymphoscintigraphy does not show drainage to the internal mammary chain, it is uncertain whether this implicates that there is a low risk of tumour dissemination to this region. The role of IMC node biopsy is currently under investigation.

The value of elective irradiation of the internal mammary chain nodes is currently investigated in a large European Organization for Research and Treatment of Cancer (EORTC) trial in patients with a positive axilla or medial located tumours.

OUTCOME MEASURE: For patients with invasive breast cancer of less than 2 mm or tubular cancer of less than 10 mm do not need lymphatic mapping or elective treatment of axillary lymph nodes.

OUTCOME MEASURE: For patients with an invasive cancer, information on the nodal status should have been obtained (lymph node sampling >4 nodes, ALND more than 10 nodes, sentinel node procedure).

OUTCOME MEASURE: More than 90% of the patients with invasive cancer and proven lymph node metastasis should have had axillary treatment (ALND, radiotherapy to the axilla or combined in extensive nodal involvement).

10. Ductal carcinoma *in situ*

Ductal carcinoma *in situ* (DCIS) is defined as a malignant transformation of the ductal lining cells within an intact basal membrane. DCIS is more frequently diagnosed following the increased breast screening. Nowadays, over 15% of the screen-detected malignancies are DCIS [42]. DCIS may appear in different histological variants with specific cyto-nuclear, architectural and molecular — pathological features [43]. As invasive cancer, poorly differentiated DCIS is related to a more aggressive behaviour, particularly with respect to an invasive recurrence and consequent metastatic disease.

The aim of surgical treatment of DCIS is to achieve tumour-free margins [44,45]. To reach this goal, all requirements related to the treatment of invasive cancer are applicable to DCIS [42]:

- Optimal imaging (including magnification views in cases of microcalcifications).
- Presurgery diagnosis of microcalcifications or density by histological core (stereotactic or ultrasound-guided) biopsies.
- Discussion of the patient in the multidisciplinary team.
- Specimen radiography after diagnostic and/or therapeutic excisional surgery.
- Guide-wire localisation preceding any surgery of a clinically-occult lesion.
- The surgical resection should aim to result in at least 1-cm tumour-free margin.
- Marking of the specimen after excision to guide the pathologist.
- Diagnostic work-up by the pathologist according to established guidelines.

DCIS should be excised completely. If margins are involved a re-excision (guided by post-operative mammography and if necessary again a guide-wire localisation) should be attempted. When a re-excision will result in poor cosmesis, a mastectomy (with or without reconstruction) should be considered and offered. If on basis of mammographical findings, the DCIS is considered to be too large for breast conservation (usually exceeding a 3 cm area of microcalcifications) immediate mastectomy with or without reconstruction should be discussed. In ‘true’ DCIS, treatment of the axilla is not recommended [42].

Radiotherapy reduces breast relapse rates by 40% after a complete excision of DCIS, irrespective the histological features of the DCIS [46,47]. Therefore, the possibility of radiotherapy should always be discussed with the patient who desires to conserve her breast after complete excision of DCIS. There are instances where the risk of invasive local relapse, which may lead to dissemination, is extremely low [44]:

- Small (<2 cm) foci of DCIS
- Low grade of DCIS
- Histologically-confirmed wide margins more than 10 mm.

In these situations, the adjuvant value of radiotherapy is very limited.

After BCT for DCIS, patients should be followed carefully with at least annual mammography. It should be kept in mind that DCIS is a potentially curable disease (by mastectomy). Therefore, BCT should carry a very limited risk for the development of invasive cancer.

Recommendation: After complete excision of DCIS, adjuvant radiotherapy of the breast should be discussed with the patient.

OUTCOME MEASURE: The breast relapse rate (invasive cancer) after BCT for DCIS should be less than 10% at 10 years.

OUTCOME MEASURE: The chest wall relapse rate after mastectomy for DCIS should be less than 5% at 10 years.

11. Follow-up

Follow-up after treatment for breast cancer is mandatory for the following reasons [48]:

- For the measurement of outcome, at least annually, indefinitely.
- For the measurement of recurrences.
- For screening for second primaries:
 - Annual mammography is advised.
 - For screening for distant disease.
 - Asymptomatic detection of distant disease does not lead to a prolonged survival.
 - Other diagnostic means should be applied in cases of symptoms.

12. Participants

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