IEO Breast Cancer Treatment Recommendations

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The Division of Senological Radiology has 4 digital mammography machines, 8 echo color Doppler devices, 1 stereotactic biopsy machine, 2 devices for vacuum assisted biopsy, 1 ultrasound guide and 1 stereotactic guide. For MRI examinations of the breast a 1.5 Tesla machine is used with coils for MRI-guided biopsy. Each year the Division performs about 42,000 diagnoses and 750 biopsies (vacuum assisted, stereotactic or US guided).

**Vacuum Assisted Biopsy**

The growing use of imaging modalities combined with continuing technological improvements in imaging technology and widespread introduction screening has meant that an increasing proportion of diagnosed breast lesions are non-palpable. The advent of vacuum-assisted biopsy and so-called microhistological examination for suspicious and non-palpable breast lesions has largely replaced open biopsies and has considerable advantages over the core biopsy procedure.

The Division of Senological Radiology has adopted vacuum-assisted biopsy for all non-palpable lesions (thickenings or usually microcalcifications) evident on mammogram and not visible by ultrasound. In selected cases, US-guided vacuum-assisted biopsy is performed to investigate non-palpable lesions evident ultrasonically. Use of vacuum-assisted biopsy avoids multiple passes with the needle and removes a larger sample than does core biopsy, so that the sufficient material is almost always available for histological characterization. Studies indicate that vacuum-assisted biopsy is more reliable than core biopsy in distinguishing the various DIN subtypes and that rates of underestimation correlate inversely with the quantity of tissue removed. Vacuum-assisted biopsy also identifies neoplasia and carcinoma more frequently than core biopsy reducing the rate of false negatives.

Furthermore the quantity of tissue removed allows analysis of hormone receptors, HER2 and Ki67. Advantages of vacuum-assisted biopsy over open biopsy are no requirement for general anaesthesia, removal of less (healthy) perilesional tissue, better cosmesis, reduced cost, and good patient acceptability with reduced patient stress. Although imaging after vacuum-assisted biopsy often shows complete lesion removal the technique should be considered diagnostic not therapeutic. The technique has high sensitivity and specificity - in our experience around 97% and close to 100%, respectively for procedures executed both under US guidance and by stereotactic mammography.

The drawbacks of vacuum-assisted biopsy are that it is relatively invasive, equipment costs are high, and it is more technically demanding for the physician than fine needle aspiration and core biopsy, with a longer learning curve. Complications are than 10% and are almost always hematoma, venous bleeding and displacement of the clip or marker. In addition to US guidance and stereotactic mammography, vacuum-assisted biopsy can now be performed under MRI guidance. We normally use...
Mammotome biopsy devices with 11G needles. Larger (8G) needles are used to remove diffuse microcalcifications. The patient is placed in the prone position when stereotactic mammography is used and is supine if US-guidance is used. These positions are comfortable for the patient, facilitate correct positioning of the breast and seem to be associated with fewer cases of syncope. US is a relatively low cost technology that does not employ ionizing radiation and has developed rapidly in recent years.

We use US-guided vacuum-assisted biopsy for the diagnostic investigation of a high proportion of breast lesions. Indications are as follows: reassessment of lesions that are C3 at US-guided fine needle aspiration cytology; investigation when fine needle aspiration cytology material is inadequate (C1); discrepancy between radiological and cytological findings (e.g. bi rads 4 on mammogram and C2 on FNAB); distinguish surgical scar from recurrence; and evaluation of small lesions evident on US. After complete lesion removal we usually introduce radiopaque marker to the biopsy site (also visible on US for a short time) to assist localisation if open surgery is required.

Management after biopsy depend on the pathological findings:

- Patients with a benign lesion or atypical lobular hyperplasia are asked to return for a mammogram after 6 months.
- For atypical ductal hyperplasia wide excision of the lesion area by open surgery is recommended in all cases.
- Wide excision of the lesion area by open surgery is also recommended for cases with discordant mammographic (e.g. BI-RADS 4) and cytological (e.g. FNAB C2) findings.
References

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- American College of Radiology (ACR) Illustrated breast imaging reporting and data system (BI-RADS), 4th edn. 2003; American College of Radiology, Reston, VA.
MRI of the breast

Use of US and MRI have made improved the possibilities for early diagnosis of breast cancer. MRI in the more sensitive (around 88%-100%) than US or mammography for the local staging of breast lesions, but has only modest specificity 37-70%.

The Division Senological Radiology of IEO adheres to the recently published recommendations from the EUSOMA working group on MR imaging of the breast. These recommendations confirm that for breast investigation a 1.5 Tesla machine is optimal and gadolinium contrast is necessary except when assessing a breast with prosthetic implant, when MRI without contrast is sufficient. To reduce the percentage of false positives, diagnostic MRI should generally only be performed in premenopausal women, preferably from the 6th to 13th day after menstruation. Preoperative breast MRI can be informative in several situations particularly: high risk patients (family history of breast cancer), lobular carcinoma, patients under 60 years with >1 cm discrepancy between mammogram and US; with multifocal, multicentric or bilateral lesions suspected on mammography/US/clinical examination. At the IEO we also use preoperative breast MRI in young women with operable breast cancer being considered for intraoperative radiotherapy (IORT).

In patients with a family history of breast cancer, annual MRI from age 30 years may be useful as part of a surveillance program that includes clinical examination, mammography and ultrasonography. In women with deleterious BRCA 1 or 2 mutations, annual MRI should be considered starting from 25 years, and in women with a TP53 mutation annual MRI should start from 20 years.

For women undergoing neoadjuvant therapy with a view to subsequent conservative breast surgery,
we perform MRI before starting the neoadjuvant treatment repeated 2 weeks after the completion of
the last cycle and two weeks before surgery. Our experience is that US or mammography persistently
underestimate lesion size after neoadjuvant, but MRI does not. Another major indication for MRI is lo-
coregional lymph node involvement in the absence of a detectable breast primary on mammography/
US (CUP syndrome. MRI is also indicated in women suspected for recurrence after previous conserva-
tive surgery, in view of the superior ability of MRI to distinguish scar tissue from recurrence.

Axial MR images showing carcinoma of the right breast. Early contrast uptake by the lesion is evident on the left image and slow washout is evident on the right.

Axial MR images of DIN2 in the lower our quadrant of the left breast. The left image is T1-weighted; the right is an MIP of a contrast enhanced fat suppressed image.
At the IEO we also use MRI without contrast to investigate a suspected ruptured prosthesis (suggested for example by development of altered breast shape or asymmetry, and palpable lymph nodes perhaps due to silicone uptake). A sensitivity of 89% and specificity 97%, have been reported for diagnosing prosthesis rupture.

References

Quadrantectomy

- Standard breast conservation procedure

Quadrantectomy has become the treatment of choice not only for small breast cancers (diameter less than 2.5 cm) but also for larger tumours, breast volume permitting, and for tumours up to 5 cm treated by pre-operative (neo-adjuvant) medical treatment. The revolution in breast cancer treatment began in the 1980s with the Milan I trial which randomized 701 patients to either breast-conserving surgery (quadrantectomy, complete axillary dissection plus breast radiotherapy, QUART) or Halsted mastectomy. Eligible patients had infiltrating carcinoma up to 2 cm, without clinically evident axillary involvement (T1N0), and were randomized in the operating room after excisional biopsy had confirmed histology and tumour size. The results, which ushered in the era of conservative surgery for all types of cancer, showed no difference in survival between the 2 arms. The most recent analysis of the Milan I results, after more than 20 years of follow-up confirmed indistinguishable survival for the 2 arms, but these events had no impact on survival. The low rate of adverse events in the QUART arm was partly attributable to the quadrantectomy operation, which was developed with the aim of achieving effective local control. Earlier studies had indicated that intraductal spread was relatively frequent in breast cancer, and in quadrantectomy, the entire portion of the ductal tree (up to the nipple) involved by the carcinoma is excised.

- Complete axillary dissection

Before the validation of sentinel node biopsy, complete axillary dissection was a cornerstone of the Veronesi breast conservation protocol. If the nodes are clinically positive they must be treated, however...
the indications for and techniques of axillary clearance in a clinically clear axilla have been matters of intense controversy. Our point of view is that the indications for axillary dissection have changed in recent years, however when axillary dissection is performed, clearance must be complete: all three levels defined by Berg must be removed: the first level comprising all lymph nodes lateral to the lateral margin of the pectoralis minor muscle; the second level comprising the lymph nodes behind the pectoralis minor; and the third level comprising the nodes medial to the medial margin of the muscle, in the space commonly called as the apex of the axilla. Axillary lymph node dissection is performed in continuity with the breast incision when the tumour is in the upper-outer quadrant and by separate incision when it is located elsewhere. Performed in this way, sparing all vascular and nervous structures of the muscles, axillary clearance causes side effects (arm lymphedema, pain and paresthesia) in less than 6% of cases, yet provides maximum possible prognostic information.

• Radioguided occult lesion localization (ROLL)

Radioguided occult lesion localization (ROLL) is a simple-to-perform surgical technique employing radioactive tracer and a γ-ray-detecting probe for the intraoperative localization and removal of non-palpable breast lesions. The technique, developed at the IEO, involves injection of immobile radioactive tracer (as opposed to the mobile radiotracer used to identify sentinel nodes) into the lesion under mammographic or ultrasonographic control. The γ-ray probe is used intraoperatively to locate the lesion and guide its removal. ROLL has proved to be an accurate method for localizing occult lesions which facilitates complete lesion removal yet minimizes the amount of healthy tissue removed.

Surgical References


SENTINEL NODE BIOPSY

Sentinel node biopsy (SNB) is the standard of care for axillary staging in breast cancer. SNB can be performed in a wide range of practice settings, providing good results notwithstanding considerable variations in technique. SNB increases staging accuracy, mainly because sentinel nodes (SN) undergo exhaustive pathologic analysis, has less morbidity than complete axillary dissection, and affords local control comparable to that of axillary dissection. Although SNB has been a routine part of clinical practice for several years, indications for SNB remain the subject of debate.

In the developmental and validation phase of SNB (the 1990s), to ensure that a sentinel node was found in the highest possible proportion of cases and that the false-negative rate was low, SNB was only performed on patients with small non-multifocal/non-multicentric breast tumor and clinically negative axillary lymph nodes. However, as the technique came into widespread use and experience increased, indications progressively expanded to include most patients with non-metastatic disease. Today the question tends to be; “are there any situations when SNB in not indicated?” while in the past it was “who qualifies for SNB?”

Our attitude is that whenever, from the clinical or oncological point of view, knowledge of axillary node status is useful, SNB is the best way determining axillary status, in most patients with non-disseminated breast cancer.

Although the role of SNB in large primary breast cancer remains controversial, published data show that for these large tumors, SN identification, accuracy, and false negative rate compare favorably with those in studies on patients with smaller cancers, permitting avoidance of axillary dissection in nearly a third of patients with large tumors.

Multifocal/multicentric disease

Multifocal or multicentric invasive breast cancer has been considered a relative contraindication for SNB based on concerns that these cancers may involve multiple lymphatic tracts draining to multiple SNs. However, there is now good evidence that in many cases tumors of the breast drain through relatively few common lymphatic channels to a common axillary SN, regardless of the precise location of the tumor. Studies that compared subareolar injection with peritumoral injection of radioisotope or
blue dye for SN mapping (without completion lymphadenectomy) demonstrated 90% or greater concordance of SNs identified with the two methods, irrespective of tumour location. A common afferent lymphatic channel to the axillary SN would explain successful localization of the SN using various injection techniques, including intraparenchymal, subdermal, intradermal, and subareolar injection. Our experience in 42 patients with multicentric breast cancer and clinically negative axilla who underwent lymphatic mapping either by a single subareolar or a double peritumoral/subdermal injection of 99Tc-labelled nanocolloids is that the number of SNs found does not depend on the number or site of injections: the mean number of hot spots identified by lymphoscintigraphy was similar in patients who received single and double injections (1.36 and 1.35, respectively). SNB is our standard procedure for axillary staging in patients with multicentric breast cancer and a clinically negative axilla.

SNB and DIN

The role of SNB in the management of ductal intraepithelial neoplasia (DIN) has not been established. IEO investigated 854 patients with pure DIN (microinvasion excluded) who underwent SNB. Only age, clinical presentation, and tumor size were predictive of SN involvement in these patients. Consistent with most other reports, the SN was the only metastatic node in all patients who underwent axillary dissection. This finding renders the utility of routine axillary dissection questionable in pure DIN cases with a metastatic SN, particularly when only micrometastases are present in the SN.

- IEO recommends that:
  1. SNB should not be a standard procedure for all patients with DIN. If the DIN is completely excised by radical surgery (free resection margins), or completely (macroscopically) removed by core needle biopsy or vacuum assisted biopsy (limited clusters of microcalcifications or small solid lesions <2 cm) then diagnostic underestimation and the risk an invasive component at final histology is very unlikely and SNB is not indicated.
  2. The principal reason for performing SNB in DIN is diagnostic uncertainty at final histological examination. This happens when DIN is not completely excised by conservative surgery (positive margins of resection or residual microcalcifications at postoperative mammogram), or in large solid tumors or diffuse, multicentric microcalcifications not macroscopically removed by core needle biopsy or vacuum assisted biopsy. In these cases, the risk of finding invasion at final histology is much higher (10% to 20%) depending on lesion size.
  3. In cases of mastectomy for DIN, SNB is mandatory. Upstaging to invasive cancer has been reported in 28% to 48% of patients after mastectomy for extensive DIN.

Previous breast and axillary surgery

Most authorities consider previous axillary surgery after breast cancer treatment an absolute contrain-
dication for SNB, but no data are available to support or refute this. The SN is, by definition, the first node or nodes directly receiving lymph from area around the tumour. To correctly predict the histological status of the axilla, SNB requires the presence of an intact lymphatic path from the site of the primary tumour (or recurrence) to the axilla. Previous axillary surgery could partially or temporarily interrupt or modify this lymphatic path, compromising the ability of SNB to identify the “real” SN - that which reliably predicts axillary status. Data suggest however that a new lymphatic system develops shortly after surgery has removed tissues or disrupted lymphatic flow. Such a pathway allows us to identify a new SN for the new tumor. These considerations suggest a new dynamic concept of the SN: not “only one SN, ever” but “always a new SN”. The IEO recommends that second SNB can be offered to selected women with ipsilateral breast cancer recurrence after previous conservative breast surgery and a negative SN followed by adjuvant radiotherapy. Previous mastectomy is unanimously considered to be an absolute technical contraindication to SNB. However, we have found that in selected mastectomized patients with recurrence, subdermal injection of radioisotope permits identification of an axillary SN. We believe there are no anatomical or physiological reasons to exclude this diagnostic opportunity “a priori”; nevertheless, only a larger study with longer follow up will reveal the true predictive value of SNB in such patients.

Pregnancy

Several authors have suggested that SNB with radiotracer can be performed in pregnancy with negligible risk to the fetus. Since the injected radiotracer remains at the injection site, within the lymphatic ducts or in the sentinel nodes, fetal exposure should be essentially zero. We carried out a pilot study on non-pregnant patients undergoing SNB, in which we measured intrauterine doses. The findings indicated that SNB can be safely performed in pregnancy, in any phase of gestation, since doses to the uterus were well below threshold values for deterministic effects. More recently we published our experience on 12 pregnant patients with breast cancer who received SNB. Ten had a negative sentinel node; 1 had micrometastasis in one of the four sentinel nodes and 1 had frank metastasis and underwent axillary clearance. From the 12 pregnancies, 11 healthy babies were born. One baby operated on at 3 months for a ventricular septal defect and at 43 months was in good health. This malformation was suspected at US examination during week 21, well before lymphoscintigraphy, and confirmed a posteriori by an independent observer. This experience further supports the safety of SNB in pregnancy.

Precautions to further minimize fetal exposure include avoiding contact with other patients as potential sources of radioactivity (e.g. by scheduling the pregnant patient as first procedure of the day and accommodating her in a single-bed room), reducing the time between lymphoscintigraphy and surgery, and possibly also using administering less activity. In pregnant patients, surgery with SNB should be performed 2-3 hours after injection of 3-5 MBq of 99mTc-labelled tracer.
Neo-adjuvant treatments

Early studies on SNB after primary chemotherapy found that the false negative rate of SNB was higher in patients who had received chemotherapy than those who did not. More recent and larger studies demonstrate that, with increasing experience, the identification and false-negative rate of SNB are similar to those in the absence primary chemotherapy. It is useful to obtain pathologic information on nodal status (by SNB under local anaesthesia) before starting preoperative treatment, since such information provides prognostic information that could be absent after preoperative chemotherapy.

If the SNs were negative, axillary dissection after neo-adjuvant treatment could be avoided, whereas, for a positive SN, axillary dissection must be performed. This approach would also address the concern that the identification rate and sensitivity of SNB after neoadjuvant treatments are lower. By contrast however, it is conceivable that the prognostic value of SNB after neoadjuvant treatments will be even greater, since it indicates response to treatment. Furthermore, performing SNB before neoadjuvant treatment would lead to complete axillary dissection in all patients with positive SNs, and therefore to a higher fraction of patients receiving this intervention.

Our experience is that SNB is useful after neoadjuvant chemotherapy in patients a clinically involved axilla at presentation. We found that SNB accurately identified all cases (32%) that had been down-staged to a node-negative axilla (confirmed by axillary dissection). We therefore propose foregoing axillary dissection after neoadjuvant chemotherapy in women with a negative sentinel node.

Male breast cancer

Male breast cancer is rare, accounting for fewer than 1% of all breast cancers and fewer than 1% of all annual cancer deaths in males. Because of the low number of patients with this disease, treatment for breast cancer in males has been extrapolated from treatment protocols for breast cancer in females. Men are more likely than women to have a delay between symptoms onset and diagnosis, so that men present with more advanced disease than women. For example nodal involvement is present in up to 60% of male breast cancer patients. The main reason for this diagnostic delay is probably widespread lack of awareness of this disease in men. Since there are no biological or anatomical reasons why lymphatic drainage should differ in men compared to women, we recommend SNB in males with breast cancer and a clinically negative axilla.

Internal mammary node biopsy

We generally perform biopsy of the internal mammary chain lymph nodes in patients with breast cancer in inner quadrants. Biopsy is performed during breast surgery with minimum increase in operating time. The IMC nodes are easily accessed through the intercostal space. Fatty tissue containing the node to be examined is carefully freed from blood vessels, and care is taken to avoid damaging to the underlying pleura. If an involved IMC node is found (even if the axilla is disease free) the disease is upstaged so that adjuvant treat-
ments (CT, RT to internal mammary) must be given. According to current treatment guidelines, a clinically- or ultrasound-positive axilla is a contraindication to SNB. However clinical examination of the axilla is imperfect and the results of several studies from the era of axillary lymph node dissection (spanning 50 years) indicate that palpable nodes in the axilla have a positive predictive value of 64% to 82%, a negative predictive value of 50% to 63%, and an overall accuracy of 63% to 68% for cancer. In fact normal lymph nodes vary widely in size, consistency, and fat content clinically suspicious axillary nodes turn out to have a wide spectrum of pathologic findings with lymphadenopathy a feature of several non-malignant diseases. Even at surgery, reactive adenopathy may be indistinguishable from metastasis, while frankly malignant nodes may appear completely normal.

These considerations suggest a possible role for SNB in selected patients with clinically suspicious nodes. We emphasize however that many breast cancer patients with clinically suspicious axillary nodes do not require SNB at all and should proceed directly to axillary dissection: first because fine needle aspiration can confirm axillary involvement; second because imaging can provide preoperative diagnoses of axillary involvement in considerable numbers of patients.

**Sentinel Node Biopsy References**


Radiotherapy after quadrantectomy for early stage primary breast cancer is an essential adjunct to conservative surgical treatment, as it ensures good local control and survival. It is important, however, to minimize radiation-related complications. Recent technological advances in computerized treatment planning and delivery systems have made it possible to provide more accurate conformation of the prescribed dose to the anatomic boundaries of the tumor volume, while excluding radiation from surrounding tissues. These advances also are opening up new possibilities in terms of the volume to be treated, fractionation regimens, and use of concurrent chemotherapy and radiotherapy.

We recommend that three dimensional conformal radiotherapy and intensity-modulated radiation therapy (IEO 3D-CRT/IMRT) should be introduced as routine for patients with breast cancer. The use of CT simulation and new algorithms for 3D dose calculation and delivery have made it possible to precisely sculpt the dose to target volumes of almost any shape. Quantitative dose-volume information on heart and lungs is critical in RT for breast cancer. The heart volume can be delineated (and hence totally spared) by optimizing beam angles, in nearly half the patients with left breast cancer, and significantly reduced in the others. Furthermore, in 3D techniques, the posterior and superior borders of the tangential breast fields are made non-divergent and coplanar, to thereby limit the dose to the lung.

Heart and lung dose-volume histograms are a simple and useful way of estimating the irradiated volume of these critical organs and complication probability of normal tissue. With regard to locoregional irradiation, we are of the opinion that the availability of new biologic predictors and new chemotherapy regimens should prompt re-examination of the concept of regional lymph node irradiation. We are designing studies to define the role of adjuvant locoregional irradiation in more advanced disease.

**Fractionation schedules**

The need for a protracted (5-7 week) radiation course is a major obstacle to the use of breast-conserving surgery in many areas of the world, including some that are relatively affluent. The standard conventional fractionation schedule has several disadvantages: psychological distress, considerable financial burden for the woman and the health care system, and delayed return to normal life. To address this problem, several centers in Canada and UK have explored shorter external beam radiotherapy regimens. It was found that delivery of a reduced total dose in a rapid schedule of slightly more than three weeks, did not result in an excess ipsilateral recurrences, indicating substantial equivalence to the longer fractionation schedule, as also noted for other cancer sites. We have adopted shorter schedules at the IEO. The majority of patients now receive only 20 daily sessions of external beam radiotherapy. However on one day a week there are two RT sessions (6 hours apart) with a boost to the tumor bed being given in one of these sessions. In selected patients the boost to the tumour bed is given by a new method called “accubooost” employing high-dose rate projection brachytherapy.
Optimal sequence of multimodality therapy

The relative timing of chemotherapy, endocrine therapy, and radiotherapy in the postoperative setting remains a matter of debate; in particular the best timing of radiotherapy, when indicated, remains a major issue. All possible permutations have their theoretical justifications, but concomitant chemotherapy and radiotherapy has the advantages of optimising efficacy and shortening overall treatment time. Currently only CMF is recommended with concurrent radiotherapy in view of acceptable toxicity without compromising dose intensity. Anthracyclines and taxanes are not recommended because of the relatively high risk of acute (skin) and late (cardiac and lung) side effects, and poor cosmetic outcomes.

However, with three-dimensional visualization and beam contouring technology it is possible to prevent the heart, lungs and other normal tissues from receiving major doses of radiation; breath holding can also be used to further improve the precision of radiation targeting. These increasingly precise radiation targeting techniques suggest it may be time to re-examine the concomitant administration radiotherapy with anthracyclines or taxanes.
RECONSTRUCTIVE SURGERY

Oncoplastic surgery

Oncoplastic surgery combines breast-conserving surgery with plastic reconstruction. It allows a wide excision yet prevents breast deformities by immediate reconstruction of the large resection defect. Oncoplastic procedures are mainly applied when 20% to 40% of the breast has to be removed - such patients were normally treated by mastectomy in the past.

Four features are fundamental to oncoplastic breast surgery:

1. the extent of surgery is appropriate to the size of the tumor;
2. partial reconstruction is used to correct wide excision defects;
3. reconstruction (immediate or delayed) employs the full range of available plastic techniques;
4. volume and shape asymmetries are corrected typically by intervention on the healthy contralateral breast.

There are two fundamentally different approaches: (1) volume-replacement procedures, which combine resection with immediate reconstruction using local flaps (glandular, fasciocutaneous and latissimus dorsi mini-flaps), and (2) volume-displacement procedures, which combine resection with a variety of breast reduction and reshaping techniques, depending on the location of the cancer. Oncoplastic surgery augments the oncological safety of breast-conserving treatment since a much larger breast volume is excised, and wider surgical margins are achieved. In addition, the contralateral breast undergoes “surgical screening” allowing the diagnosis of occult cancers in the contralateral breast. The IEO recommends oncoplastic approaches for large breasts, for cancers treated by pre-operative medical therapies, for cancers located in quadrants (inferior quadrants) that do not usually afford a good cosmetic result with standard breast conservation, and for small-to-medium size cancers in small breasts to avoid breast deformities.

Implant reconstruction

After mastectomy, the choice of the reconstructive technique depends on the patient’s preferences, the condition of the thoracic tissues, and the surgeon’s experience and skills. Breast implants are now popular and widely used for breast reconstruction and are of various types: (1) temporary (expanders) vs. definitive; (2) saline (now rarely used) vs. silicone; (3) rounded vs. anatomically shaped. In all cases, the implant should be placed behind the pectoralis major and serratus anterior muscles. Breast reconstruction can be performed at the time of mastectomy (immediate) or in a second surgical procedure (delayed). While there is general agreement that immediate reconstruction is appropriate for in situ neoplasms, many surgeons prefer to delay reconstruction for invasive cancer. The IEO re-
commends immediate reconstruction for both in situ lesions and invasive cancers, since reconstruction has no adverse effect on patient prognosis. Immediate reconstruction offers several benefits over delayed reconstruction: technically easier, reduced patient hospitalization and time in surgery, lower cost, and not least immediate restoration of the breast mound which has a positive psychological impact on the patient, contrasting the negative impact of mastectomy.

The IEO does not recommend implants after standard conservative treatment for breast cancer, in view of the fact that fractionated large field irradiation (standard treatment following conservative surgery) is associated with a relatively high risk of capsular contracture, resulting in poor cosmetic outcomes.

By contrast, intraoperative radiotherapy (e.g. ELIOT) spares surrounding tissues from irradiation and carries no increased risk of capsular contracture compared to conventional radiotherapy.

**Flap reconstruction**

Autologous reconstructions use various flaps (fasciocutaneous, musculocutaneous, pedicled free flaps) which are transferred to the thoracic region to recreate the breast mound as an alternative to implant. The choice of flap depends on patient preference, patient anatomy, what tissues remain after mastectomy, and the surgeon’s experience and skill (microsurgical techniques are necessary for free flap transfers). It is generally agreed that flap reconstructions are superior to implant reconstructions in terms of softness, appearance and durability (changes over time are similar to those undergone by a natural breast). Flap reconstructions are particularly recommended for irradiated tissue, large defects after extensive mastectomies, and poor vascularised mammary tissue.

**References - Oncoplastic Surgery**

References - Implant Reconstruction


References - Flap reconstruction

ELIOT (intraoperative therapy with electrons) is the application of electron radiation targeted to the tumor bed during surgery. A major advantage of ELIOT is that it can provide full-dose radiotherapy during the breast-conserving surgical session, solving the problem of difficult access to radiotherapy centers experienced by many women post surgery. ELIOT uses a mobile accelerator with a robotic arm, present in the operating room, that produces an electron beam of variable energy (3-12 MeV). After tumor removal the surgeon detaches the residual breast from the thoracic wall and inserts aluminum and lead shielding discs between the gland and the thoracic wall, to protect deep structures. The gland is temporarily re-sutured together. The depth of the breast tissue is measured at the site of the tumor bed to determine the energy of the beam. The electrons are directed to the open breast (the skin is held away) by means of cylindrical Perspex applicators of variable diameter (4-10 cm) and variable bevel angle where they contact the breast (perpendicular or 15°-45° relative to the applicator axis). ELIOT is extensively employed at the IEO. From 2000 to 2007 we randomized 1306 patients, in a prospective phase III trial (ELIOT trial), to receive conventional external beam radiotherapy (50 Gy to the whole breast plus a 10 Gy boost to the tumor bed) or a single dose of 21 Gy of ELIOT. All patients received quadrantectomy followed by SNB, with axillary dissection if the sentinel node was positive. The trial is in follow-up. However numerous patients, who did not fulfil trial eligibility criteria or refused to enter (opting for ELIOT rather than randomization), also received ELIOT. From January 2000 to December 2008, 1,822 out-trial patients with primary unicentric breast cancer <2.5 cm, received ELIOT. A non-randomized comparison with similar patients who received external beam radiotherapy suggests equivalent survival (see survival curve).
Our expectation is that ELIOT will be shown to be as effective as external beam radiotherapy as a treatment for small size breast cancer. If this is the case it will be employed to solve the problem of difficult access to radiotherapy centers.

**Partial Breast Irradiation**

Most randomized trials support the use of whole breast irradiation after breast conserving surgery. However several centers, including the IEO, are examining modifications to irradiation, in particular the use partial breast irradiation (PBI). In PBI only the tumor bed and a limited volume of adjacent tissue are irradiated. There are various techniques for giving PBI including brachytherapy techniques, intraoperative radiation therapy (IORT) and high precision external beam irradiation. All afford a shorter schedule (no more than 10 sessions).

PBI has other advantages including decreased morbidity by reducing irradiation to non-target tissues and avoiding the timing clash with systemic therapy which can delay the initiation of combined adjuvant chemo-radiotherapy. At the IEO the most-used PBI technique is ELIOT, but interstitial (with iridium sources) and endocavitary (Mammosite balloon) brachytherapy, and 3D conformal irradiation are used in selected patients. We are also experimenting with intraoperative avidination for radionuclide therapy (IART) as described below. Preliminary data from recent studies on PBI suggest that a change in irradiation treatments can be expected soon for the management of limited breast disease.

**ELIOT Boost**

There are several techniques for delivering a boost in breast radiotherapy. The main problem is accurately defining the boundaries of the tumor bed after surgery. This can be difficult, particularly when the breast has been reconstructed, when marker clips have not been placed, or when there is no imaging evidence of tumor location (scarring or seroma cavity). Enlarging the volume of irradiated tissue can reduce targeting errors but may increase the risk of late tissue reactions or poor cosmetic outcome. ELIOT offers important advantages compared with conventional external beam radiotherapy in this area. Direct exposure of the tumor bed during the operation overcomes localization inaccuracy, allowing treatment of a more limited breast volume. Critical structures (heart and lung) are spared by shielding, and the skin is moved away from irradiated field, minimizing late skin sequelae. Accumulating evidence suggests that ELIOT boost is well tolerated, with good cosmesis and good local control. We started a non-randomized trial with ELIOT boost in 2004. ELIOT is used to give a 12 Gy intraoperatively, followed 3-4 weeks later by hypofractionated external beam radiotherapy to the whole breast in 13 fractions over 2.5 weeks, up to
a total dose of 37 Gy. Eligible patients are premenopausal women below 48 years of age, with cT1-T2 clinically cN0-1 breast cancer, scheduled for breast-conserving surgery. Data on the first 211 patients show high compliance with treatment and acceptable acute/intermediate toxicity. Thus ELIOT boost appears to be an effective alternative to conventional external beam radiotherapy. Giving the boost in a single intraoperative session only modestly increases operative (by 15–20 minutes). This approach not only reduces the total time of external treatment to 2-3 weeks, with consequent cost savings and improvement in patient well-being, but also seems to afford a local control rate that is similar to or better than other boost techniques.

**Nipple-sparing mastectomy**

Despite the increasing indication for conservative breast surgery, mastectomy remains the most appropriate treatment for large or multicentric tumors, medium size tumors in a very small breast or recurrences after conservative treatment. At the IEO, 72% of the new cancers receive breast preserving surgery, and the remaining 28% receive mastectomy. Skin-sparing mastectomy was a significant advance on mastectomy. Preservation of the skin envelope enhances the quality of the breast reconstruction, enabling the reconstructed breast to retain a more natural shape. The nipple-areola complex is an identifying characteristic of the breast and conserving it decreases the woman’s feeling of mutilation when mastectomy is required. However conservation of the nipple-areola complex when mastectomy is indicated has always been criticized because of the high risk of recurrence.

By giving additional radiotherapy, in the form of ELIOT, to the nipple-areola complex after skin-sparing mastectomy, the risk of local recurrence should be substantially reduced. ELIOT would be followed by immediate breast reconstruction using a myocutaneous flap.

In our experience with nipple-sparing mastectomy and ELIOT, no local recurrences to the nipple-areola complex have occurred, although follow up is short. These encouraging results are particularly important since in 160 cases the tumor was in the retro areolar area, very close to the areolar dermis. Longer follow up is required to confirm the efficacy of the ELIOT to the nipple-areola complex, and only a randomized trial comparing nipple-sparing mastectomy with or without ELIOT can provide definitive indications.
Radiotherapy References


Trial IBCSG 23/01

Trial 23-01 of the International Breast Cancer Study Group (IBCSG) is a multicentric randomized trial on axillary dissection versus no axillary dissection in patients with clinically node negative breast cancer and only micrometastases in the sentinel node. The trial, which closed recently and is now follow-up, was designed to determine the prognostic significance of minimal (<2mm) metastatic involvement of sentinel nodes in breast cancer.

The nodes are examined extensively by staining multiple sections with hematoxylin and eosin; immunostaining for cytokeratin is used only when the hematoxylin and eosin findings are not clear. This important trial began in April 2001, initially with a single center (IEO). In order to have sufficient power to answer the questions posed, the trial must recruit a considerable number of patients.
Intraoperative Avidination for Radionuclide Therapy

Intraoperative avidination for radionuclide therapy (IART) is another partial irradiation technique under development at the IEO. There are two steps. The first is “avidination” in which native avidin is injected by the surgeon directly into and around the tumor bed. The second step is intravenous injection of 90Y-labeled biotin, one day later. Avidin injection requires no more than 10 minutes and is done after cancer removal (quadrantectomy), while the surgeon is waiting for the result of the intraoperative pathological analysis of the sentinel node, or after axillary dissection. Following avidination the wound is closed as normal. Radiolabelled biotin, injected intravenously the day after surgery, binds to the avidin in the operated breast, bringing a significant quantity of radionuclide whose radioactive decay kills residual tumor cells. In preliminary studies, scintigraphic images demonstrated fast and stable uptake of radiolabelled biotin at the injection site, but without significant localization of radioactivity in the rest of the body. A phase II study demonstrated that IART combined with reduced external beam radiotherapy is a safe procedure without systemic toxicity that produces a good aesthetic outcome to the treated breast. IART is an interesting nuclear medicine approach that may have a role in the management of early breast cancer.

It provides a radiation boost that reduces the duration of conventional external beam radiotherapy and allows patients who have difficulty attending a radiotherapy centre (particularly the elderly, and those who live a considerable distance from the facility) to be treated optimally.

IART References

NUCLEAR MEDICINE

Sentinel node biopsy

The procedure we use to visualize the sentinel node was developed in house in the early 1990s and has been in use since 1995. The failure rate non identification of the sentinel node is less than 1% in over 20,000 lymphoscintigraphic scans and biopsies.

On the day before surgery (or in the morning of the same day if surgery is in the afternoon) 12-15 MBq of technetium-99-labelled particles of human colloidal albumin in 0.2 ml of saline are injected in the subdermis above the tumor followed by gentle massage. Lymphoscintigraphy is performed 20-30 minutes later to reveal the dynamics of lymphatic flow; anterior and anterior-oblique projections of the breast and axilla are obtained to determine the exact position of the sentinel lymph node.

The skin projection of the lymph node is then marked and used as a landmark when beginning sentinel node removal during surgery.

The axilla after neo-adjuvant treatment

We are evaluating the role of positron emission tomography with $^{18}$F-2-fluoro-2-deoxy-D-glucose (FDG-PET) in determining the approach to the axilla in breast cancer patients who have received neo-adjuvant therapy.

Preliminary results on 44 patients demonstrate a relatively high positive predictive value of FDG-PET for the detection of metastatic axillary lymph nodes after neoadjuvant therapy. These data suggest a possible role of FDG-PET in selecting patients who, after neoadjuvant therapy, should proceed directly to axillary lymph node dissection, avoiding SNB, and shortening surgery time. However this approach requires validation on a larger series of patients and enrolment is ongoing.

Nuclear Medicine References

The first histopathologic approaches to the sentinel node were the same as those used for the routine assessment of regional lymph nodes: assessment of 1-3 sections cut from frozen (for intra-operative diagnosis) or paraffin-embedded lymph nodes. However the high false-negative rate of this approach soon became apparent when compared with the results of early studies which used more extensive methods of histopathologic examination. Subsequently, numerous studies were performed to maximize the positive and negative predictive value of sentinel node biopsy, in a cost effective way that did not unacceptably increase the workload of the pathology laboratory. The main techniques employed were to increase the number of sections taken and examined (sub-serial sectioning of the entire sentinel node) and the use of immunohistochemical staining.

The cost-benefit ratio of extensive sentinel node examination varies with the number of patients evaluated, the reimbursement rate, and the availability of personnel and equipment. It has been shown that the detection rate for metastases depends on the number of sections examined from a lymph node, and on the examination procedure used. To ensure optimization of patient management across treatment centers it would be useful to agree upon a standard protocol.

At the IEO we devised one of the most demanding sentinel node examination protocols, that is suitable for both frozen and paraffin-embedded nodes. The sentinel node is bisected along its longest axis, and cut into 2-3 mm thick slices if thicker than 5 mm (thinner nodes are processed uncut), with care taken to preserve intact the nodal capsule and the peripheral sinuses – where metastatic foci commonly occur. Sections are cut at 50-100 μm intervals, along the entire length of the node consuming it completely. Formerly spare sections for immunohistochemistry were cut at each interval, but we now perform immunohistochemical examinations on de-stained sections, where necessary, to confirm the metastatic nature of morphologically atypical cells (approximately 5% of cases).

The need for complete examination of the sentinel node derives from the observation that, while foci measuring 2 mm or more (macrometastases) are almost always present in the initial sections cut from the middle area of a node, foci less than 2 mm (micrometastases) are distributed randomly throu-
ghout the node, and cannot be reliably detected by examining sections from the central part of the node. The choice of cutting sections at 50-100 μm intervals is dictated by the requirement to identify even minimal nodal involvement (isolated tumor cells and micrometastases), which are often not detected if the node is sectioned at larger cutting intervals.

**Pathology References**

Adjuvant systemic therapies have improved disease-free and overall survival in breast cancer. The 11th St Gallen Consensus conference held in March 2009, emphasized the need to use predictive markers to identify early breast cancer patients who might benefit from systemic therapies.

All patients operated on at the IEO are discussed at multidisciplinary meetings, and algorithms are applied to identify the best adjuvant treatments in accord with the recommendations of the 11th St Gallen Consensus Conference, which are as follows:

1. Any level of estrogen receptor expression is considered to justify endocrine therapy.
2. Overexpression or amplification of HER2 indicates anti-HER2 therapy. This marker must be reliably and accurately determined according to ASCO/CAP guidelines with positivity defined immunohistochemically as intense uniform membrane staining by >30% of the tumor cells; by fluorescence in situ hybridization (FISH) as a HER2 gene copy to chromosome 17 centromere ratio of >2.2; or by chromogenic in situ hybridization (CISH) of >6 HER2 signals/cell.
3. Chemotherapy is indicated for patients with higher risk of relapse, but the threshold for its use is difficult to define. Patients receiving anti-HER2 therapy conventionally also receive chemotherapy, and anti-HER2 therapy with endocrine therapy is not considered. Chemotherapy is usually indicated for patients with triple-negative disease, as most of these patients are at sufficient high risk to justify chemotherapy. However, rare breast cancer phenotypes such as medullary, apocrine, or adenoid-cystic carcinoma are low risk and do not require adjuvant treatment even if triple negative. Similarly, patients with cancers <1 cm, without axillary nodal involvement and without other features indicating increased metastatic potential (e.g. perivascular invasion) may not need chemotherapy. Decisions must be made on an individual basis.

It is difficult to assess the real benefit of chemotherapy in patients with endocrine responsive, HER2-negative disease. Features supporting addition of chemotherapy to hormone therapy include grade 3 tumors, high proliferation rate (as measured by Ki67 or genetic assays), low expression of estrogen or progesterone receptors, extensive axillary involvement (usually four or more involved nodes), peritumoral vascular invasion, and tumor size >5 cm. Conversely, patients with grade 1 tumors, low proliferation, high expression of estrogen and progesterone receptors, negative axillary nodes, no peritumoral vascular invasion, and tumor, 2 cm should receive endocrine therapy alone.

Patients with intermediate risk disease (grade 2, intermediate proliferation index, tumor between 2 and 5 cm, and 1 to 3 involved lymph nodes) are problematic as regards the indication to add chemotherapy. However, if all these characteristics are present, chemotherapy is probably indicated. In uncertain cases, gene expression profiling, if available, may help to determine whether chemotherapy
is likely to reduce the risk of relapse. New tools include predictive models which consider clinical, pathological and molecular data.

**Adjuvant systemic therapies: Endocrine therapy**

**Premenopausal patients:** We recommend either tamoxifen plus ovarian function suppression (especially in patients at high risk of relapse or with HER2-positive disease) or tamoxifen alone (low risk, age >40 years), both for 5 years. Ovarian function suppression alone is sometimes considered in selected cases. Aromatase inhibitors are not indicated in premenopausal women. When tamoxifen is contraindicated, aromatase inhibitors may be administered together with ovarian function suppression, with estradiol monitoring during treatment. Based on limited evidence, we prefer GnRH analogue concurrently with chemotherapy (if indicated) particularly in younger patients.

**Postmenopausal patients:** Recent results from trials support aromatase inhibitors in postmenopausal women with receptor-positive breast cancer. The benefit may be particularly marked for women at high risk of relapse, whereas for women at low risk, tamoxifen is still a reasonable option. For patients at high risk of relapse aromatase inhibitors (anastrozole, letrozole) are recommended for five years, whereas in lower risk patients, 2 to 3 years of tamoxifen should be followed by aromatase inhibitor ( exemestane, or anastrozole) to complete 5 years of treatment. We also favor aromatase inhibitors initially in patients being prescribed selective serotonin reuptake inhibitors. Sequential rather than concurrent administration of cytotoxic and endocrine therapies should be considered.

For patients who have completed 5 years of endocrine treatment, we support the addition of continuation of aromatase inhibitors for a further period only in high risk patients (with node-positive disease). We consider it wise to check for ovarian function suppression in younger postmenopausal women receiving aromatase inhibitors. We support the evaluation of bone mineral density prior to starting aromatase inhibitors, together with use of calcium and vitamin D supplements and especially physical exercise, to reduce the risk of bone loss and treatment-related symptoms.

**Anti-HER2 therapy**

In patients with HER2-positive early-stage breast cancer, trastuzumab improves disease-free and overall survival. Trastuzumab for one year is currently prescribed to all patients with HER2 overexpressed or amplified, if the tumor is >1 cm or axillary nodes are positive. Evidence regarding the utility of trastuzumab in patients with HER2-positive tumors <1 cm and no nodal involvement is limited, and we make no define recommendations. We usually use trastuzumab in sequence with chemotherapy,
but the benefits of sequential vs. concurrent administration are unclear. All patients eligible for trastuzumab should have baseline echocardiogram or cardiac scan to assess left ventricular ejection fraction before starting trastuzumab, with serial assessments of left ventricular ejection fraction every 3 months while receiving trastuzumab. We usually avoid trastuzumab in patients with low (<50%) left ventricular ejection fraction. If cardiac toxicity manifests, trastuzumab should be discontinued and left ventricular ejection fraction re-assessed in 4 weeks, however this decision should be made weighing individual patient characteristics considering recurrence risk and pre-existing cardiac morbidity.

**Adjuvant chemotherapy**

Chemotherapy is crucial in triple-negative breast cancer and in HER2-positive breast cancer. Decisions about adjuvant chemotherapy are more difficult in patients with endocrine responsive, HER2-negative disease. We use several chemotherapy regimens at the EIO but we do not have systematic criteria or specific predictive markers indicating particular regimens. Low ER, HER2 overexpression and high proliferation rate predict a good response to chemotherapy generally.

Patients with tumours expressing high levels of estrogen receptor derive less benefit from adding chemotherapy to endocrine therapy. However in the presence of endocrine responsive high risk disease, chemotherapy is indicated in addition to hormonotherapy, although the more intensive regimens (adding taxanes or using a dose-dense schedule) may not be more effective than the ‘basic’ (once every 3 weeks) anthracycline-based regimen. Less intensive regimens like anthracycline for 4 courses or classical CMF for 3 courses are typically used for patients with endocrine responsive disease who require chemotherapy. More intensive regimens should be offered to patients with high risk disease.

In particular, we consider anthracycline-containing chemotherapy for 6 months as first option in patients with HER2 overexpression and no hormone receptors. Examples of such regimens include anthracycline for 4 courses followed by classical CMF for 3 courses; Canadian CEF for 6 courses; and sequential adriamycin, docetaxel and classical CMF for 3 courses. These regimens have been shown in comparative trials to yield superior results, but with greater cost and toxicity. For patients with triple negative tumors, DNA damaging compounds might be considered: classical CMF for 6 courses is a reasonable option.

Chemotherapy may be offered to fit elderly patients with sufficient life expectancy, and higher risk of relapse for various reasons including absence of endocrine receptors. Shorter duration chemotherapy (e.g. 12-16 weeks of weekly epirubicin or paclitaxel) is suitable for elderly patients. Chemotherapy should start earlier (within 3-4 weeks of surgery) in patients with no endocrine receptors. We do not recommend routine use of hematopoietic growth factors in patients with early breast cancer.
Neo-adjuvant systemic therapy

Neo-adjuvant systemic therapy should be considered to enhance the possibility of breast conserving surgery and to acquire early information on the responsiveness and biology of the disease. Before starting neo-adjuvant therapy, core biopsy should confirm the diagnosis and obtain predictive markers. Preoperative chemotherapy is less effective for tumors expressing high levels of estrogen receptor. Neo-adjuvant endocrine therapy without chemotherapy is reasonable for patients with strongly receptor positive disease, particularly if postmenopausal, and should continue for 5 to 8 months or until maximum tumor response.

Acceptable chemotherapy regimens should include taxane or anthracycline. In some cases (e.g. some endocrine responsiveness, elderly patients, patient preference) tailored chemotherapy (e.g. capecitabine and navelbine; fluorouracil, lederfolin and navelbine) can be considered.

Six chemotherapy courses should be administered. Infusional chemotherapy (regimens containing fluorouracil as continuous infusion) is preferred for large cancers or inflammatory disease. In inflammatory breast cancer the treatment should last 6-8 courses. If the inflammatory disease is also HER2-positive, an anti-HER2 drug should be administered together with chemotherapy.

Medical Oncology References


RETHINKING THE TNM BREAST CANCER CLASSIFICATION

For breast cancer, as for most cancers, the tumor size, regional lymph node involvement, and distant metastases have prognostic and therapeutic implications, and form the TNM classification, whose latest revision was published at the end of 2009 by the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC). Most medical facilities use the TNM system as their main method for cancer reporting. However, additional information is necessary to serve as a useful guide to therapy. Thus, estrogen and progesterone receptor (ER, PgR) status and HER2 overexpression/amplification are important guides to treatment, but are not part of current TNM classification.

We believe it would be convenient to enlarge the current TNM by adding flexible “place holders” to accommodate indicators of prognosis and treatment response as they are validated and can be changed to accommodate new ones at a later date. There are other aspects of the TNM cancer classification, first published 70 years ago by the AJCC, which we consider to be in need of overhaul. Most fundamentally, we need a classification that takes account of the fact that biology rarely has clean cut-off points, so basic information on tumor size should not be presented as categories, but as points on a continuum to convey precise size and hence more detailed prognostic information.

We also need a classification that employs a rigorous and unambiguous language so as not to engender confusion and distress in our increasingly informed and aware patients. Finally, we need a system that is sufficiently similar to the old classification that valid comparison of new data with old is possible. We have therefore developed a new TNM classification, which we call the TNM\textsubscript{IEO} classification.

**TNM\textsubscript{IEO} classification**

We propose modifying the present TNM\textsubscript{UICC} classification in the following five ways: using more rigorous and unambiguous language that our increasingly informed and aware patients can understand; presenting tumor size exactly in cm, instead of as categories, thereby providing a more precise indication of prognosis; specifying the number of lymph nodes examined; specifying the site of any distant metastases; and specifying hormone receptor status.

Such changes would result in a system that is sufficiently similar to the old classification for valid comparison of new data with old to be possible but is an important advance on the current classification as it provides considerably more information, yet simplifies T, N, and M specification. More tentatively, we also suggest it would be useful to develop a TNM classifi-
cation that serves as a useful guide to treatment by incorporating new biologic indicators of treatment response and prognosis as they are validated.

References

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