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Review Article

Local Breast Cancer Treatment based on Targeted Oncoplastic Breast Surgery (TOBS) and Breast Imaging

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Abstract

Preoperative staging of breast cancer based on breast imaging (mammography, breast sonography and breast magnetic resonance tomography (MR-mammography)) is mandatory. Earlier diagnosis of breast cancer leads more likely to favourable oncological outcome. Histological results of different Interventional procedures guided by ultrasound, stereotactic mammography or magnetic resonance in sense of image-guided wire markings are the basis for planning surgical resection margins in oncoplastic breast-conserving surgery. A new concept of targeted oncoplastic breast surgery was developed to standardize published surgical methods, and to optimize oncological and aesthetic outcomes during breast-conserving therapy in an academic breast center. Even after the new SSO-ASTRO-consensus guideline on margins for breast-conserving surgery with whole breast irradiation in stage I and II invasive breast cancer, a practice-relevant rational and indication for targeted oncoplastic breast surgery can be demonstrated.

This review gives an overview about the influences of breast imaging, interventional procedures and wire markings on the breast-conserving therapy of breast cancer in the sense of targeted oncoplastic breast surgery.

Breast Imaging

It is known that earlier diagnosis of breast cancer is more likely to result in a favourable outcome. Tumor size at diagnosis and lymph node stage are the best predictors of outcome. Regardless of tumor type or grade, the smaller a breast cancer is at the time of diagnosis, the more likely it is that it has not spread beyond the breast. As a result the current strategy for reducing breast cancer mortality is to seek diagnosis as early as possible. Early diagnosis is achieved by encouraging women to present as early as possible to breast clinics when they develop breast symptoms and through breast cancer screening. Breast imaging is fundamental to both.

Breast imaging is a more general term that encompasses mammography, breast sonography, breast magnetic resonance imaging (MRI) and other emerging technologies. To provide uniformity in the assessment of breast imaging findings, the American College of Radiologists (ACR) established final assessment classifications (Breast Imaging Reporting and Data System; BI-RADS) [1-3]. The final assessment categories are as follows: Category 1, negative; Category 2, benign; Category 3, probably benign (risk of malignancy < 2%); Category 4, suspicious abnormality (biopsy should be considered); Category 5, highly suggestive of malignancy.

Category 4 and 5 assessments indicate abnormalities that require tissue biopsy for diagnosis. These categories represent a broad range (3% to 100%) of risk of cancer.

Mammography

X-ray mammography has been the basis of breast imaging for more than 30 years. The sensitivity of mammography for breast cancer is age dependent. The denser the breast, the less effective this method is for detecting early signs of breast cancer. Breast density tends to be higher in younger women and increased density obscures early signs of breast cancer [4]. The sensitivity of mammography for breast cancer in women over 60 years of age approaches 95%, while mammography can be expected to detect less than 50% of breast cancers in women under 40 years of age [5]. Mammography uses ionising radiation to obtain an image and therefore should only be used where there is likely to be a clinical benefit. Consensus is that the benefits of mammography in women over the age of 40 years are likely to far outweigh any oncogenic effects of repeated exposure. Screening of women over the age of 40 by mammography is accepted practice. However, in symptomatic practice there is rarely an indication for performing mammography in women under the age of 35 unless there is a strong clinical suspicion of malignancy. Practice is changing and ultrasound is being increasingly used for the assessment of women with focal breast symptoms in this age range. Mammography is routine in all women in the screening age group [6].

Major benefits have been predicted from acquiring mammograms in direct digital format [7]. Compared with conventional mammography, the predicted benefits of full-field digital mammography include better imaging of the dense breast, the application of computer-aided detection and a number of logistical advantages providing potential for more efficient mammography services. In the clinical setting, comparative studies have shown that digital mammography performs as well as film/screen mammography [8-11].

Mammographic preoperative evaluation defines the extent of a patient´s disease, the presence or absence of multicentricity and other factors that might influence the treatment decision, and evaluates the contralateral breast. The size of the tumor should be included in the mammographic report. If the mass is associated with microcalcifications, an assessment of the extent of the calcifications within and outside the mass should be made. Magnification mammography is important for characterizing microcalcifications.

Mammography is the basis of stereotactic breast biopsy. Stereotactic biopsy can be carried. This technique is used for biopsy of unpalpable lesions that are not clearly visible on ultrasound (e.g. microcalcifications) [12].

Ultrasound

High-frequency (≥ 7,5MHz) ultrasound is a very effective diagnostic tool for the investigation of focal breast symptoms. Ultrasound does not involve ionising radiation and is a very safe imaging technique. It has a high sensitivity for breast pathology and also a very high negative predictive value. High-resolution ultrasound easily distinguishes between most solid and cystic lesions and can differentiate benign from malignant lesions with a high degree of accuracy. Ultrasound is the technique of choice for the further investigation of focal symptomatic breast problems at all ages. Under 35 years of age, when the risk of breast cancer is very low, it is usually the only imaging technique required. Over 35, when the risk of breast cancer begins to increase, it is often used in conjunction with mammography. Ultrasound is less sensitive than mammography for the early signs of breast cancer and is therefore not used for population screening. However, ultrasound does increase the detection of small breast cancer in women who have a dense background pattern on mammography [13-15]. In the screening setting, there is currently insufficient evidence of any mortality benefit and insufficient resources to allow for routine ultrasound screening of women with dense mammograms. Ultrasound is the technique of first choice for biopsy of both palpable and impalpable breast lesions visible on scanning [16]. Ultrasound is being increasingly used to assess the axilla in women with breast cancer. Axillary nodes that show abnormal morphology can be accurately sampled by needle core biopsy.

Doppler ultrasound adds little to breast diagnosis and is not widely used. Three-dimensional ultrasound of the breast is said to increase the accuracy of biopsy and the detection of multifocal disease but again is not widely available [17,18]. Elastography is a new application of ultrasound technology that allows the accurate assessment of the stiffness of breast tissue. It is being evaluated at present and may prove to be a useful tool in excluding significant abnormalities, for instance in assessment of asymptomatic abnormalities detected by ultrasound screening.

Magnetic Resonance Mammography

Magnetic resonance imaging (MRI) is now widely available. A variety of possible clinical indications for contrast-enhanced MRI of the breast have been reported. These include screening for breast cancer, determining the local extent of malignant disease, identifying an occult primary, assessing response to neoadjuvant chemotherapy, identifying local recurrences after breast-conserving therapy, breast imaging after implant reconstruction or breast augmentation, and the detection of ipsilateral breast cancer in patients presented with axillary lymph node metastases (CUP-syndrom) [19-23].

MRM is the most sensitive technique for detection of breast cancer, approaching 100% for invasive cancer and 60-70% for ductal carcinoma in situ (DCIS), but it has a high false-positive rate [24-28]. Rapid acquisition of images facilitates assessment of signal enhancement curves that can be helpful in distinguishing benign and malignant disease. However, significant overlap in the enhancement patterns usually means that needle sampling is required. Breast lesions seen on MRM that are larger than 10mm can be seen on ultrasound if they are clinically significant. MRM is likely to prove the best method for screening younger women (under 40 years) at increased risk of breast cancer but, because of cost, it is unlikely to be used for general population screening. MRM is the best technique for imaging women with breast implants. It is also of benefit in identifying recurrent disease where conventional imaging and biopsy have failed to exclude recurrence. Provided it is carried out more than 18 months after surgery, MRI will accurately distinguish between scarring and tumor recurrence [29,30]. MRI is being increasingly used to examine women for multifocal disease prior to conservation surgery, although the lack of evidence of efficacy means that it is not routine in this clinical setting. MRI of the axilla will demonstrate axillary metastatic disease but its sensitivity is not sufficient for it to replace surgical staging of the axilla.

The rate of MRI-detected multifocal disease, which ranges from 16% to 37%, is clearly much higher than the rate of in-breast recurrence after breast-conserving therapy, with reported rates in two studies with a 20-year follow-up of 8.8% and 14.3%, respectively [31,32]. This strongly suggests that in some, and perhaps many cases, the additional foci of cancer identified only on MRI, especially those that prove to be in situ disease, would likely be successfully treated with postoperative radiation.

Treatment decisions with regard to the recommendation of mastectomy or breast conserving surgery must be made on a case-by-case basis, with careful review of the imaging, pathologic, and surgical findings [33,34]. There are additional questions concerning patient selection. Which are the patients at highest risk for having multifocal or multicentric cancer who would benefit most from MRI (palpable cancer, young patients, patients with dense breasts, patients with lobular cancer)? Based on the current success of breast-conserving surgery, it is unlikely that MRI of the breast is warranted in all patients with newly diagnosed breast cancer [20,34]. Clinical investigation continues in an effort to find answers to these questions.

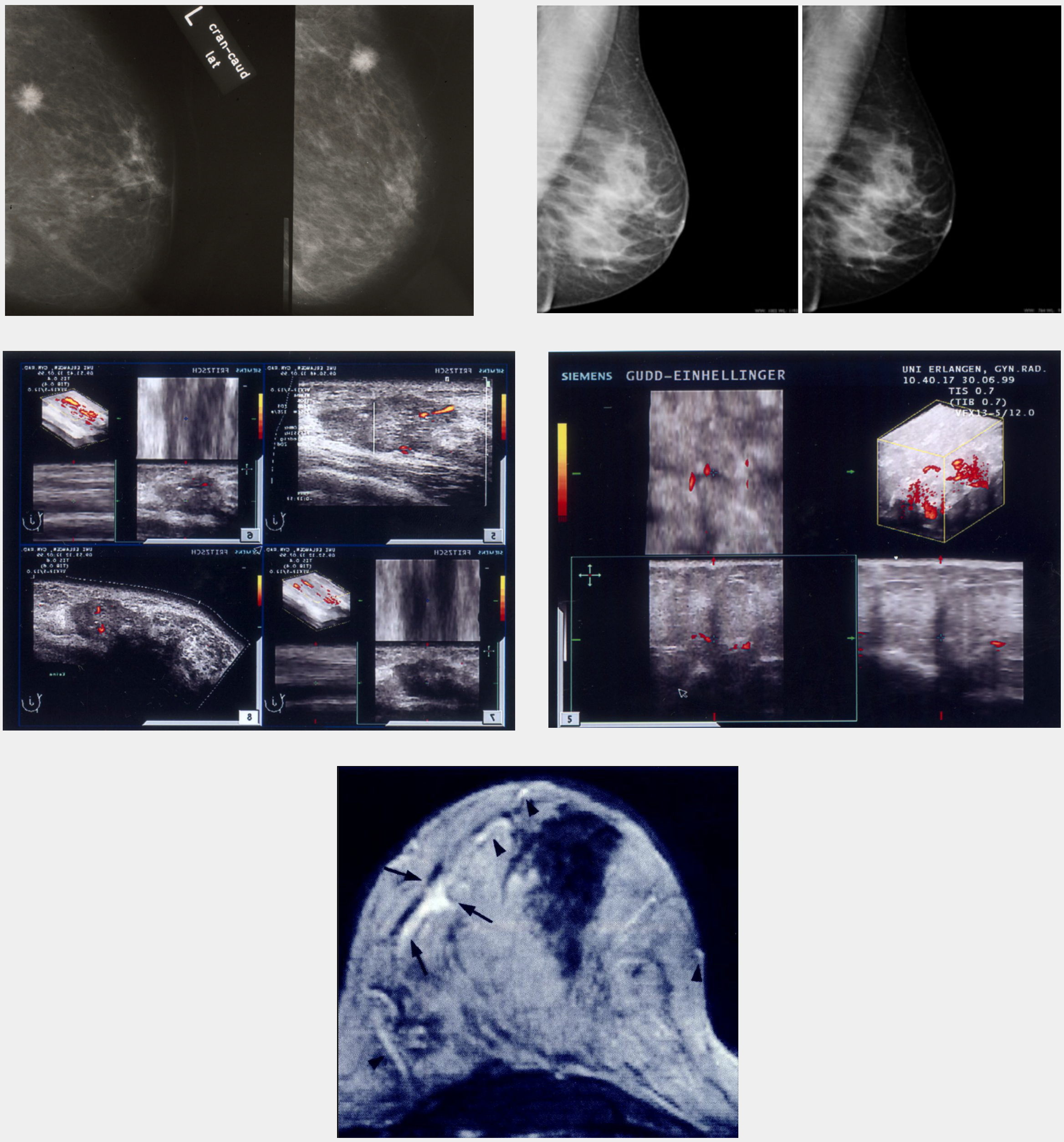

Figure 1: *Complementary breast imaging*

Breast Cancer Screening

The aim of breast cancer screening is to reduce mortality through early detection. Randomised controlled trials and case-control studies demonstrated that population screening by mammography can be expected to reduce overall breast cancer mortality by around 25% and by 35-40% in those who participate [35,36]. The validity of these trials was questioned in 2000-2002 but subsequent reviews by the Swedish combined trials group and a WHO International Agency of Research on Cancer committee of experts have reaffirmed the mortality benefit of mammographic screening and determined that criticisms of the mammographic screening trials were unjustified [37,38]. The mortality benefit of screening is greatest in women aged 55-70 years. The mortality benefit of screening women aged between 40 and 55 is approximately 20%. Screening women under the age of 40 has not been shown to provide any mortality benefit [39-41].

The screening method is two-view mammography; clinical examination of the breast and breast-self examination have not been shown to contribute to mortality reduction through early detection and so are not included.

Women at increased risk of developing breast cancer due to a proven inherited predisposing genetic mutation, family history, previous radiotherapy or benign risk lesions may be selected for screening at young age [42,43]. There is evidence that MRM is the most sensitive method of imaging young women but has significant resource implications [44]. The specificity of MRM has been a concern, although with second-look recall, targeted ultrasound and the slowly increasing availability of MRI-guided biopsy this may be less of a problem than initially thought.

Image-Guided Breast Biopsy

Needle biopsy is highly accurate in determining the nature of most breast lesions classified as BIRADS 4 or 5. Patients with benign conditions avoid unnecessary surgery; carrying out open surgical biopsy for diagnosis should be regarded as a failure of the diagnostic process. For patients who prove to have breast cancer, needle biopsy provides accurate understanding of the type and extent of disease so ensuring that patients, and the doctors treating them, are able to make infomed treatment choice. Needle biopsy not only provides accurate information on the nature of malignant disease, such as histological type and grade, but also facilitates pre-treatment assessment of tumor biology (hormone-receptors, HER-2/neu receptor, genetic profiling etc.) [45,46].

Breast needle biopsies of nonpalpable lesions require imaging to guide needle placement. Imaging guidance can be performed with ultrasonography, stereotactic mammography or MRI. Ultrasound guidance is the technique of choice; it is less costly and easy to perform. Ultrasound provides real-time visualisation of the biopsy procedure and visual confirmation of adequate sampling. Between 80 and 90% of breast abnormalities will be clearly visible on ultrasound and amenable to biopsy using this technique [47]. For impalpable abnormalities not visible on ultrasound, stereotactic X-ray-guided biopsy is required. A few lesions are only visible on MRI and require magnetic resonance-guided biopsy.

The technique used for ultrasound-guided biopsy [48] consists of the following steps: imaging the lesion, finding the needle in the longitudinal plane through the breast, maximally visualizing the needle tip, and placing the needle in the lesion. Development of good hand-eye coordination is crucial to a successful lesion sampling [49].

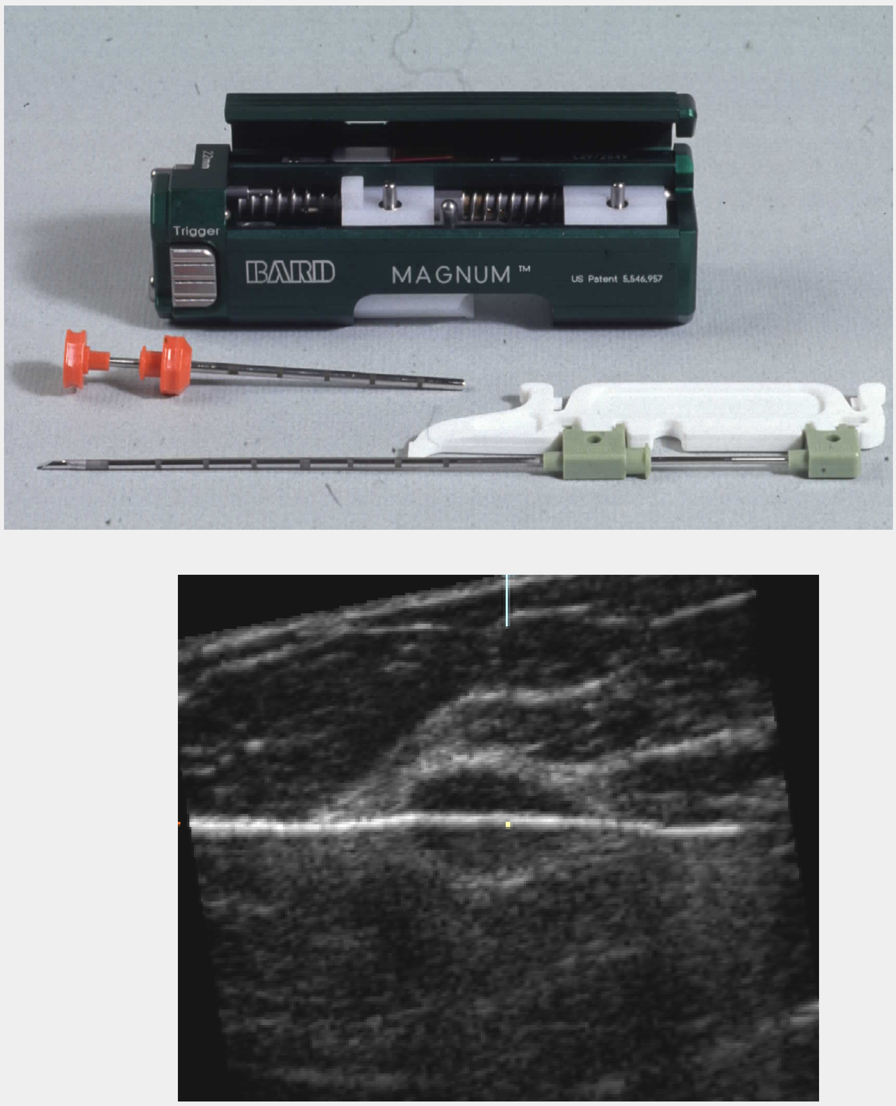

Figure 2: *US-guided breast core biopsy (14-g)*

Using the 14-gauge needle, multiple core biopsy samples are necessary to ensure accurate sampling of different areas of the lesion. In most cases, accurate lesion sampling can be achieved by obtaining 5 core samples for masses and 5 to 10 core samples for microcalcifications [50,51].

To improve sampling of microcalcifications using digital, stereotactic mammography guidance the vacuum-assisted biopsy instrument with probes coming in 11-gauge size has been developed [12].

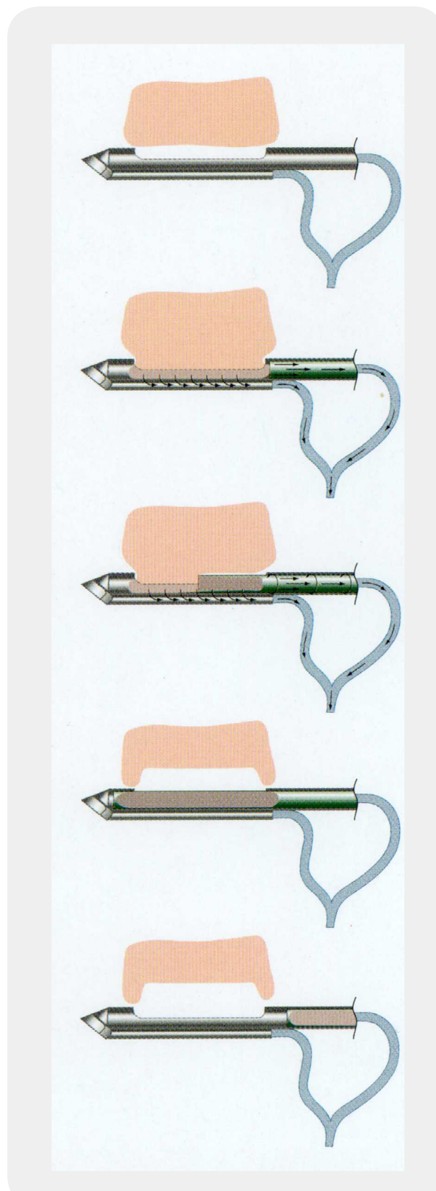

Figure 3: *Vacuum-assisted core biopsy (11-g)*

Studies have shown improved sampling of microcalcifications with the vacuum-assisted biopsy instrument [52,53]. For calcifications it is imperative that there is proof of representative sampling with specimen radiography. If calcification is not demonstrated on the specimen radiography and the histology is benign, then management cannot be based on this result as there is a high risk of sampling error; the procedure must either be repeated or open surgical biopsy carried out [54-60].

An 8-gauge vacuum assisted biopsy probe is preferred for therapeutic removal of breast lesions such as fibroadenomas [61-63].

Although not approved by the FDA for this function, in certain cases the ABBI biopsy could serve as an excisional biopsy and obviate the need for additional surgery [64]. If, after the ABBI procedure, patients also require surgical biopsy, the procedure is then, in effect, a more expensive and more invasive core biopsy method for obtaining diagnosis.

The low specificity of MRI requires the ability to perform MRI-guided biopsies, which require an additional specialized MRI biopsy coil and MRI-compatible wires and needles for localization and core biopsies [65-67]. Centers that cannot perform MRI-guided localization and biopsy lack the ability to manage lesions visible only with MRI and are at a clear disadvantage.

In cases of complete radiological removal of small occult breast lesions with needle biopsies, clip marking with the possibility for re-localization in cases of necessary therapeutic open surgical resection is mandatory. Core needle and vacuum-assisted biopsy is extremely useful in the evaluation of patients with multiple suspect lesions. Tissue samples can be obtained without having to perform multiple surgical biopsies. Establishing the extent of a patient´s cancer allows surgical mapping; optimal resection can help determine the most appropriate surgical therapy (e.g. oncoplastic breast-conserving surgery).

It is important that the result of needle breast biopsy is always correlated with the clinical and imaging findings before clinical management is discussed with the patient. This is best achieved by reviewing each case at prospective multidisciplinary meetings.

Wire-Guided Surgical Excision

The number of clinically occult breast lesions is increasing. Accurate localisation techniques are required to facilitate their surgical excision as the therapeutic part of a planned oncoplastic breast-conserving procedure [68]. The hooked wire is the most commonly employed technique and has proved very reliable but does have inherent associated problems. There are various designs of localisation wire in common use. All have some form of anchoring device such as a hook with a splayed or barbed tip. The wire is deployed under ultrasound or stereotactic guidance (for mammographic lesions only) within a rigid over-sheath cannula, which is then removed once positioning is satisfactory. Most wires are very flexible and when the cannula is removed the wire may assume a quite circuitous course, especially after stereotactic insertion when the breast is released from compression. In a very fatty breast in which there is no solid lesion or the wire has not transfixed the lesion, care must be taken to avoid displacing the wire.

Accurate wire placement is essential and ideally the shortest possible length of wire should be within the breast. Procedures that can be surgically more challenging are wide local excisions (segmental resection) for DCIS with no mass lesion. In such cases, where the distribution of disease is often more eccentric, careful three-dimensional excision planning expecially in oncoplastic procedures is necessary. Inserting more than one wire and even bracketing the lesion with three or four wires can occasionally be useful.

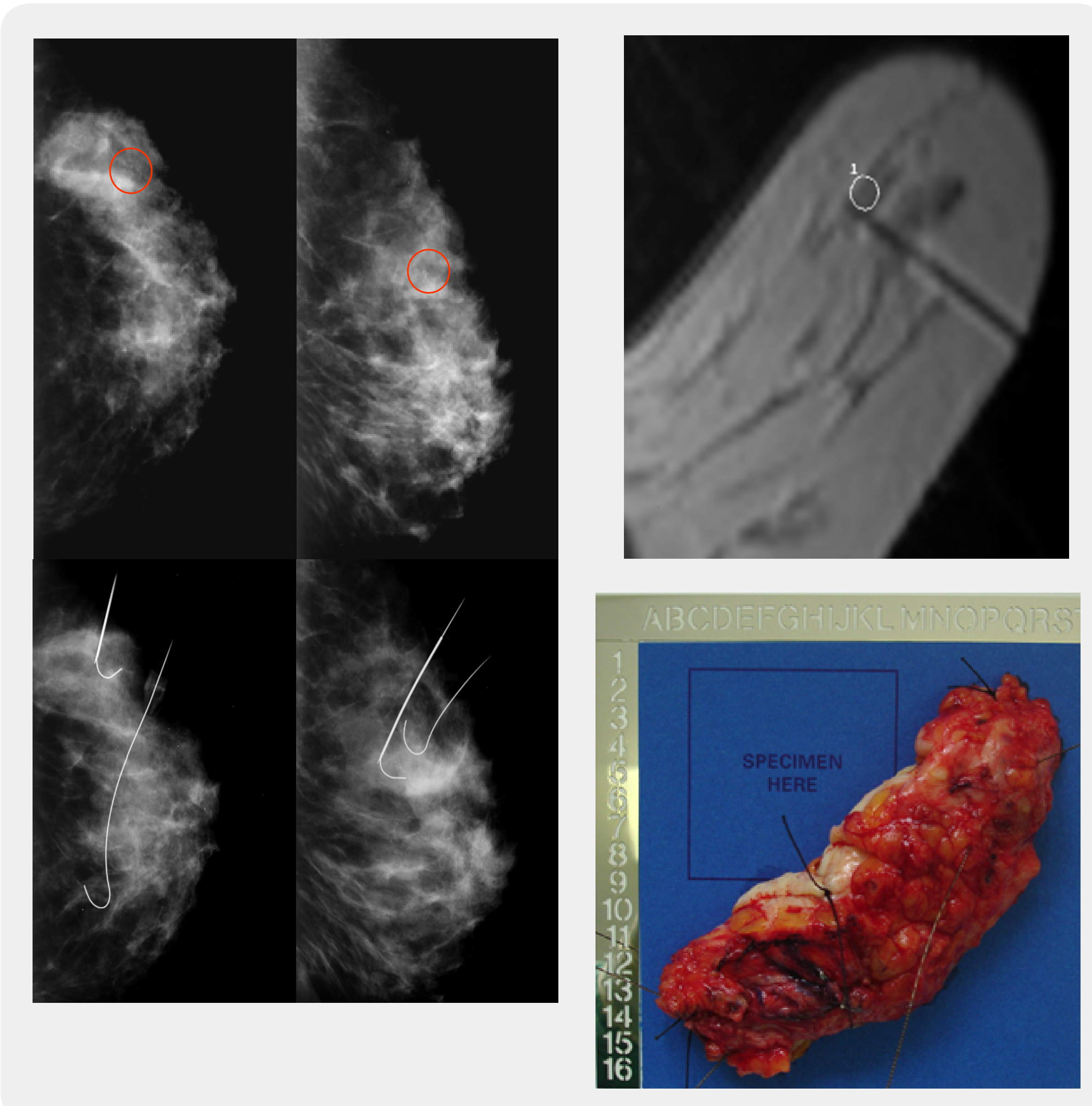

Figure 4: *Wire-guided (mammography and MRI) segmental excision*

Intraoperative specimen radiography is essential, both to check that the lesion has been removed and, if cancer has been diagnosed, to ensure that adequate radiological resection margins have been achieved. We have to consider that especially in DCIS the proved radiological resection margin (specimen radiography) sometimes differs from the histological resection margin [68-71].

Breast Imaging in the Preoperative Setting

Advances in breast imaging have led some to question whether whole-breast ultrasound or MRI should be part of the standard preoperative evaluation of a patient with breast cancer. Golshan *et al.* [72] reviewed the impact of ipsilateral whole-breast ultrasound on the surgical management. 18% of the patients had additional lesions identified by ultrasound. The role of ultrasound as a diagnostic tool for the evaluation of breast masses is well established (as is its role in defining lesions that are poorly seen on mammogram or mammographically occult) and the available data support its use as a routine tool when evaluating patients for breast-conserving therapy.

Tillmann *et al.* [73] reported the results of the impact of breast MRI on the surgical management and could show that the MRI findings affected clinical management in 20% of cases. In 11%, the effect of MRI was jedged to be beneficial due to the identification of cancer that was confirmed histologically. In 2% of cases, the benefit of MRI was uncertain, and in 6%, MRI had an unfavourable effect due to false-positive findings that resulted in unnecessary mastectomy or additional breast biopsies.

The work of Holland *et al.* [33] clearly indicates that microscopic foci of invasive and non-invasive cancer are present at a distance from apparently localized primary tumors in a significant number of patients. Only 39% of specimens showed no evidence of cancer beyond the reference tumor. The percentage (41%) of patients with residual cancer more than 2cm from the reference tumor corresponds well to the rate of local failure reported in patients treated with excision of the primary tumor alone. However, radiotherapy is effective in controlling the majority of these occult foci of carcinoma. The importance of these microscopic foci of tumor in the patient treated with excision and radiotherapy has again become an issue of clinical significance with the development of imaging modalities, such as magnetic resonance (MRI) and ultrasound, which allow preoperative detection of very small foci of cancer.

Clinical experience has demonstrated that the majority of this disease is controlled with radiotherapy. The ability of MRI and ultrasound imaging to identify these microscopic tumor foci raises the possibility that significant numbers of women who could be treated with lumpectomy / segmentectomy and radiotherapy will be subject to mastectomy.

Histologic subtype other than invasive ductal carcinoma does not appear to be associated with an increased risk of recurrence. Because of the increased incidence of multicentricity and bilaterality, invasive lobular cancer associated with increased mammographic density (ACR 3 and 4) is an accepted indication for preoperative MRI before breast-conserving therapy.

TOBS Based on Breast Imaging

Breast-conserving therapy (BCT) consisting of surgical removal of the primary tumour followed by whole breast irradiation is an alternative to mastectomy which results in equivalent long-term survival [74]. Although rates of BCT have increased over time worldwide, there remains remarkably little consensus about what amount of normal breast tissue should be removed as a margin to minimize the risk of local recurrence. The conclusion of the SSO (Society of Surgical Oncology) - ASTRO (American Society of Radiation Oncology) Consensus Panel reinforced the importance of obtaining negative margins defined as no ink on tumour (invasive cancer or DCIS), to optimize local control [75]. The most important and potentially practice-changing conclusion was based on the finding in the meta-analysis of Houssami *et al.* that margins of 1, 2, or 5mm were not associated with significantly different risks of local recurrences [76]. This meta-analysis could not be used to demonstrate whether a margin of no ink on tumour is adequate for patients with invasive lobular cancer, an EIC in association with invasive cancer, tumors of unfavourable biologic subtype (i.e., triple negative breast cancer), and in young patients.

Oncoplastic principles were introduced into breast-conserving surgery 15 years ago to allow oncologically safe breast conservation, by performing a wide excision for larger or poorly located tumours, while limiting the risk of postoperative deformities [77]. Numerous surgical techniques with tissue displacement and tissue replacement have been published with different indications, incision lines and suggested rotation techniques, missing a systematic and structured approach for oncoplastic breast surgery [78]. During the last years five reconstruction principles introducing a new concept of breast-conserving surgery, termed targeted oncoplastic breast-conserving surgery have been defined [79]. These major principles were: BCT-glandular rotation, BCT-dermoglandular rotation, BCT-tumoradapted reduction mammoplasty, BCT-thoracoepigastric flap, BCT-latissimus dorsi flap (Figure 5). Partial mastectomy defects could be reconstructed during BCT with these five oncoplastic principles in 97%. The cosmetic results were good or excellent in 95%. A tumour-free resection margin of 1mm was mandatory (according to german guidelines) and achieved in 91% during first surgery, while in 5% secondary mastectomy was required. Local-recurrences were diagnosed in 1,9% with a median follow-up of 4,2 years [80].

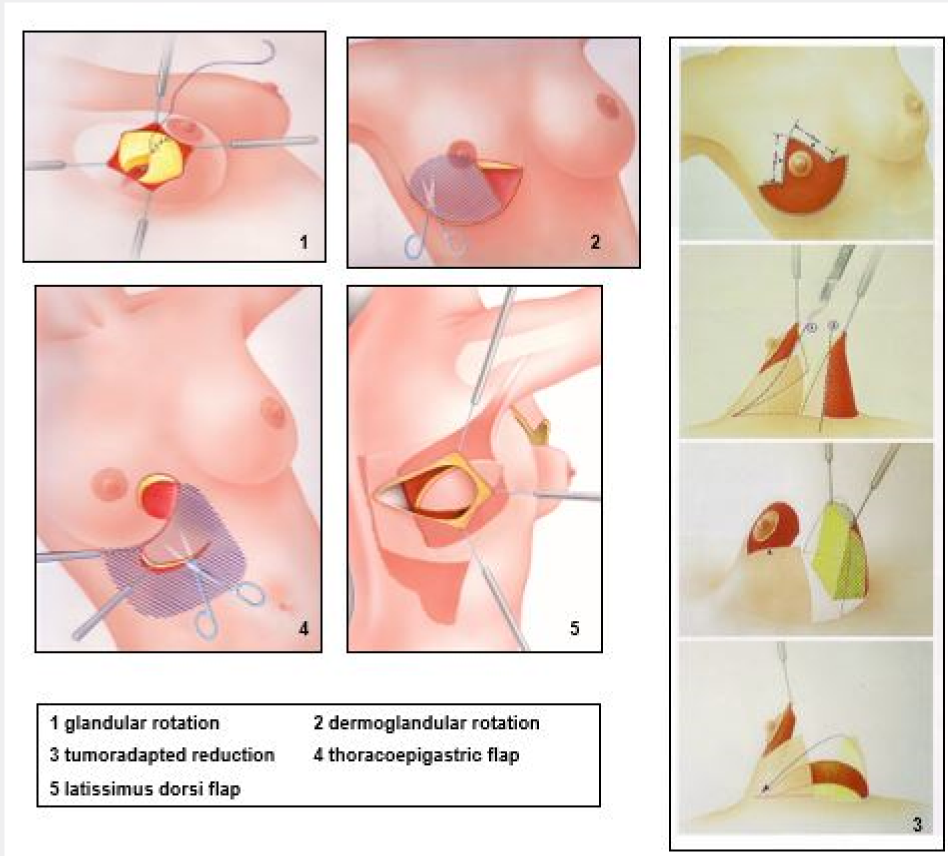

Figure 5: *Targeted oncoplastic breast-conserving surgery*

Further development of the traditional concept of oncoplastic breast surgery to a concept of targeted oncoplastic breast-conserving surgery with five defined oncoplastic principles allows the reconstruction of segmental resection defects during breast-conserving therapy with highest clinical applicability and results in favourable oncological and aesthetic outcomes. This approach might be useful in extending the indications for breast-conserving therapy. The adoption of a minimal margin definition does not remove the rational for a new concept of targeted oncoplastic breast surgery. Targeted oncoplastic breast surgery depends on the anatomical, pathological and reconstructive aspects of breast cancer to achieve favourable local outcomes for the patients - combining oncological and aesthetic prerequisites.

Conclusion

The translation of breast imaging, interventional procedures and wire-guided surgical excision into a concept of targeted oncoplastic breast-conserving surgery is mandatory and an interdisciplinary task for the breast radiologist and the breast surgeon to achieve the best oncological and aesthetic outcomes for patients with breast cancer.

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