New Technologies in Breast Cancer Surgery

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Keywords

Breast cancer · Intraoperative surgical margin assessment · Radiofrequency spectroscopy · Sentinel node detection · Acellular dermal matrix

Summary

Since breast-conserving surgery has become the gold standard for early breast cancer, the development of less radical or less burdensome technologies has been pressed for in order to preserve the patient from unnecessary harm through the operative procedure. Different technical approaches are under evaluation, and some of them are already being used in the clinical setting. The aim of this article is to present a perspective on future breast cancer surgery by shedding light on the current innovative and new techniques.

Introduction

Despite the multitude of biological systemic treatment options in breast cancer that have been developed in the last decade, the development of innovative technologies for diagnostics and surgery of breast cancer has also increased. The current discussion about axilla management, intraoperative margin assessment, and nipple-sparing mastectomy combined with immediate reconstruction and intraoperative radiotherapy confirms the enhancement of surgical strategies. Since the introduction of different screening programs and the increased detection of non-palpable premalignant and early malignant lesions of the breast, it is necessary to provide technologies to support the breast surgeon in handling this ambitious situation in a competent way. Some of the described techniques are already used in the clinical setting, some are still under evaluation, and for some techniques it is unclear whether they will reach the operation room sometime in the future.

Schlüsselwörter

Mammakarzinom · Intraoperative Resektionsrandbestimmung · Radiofrequenzspektroskopie · Sentinel-Node-Detektion · Azelluläre Matrix

Zusammenfassung

Seitdem die brusterhaltende Operation beim frühen Mammakarzinom als Goldstandard etabliert ist, wird die Entwicklung weniger radikaler und schonender operativer Techniken zum Schutze der Patientin kontinuierlich vorangetrieben. Verschiedene Technologien sind zurzeit unter Beobachtung und werden in Studien geprüft, manche von ihnen werden bereits im klinischen Alltag angewendet. Ziel dieses Artikels ist es, aktuelle innovative und neue Technologien zu beleuchten und damit einen Ausblick auf die zukünftige operative Therapie des Mammakarzinoms zu geben.

Intraoperative Surgical Margin Assessment

A sufficient surgical margin assessment in breast-conserving surgery (BCS) for invasive cancer and ductal carcinoma in situ (DCIS) is an intensely discussed subject. It is well known that insufficient or positive margins are the strongest predictor for risk of local recurrence.

Reexcision rates in BCS for pure DCIS are reported as ranging from 36 to 46% [1, 2] and as 23% for invasive carcinoma and DCIS [2]. Therefore, performing a surgical margin assessment intraoperatively is important. Frozen-section procedures are time consuming and unreliable in assessing DCIS, and intraoperative ultrasound or intraoperative radiography of the specimen provides information only about the size of the noticed lesion or the microcalcifications.

Spectroscopy is a promising technique for intraoperative margin assessment and is currently under evaluation. 5 different groups are working on different devices, but most of these devices have not yet been tested in clinical trials and are therefore not yet usable in the operation room (OR).

Radiofrequency Spectroscopy – MarginProbe®

There are several devices for intraoperative margin assessment that are under evaluation, but the only device that is used in the OR today is the MarginProbe® (Dune Medical Devices, Framingham, MA, USA). This device consists of a disposable hand-held probe and a console (fig. 1).

The probe measures a tissue area of 7 mm in diameter and a depth of a few millimeters. Measurements are performed on the excised tissue. The device quantifies the dielectric properties of malignant and normal breast tissue with radiofrequency spectroscopy and identifies malignant cells in the surgical margin. The measurements are then compared with the electric properties of known tissues in the database of the console and are classified as either normal (negative) or malignant (positive). The console provides a binary representation of the measurement result (fig. 2). Each measurement takes no longer than 1.5 s; so the results can be read by the surgeon in real time.

Three clinical trials have been conducted and the results are consistent with a significant reduction of the reexcision rate by > 50% (table 1). In our German multicenter study that was conducted with only DCIS patients, the results showed a 52% ($p < 0.01$) reduction [5, 6]. Similar data were found in an unplanned subanalysis of the DCIS cases of the US Pivotal trial; the reexcision rate dropped from 37.2 to 13.3% [7].

It is anticipated that the results of the US Pivotal study will lead to the approval of the MarginProbe in the USA in this year.

Diffuse Reflectance and Intrinsic Fluorescence Spectroscopy – a Spectroscopic Tissue Scanner

Another device that is still under evaluation is an optical fiber probe-based spectroscopic tissue scanner. This device combines both diffuse reflectance spectroscopy (DRS) and intrinsic fluorescence spectroscopy (IFS). These spectroscopic tech-

niques are being actively pursued as tools for real-time cancer diagnosis [8]. The combination of both techniques provides information on the metabolic, biochemical and morphological states of tissues, which can differ between malignant and normal tissue. However, both techniques have a relatively short tissue penetration (≤ 1 mm), and conventional fiber probe-based spectroscopic techniques can only examine a small area of tissue (~ 1 mm) at a time [9].

In a recently published paper, Lue et al. [9] presented a portable tissue scanner that is able to scan large tissue samples of up to 20×20 cm (less than 20 min for an area of 8×8 cm). The authors tested the scanner with tissue-simulating phantoms from animal and human breast tissue. They could clearly distinguish between cancerous and normal breast tissue by employing the physicochemical fitting parameters of the tissue using DRS and IFS [9].

To save time, the authors want to further develop the system in order to image up to 6 separate tissue sites simultaneously [9].

Hand-Held Spectroscopic Pen Device – SpectroPen

Another tool currently under evaluation is a hand-held spectroscopic pen called SpectroPen [10]. The device works by using exogenous near-infrared (NIR; 700–900 nm) contrast agents (i.e. indocyanine green, ICG) for the intraoperative detection of malignant tumors. Mohs et al. [10] recently presented their results from using this technique in vitro and in vivo in mice bearing breast tumors. The SpectroPen connects a hand-held sampling head to a spectrometer. This spectrometer can record fluorescence and Raman signals by utilizing an NIR diode laser (emitting at 785 nm). The goal of this technique is to detect tumor cells in the margins of the excised tissue, supported by using albumin-bound ICG or surface-enhanced Raman scattering (SERS) nanoparticles as contrast agents. The device, which is held on the tissue, measures the

Fig. 1. MarginProbe® system.

Fig. 2. Measurement of the dielectric effects of tissue and presentation of the results on the console display.

Table 1. MarginProbe® trial overview

Studies	n	Countries (sites)	Study design	Notes	Positive margin definition	Reexcision rate reduced by
Pre-market						
MAST (Allweis et al., 2008) [3]	293	Israel (11)	device performance as adjunct to SOC vs. SOC, all BCS patients	pilot randomized trial, looking at reexcision rates, tissue volumes, and cosmesis (at 6 months)	1 mm	56% ($p = 0.039$)
Pivotal (Schnabel et al., 2011) [4]	596	USA, Israel (21)	device performance as adjunct to SOC vs. SOC, non-palpable lesions	device used on main specimen only; complete surgical resection is the primary endpoint	1 mm	50% ($p < 0.001$)
Post-market						
German (Thill et al., 2012) [5, 6]	55 ^a	Germany (3)	single arm, pure DCIS patients	device used on main specimen, optional on additional resected tissue	5 mm	52% ($p < 0.01$)

SOC = Standard of care.

^a39 patient interim data reported.

spectroscopic differences of the ICG contrast between the tumor tissue and the normal tissue very clearly and strongly. The tissue penetration depth is about 5–10 mm, depending on the optical properties of the tissue. So far, this device has only been used in animal models; thus, further examinations are necessary [10].

Automated Touch Prep Cytology

Another method for performing an intraoperative margin assessment is the examination by touch prep/imprint cytology. The touch and scrape prep technique are the two different techniques commonly used. During touch prep, the tissue margin is dabbed on a glass slide and fixed afterwards. The scrape prep technique is performed using a scalpel to scratch cells from the margin surface and to transfer them to a glass slide [11]. The largest trial by Klimberg et al. [11] enrolled 428 patients and had an accuracy rate of 99% in correctly diagnosing cancer. However, an experienced cytopathologist is necessary because correct interpretation can be challenging [12].

On this account, studies were conducted that have evaluated automated intraoperative microscopy with the use of immunofluorescent staining to increase the detection rate of cancer cells. The staining protocol takes 20–25 min and an automated microscopic scan of 1 complete glass slide takes between 5 and 45 min, depending on the equipment used. First data showed that this technique renders a cytologist unnecessary [13]. It is expected that, in the future, surgeons will be able to use such an automated microscope in the operating room; however, these results are premature and still in experimental stages.

Radioguided Occult Lesion Localization

For the management of non-palpable breast cancer, accurate localization is essential to achieve complete resection with acceptable cosmetic results. Radioguided occult lesion localization (ROLL) takes advantage of the intra- or peritumoral

injected radiotracer that is already used for sentinel lymph node biopsy (SLNB) to localize the tumor intraoperatively. It is common to use a ^{99m}Tc-labeled human serum albumin macroaggregate, which is injected using ultrasound guidance or by mammographic guidance. The lesion is detected by using a hand-held gamma probe intraoperatively. The edges of the excision are defined as the locus of points surrounding the hot spot where the radioactivity falls off sharply. After specimen excision, the probe is used to check for residual radioactivity at the excision site; if this is present, the excision is enlarged [14, 15]. A recently published study by the European Institute of Oncology in Milan, Italy, enrolled 1,258 patients and described ROLL as a safe and easy technique for managing non-palpable lesions of the breast [15].

Several studies have compared ROLL to wire-guided localization. Most of the studies show a shorter duration of surgical excision and a lower weight of the excised tissue (summarized in [14]). This is confirmed by the data of Martinez et al. [14] who found a significantly shorter mean duration for ROLL but no other statistical differences in other parameters [14]. The ROLL trial from The Netherlands that was presented with preliminary results at the San Antonio Breast Cancer Symposium showed no superiority of ROLL in terms of reexcisions and complete tumor excision [16].

However, in extensive microcalcifications, and especially with the use of multiple wires, the wire-guided localization seems to be superior.

New Techniques in SLNB

Sentinel Lymph Node Detection by ICG Fluorescence Technique

In contrast to the margin assessment, the use of ICG for detecting sentinel lymph nodes (SLNs) is quite well known. It is an appropriate alternative to the common method with ^{99m}Tc; however, the false-negative rate has still a wide range

and the corresponding SLN detection is technically not as precise as detection of a radioactively marked SLN with a gamma probe. Nevertheless, development continues and the technique does not require a facility that is equipped to use radioisotopes. The fluorescence-assisted resection and exploration (FLARE) imaging system is able to visualize for human eyes the invisible NIR region, in video-assisted and real-time mode. Furthermore, it allows an anatomically correct presentation of the SLN [17]. The signal remains in the tissue for only 30 min, which leads to a quick detection of the SLN. Recently published data has shown an excellent detection rate for ICG alone of 100%, ICG and blue dye of 95.0%, ICG radioisotope of 77.2%, and ICG and blue dye and radioisotope of 73.1% [18]. Another study presented a detection rate for ICG of also 100% [19]. If such results are reproducible, then the future use of ICG for detecting SLNs will become more and more common.

Hand-Held SPECT for Three-Dimensional Visualization of the SLN – declipseSPECT

The hand-held single-photon emission computed tomography (Freehand-SPECT) is an extension of the gamma probe by additional use of a navigation unit to generate a three-dimensional (3D) presentation of the radiolabeled SLNs intraoperatively [20]. There are systems used as a top piece in addition to a normal gamma probe.

The declipseSPECT (SurgicEye GmbH, München, Germany) allows the 3D reconstruction of low-energy gamma radiation in the operation field and correlates it anatomically with the patient (fig. 3).

The localization system consists of an optical camera and an infrared localization device. The navigation unit of the system is placed over the patient, and a referencing system is also fixed on the patient. After scanning the operation field with the gamma probe, 3D images can be generated with this device and are visualized on the screen. They can be displayed in real time and information on the depth of a sentinel node is available.

A study conducted by Wendler et al. [21] demonstrated that the 3D images were equivalent to those produced by

scintigraphy and comparable to the gold standard SPECT/CT regarding the visualization of SLNs.

However, the shift of the soft tissue during axilla operation is quite a problem in reconstructing an image, as it comes to a movement of the tissue and the primarily reconstructed image is not consistent with the real tissue localization. To solve this problem, a real-time reconstruction has to be generated. If this will work out in the future, this technique will be used especially for obese patients in order to improve the detection of SLNs.

The SentiMag® System in SLNB

A very interesting device is the SentiMag® probe (Endomagnetics Ltd., Cambridge, UK; Sysmex GmbH, Norderstedt, Germany), which is under evaluation for SLNB and works together with a magnetic tracer (Sienna+™). The SentiMag® system is a non-radioactive system for the detection of lymph nodes based on a magnetic detection principle. It consists of the SentiMag® detector, a hand-held probe, and the magnetic tracer Sienna+. The magnetic tracer that has been used for several years in magnetic resonance imaging (MRI) is injected subcutaneously in or around the lesion the same way as is the radiolabeled tracer. However, the injection can be done by the surgeon himself at least 30 min before surgery. The probe that detects magnetic fields is used equivalently to the common gamma probe.

The results of two unpublished studies from the University College London Hospital (n = 10) and Guy's and St. Thomas Hospital London (n = 53) showed encouraging results, with good concordance to the radioactive method. A multisite European trial (n = 160) is going on. The goal of the study is to establish statistical equivalence for the SentiMag® instrument and the optimally sized tracer Sienna+ to the conventional ^{99m}Tc/Blue Dye combination-based SLN detection (patients receive a triple injection of Sienna+/^{99m}Tc/Blue Dye). If data from the upcoming studies is consistent, this technique will allow an SLNB to be performed anywhere, without substantially changing the working practice.

One-Step Nucleic Acid Amplification

Sensitivity and specificity of the histopathological examination are the fundamental quality criteria for a sufficient intraoperative diagnosis. The one-step nucleic acid amplification (OSNA) assay (Sysmex, Kobe, Japan) is an automated system for the rapid and quantitative detection of cytokeratin 19 (CK19) mRNA with the reverse transcription loop-mediated isothermal amplification (RT-LAMP) method. The amplification is processed isothermally by means of 6 primers and can detect mRNA of CK19 quantitatively without interference by pseudogenes. Calibrated with conventional postoperative histology, this molecular technique yields comparable results intraoperatively and is expressed as micrometastasis, macrometastasis, or no metastasis, depending on the CK19 mRNA copy number amplified in the SLN lysates [22–24].

Fig. 3. In situ visualization of the tumor and the SLN with declipseSPECT.

Fig. 4. Harmonic Focus® curved shears.

This method has been shown to feature high specificity with a low false-positive rate [22–24]. In comparison to an extensive histological examination, several studies have described a sensitivity between 95.6 and 100% and a comparable specificity of 95% [24–26]. The time from the intraoperative SLN assessment to the definite result varies according to the number of SLN (median 37 min for 2 SLN). Isolated tumor cells are not detected due to the set cut-off.

Because of the recent convincing results [23, 24], this technique has been accepted more and more in different countries. In Germany, OSNA is still under evaluation in some single institutions and in the OSNA subprotocol of the SENTINA trial (www.germanbreastgroup.de).

New Surgical Tools

Ultrasonic Dissection – the Harmonic Focus® Device

Ultrasonic dissection is a well-established technique in different surgical fields such as endoscopic and abdominal surgery. The use in breast surgery was evaluated in different studies that focused on mastectomies or axillary dissection (summarized in [27], meta-analysis [28]), but a recently published study by Böhm et al. [27] evaluated the use of ultrasonic dissection in BCS. The authors used the Harmonic Focus® Curved Shears (Ethicon Endo-Surgery, Norderstedt, Germany) (fig. 4) and compared them with scissors in combination with mono- and bipolar electrocautery. The device works with low-frequency ultrasonic energy which creates cellular friction and seals vessels. Moreover, it causes less thermic effects on neighboring tissue because of the lower temperature compared with electrocautery. In their prospective randomized trial, Böhm et al. found no difference regarding the operative time, but less drainage volume in the breast and the

axilla, less intramammary seroma and hematoma, less axillary seroma and less pain in the Harmonic surgery arm. These differences were all statistically significant and the risk of an axillary seroma was even lowered by 70% using the Harmonic scalpel [27]. In contrast to these findings, a recently published meta-analysis including 6 studies comparing electrocautery with ultrasonic dissection in mastectomy did not find any differences [28].

Use of Acellular Dermal Matrices in Breast Reconstruction

The use of acellular dermal matrices (ADMs) in breast reconstruction has increased dramatically in recent years. The ADM has added a new tool to achieve lasting, predictable results in expander/implant reconstruction. The clinical benefits are multiple and include:

- an increased ability of the breast surgeon to define the placement of the inframammary fold (IMF) and the expander/implant position,
- an additional layer of material between the expander/implant and the thin and poorly vascularized skin after mastectomy,
- a larger submuscular pocket,
- a quicker tissue expansion and less time needed to final reconstruction [29],
- and an increased potential for reduction of capsular contracture incidence [30, 31].

ADMs are biological allografts that are produced from cadaveric human skin or animal skin. They are purified extensively; thus, they have no remaining living cellular elements and consist of the original dermal collagen matrix. This matrix is infiltrated by fibroblasts and is revascularized by the host's vessels once it is placed in the patient [32].

To date, there are several ADM products that are commercially available. These include Strattice® and Alloderm® (LifeCell™ Corp., Branchburg, New Jersey), an allograft from pig skin, SurgiMend® (Polytech Health and Aesthetics GmbH, Dieburg, Germany), an allograft from beef skin, Epiflex® (DIZG, Deutsches Institut für Zell- und Gewebeersatz GmbH, Berlin, Germany), an allograft from human skin, and others.

The most common reason to use ADMs in breast reconstruction is to build a subpectoral pocket by fixing the relieved pectoralis muscle in the IMF. The ADM is sutured in between the inferior margin of the pectoralis muscle and the IMF in order to cover the lower pole of the implant/expander that is placed underneath. This technique improves the control of the IMF and leads to a better preservation of the implant location. In case of using an expander, this technique provides additional space to instill more volume at the time of surgery [33].

Since the increased use of ADMs in the last years, their safety and efficacy is well documented in the literature. Sbitany and Langstein [32] summarized the complication rates of 9 studies (table 2) and found the only statistical significant difference to occur in the incidence of seroma.

Outcome	Cohort		p
	Submuscular coverage, %	ADM assisted, %	
Cellulitis/wound infection not requiring surgical intervention	2.8 (1.7–4.0)	3.4 (0.9–6.0)	0.09
Hematoma	1.2 (0.8–1.7)	2.0 (1.8–2.1)	0.11
Seroma	4.3 (2.0–6.6)	8.4 (2.3–14.6)	0.03
Infection requiring expander/implant removal	3.2 (1.5–5.0)	3.4 (2.1–4.8)	0.18
Partial mastectomy flap necrosis	7.2 (4.9–9.2)	9.3 (4.8–13.9)	0.08

Table 2. Complication rates for submuscular versus ADM-assisted reconstruction cohorts in 9 studies (modified from [32])

Complications following revisions with ADM can sometimes occur, such as cutaneous erythema, seroma, and exposure. A cutaneous erythema is most likely associated with an inadequate hydration of the ADM because of persistent cryopreservatives. It is therefore an inflammatory reaction without being a definite infection. Anyway, the use of antibiotics is recommended. Seromas can be avoided or minimized by leaving the drains in the wound for at least 2 weeks. Small seromas (< 20 ml) may disappear without intervention, but larger seromas have to be treated with aspiration [34].

New diagnostic and surgical techniques pose both a challenge and a chance on different levels. In times of a stratified and personalized medicine regarding systemic treatment, these new techniques provide more individuality and less radicality also in breast surgery. In times of short financial resources on the one hand and scientific thirst for knowledge on the other hand, costs and efficacy should be brought into a well-balanced relation.

Disclosure Statement

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Concluding Remarks

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