Abstract: Breast sentinel lymph nodes are still commonly assessed through complete lymph node dissections, which is a time-consuming and radical approach because the nodes are difficult to identify. To prevent false diagnosis and achieve accurate results, minimally invasive, image-guided procedures are applied and constantly improved. The purpose of this paper is to present the currently used imaging modalities ultrasound, fluorescence, single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI) and hybrid imaging methods and comparing their effectiveness for breast sentinel lymph node biopsy. A definition for an ideal imaging system combining efficient minimally invasive techniques with workflow considerations is also discussed. As a conclusion, upcoming imaging methods and their future outlook with areas of advancement are presented.

Keywords: biopsy; breast cancer; image guidance; minimally invasive; sentinel lymph node.

Introduction

In 2015, an estimated 1,658,370 new cases of cancer were diagnosed in the United States, and it is expected that 589,430 people will die from breast cancer. The number of people diagnosed reached nearly 14.5 million in 2014 and is expected to rise to more than 19 million by 2024 in many other countries [5].

In most of the cases, the cancer spreads from loci to other regions of the body through the lymphatic system.

Clinical setup

SLN status remains one of the most important prognostic factors in breast cancer. A negative SLNB result indicates that cancer has not developed the ability to spread to nearby lymph nodes, whereas a positive result indicates that cancer is present in the SLN and may also be in the nearby lymph nodes. Hence, it is very essential to navigate all the SLNs in the breast cancer to prevent from omitting metastasis [1, 11, 18].
Methods

The clinical workflow for image-guided breast SLNB is as follows:

- Injecting tracer: The surgeon injects (see Figure 2A) a blue dye and radioactive material (e.g., Tc-99m) into the tissue next to the tumor. The tracer gathers in the SLN and serves as an indicator for the navigation as shown in Figure 2B.

- Identification: The surgeon uses an imaging modality to identify the SLN or looks for lymph nodes that are stained with the tracer. Then, the SLN samples are collected using the biopsy procedure.

- Pathological assessment: The SLNB specimen is pathologically assessed to determine the presence of tumor cells or micrometastases, which is used as an indicator for the SLN staging; hence, hematoxylin and eosin (H&E) staining is applied. Tests on estrogen, progesterone receptor, HER2 and Ki-67 are performed as well to determine the biological subtype of the breast cancer when tumor cells or micrometastases are present in the specimen [11]. Based on the resulting definition of the tumor subtype, the extent of disease is determined, followed by subsequent therapy [22].

Systems and tools

Currently, SLNB is performed as an open surgery (Figure 2B) and, with image guidance, could lead to a true minimally invasive procedure, maybe even in an outpatient setup. The below-listed imaging systems are the most commonly used image guiding systems for SLNB procedures. The imaging system is chosen based upon some of the many parameters like specificity, sensitivity, accuracy, availability, economics, procedure correctness and quality assurance in the diagnosis.
Ultrasound (US)

Alvarez et al. reported a reduced level of false negative SLNs with 94.8%–100% specificity but low sensitivity using intra-operative ultrasonography [1]. Figure 3A shows the US image of a fine biopsy needle in sampling the SLN under US guidance.

Contrast-enhanced ultrasound (CEUS)

CEUS can also be used to identify SLNs. Microbubbles composed of phospholipid-stabilized membranes and sulfur hexafluoride gas are usually used as the contrast agent. The areas of contrast agent accumulation in the SLN can be detected when the US probe is moved along the lymphatic channels. In many cases, the contrast agent remains in the SLN for a few minutes; when no lymphatic vessel is located, more microbubbles are injected. The conventional grayscale window of the US image is synchronously applied to confirm the presence of a defined SLN. Xie et al. recorded 81.8% and 86.2% of sensitivity and specificity using CEUS, respectively [38].

Photoacoustic tomography-ultrasound (PAT-US)

Photoacoustic imaging is an emerging hybrid technology that uses short laser pulses to irradiate chromophores in the targeted tissue. Laser pulses induce higher localized thermo-elastic expansion in the region of the SLN. The selectivity of the laser in this method is very high, which enables differentiation between the SLN and the surrounding tissue. The procedure is navigated by an US transducer placed on the breast. Hence, deep SLN mapping can be measured using the photoacoustic signals non-invasively. Figure 3B shows an in vivo PAT-US image of the SLN and needle for various photoacoustic amplitudes [10, 17].

Fluorescence imaging

Fluorescence imaging is used for detecting the tumor and nodal margins for navigating the SLN or the nearby SLN. Near-infrared (NIR) light in the wavelength of 700–900 nm causes low tissue autofluorescence because of reduced absorbance and scattering. Fluorescence mapping causes low tissue autofluorescence with good penetration depth and relatively high signal-to-noise ratio. Simultaneous color video is also acquired and merged by superimposing in real-time with the NIR image to mark the SLN location. Troyan et al. reported 100% sensitivity to visualize the SLN clearly. NIR fluorescence and color-coded images of the lymphatic vessel draining the SLN are shown in Figure 4 [33].

Scintigraphy

In lymphoscintigraphy, the patient is imaged using a hand-held gamma camera with the low-energy, high-resolution parallel hole collimator as shown in Figure 5 [34].

Freehand single-photon emission computed tomography (Fh SPECT)

An IR optical tracking system is used to determine the relative position and orientation of the patient in relation to the probe. Creating a Fh SPECT image is shown in
Figure 5: The surgeon traces the radioactive material using the hand-held gamma camera to identify the breast SLN [30].

Figure 6: Fh SPECT procedure and scintigram for identifying SLN in the breast tumor. (A) Surgeon holding freehand SPECT (Fh SPECT), with the postoperative image showing no remaining activity along the radioactive injection site marked with a black star, (B) preoperative scintigram from the Fh SPECT of a patient with SLN (arrow) [4].

Figure 4: From left to right: color-coded image of SLN, NIR fluorescence image of the lymphatic vessel (arrowhead) draining to the SLN (arrow) located deeper into the tissue and color- and NIR-merged image of draining lymphatic channel into the SLN [29].

Figure 6A, with the preoperative three-dimensional (3-D) image reconstructed along with preoperative scintigraphy as shown in Figure 6B. The scintigram image localizes the region of the SLN near the tumor spot. Bluemel et al. reported a >89.7% SLN detection rate using the conventional gamma probe and Fh SPECT [4]. In a mobile hybrid Fh SPECT system, the tumor density is staged, enabling registration of a Fh SPECT image on the US plane as shown in Figure 7. Here, the image is superimposed with a real-time intervention needle guidance in the US plane [15].

Magnetic resonance imaging (MRI)

In the MRI of the breast, an intravenous contrast agent like gadolinium diethylenetriamine pentaacetic acid
(DPTA) or a sterile aqueous suspension of 60-nm superparamagnetic carboxydextran-coated iron oxide particles is injected. These contrast agents have a diameter similar to that of the standard particle size of a radioisotope tracer. The particles gather in front of SLN as a contrast to the surrounding tissue. The radio frequency signals are generated by excitation of the magnetic particles in tissues exposed to the strong magnetic field. The constructed images localize the tumors by highlighting areas containing dense SLN network [14]. Reddy et al. reported 94%–100% sensitivity, with a lower specificity of 37%–97% [28].

### Ultrasound-magnetic resonance (MR-US)

In modalities like US and real-time MR, vitamin E soft gel is used for registration of the breast region. Electromagnetic sensors are coupled to the ultrasound probe and for navigation. Pons et al. reported 96.3% sensitivity and a very low specificity of 18.8%. In a few systems, color change in the lymph nodes also helps in faster SLN identification [2]. Figure 8 shows real-time MR-US mapping of the lymph node [24].

### SLNB image modality assessment

Table 1 gives an overview of the clinical results from the recent years for all the mentioned imaging modalities.

Table 2 shows the comparison of the suitable imaging modalities based upon the clinical data, literature and personal experiences. Certain clinical parameters are considered for assessing the imaging modality based on various criteria applicable in clinical practice. The “+” sign in the assessment shows the increasing level of preference to choose any mentioned imaging system and the “−” sign indicates the decreasing level of chances to reject the imaging method, with “0” as the mid-point to the choice.
of acceptance. The outlook table is considered for identifying a preferred imaging modality for breast SLNB.

Factors such as training the surgeon and gaining experience with a complex imaging method can also eliminate the choice of a costlier system. It is necessary to know whether the imaging system can improve the procedure time, specificity, sensitivity and accuracy. Radiation protection and handling of the system without any harm to the patient and the medical staff is another factor in identifying the target with higher resolution and lower artifacts. In many cases, functional activity of the SLN would be required, which is available in very few imaging methods. Consequently, it is a phenomenon to think about the evolution and development of the system to couple other imaging modalities to use with it in accordance with the available minimally invasive surgical tools.

**Guidelines on selection of imaging methods**

CEUS increases the number of patients proven to have ALN involvement preoperatively, thereby reducing the SLN biopsy rate by more than 50% using conventional gray-scale sonography [32]. Fluorescence imaging precisely guides intraoperative positioning, thereby helping the surgeons to distinguish between normal and malignant tissues with labels [7].

The following are significant factors ordered by importance for choosing the image guidance method in breast SLNBs:

1. Highly targeted
2. Short procedure duration
3. Spare healthy lymph node
4. Quick recovery
5. Real-time intervention and biopsy
6. Minimally invasive protocol
7. Molecular-level differentiation
8. Reduced radiation exposure

**Limitations**

The human eye cannot see deeper than the tissue surface, while palpation may be able to distinguish tumor nodes from the surrounding tissue, in a few cases, better than imaging. There are several chances to get false-negative results because multiple lymph nodes are removed at the same time in a few systems [31]. Preoperative interventions are currently limited to use in the operating room because of their large hardware footprint, slow image reconstruction, lack of resolution, use of ionizing radiation, prohibitive cost and specialized operator requirement. The relatively low sensitivity and limited spatial and temporal resolution in the following image guidance systems limit in vivo applications, which are not favorable in some cases. Similarly, MRI examinations are too expensive to be routinely implemented in all patients.

US: US requires direct contact with tissue and only visualizes a thin slice of the surgical field-of-view (FOV). In ultrasonography, signals overlap sometimes, limiting the ability of US to accurately stage the SLN even when there are signs of metastatic disease. US cannot differentiate SLNs from downstream lymph nodes.

Fluorescence imaging: NIR light is invisible to the human eye, so a special optical imaging system is required in addition to seeing it in the surgical field. A surgeon would feel uncomfortable to simultaneously switch and

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**Table 2:** Outlook table: Assessment of imaging modalities suitable for breast SLN biopsy – a method of approach for the decision-making process in choice of preference based on required criteria [9, 12, 20, 26, 27].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ultrasound</th>
<th>Fluorescence imaging</th>
<th>Scintigraphy</th>
<th>Fh SPECT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability in surgery</td>
<td>0</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Complexity/training</td>
<td>0</td>
<td>0</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Cost</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>−</td>
</tr>
<tr>
<td>Resolution</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Time</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Harmfulness</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Artifacts</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Anatomical information</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>Functional imaging</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>−</td>
</tr>
<tr>
<td>Use of minimally invasive tools</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Fusion with other imaging modalities</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

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operate with different tools in a sterile environment. In optical-based imaging systems, sensors try to mitigate its effect via various vertical trenches between photo diodes. Optical crosstalk is not completely eradicated; this effect causes light to reflect and refract multiple times within the imaging system, such that light to be absorbed by one photo-detector will be absorbed by other neighboring photo-detectors [23].

**Recommendations**

Imaging methods are expected to be real-time with high sensitivity and specificity. Lymphoscintigraphy and US-guided SLNB are safe, simple and highly reliable, with minimal morbidity or complications in patients, scintigraphy being a recommended system [11]. By coupling scintigraphy with optional therapy, it is anticipated that the procedure will also guide treatment planning and monitor treatment response. This could improve patient outcomes, reduce hospital revisits and enhance the quality of life, with less lymphedema or tissue swelling. Table 3 shows the recommended essential characteristics and the features for an ideal imaging system that could be better suited for breast SLNB. An overview of the expected image guidance system for future breast SLNBs is shown in Figure 9 [7].

**Summary**

Breast tumor metastasis usually spreads primarily via the lymphatic system. Image-guided SLN mapping and biopsy is a relatively new technique for staging and treating patients with breast cancer. SLNB has become widely adopted for selective lymph node dissection, with maximum benefits and minimal risk for the patient. Visualization of SLNs at distant depths using US, scintigraphy, Fh SPECT, fluorescence imaging and MRI provides helpful guidance for SLN mapping and diagnosis as well as guiding the surgeon in the biopsy procedure.

**Table 3:** Characteristics of an ideal real-time image guidance for breast SLNB [23].

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative</td>
<td>Use in the operating room</td>
</tr>
<tr>
<td>Real-time</td>
<td>Simultaneous image acquisition, display</td>
</tr>
<tr>
<td>Miniaturized</td>
<td>Hand-held applicator</td>
</tr>
<tr>
<td>High specificity</td>
<td>Low false-negatives</td>
</tr>
<tr>
<td>High sensitivity</td>
<td>Detection sensitivity</td>
</tr>
<tr>
<td>High resolution</td>
<td>Interrogation of the tumor boundary</td>
</tr>
<tr>
<td>Wearable</td>
<td>Ergonomic, hands-free movement</td>
</tr>
<tr>
<td>User-friendly</td>
<td>Minimal training and less-specialized operator</td>
</tr>
</tbody>
</table>

**Figure 9:** Outlook of the future hybrid breast SLNB system.
Educating the surgeon is also a crucial factor in handling the patient during the interventional procedure. There is significant clinical evidence investigating the utility of breast SLNB, although larger studies and clinical evaluations are required to assess any individual image guiding system to gain additional breast sentinel biopsy accuracy. If the clinical value is determined and the imaging systems can provide further information to avoid false negatives, the surgeons would desire to have such a system in a minimally invasive surgical environment [7, 8, 22, 25].

Conclusion

In patients with early breast cancer and small-volume locoregional disease, mastectomy has shown to offer no survival benefit and has largely been abandoned. It is of great clinical relevance to select the appropriate imaging tool to perform breast SLNB, avoiding ALND. This could impinge cost-saving and patient health factors. It also depends on the surgeon’s skill and experience in operating the instrument. Through the development of better intraoperative imaging systems and other technologies in breast SLNB, surgeons can reduce false-negative results.

With current efforts to miniaturize the technology, it is evident that imaging-assisted methods could become an enabling platform for oncological intervention, therapy and diagnosis. Superimposing the intraoperative and preoperative images with the real-time simulated results on virtual reality spectacles could give the surgeon a precise location of the SLN. A hybrid imaging system with accurate visualization, thus enabling a faster intervention in a miniaturized setup, is required. It could enable SLNB in an ambulatory setup, bringing the procedure out of the hospital in a low-cost atmosphere. If the ongoing clinical studies can prove the beneficial features of image-guided SLNB, the trends of reliable, rapid diagnosis in an ambiance with faster biopsy and minimally invasive therapy would be the next decade’s breakthrough [1, 11, 19, 27].

Acknowledgments: The authors would like to thank all the researchers from INKA Intelligent Katheter, Otto von Guericke University, Magdeburg, Germany, who helped and supported in the writing of this paper.

Conflicts of interest: Michael Friebe is on the advisory board of Surgiceye GmbH, Munich, Germany, a startup company developing diagnostic imaging systems.

References


