Sentinel Lymph Node Mapping: Current Practice and Future Developments

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Anatomy

Historically, lymph node groups are designated based on anatomical location. The axillary vein group is located superior and lateral to the axilla and runs along the axillary vein. However, these nodes may course lower below the vein as much as 3–4 cm, as an apron of nodes, or as a linear chain of nodes. It has always been taught that these lymph nodes receive most of the lymph draining from the upper extremity. The external mammary or anterior or pectoral groups are located at the border of the pectoralis minor muscle in association with the lateral thoracic vessels. These are the primary lymph nodes receiving lymph drainage from the breast. The scapular or posterior or subscapular group, located posteriorly in the axilla is closely associated with the subscapular vessels. These lymph nodes drain the posterior region of the neck and the posterior aspect of the shoulder region. Collectively, these nodes are termed level I nodes. The central group nodes, located posteriorly to the pectoralis minor group along with the interpectoral nodes of Rotter's nodes comprise the level II axillary nodes. The subclavicular or apical group, located medially to the pectoralis minor muscle and extending to the apex of the axilla, are considered level III nodes. These nodes receive lymph from all the other groups of axillary lymph nodes and become the lymphatics forming the thoracic duct on the left and on the right, the right lymphatic duct (Fig. 20.1). In addition to the axillary nodes, the breast lymph also drains into internal mammary nodes located retrosternal between the costal cartilages commonly to the second and third intercostal spaces approximately 2–3 cm lateral to the sternal margin.

Until recently, the lymphatic drainage of the arm was not considered when removing lymph nodes. The majority of draining lymphatics from the distal arm enter the axilla along the volar surface of the upper arm [1]. Axillary reverse mapping (ARM) maps the drainage of the arm as it traverses the axilla. Figure 20.2 demonstrates that this anatomy varies substantially from the traditional teaching, that the arm lymphatics course within a centimeter of the axillary vein (Fig. 20.2).

Indication for Staging Lymph Nodes and Development of SLNB

The current practice of staging the axilla varies widely, but for the clinically node-negative patient with invasive ductal cancer, should almost always include a sentinel lymph node biopsy (SLNB). The primary route of lymphatic drainage

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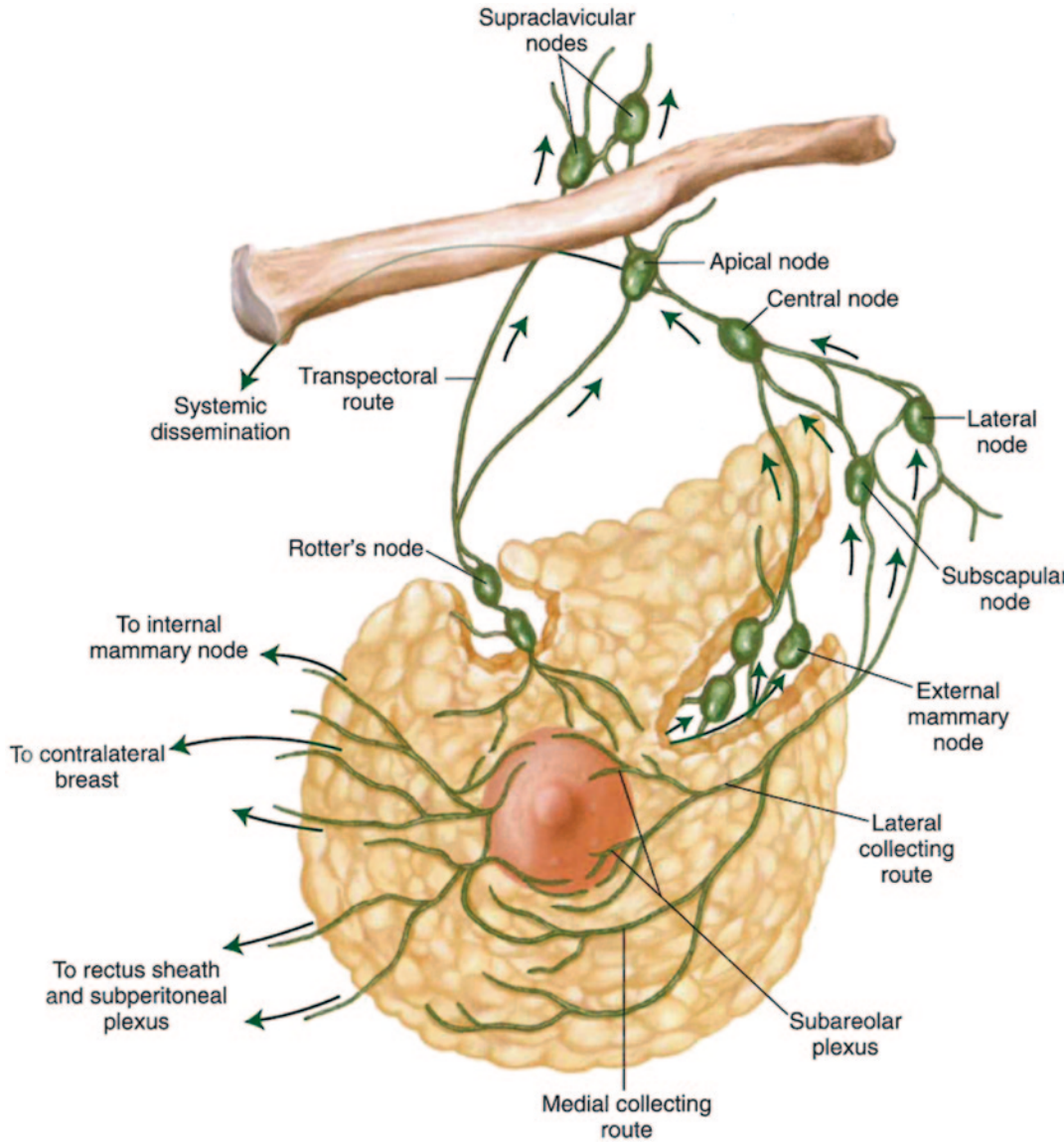

Fig. 20.1 Lymphatic drainage of the breast [33]

of the breast is through the axillary lymph nodes with more than 75 % of the lymph from the breast passing to the axillary lymph nodes [2]. Separate lymphatic drainage pathways for the breast and the upper extremity as well as the back can run side by side when crossing the axilla. It has also been demonstrated that the lymphatic drainage is highly variable between subjects. Only in a small percentage of cases (<5 %) the lymphatic drainage of the breast and the arm completely overlap [3]. SLNB should be considered in clinically node-negative patients T1–3 regardless of multicentricity who have not had previous axillary surgery. It may also be useful in patients with aggressive large (>2.5 cm) ductal carcinoma in situ [4]. Axillary status in breast cancer patients continues to serve as a major predictor of outcome while also influencing decisions for adjuvant therapy.

The potential sequele of axillary lymphadenectomy includes local sensory dysfunction, reduced shoulder mobility, and lymphedema. Ranging

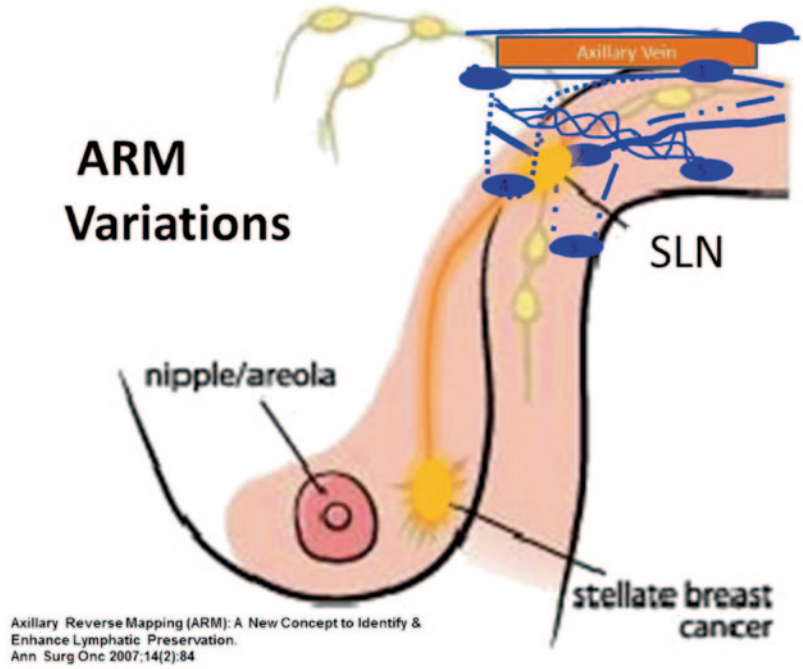

Fig. 20.2 Variations in the lymphatics draining the arm as they course through the axilla [31]

from 13 to 77 % after axillary lymph node dissection (ALND), lymphedema is the patient's most dreaded side effect of axillary surgery adversely affecting quality of life, job performance, and health-care costs. SLNB was designed to ameliorate the morbidity of ALND while still offering accurate staging of the patient. Despite the less invasive dissection, reported lymphedema rates for SLNB still range from 0 to 13 %, with larger studies reporting a range of 7–8 %.

Many different variations in mapping technique have been described. Type and number of agents, including dual versus single agents have been researched, as well as the site and timing of the material that is injected (i.e., injectate).

Agents

SLNB was originally described by Krag et al. with unfiltered 99m Technetium sulfur colloid (Tc99) [5, 6, 7] which has been validated in multiple studies and has become the gold standard with or without blue dye. Variations of Tc99 using filtered or unfiltered or as a nanocolloid in a human albumin base have also been used. Radioactive handling difficulties and potential radiation exposure have led to a plethora of ways to map lymph nodes without radioactivity.

Giuliano et al. first reported the use of isosulfan blue dye for mapping SLNB in breast cancer [8]. Since that time, other blue dyes used have included patent blue dye, which is the gold standard in the UK and Europe as opposed to its isomer isosulfan blue which is mainly used in the USA [9]. Increasingly, many countries have been using diluted methylene blue for SLNB as it is a cheaper alternative and more readily available although more caustic with higher reported local reactions and necrosis. Indigo carmine is also used primarily in Asia for SLNB with reportedly good localization rates [10]. The main drawbacks to blue dye are major allergic reactions, which occur with less than 1 % frequency but have resulted in death [11].

Recently, studies have used a Lymphoseek (technetium Tc99m tilmanocept) injection for subcutaneous, intradermal, subareolar, or peritumoral use. Lymphoseek with 0.5 mCi of radioactivity is given at least 15 min to within 15 h prior to SLNB [12]. In this small study, 13 centers contributed 148 patients given Lymphoseek and vital blue dye with a 99 % concordance rate.

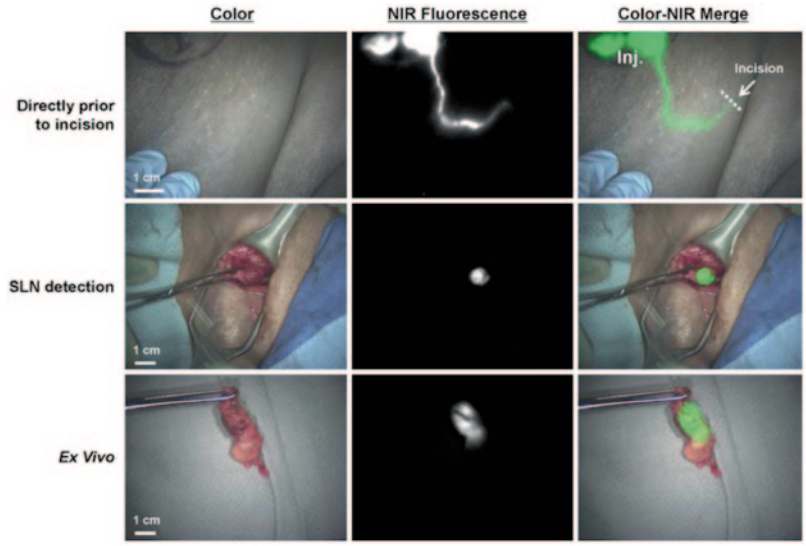

Fig. 20.3 Near-infrared (NIR) fluorescence-guided sentinel lymph node (SLN) mapping. The *top row* shows percutaneous NIR identification of afferent lymphatic channels flowing away from the injection site (*Inj.*). The planned incision site, based on the presumed location of the SLN, is shown as a *dashed line*. *Middle row:* real-time fluorescence identification of the SLN directly after incision. *Bottom row:* ex vivo image of the SLN. Scale bars 1 cm. Camera exposure times were 150 ms (*upper row*), 55 ms (*middle row*), and 50 ms (*bottom row*) [14]

Fluorescent dyes in particular isocyanogreen dye (ICG) have been used for SLNB, particularly in Asia. Until recently, ICG was used only experimentally when a handheld device (PDE®, Hamamatsu, Japan) to image near-infrared fluorescence attained Food and Drug Administration (FDA) approval and began to be marketed in the USA [13]. ICG mapping can be seen through the skin but tends to map to more nodes than other agents (Fig. 20.3) [14].

Recently, magnetic particles (superparamagnetic iron oxide, SPIO) have been used for sentinel lymph node (SLN) localization in the SentiMag study which compared SPIO to radioguided localization. This prospective multinational noninferiority study demonstrated a similar detection rate with the magnetic tracer (Sienna+®, Endomagnetics, Basel, Switzerland) and a handheld magnetometer, the SentiMag®. A similar average number of SLNs was detected and a higher per patient malignancy detection rate was found for the SPIO tracer [15]. The technique is straightforward and there is no associated radioactivity. SPIO is not FDA approved for SLNB in the USA.

As of yet the optimal size of particles and volume of injectate is not settled and will be the reason for further development of methods and tracers for SLN mapping.

Site and Timing of Injections

A plethora of studies have been generated describing various sites of injection including peritumoral, subareola, dermal, subdermal, and intratumoral [16]. Even the timing of injection has come under scrutiny with studies performing the injection of radioactive colloid anywhere from 30 min to 24 h preoperatively. Most recently, studies have described intraoperative injection of technetium, which can be performed dermally or in the subareolar complex with great success and accuracy and with the added advantage of being painless for the patient, avoiding vasovagal episodes and avoiding scheduling coordination issues with the operating room. In a study of 699 patients, intraoperative injection of Tc99 identified 98.6% of SLNs, 100% of intraoperative dermal injections (only used in six patients

with upper outer breast scars) and dual tracer with isosulfan blue dye in 94.8% [17].

Lymphoscintigraphy before SLNB is not uniformly performed and is of questionable value in mapping the breast [18]. Klauber-deMore et al. reviewed 13 studies in which lymphoscintigraphy was performed. The lymphoscintigram mapped to the internal mammary node (IMN) in 12.7% (0–35%) of patients. Eight of the studies report on IMN status and showed an18% IMN positivity (15/83 patient). In five studies that evaluated lymphoscintigraphy mapping, only 2 of 15 patients had positive IMN when the axilla was negative. In addition, techniques other than peritumoral injection map to these nodes even less [19, 20].

In cases where there is potential for significant drainage to the internal mammary vessels we recommend ultrasound (US) of the second and third intercostal spaces for visualization of suspicious internal mammary nodes.

When the breast fails to map additional injection of saline (20–40 cc) can be performed with massage to increase chances of mapping. When no SLN is found, ALND is performed [21].

Mapping of Multicentric Lesions

The drainage of the breast seems to be more important than the location of the tumor and thus localization of the SLN [22]. Within the EORTC 10981−22023 (AMAROS) trial the SLN was identified in 96% of patients with known multicentric tumors and 98% with unifocal tumors demonstrating an expected higher rate of positivity with multicentric disease (51%) compared to 28% in the unifocal group [23]. Importantly, the percentage of nonsentinel nodes were similar in each group, 40 and 39%, respectively.

Mapping After Neoadjuvant Chemotherapy

At this time, there is no consensus whether and when to perform a SLNB in patients receiving neoadjuvant chemotherapy. It has been shown that about 40% of known positive lymph nodes are converted to negative with chemotherapy and advocates of SLNB after chemotherapy point out that these patients could be spared an ALND. However, reported false negative SLNB rates after neoadjuvant chemotherapy are higher than those performed before systemic chemotherapy [24]. Dual mapping is recommended as the results of the ACOSOG Z1071 (Alliance) clinical trial study demonstrated improved sensitivity with radioactive and blue dye mapping [25].

Axillary Recurrence After a Negative SLNB

There have been seven randomized controlled trials demonstrating that patients with negative SLNs do not require ALND despite the known ~10% false negative rate. The rate of axillary recurrence is referred to as the clinical false negative rate. Van der Ploeg and colleagues performed a systematic review and meta-analysis of axillary recurrence in SLNB negative breast cancer patients [26]. In 48 studies encompassing 14,959 SLN negative breast cancer patients followed for a median of 34 months, 0.3% of patients had an axillary recurrence with the highest sensitivity rates and lowest recurrence rates seen with Tc99, superficial versus deep injections and the use of immunohistochemistry staining.

Completion ALND with Positive Nodes

In 2011, Giuliano et al. reported on the ACOSOG Z-0011 trial including patients with tumors smaller than 3 cm and a clinically node-negative axilla. Patients, who had one or two positive nodes at SLNB, were randomized to breast conservation therapy (BCT) with completion ALND or BCT with no further treatment of the axilla. The study did not accrue all its patients and may be underpowered. However, at 6.3 years median follow-up no statistically significant difference was found in regional recurrence or survival. Details of the radiation fields have not been reported, but by protocol axillary radiation was not

planned. Multiple small retrospective articles totaling 1035 patients with positive SLNB and no ALND report less than 2% axillary recurrence with 28–82-month follow-up [27]. In general, Europe has been less accepting of these data than the USA where many surgeons have stopped doing ALND under Z-0011 criteria.

Failure of Mapping

Technical factors including surgical experience and the 20–30 cases that it takes to become proficient in SLN mapping are the only ones that surgeons can predict and control. Dual versus single injection can aid the novice in locating SLNs. The inexperienced surgeon can validate his technique with a completion ALND. Palpation as well as intraoperative US of the axilla can help locate nodes that have low counts and are hard to find as well as nodes with high tumor burden that did not take up the radioactivity or blue dye or were just a technical miss (took up the dye but were not located by the surgeon) [28].

Factors that cause false negative SLNB and therefore not under control of the operator are tumor/patient factors including large size, upper outer location, older and obese patients, lobular or poorly differentiated ductal histology or partial to complete replacement of non-SLN with tumor and larger tumor size [29, 30].

Axillary Reverse Mapping

ARM has been described by Klimberg and colleagues as a technique to identify and separate the lymphatic drainage of the arm from that of the breast in an attempt to minimize unnecessary disruption of the arm lymphatics [31, 32, 33]. It is useful for ALND as well as SLNB, allowing visualization and protection of the arm lymphatics during lymphadenectomy, resulting in significantly reduced postoperative lymphedema while maintaining oncologic safety. It involves injection of blue dye in the upper inner volar surface of the arm simultaneously with breast lymphatic mapping. When performing SLNB, blue

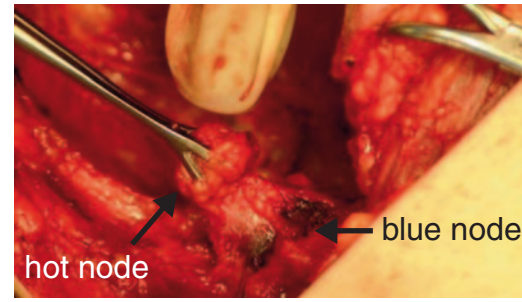

Fig. 20.4 Hot radioactive node in Babcock being dissected free from the blue nonradioactive arm node

lymphatics can be seen in ~30% of patients and during an ALND greater than 70% of the time. In ~10% of patients, the ARM node was separate but juxtaposed to the SLN and therefore potentially in harm's way if not distinguished by the blue dye (Fig. 20.4). When non-SLN blue nodes were resected, the positivity rate was low as were follow-up regional recurrence rates. Lymphedema for SLNB was less than 1% and ALND lymphedema rates were less than 6%, which compares favorably with national studies. When blue nodes are resected, the remaining lymphatics are reanastomosed end-to-end, which results in a very low lymphedema rate.

Boccardo and colleagues have developed what is called lymphatic microsurgical preventing healing approach the so-called LYMPHA procedure. This is basically performing a lympho-venous anastomosis after excision of the node rather than anastomosing end to end [34]. Lympho-venous anastomosis of the lower arm has also been used for moderately successful reversal of lymphedema.

No Surgical Staging

Recurrence scores from genomic assays on the primary tumor provide a quantitative estimate of the risk of distant recurrence and reveal the underlying tumor biology that traditional measures such as patient age, tumor size, and tumor grade, cannot provide. The recurrence score does not predict lymph node involvement. In fact lymph node involvement has been shown to be additive

to recurrence scores. Therefore, at this time, prognostic information is still gained by performing an SLNB or even an ALND.

Drawbacks of axillary irradiation without dissection are that pathologic node status is unknown, complexity of matching fields, risk of arm edema, and risk of brachial plexus injury. Recurrence appears to be the same; however, mixed reports indicate that the lymphedema rate might be higher at longer follow-up. Others argue that the omission of ALND would affect the choice of chemotherapy. Preliminary reports from the EORTC AMAROS trial found no difference in use or type of systemic therapy in patients randomized to ALND versus axillary radiation therapy (XRT) [35].

Future Developments

Percutaneous biopsy of SLN is common using US (Fig. 20.5) and avoids taking the patient with a clinically suspicious axilla to the operating room prior to neoadjuvant chemotherapy. However, occult metastases require excision of the lymph node for detection. Kim and colleagues have developed a method using ICG in a rat model and a novel handheld photoacoustic probe for image-guided needle biopsy (Fig. 20.6). Optical fibers are used to deliver pulsed laser light and direct photoacoustic image-guided insertion of a needle into lymph nodes identified by ICG. This highly sensitive method is being tested in the clinic and may provide less invasive staging of micrometastases [36].

Real-time MRI-navigated US may have a role in confirming positive nodes on MRI with much greater sensitivity than second-look US. Real-time US with supine MRI using a volume navigation technique increases the detection and biopsy of positive SLNs [37].

High-resolution, handheld cameras have been developed for nonpalpable breast localization plus SLNB or the so-called SNOLL technique (sentinel node and occult lesion localization) that is common in Europe and beginning to be adopted more widely in the USA [38]. These handheld gamma cameras enable intraoperative scintigraphy in real time.

The development of hybrid single-photon emission computed tomography/computed tomography (SPECT/CT) cameras can increase the precise anatomical localization of SLNB prior to surgery as opposed to scintigraphy. They also may be important in evaluating novel tracers [39].

Eleven quality indicators for the performance of SLNB have been identified based on a consensus of Quan and colleagues [40]. These include: pathologic evaluation protocol, pathologic reporting by AJCC guideline, protocol for injection of radiocolloid, proper identification of SLN, SLNB performance in eligible patients, SLNB concurrent with lumpectomy/mastectomy, completion of ALND for positive SLNB, SLNB performance in ineligible patients, axillary node positivity rate; number of nodes removed; axillary recurrence rate.

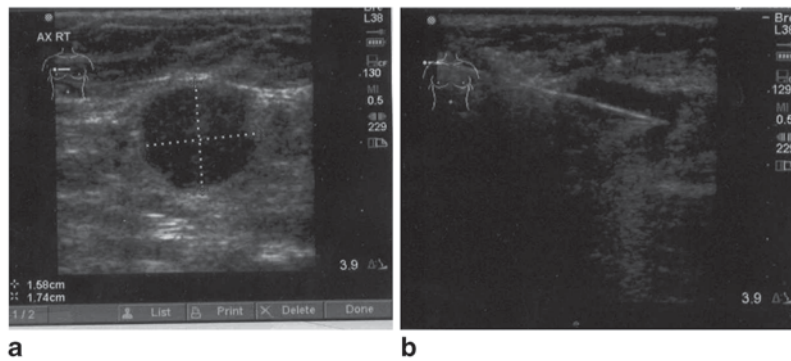

Fig. 20.5 **a** Ultrasound (US) demonstrating a positive node with rounded shape, hypoechoic, and without cortical structure. **b** US-guided needle biopsy to confirm nodal positivity

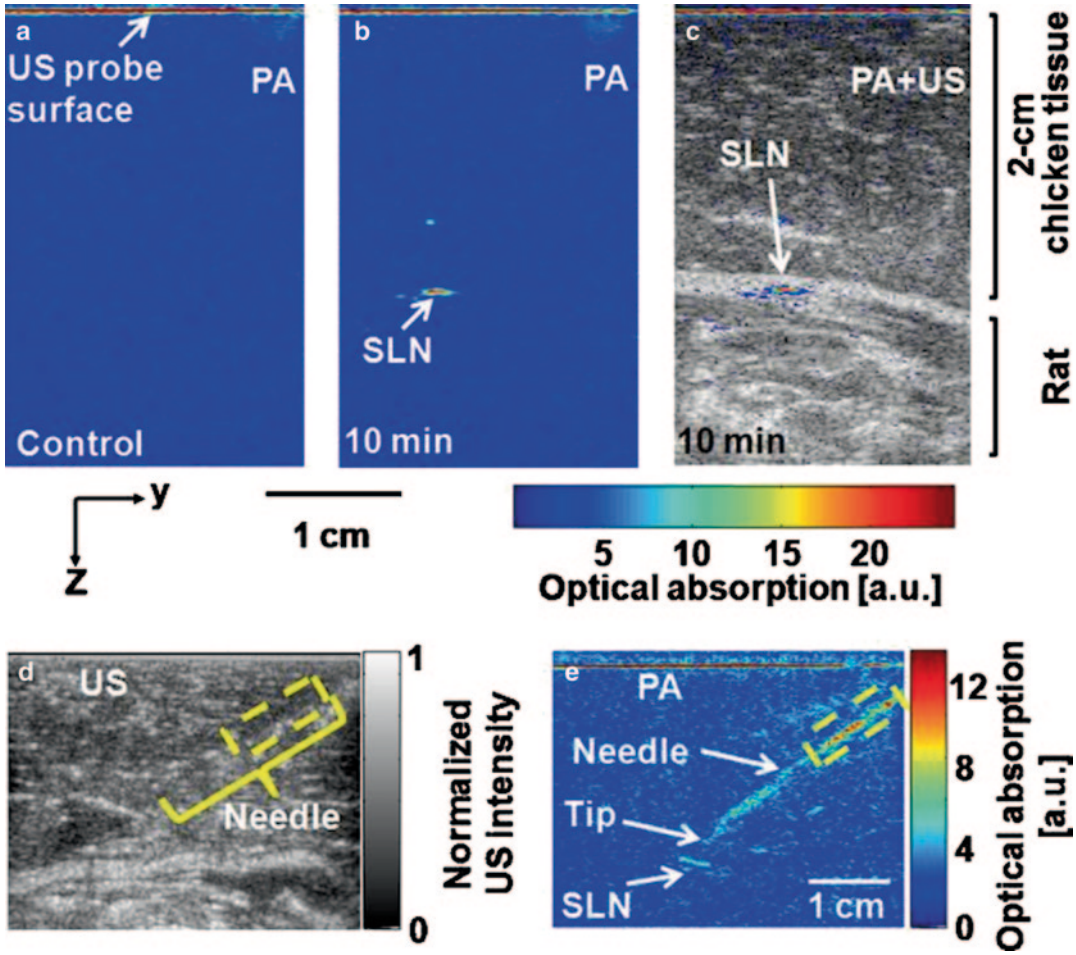

Fig. 20.6 Handheld array-based photoacoustic probe for guiding needle biopsy of SLN In vivo photoacoustic (*PA*) and ultrasound (*US*) B-scan imaging of an sentinel lymph node (*SLN*) dyed with indocyanine green (ICG) and guiding of a biopsy needle: **a** control PA image acquired before ICG injection, **b** PA image taken 10 min after ICG injection, **c** overlaid PA (pseudocolor) and US (*gray* scale) images, **d** US guidance of a biopsy needle, and **e** PA guidance of a biopsy needle. The image contrasts were calculated using the values within the regions of interest indicated by the *yellow dotted boxes* in **d** and **e**. (Color online only.) [36]

Summary

The literature will continue to be showered with various conjugates to Tc-99 and new dyes as well as new scanning devices in an effort to improve detection and accuracy of SLNB. At this time SLNB remains an important addition to hormonal and genomic information on tumors, however, as oncogenomics becomes more accurate SLNB may become obsolete.

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