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New Technologies for Sentinel Lymph Node Detection

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Keywords

Computed tomography lymphography · Fluorescein · Indocyanine green · Microbubbles · Sentinel lymph node biopsy · Superparamagnetic iron oxide, SPIO

Summary

The 'standard of care' method for sentinel node mapping is the combination technique using radioisotope and blue dye although some centres use radioisotope or blue dye alone. Radioisotope usage requires licensing, has regulatory issues around handling and disposal of waste, and logistically may be unavailable or difficult to implement in some centres or less developed country. This has led to the development of alternative methods such as superparamagnetic iron oxide (SPIO), fluorescence techniques using indocyanine green (ICG) or fluorescein, computed tomography lymphography, and contrast-enhanced ultrasound scan (CEUS) using microbubbles. The newer techniques will potentially enable a more widespread adoption of this procedure; however, a common barrier for these techniques is the lack of standardisation and no randomised trials to evaluate their effectiveness against the current standard of care. Furthermore, many of these techniques are more costly and may become redundant in node-negative patients with small tumours if ongoing trials show that sentinel node biopsy offers no additional benefit to grey-scale axillary ultrasound. This review discusses the new techniques for sentinel node mapping that have emerged including their pros and cons.

Introduction

Sentinel node biopsy has become cemented into routine practice and the management of early breast cancer. The 'standard of care' method for mapping is the combination technique using radioisotope and blue dye although some centres use radioisotope or blue dye alone. These methods have stood the test of time and consistently achieve a more than 90% identification rate, less than 10% false-negative rate, and have demonstrated oncological safety in randomised trials compared with axillary lymph node dissection [1–5]. Radioisotope usage requires licensing, has regulatory issues around handling and disposal of waste, and logistically may be unavailable or difficult to implement in a small centre or less developed country with limited or no nuclear medicine capacity. There are access issues even in the UK, and in some countries like India less than 1% of centres use radioisotope for sentinel node biopsy. The gamma probe costs more than EUR 15,000. Radioisotope exposes both staff and patients to ionising radiation (below the permissible limits), and a formal risk assessment is mandatory. Some surgeons use blue dye alone (Patent Blue V, methylene blue, isosulfan blue), but this is associated with lower (but acceptable at more than 90%) identification rates [6] and a small risk of allergic reactions [7].

This has led to the development of alternative methods including non-operative techniques for axillary staging. This review discusses the new techniques for sentinel node mapping that have emerged including their pros and cons.

Superparamagnetic Iron Oxide

Superparamagnetic iron oxide (SPIO) nanoparticles have been used as magnetic resonance imaging (MRI) contrast agents. Sienna+® (Endomagnetics Ltd, Cambridge, UK) is a brown liquid SPIO tracer with a particle size of 60 nm and has been used for sentinel node mapping. 2 ml of Sienna+ diluted to 5 ml with saline

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is injected into the breast (similar to other tracers) after induction of anaesthesia. The injection site is massaged for around 5 min. The SPIO particles travel through the lymphatics and concentrate in the sentinel node/s. The sentinel nodes may stain brown and the tracer can be detected using the hand-held Sentimag® (Endomagnetics Ltd) magnetometer probe similar to the gamma probe for radioisotope after allowing for a migration time of 20 min. The ferromagnetic signal is distorted by metal instruments, and these need to be removed or replaced with plastic instruments at the time of localisation. The technique is contraindicated in those with an allergy to iron or dextran compounds, iron overload disease, pacemaker, or ferrous metal-containing devices in the chest wall.

The sentinel node detection rates per patient range from 94.4 to 98% [8–14]. A recent meta-analysis [14] including 7 non-randomised studies [8–14] showed that Sienna+ is non-inferior to standard mapping techniques for sentinel node detection. There was no difference in detection rate per patient (fixed odds ratio (OR) 1.10; 95% confidence interval (CI) 0.67–1.79; p = 0.71) between Sienna+ and the standard tracer technique. However, the detection rate per node was better with Sienna+ (random OR 1.84; 95% CI 1.37–2.47; p < 0.0001). Sienna+ identifies more nodes compared with the standard technique, but, reassuringly, there is high concordance in the detection of malignant nodes, suggesting the false-negative rate is no different to that of the standard technique.

The SPIO tracer is not associated with radioactivity, easier to implement without the regulatory issues of radioisotope, available in around 30 countries, and, reassuringly, data from multiple studies show non-inferior detection rates compared with standard tracer techniques. It can be stored conveniently because of the long shelf life. However, the transcutaneous signal detection is less favourable for SPIO compared with radioisotope, and the magnetic signal attenuates significantly with increasing depth as seen in obese patients, suggesting radioisotope may be more useful to guide the incision in the axilla and sentinel node biopsy in the obese. Additionally, the brown skin discolouration with detectable magnetic activity has been found to persist for more than 1 year in 1 in 5 patients making postoperative breast MRI difficult if needed [14]. It is associated with significant costs; the probe costs around EUR 25,000 and Sienna+ costs around EUR 250 per patient in addition to the cost of disposable plastic instruments. It remains to be seen if the higher nodal yield with SPIO leads to an increase in arm morbidity.

Overall, SPIO tracer appears to be a viable alternative to the current standard of care; however, it remains to be seen whether this technique will eventually replace radioisotope or whether its use is restricted to sites that do not have access to radioisotope. The safety of the standard tracer techniques has been confirmed in multicentre randomised trials comparing them with axillary lymph node dissection, but there are no randomised trials comparing SPIO to the standard tracers and data on locoregional recurrence is lacking.

Fluorescence Techniques

Indocyanine Green

Indocyanine green (ICG) is used for assessing liver function and cardiac output and more recently to monitor free flap perfusion. Unlike fluorescein, ICG is completely bound to plasma proteins and fluoresces in the near-infrared wavelength. This fluorochrome absorbs light at a wavelength of approximately 800 nm with emission of a fluorescent signal when subatomic particles return from an excited to a ground state. 1–5 ml of ICG (5–15 mg) is injected subdermally or intradermally into the retroareolar or periareolar breast tissue after induction of anaesthesia. The breast is massaged for 2 min. The fluorescence is not visible directly and commonly the operating lights are dimmed and the Photodynamic Eye (PDE; Hamamatsu Photonics, Hamamatsu, Japan) system is used to see the black and white images of fluorescent lymphatics and sentinel nodes on a monitor. Some surgeons find the PDE system difficult and cumbersome. The Medical Imaging Projection System (MIPS; Panasonic Connected Solutions Company, Japan) used in liver surgery may be used to see the fluorescence [15]. It detects fluorescent emission from the organ and projects the images on the location of the fluorescence emission. The HyperEye system (Mizuho, Tokyo, Japan) allows transcutaneous visualization of lymphatic vessels under light conditions and displays coloured images on an external monitor [16]. Alternatively, a laparoscopic camera with infrared filter may be used so that coloured images can be seen on a high definition monitor [17]. ICG cannot be used in patients with iodine allergy as it contains sodium iodide. Transcutaneous fluorescence of lymphatic vessels facilitates the location of axillary incision. It is necessary to allow 3–10 min migration time before skin incision. After incision, sentinel nodes are localised using an infrared torch PDE and subsequently removed.

ICG has emerged as a simple and efficient method; however, there are no randomised trials comparing it with standard tracer techniques. It has been used alone or in combination with blue dye or radioisotope [18–22]. The published studies use a wide range of ICG doses, and standardisation in terms of concentration and volume injected is vital. A concentration of <5 mg/ml and volume of ≥2 ml have been found to improve the detection rate [20]. The studies are heterogeneous and often have poor methodological quality. Similar to SPIO studies, authors have used the ICG and standard tracer techniques simultaneously in the same patient, and therefore the sentinel node detection rate of one technique may be influenced by the other. The sentinel node detection rates range from 93 to 100% (pooled detection rate 98%, 95% CI 96–99%) [23]. A review found that ICG is superior to blue dye in terms of sentinel node identification rate (fixed OR 18.37, 95% CI 8.63–39.10; p = 0.0001) and comparable to radioisotope (random OR 0.81; 95% CI 0.03–24.29; p = 0.90) [24]. A recent meta-analysis confirmed that the sentinel node detection rate is similar for ICG and radioisotope (fixed OR 1.29, 95% CI 0.87–1.90; random OR 1.32, 95% CI 0.54–3.18) [25]. More importantly, ICG and radioisotope were comparable for detection of tumour-positive sentinel node (random OR

1.90, 95% CI 0.74–4.86) [25]. ICG's smaller molecular size can result in faster migration in the lymphatics and identify more nodes (mean number of nodes excised 3–5.4 for ICG and 1–2.4 for blue dye) [24]. It is not known whether the increased node yield adversely impacts on arm morbidity. Additionally, leakage into surrounding tissue at the time of sentinel node biopsy may impair sentinel node detection.

The PDE system costs around EUR 50,000 and ICG costs around EUR 25 per patient. Therefore, ICG sentinel node mapping may not be cost-effective in hospitals with established nuclear medicine departments or in developing countries. However, it offers a satisfactory alternative to conventional methods without the use of radioactive tracers. There are no reported serious adverse events related to hypersensitivity to ICG.

In summary, ICG sentinel node mapping appears to be reproducible and safe and eliminates exposure to ionising radiation. The technique needs to be standardised to ensure best performance and easy adoption. Future large methodologically sound studies are required before ICG mapping will be ready for prime time.

Fluorescein

10% fluorescein is a widely available, low-cost fluorescent dye that is widely used in ophthalmology [26] and malignant brain tumour surgery [27, 28]. A blue light source is required to excite fluorescence. It has been successfully used for sentinel node mapping in colorectal tumours [29].

The cost of fluorescein is less than EUR 1, and, unlike ICG, fluorescence is visible directly and no imaging system is needed. Similar to ICG, fluorescein is not associated with adverse reactions. The molecular weight is lower than that of ICG, which may lead to a higher number of nodes removed at sentinel node biopsy. Early results from a randomised trial showed similar detection rates for fluorescein combined with methylene blue dye compared with the standard combination technique (radioisotope and methylene blue dye) [30]. This is an attractive option for developing countries because of low cost and easy availability; however, apart from conference proceedings by one author, there are no published papers. Further studies are needed to standardise the technique and demonstrate its reproducibility and effectiveness.

Non-Operative Axillary Staging

Sentinel node biopsy is minimally invasive but is associated with a small risk of arm morbidity. The role of further axillary treatment in women with 2 or less positive nodes at sentinel node biopsy was challenged by ACOSOG Z0011 [31] and is being studied in the confirmatory POSNOC study [32]. Therefore we are now questioning the role of removing the sentinel nodes, and efforts are underway to stage the axilla without surgery [33].

Computed Tomography Lymphography

This method has been pioneered in Japan to aid sentinel node detection using blue dye or ICG alone, as many institutions cannot use radioisotope because of regulations. 3-dimensional (3D) computed tomography lymphography (CTLG) is performed 1 day before surgery. 4 ml of iopamidol is injected intradermally into the periareolar skin or subareolarly. The breast is massaged for about 1 min to facilitate the migration of the contrast agent into the draining lymphatics. CT scan is performed and 3D CT images are reconstructed to identify the lymphatics and sentinel nodes. Sentinel nodes that are not stained or poorly stained (<50%) suggest presence of metastasis [34]. Other criteria used by some authors are partial staining of sentinel nodes (stain defect, mottled or 'crab claw' stain), stagnant or dilated lymph vessels, and detoured lymph vessels [35]. The sentinel nodes are marked on the skin using a laserlight navigator system. Sentinel node biopsy is performed using blue dye or ICG.

The sentinel node detection rate for CTLG preoperatively ranges from 98 to 100% and for CTLG-assisted sentinel node biopsy is 100% [34–36]. However, CTLG alone has an unacceptably high false-negative and false-positive rate for macrometastases (17.9 and 16.4%, respectively) [34]. No adverse events have been reported.

Published literature demonstrates that CTLG is feasible and safe and complements blue dye or ICG mapping techniques. However, it exposes the patient to radiation, puts increasing pressure on already stretched radiology services, and is costly. It is difficult to see a role for CTLG in combination with other tracers for operative sentinel node biopsy as the identification rates can be improved by combining blue dye and ICG in the absence of radioisotope or using SPIO. There may be a role for CTLG alone for staging the axilla without sentinel node biopsy if the false-negative and false-positive rates can be improved by refining the criteria to define a node with metastases in future studies.

Contrast-Enhanced Ultrasound Scan

By using an ultrasound (US) contrast agent and the contrast-specific mode of the US machine, dynamic contrast-enhanced ultrasound scan (CEUS) images can be obtained to identify and biopsy the sentinel nodes non-operatively. Second generation US contrast agents (e.g., SonoVue®; Bracco, Milan, Italy; Definity™; Lantheus Medical Imaging, North Billerica, MA, USA; and Sonazoid™; Daiichi Sankyo, Tokyo, Japan) consist of microbubbles containing various gases within a shell. Definity consists of octafluoropropane gas within a lipid shell, and SonoVue consists of sulphurhexafluoride(SF6) within a phospholipid shell. SF6 is an inert molecule that does not interact with any other molecule in the body [37]. After destruction of the microbubble, SF6 gas is excreted only through the lungs without any excretion through the kidney or the liver. Sonazoid consists of perfluorobutane within a hydrogenated egg phosphatidylserine (HEPS) shell. Although no adverse effects have been reported after use in the breast, these can be regarded as a foreign material by the immune system; therefore, a hypersensitivity reaction is possible [38]. SonoVue and Sonazoid should be avoided in <18-year old, pregnant, and breast-feeding women because of a lack of safety data. Although not yet proven in vivo in humans, there is a possibility that microbubbles with in-

sonation can cause harmful effects on cells or tissues, such as microvascular rupture and increased heating around the US contrast agent [39]. In contrast to its use in few centres in Europe and Asia, CEUS has not been used in North America for axillary staging [40].

The US contrast agent (SonoVue 0.2–0.5 ml [41], Sonazoid 2 ml [42]) is injected intradermally or subdermally at the upper outer periareolar skin or subareolarly. The breast is massaged for a few seconds. The lymphatic channels are visualised on contrast pulse sequencing and followed into the axilla to the draining sentinel node that accumulates the contrast agent. The injection may be repeated in failed localisations; however, safety may be a concern because of the potential harmful effects on the microvasculature. A fine needle aspiration or core biopsy is performed of the draining node using conventional grey-scale US to stage the axilla [41].

CEUS has the potential to stage the axilla without surgery by identifying and percutaneously sampling the sentinel nodes. The preoperative identification and localisation rates for sentinel nodes using CEUS range from 70 to 100% [40]. A recent meta-analysis of 4 studies found a low pooled sensitivity of 54% for identification of nodal metastases (95% CI 47–61%) and pooled specificity of 100% (95% CI 99–100%). The authors report the false-negative rate of CEUS-guided core biopsy to detect nodal metastases as 8–17% [40]. However, this is misleading as the false-negative rate should be 1 – sensitivity = FN/TP + FN = 46%, which is unacceptably high. Additionally, we need to adjust for the number of non-diagnostic or inadequate biopsies.

Nevertheless, CEUS has several advantages over CTLG, such as no radiation, no harmful effects on the kidney or thyroid, and easy accessibility. However, the technique has failed to gain support and remains limited to a few centres. Further research is needed to standardise the technique and improve the sensitivity, followed by randomised trials comparing it with sentinel node biopsy for axillary staging.

Conclusion

Sentinel node biopsy has revolutionised axillary treatment in breast cancer. The newer developing techniques will potentially enable a more widespread adoption of this procedure, and for many sites with no access to radioisotope Sienna+ or ICG are being used routinely. A common barrier for these techniques is the lack of standardisation and evaluation in randomised trials that include cost-effectiveness as one of the outcomes. Furthermore, many of these techniques are more costly, and it is difficult to envisage how they will replace the less costly standard mapping techniques in countries with limited resources. Future large collaborative randomised trials will help these techniques to be established in standard practice.

There is an increasing interest in non-operative axillary staging as studies show that no axillary treatment may be needed for patients with low-burden nodal disease (micro- or macrometastases) [31, 43]. CEUS has the potential to improve the sensitivity of conventional grey-scale US and stage the axilla non-operatively. The danger is that CEUS and other new techniques may become redundant in node-negative patients with small tumours if ongoing trials comparing grey-scale US versus sentinel node biopsy for axillary staging show that sentinel node biopsy offers no additional benefit to axillary US [33]. The future is likely to be an individualised approach to axillary staging based on tumour size and molecular profile rather than one size fits all.

Disclosure Statement

The author declares no conflicts of interest.

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