Sentinel Lymph Node Biopsy in Breast Cancer Surgery

J. Michael Dixon, BSc (Hons), MBChB, MD, FRCS, FRCSEd, FRCP, OBE

Edinburgh Breast Unit, NHS Lothian, Western General Hospital, Edinburgh, Scotland, UK

Bartholin first noticed the existence of the lymphatics in 1653 and, in the 1700s, Sappey first mapped breast lymphatics. In the 19th century, Virchow put forward the view that lymph nodes filtered lymph¹ and, in 1940, Gilchrist showed that when injected, carbon traveled and was retained in the regional lymph nodes.² In 1954, Zeidman and Buss reported that injected cancer cells arrested in lymph nodes and these cells remained in the first regional draining node for 3 weeks. In 1967, Fisher and Fisher reported that 40 % of radiolabeled cancer cells were retained in the node or nodes that drain a cancer.^{3,4} These observations provided the basis for the sentinel lymph node concept. The validity of sentinel node biopsy is based on two principles: first, the existence of an orderly and predictable pattern of lymphatic drainage to a regional node basin and, second, that the first node or nodes act as an effective filter for tumor cells. Sentinel lymph node biopsy was first introduced as part of breast cancer nodal staging by Giuliano et al. in 1994 using blue dye alone.⁵ Simultaneously, the use of isotopes was developed by Krag et al., and together these studies established the role of blue dye and radioisotope in sentinel lymph node biopsy in breast cancer.⁶ Anatomically, one or two large lymph trunks leave the areola and these drain mainly to the lower axillary nodes.⁷ Where there are two lymphatic trunks, these either combine and drain to one node or, more commonly, drain to two different sentinel nodes. Sentinel lymph nodes usually have a clearly defined anatomical location in the lower axilla. The presence of two lymphatic trunks in many explains why there is rarely one sentinel lymph node, and why false negatives can occur if the node draining one

trunk but not the node or nodes draining the second trunk are removed.

Since being introduced, the technique of sentinel lymph node mapping has evolved. As the authors of the accompanying article on *Troubleshooting Sentinel Lymph Node Biopsy in Breast Cancer Surgery* note, there is a learning curve, and although after a few cases surgeons rapidly became competent at the technique, there remain differences in how various surgeons find sentinel nodes, and it is not a procedure without its pitfalls.⁸ Having a troubleshooting guide to sentinel lymph node biopsy is helpful and this guide will help surgeons faced with setting up and running a sentinel node biopsy service.

The largest study on the success of sentinel lymph node biopsy was conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP).^{9,10} Data from 5536 patients in this study showed sentinel lymph nodes were identified successfully in 97.2 % of patients using a dual isotope and blue dye technique. Only 1.4 % of sentinel lymph node biopsies were outside levels I and II of the axilla. Overall, 65.1 % of the sentinel lymph nodes contained both radioactivity and blue dye, with one-third of sentinel lymph nodes containing either radioisotope or blue dye alone. Importantly, a small percentage of sentinel lymph nodes were identified by palpation alone (3.9 %). The false negative rate in this study was 9.8 % and was related to the number of sentinel lymph nodes removed, and was 17.7 % when only one node was removed, 10 % for two nodes, 6.9 % for three nodes, and 5.5 % for four nodes. There is excellent advice in the troubleshooting guide on what does and does not constitute a sentinel lymph node, but there is no specific comment on the ideal number of nodes that should be removed. One large study compared the number of sentinel lymph nodes harvested with overall survival, and demonstrated that patients who had three sentinel lymph nodes removed had a better a disease-specific survival than groups with smaller numbers of sentinel nodes (hazard ratio 0.73; $p = 0.001$).¹¹ The

conclusion of these authors was that the optimal number of sentinel lymph nodes harvested is three. They explain better outcomes for patients having three sentinel nodes removed on the basis that understaging and undertreatment is a potential issue because of the higher false negative rate in patients who have only one or two sentinel lymph nodes removed.

The authors of the troubleshooting guide acknowledge that combined radioisotope and blue dye is superior to blue dye alone, although they make it clear that some experts continue to use only blue dye alone and others use isotope with blue dye only if there are no nodes detectable on scintigraphy or using a handheld probe. A recent systematic review noted that although blue dye and isotope outperformed isotope alone in sentinel node detection, dual tracers did not result in a significantly lower false negative rate other than in exceptional circumstances such as after neoadjuvant chemotherapy.¹² Because the use of radioisotopes requires a licence, it is not available in every center. There are newer techniques that are being validated and appear to be as effective as isotope, using agents such as iron and fluorescent dyes, and this may allow those who currently use blue dye alone to use a combined technique without the need for radioisotope.

Site of injection remains variable between experts, as seen in this troubleshooting guide. A study by Chagpar et al. showed that subareolar and periareolar injection techniques produced higher sentinel lymph node identification rates than peritumoral injection.¹³ This and other studies demonstrated the validity of subareolar and periareolar injection but noted that regardless of where isotope and blue dye are injected in the breast, drainage is to the same nodes. The timing of radioisotope injection is not important and is not discussed in the troubleshooting guide. A number of studies have shown that the isotope can be injected after the patient has been anesthetized, with radioisotope reaching sentinel nodes, as does blue dye, very quickly.¹⁴

A big disadvantage of using isosulfan blue or patent blue V is the small but significant rate of adverse reactions. The authors of this troubleshooting guide discuss prophylaxis and note the low rate of severe reactions (5 grade III reactions requiring vasopressor support in the New Start Programme of 7917 patients¹⁵ and 2 of 1742 in a French series.¹⁶ Anaphylaxis can be reduced by prophylaxis, but the number of severe anaphylactic episodes is small and, although prophylaxis reduces the severity of allergic reactions, the incidence of reactions does not appear different. Prophylaxis may increase rates of infectious complications and wound dehiscence.¹⁷ I agree with the experts that, given the low incidence of adverse reactions and the potential adverse effects of steroids, prophylaxis should be considered investigational. The experts rightly

recommend that when grade III reactions occur, the operative procedure should be abandoned.

The issue of no uptake of radioactive tracer in the axilla is a scenario that all surgeons occasionally come across. The expert's tip is to inject saline after the radioisotope as larger volumes of fluid do appear to increase the rates of tracer uptake in the axillary lymph nodes. This is a technique that I use routinely. In patients with no obvious sentinel nodes, whether to proceed to an axillary lymph node dissection or an axillary lymph node sampling procedure remains controversial. However, axillary lymph node sampling has been well studied, and removing four palpable nodes from the lower axilla is effective at staging the lower axilla, and there are now long-term data on 30-year outcomes demonstrating its safety.¹⁸

Controversy continues to surround the role of the internal mammary (IM) nodes. The likelihood of identifying IM node drainage relates to where the isotope or blue dye is injected in the breast. In a study by Krynyckyi et al., IM nodes were identified in 4 of 82 patients (4.9 %) where the radioisotope was injected around the tumor and intradermally, and in 13 of 61 patients (23 %) where, in addition to peritumoral and intradermal injections, radioisotope was also injected deep to the tumor ($p < 0.001$).¹⁹ This study also noted that IM nodes were seen in 46.2 % of women with small breasts, 21.1 % with medium sized breasts, and in no patients with large breasts ($p < 0.009$).¹⁹ While current evidence suggests that the prognostic significance of sentinel lymph nodes in the IM chain is similar to sentinel nodes in the axilla, it is of concern that drainage to IM nodes may be influenced by site of isotope injection and breast size.

Although sentinel lymph node biopsy is an operation that breast surgeons perform regularly, as the troubleshooting guide notes, it is not without problems. It is for this reason that surgeons need to be aware of the pitfalls and tips to avoid such issues. The benefits of sentinel lymph node biopsy to patients are clear. Its accuracy is evident in long-term follow-up, with excellent rates of long-term control and low axillary recurrence rates.

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