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The sentinel node biopsy in patients with breast cancer; many controversies remain

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Summary

The sentinel node procedure has increasingly been used as a diagnostic tool for staging breast cancer. Although many institutes have embraced this procedure, many issues concerning the indications and the technique itself remain unsolved. In this review, several aspects regarding these controversies are discussed from the perspective of The Netherlands Cancer Institute. These include the definitions used to identify the sentinel node, the indications and contraindications for this procedure and the injection site of the tracer and blue dye. What are the clinical implications of a micro-metastasis in the sentinel node? What is the best treatment for patients with an involved axillary node? Should non-axillary sentinel nodes be pursued, and if so, what are the implications for further management of these patients? Finally, the current TNM system is discussed in perspective of the evolving sentinel node procedure. Although many questions remain to be solved, the regional recurrence rates are low when axillary clearance is omitted because of a tumor-free sentinel node.

Key words: Breast neoplasms; Lymphatic metastasis; Sentinel lymph node biopsy.

Introduction

Since 1992, the sentinel node procedure has been increasingly used as a diagnostic tool for staging. This procedure is based on the theory that metastatic spread in the lymphatics occurs in a stepwise fashion (Figure 1), which implies that the sentinel node is the first to become involved in case of disseminating disease. The first type of cancer in which this concept was proven to be successful was melanoma [1], followed by cancer of the breast, penis [2, 3] and other solid neoplasms [4, 5].

The sentinel node procedure in melanoma patients is standardized, in contrast to the procedure in patients with breast cancer. Its rapid incorporation in the diagnostic protocols of this tumor has led to the use of a wide variety of techniques, and many issues concerning the indications and techniques have yet to be solved. In the current article, some of these issues are discussed on the basis of the experience at The Netherlands Cancer Institute.

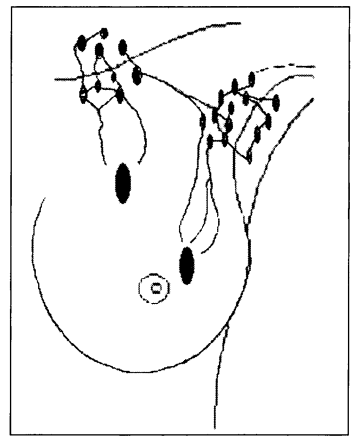

Figure 1. — Schematic representation of the lymphatic drainage of breast cancer. In the represented situation, a tumor in the upper outer quadrant directly drains toward the axilla. A tumor in the upper inner quadrant directly drains to the sub-clavicular region. Both tumors drain in a stepwise fashion towards the supra-clavicular nodes.

Definitions

The original definition of the sentinel node is "the initial node upon which the primary tumor drains" [1]. In practice, this definition is challenging, because one does not always know which node is the first draining node [6]. What the original definition intended to say was that a sentinel node receives its lymph directly from the primary lesion site, reflecting the above-mentioned hypothesis of stepwise dissemination. Several definitions have been formulated to accurately identify the sentinel nodes in clinical practice (Figure 2); some are based on lymphoscintigraphic images, some on use of a probe and others on use of blue dye.

A frequently used definition states that the sentinel node is the first node visualized on a lymphoscintigraphic image [7]. It is true that the first node that is depicted is on a direct drainage pathway, but this definition does not acknowledge that a patient may have several lymphatic ducts leading to more than one sentinel node. A second node on a direct drainage pathway might be clogged with the tumor, which slows down the accumulation of the tracer. It may also be located further away and

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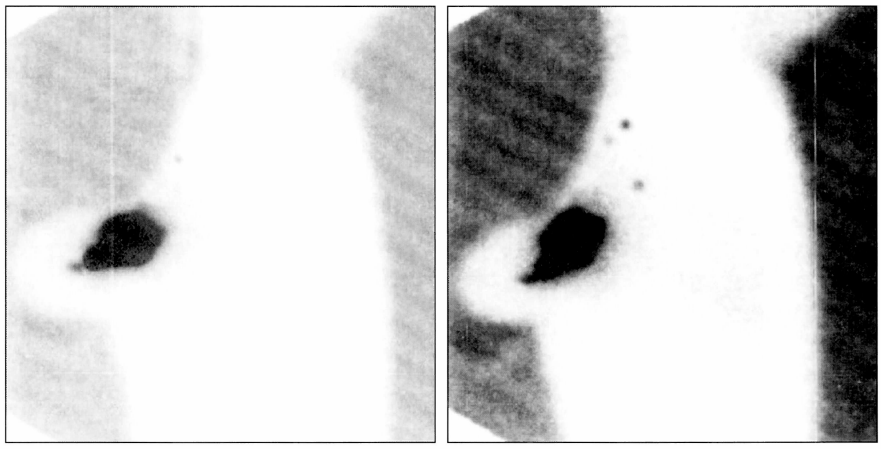

Figure 2. — Left lateral scintigrams of a patient with a left breast cancer after intra-lesional tracer administration. Three hot nodes are depicted. Which one(s) should be considered the sentinel node? The one closest to the primary tumor? The hottest node? The anterior one that was depicted first? All three, as they are all radioactive?

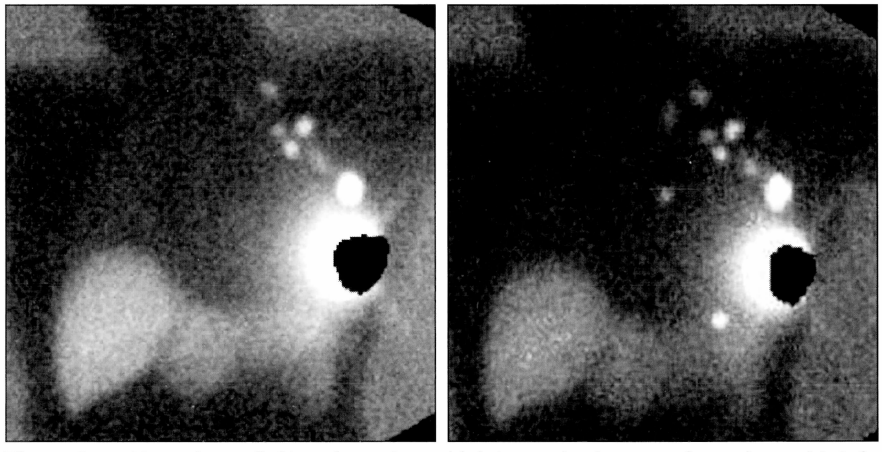

Figure 3. — Ten minute (left) and two hour (right) anterior images of a patient with left-sided breast cancer. The 10-minute image shows one sentinel node in the axilla, the 2-hour image shows a second sentinel node within the breast and another lymph node in the internal mammary chain.

take more time to accumulate the tracer. Figure 3 shows two lymphoscintigraphic images, one ten minutes after the tracer injection, the other two hours later. After ten minutes, a sentinel node is clearly seen in the axilla but after two hours, another sentinel node is seen medially within the breast and another hot spot is present in the internal mammary chain. The first two must be on a direct drainage pathway, but if surgeon had proceeded with surgery immediately after the first image was made, the second node would have been missed.

Another frequently used definition states that the sentinel node is the "hottest" node in a particular basin [8]. This definition is imperfect for two reasons. First, a tumor may directly drain towards more than one node. These need not be visualized simultaneously. A second node on a direct drainage pathway may appear faint on the scintigraphic image due to tumor interfering with the inflow [9-12]. If the surgeon were to remove only the hottest node, the tumor-filled node would be left in situ and could cause a recurrence. Secondly, a large node can retain more tracer than a small node, and if it does, may be mistaken for a sentinel node while it might in fact be a second-echelon node. As a result, some surgeons define all radioactive nodes as sentinel nodes and remove all these nodes. However, the sentinel node procedure was developed to remove as few nodes as possible, and still accomplish optimal staging. The removal of more nodes may increase the odds of complications primarily associated with axillary lymph node dissection.

Some people define the sentinel node as the one closest to the primary tumor [13]. Often this is true, but nodes located further away from the primary tumor can also be on a direct lymphatic pathway. Figure 4 shows early anterior and lateral scintigraphic images, in which two nodes are visualized, one intramammary node and one in the axilla. Both are visualized with a similar intensity, and without any lymph vessels to determine the order of drainage. Which one is the sentinel node? The axillary node could be down stream from the intramammary node but it might also be another sentinel node with its own lymphatic vessel directly from the tumor, bypassing the intramammary node.

Then, there is a sixth definition, which entails that every node which stains blue is a sentinel node [14]. Indeed, the sentinel node is often blue, but this not always the case. The blue dye is not permanently retained in the first lymph node, but it passes through and travels to the next node in the chain. After a while, a string of subsequent nodes are stained blue of which only the first one is directly at risk of harboring metastatic disease. Again, more nodes are removed than is necessary for accurate staging.

A sentinel node is a lymph node on the direct drainage pathway from the primary tumor. This is the definition that we like the most because it best reflects the concept on which lymphatic mapping is based. In clinical practice this definition requires identification of a lymphatic duct leading towards a node that originates in the primary tumor area. The blue dye offers the best chance of finding this lymphatic channel and in combination with the radioactive tracer, lymphoscintigraphic images and a probe, there is a very good chance of identifying the sentinel nodes. If one is in doubt, whether a particular node is on a direct drainage pathway, it is best to err on the safe side and remove it as such. With

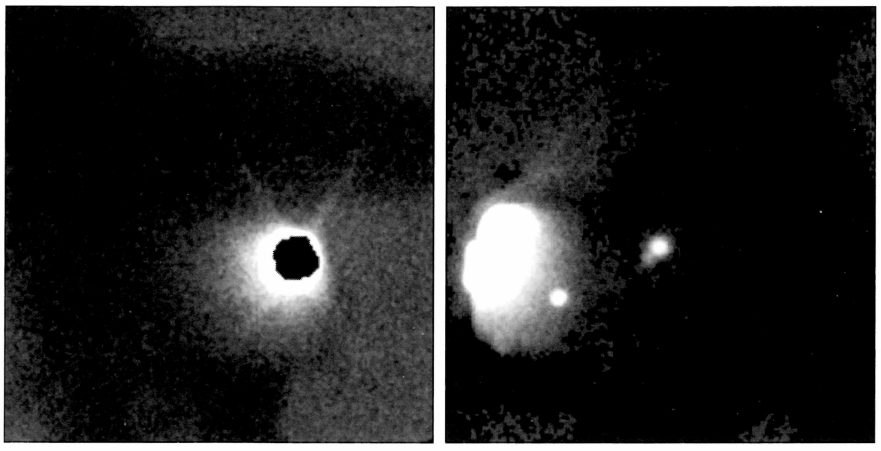

Figure 4. — The anterior image (left) does not show any sentinel nodes, whereas the lateral image (right) shows two nodes, one in the parenchyma of the breast and the other in the axilla.

this approach, one has the greatest chance of identifying all sentinel nodes without unnecessary removal of too many non-sentinel nodes.

Indications and contra-indications

As the primary goal of the sentinel node biopsy is evaluating whether the axilla contains metastasis, patients with an axilla that is obviously involved are excluded from the procedure. Unfortunately, the preoperative identification of these patients is difficult because palpation is notoriously inaccurate [15-17]. In some institutes, ultrasonographic evaluation and subsequent fine-needle aspiration cytology of suspicious axillary lymph nodes is included in the preoperative staging protocol but results are variable: in 14-26% of patients, sentinel node biopsy is avoided in lieu of axillary lymph node dissection [18-21]. At The Netherlands Cancer Institute, preoperative ultrasound identifies some eight percent of patients as having metastases and they are spared sentinel node biopsy. This gain may seem modest but the involved nodes that are identified by ultrasound are the very ones that may fail to take up the tracers due to the extensive tumor load and to cause the recurrences later on. Patients with more than four involved axillary nodes have a greater than 50% chance of non-visualization [22-24].

Patients with multifocal breast tumors are often excluded from the sentinel node biopsy. Some investigators find that in these tumors, lymphatic drainage may be variable from one tumor focus to the next. The tracer may only travel through some of the lymphatic pathways and thus not all "true" sentinel nodes may be visualized. Consequently, not all sentinel nodes are pursued and this could result in inaccurate staging and an increased false-negative rate [25-27]. Other investigators assume that the lymphatic drainage of the whole breast is uniform [28]. The site of the injection would then be irrelevant as drainage will be to the same node(s) all the time (see injection techniques). Unless the foci are near one another, the sentinel node procedure is not performed in these patients at our Institute.

Ductal carcinoma in situ (DCIS) is also often considered to be a contra-indication for the performance of a sentinel node biopsy [29]. By definition, this is not an invasive tumor, and the prognosis is generally very good [30]. The preoperative diagnosis, however, is not always accurate; the pathologist will identify invasive components in 10-29% of the patients whom preoperatively were presumed to have DCIS [30]. For these patients, the sentinel node biopsy might be beneficial but proof of a survival benefit is lacking. Sometimes, axillary metastases are detected in patients with DCIS without any histologically detectable invasive components [31, 32]. Clinical relevance of these metastases seems to be small and performing sentinel node biopsy in this group should be regarded as experimental [33]. A fundamental difference with the situation in invasive breast cancer is that axillary node dissection is not the standard of care in DCIS. With the addition of lymphatic mapping, treatment becomes more extensive in DCIS, whereas it becomes more conservative in invasive breast cancer. The situation in pure DCIS is more like the situation in melanoma and we would like to see evidence that lymphatic mapping improves the prognosis. For patients with possible or even probable invasion, the sentinel node biopsy provides valuable information, and we would consider the procedure in this patient group.

A fourth controversial indication for sentinel node biopsy is previous treatment of the breast or axilla. Neoadjuvant chemotherapy is increasingly being advocated as a means of in vivo assessment of the chemotherapy response, and also for downsizing the tumor to enable breast-conserving therapy. The identification rate of the sentinel node after neoadjuvant chemotherapy is relatively low, and the false-negative rate of the sentinel node in this situation is high [34-36]. So far, no investigator has dared to abandon axillary lymph node dissection when the sentinel node procedure was performed after neoadjuvant chemotherapy. At our institute, the sentinel node is pursued prior to neoadjuvant treatment in patients with a T2N0 tumor. Axillary lymph node dissection is omitted in case of a tumor-negative sentinel node. Previous excisional biopsy is another perceived contra-indication for sentinel node biopsy. Although some investigators have a high success rate after prior excisional biopsy [37, 38], we found a 70% discordance rate between the location of the sentinel nodes when comparing pre- and postoperative tracer injection and imaging [39]. Moreover, excisional biopsy causes non-visualization of the axillary nodes in more than one-third of cases [39]. In view of these results, it appears wise to perform the sentinel node procedure prior to a diagnostic excision and treatment of the breast and axilla.

Injection technique

One of the great controversies surrounding the sentinel node biopsy in patients with breast cancer is the technique used to identify the sentinel nodes, in particular the best location of the injection of the radioactive tracer and blue dye. Several techniques have been advocated: sub-areolar, peri-areolar, intradermal, subdermal, peritumoral, intratumoral and subtumoral [40]. The first four can be regarded as "superficial" and the latter three as "deep" [40]. The superficial techniques are based on the concept that there is a common drainage pathway from the whole breast. During the embryological development, the breast gland and lymphatic vessels are formed from one single ectodermic bud and all lymphatic vessels are assumed to travel towards the same lymph node(s) [41]. This would imply that the location of the tracer injection is irrelevant for the visualization of a sentinel node, as long as it is located within the breast. These superficial injection techniques have several advantages. They are easy to perform in all patients, including those with non-palpable tumors, and axillary nodes are rapidly and intensely visualized [42-44]. Furthermore, the radiopharmaceutical can be injected as far away form the axilla as deemed convenient to reduce the disturbing radioactive scatter. Many nuclear medicine physicians and surgeons prefer using superficial injection techniques.

The three deep injection techniques are based on the view that different parts of the breast possess their own unique drainage pathways. Several investigators have shown that lymphatic drainage of the breast varies from one part to another [28, 45-47]. Furthermore, sentinel nodes outside the axilla are primarily encountered with the deep injection technique [48, 49], and rarely with the superficial injection techniques. Consequently, if one wants to be certain to identify all the nodes where the neoplastic cells would travel to directly (and not only visualize axillary lymph nodes), the injection of the tracer should be in close proximity to the tumor.

An advantage of injecting a small volume into the tumor is that lumpectomy will remove the radioactivity at the injection site, thereby eliminating shinethrough and facilitating recovery of the sentinel node. Furthermore, the intralesional injection technique provides the opportunity to use the radioactivity to guide the segmental excision in patients with non-palpable lesions [50].

In terms of drainage patterns, there is no fundamental difference between peri-tumoral injection and intra-tumoral injection. These two techniques will identify the same nodes. Some of the tracer injected around the tumor will diffuse into it, and some of the tracer administered into the lesion will leak out into the surrounding tissue. In conclusion, the superficial injection technique may be easier but the odds of identifying the wrong nodes may be greater. In time, this might lead to an increased axillary recurrence rate in this patient group. Moreover, sentinel nodes outside the axilla are primarily identified with the deep injection technique.

Micrometastasis and non-sentinel node metastasis

One of the pressing questions in the treatment of breast cancer patients is the clinical relevance of micrometastases (0.2-2.0 mm) and submicrometastases (< 0.2 mm) in the sentinel node. Before the sentinel node era, the pathologist bisected nodes in the axillary lymph node dissection specimen, and evaluated these after staining with hematoxylin-eosin. This fairly crude method rarely identified micrometastases. Since the introduction of the sentinel node procedure, the pathological work-up has markedly changed. Fewer nodes are examined, but these nodes are examined more thoroughly. Sentinel nodes are evaluated at multiple levels, stained with both hematoxylin-eosin and immunohistochemistry (cytokeratin antibodies) and now even a single tumor cell is occasionally distinguished (Figure 5). The clinical implications of these small metastases are unknown [51]. Are isolated tumor cells capable of producing regional and distant recurrences? What is the chance that more nodes are involved? Should patients with a micrometastasis in the sentinel node be advised to undergo axillary lymph node dissection? A meta-analysis by Cserni and co-workers [52] has shown that the rate of non-sentinel node involvement in the presence of micrometastatic and submicrometastatic disease in the sentinel node is 20%. This rate is 9% if only immunohistochemically detected metastases are identified. This study might not, however, reflect the full extent of additional metastasis as none of the studies in this metaanalysis considered immunohistochemical staining of non-sentinel nodes.

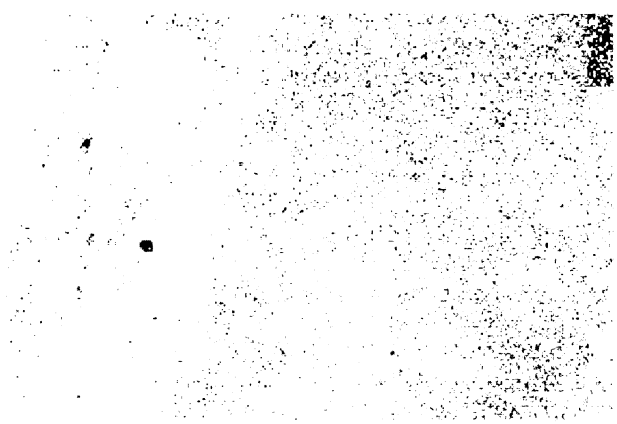

Figure 5. — Sentinel node with an isolated breast cancer cell in immunohistochemical staining with CAM 5.2.

Several studies have focused on possible factors associated with non-sentinel node metastasis [53, 54]. Degnim and co-workers [55, 56] have shown that a tumor load in the sentinel node greater than two mm is the strongest predictor of the presence of additional non-sentinel node metastasis. Other associated characteristics are extra-nodal extension of a metastasis, more than one tumor-positive sentinel node, a greater than two centimeter diameter of the primary tumor and lymphovascular invasion of the primary tumor [57-60]. Few studies on the long-term follow-up of patients with micro-metastasis have been published [61].

Some authors find that the presence of micrometastatic disease in the axillary nodes has an effect on both the disease-free survival and the overall survival [62-64]. Others find no relationship between these two, but show an association between the primary tumor characteristics and the prognosis [65-67].

Currently, this issue remains unsolved. Patients with isolated tumor cells in the sentinel node have a moderate chance of additional metastasis and may have a somewhat worse overall prognosis when compared to patients with tumor-negative sentinel nodes. For now, it seems that one should consider both the tumor-load of the sentinel node and the primary tumor characteristics when advising a patient with regard to completion axillary lymph node dissection. With regard to adjuvant systemic therapy, some patients will receive chemo- or hormonal therapy based on the primary tumor characteristics, hormonal receptor status, or the patients' age. As patients with micro- and submicrometastases are not considered N1 patients, adjuvant treatment is not routinely offered.

Non-axillary sentinel nodes

Lymphatic drainage from the breast is primarily towards the lower axilla, but other sites where metastatic tumor may travel include the internal mammary chain, level III of the axilla (subclavicular group), the supraclavicular fossa, the prepectoral nodes (intramammary nodes), and the interpectoral group (Rotter's nodes) [68-74]. Many surgeons remove only the axillary nodes because the pursuit of the other modes may be time-consuming and technically more demanding [75].

The presence of metastases in locations outside the axilla seems to indicate a worse prognosis as compared to patients with no metastases at all. Patients with tumor-negative sentinel nodes in the axilla and tumor-positive ones in the internal mammary chain have an equal prognosis as vice versa. The prognosis is even worse when both basins contain metastases [76-78]. Tumor-positive intramammary nodes are also a predictor of poor disease outcome [79].

Even though involved non-axillary nodes influence the prognosis, it is debatable whether treatment of these nodes improves survival. Some studies demonstrated a survival benefit by treating nodes in the internal mammary chain [76, 80], while others showed no difference [81]. At The Netherlands Cancer Institute, nodes outside the axilla are pursued and non-axillary sentinel nodes are visualized in approximately 27% of the patients. Two-thirds of these nodes are in the internal mammary chain. Metastases in unusually situated nodes were found in 16% of the patients in whom these were pursued. The treatment was altered in 18% of these patients to more appropriately serve their individual needs [82-84]. Since the nodes in the axilla, internal mammary chain and intramammary nodes seem to be of clinical relevance, we assume that this is true for all sentinel nodes regardless of their location.

Treatment of a nodal basin after a tumor-positive sentinel node

Usually, patients with a tumor-positive sentinel node receive a complete axillary lymph node dissection but the effectiveness of radiotherapy of the axilla in this situation is currently being investigated. It has been suggested that radiotherapy may be equally effective with regards to overall survival [85, 86], but with less morbidity [87]. As for the local-regional control, axillary lymph node dissection seems to be superior to radiotherapy [86]. Many of these trials had a short follow-up, and further trials comparing axillary lymph node dissection with axillary radiotherapy after a tumor-positive sentinel node are undertaken [88]. One of these trials is EORTC's AMAROS trial, which has already enrolled half of the required number of patients.

There are no evidence-based rules for treatment of patients with involved sentinel nodes outside the axilla. Therefore, decisions should be based on common sense [89]. For instance, we give radiotherapy to the internal mammary chain if a sentinel node there is involved [90]. We will not hesitate to perform axillary node dissection if an intramammary sentinel node in the upper outer quadrant of the breast is tumor-positive.

TNM system

The pN-category is defined by the number of nodes involved, their location and the size of the metastasis. Internal mammary chain nodes have been assigned specific denotations when identified using the sentinel lymph node biopsy. Lymph node metastases in locations other than the axilla or internal mammary chain are either not mentioned in the TNM system or carry notations implying that some lymph node sites have greater prognostic implications than the others, despite the fact that all these nodes are on a direct drainage pathway from the tumor. For instance, a supraclavicular metastasis is currently classified as N3 because it traditionally carries a poor prognosis. A metastasis detected in such a lymph node has always been palpable and the disease usually passed through a series of involved axillary or internal mammary chain nodes to get there [68]. However, a metastasis in a supraclavicular sentinel node is not palpable and, by definition, has reached that node directly, without initially passing through other nodes first.

Currently, metastases smaller than 0.2 mm are denoted as pN0(i+) and metastasis between the 0.2 and 2 mm as pN1mi. The N0 notation implies that these patients have an equal prognosis as patients with no metastasis at all. However, there are some studies suggesting that patients with even these very small metastases have a worse prognosis than true N0 patients [92, 93]. A future TNM classification may reflect the more accurate staging resulting from lymphatic mapping.

Conclusions

In many institutes, the sentinel node procedure has been incorporated in the standard protocol for the management of patients with breast cancer. Many patients are spared an unnecessary axillary node dissection that they do not need because they do not have metastases there. Despite the many controversial issues concerning indications and technique, axillary recurrence rates in these patients are extremely low. This suggests that the technique is forgiving. Perhaps the radiotherapy to the breast and the systemic treatment that many of these patients receive, remove some of the metastases that surgeons leave behind. One should bear in mind that the recurrence numbers might go up because follow-up is not yet that long. The high false-negative rates that melanoma surgeons are experiencing may serve as a warning. Despite its rapid incorporation in the diagnostic protocols and even if this procedure seems to be very promising, many controversies remain and more research and a longer follow-up are needed to solve these issues.

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