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Update on Detection of Sentinel Lymph Nodes in Patients With Breast Cancer

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Sentinel lymph node biopsy is now the practice of choice for the management of many patients with breast cancer. This was not true in the early 1990s, when the first such procedures were performed and protocols for such were refined often. This was also not true in the first years of the 21st century, when a decade of collective experience and information acquired from numerous clinical investigations dictated additional subtle and not-so-subtle refinements of the procedures. However, it is true today; reports of the latest round of clinical investigations indicate that there are several breast cancer sentinel node procedures that result in successful identification of potential sentinel nodes in nearly all patients who are eligible for such procedures. A significant component of many of these successful sentinel node procedures is a detection and localization protocol that involves radiotracer methodologies, including radiopharmaceutical administration, preoperative nuclear medicine imaging, and intraoperative gamma counting. The present state and roles of nuclear medicine protocols used in breast cancer sentinel lymph node biopsy procedures is reviewed with emphasis on discussion of recent results, unresolved issues, and future considerations. Included are brief reviews of present radiotracer and blue-dye techniques for node localization, including remarks about injection strategies, counting probe technology, and radiation safety. Included also are discussions of on-going investigations of the implications of the presence of micrometastases; of the management value of detection, localization, and excision of extra-axillary nodes such as internal mammary nodes; and of the broad range of recurrence rates presently being reported. Remarks on the present and possible near- and long-term roles for nuclear medicine in the staging of breast cancer patients including comments on positron emission tomography and intraoperative imaging conclude the article.

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There are in MEDLINE, as of the end of 2004, more than 1,500 citations to documents that comment on some aspect of the detection, localization, excision, and assessment of sentinel lymph nodes in breast cancer patients. The 1,500-plus documents discuss aspects of the roles of nuclear medicine, surgical oncology, pathology, genetics, medical oncology, radiation oncology, and radiology in the use of sentinel lymph node protocols in the management of breast cancer. There are less than 25 citations to documents from 1993 to 1996, approximately 500 citations to documents from 1997 to 2000, and perhaps 1,000 citations to documents from 2001 to 2004. The rapid increase in the number of publications during the last decade attests to the rapid expansion of the use of sentinel node protocols in breast cancer management and to an ongoing aggressive search for protocol refinements that result in the accurate staging of even more patients.

Background

The history of breast cancer management during the past few decades has been one of decreasing invasiveness, decreasing morbidity, and increasing effectiveness. Absent the latter result, the former 2 are partial successes, but it is the latter that is the most desired and most beneficial. Today, women diagnosed with breast cancer survive, on average, longer than ever before. This is, in part, a result of the broad multidisciplinary approach now used in the evaluation and treatment of patients—an approach that includes surgical oncology, medical oncology, radiation oncology, radiology, nuclear medicine, genetics, and pathology. During the last decade, the prognosis for all patients has improved much and for patients younger than 50 improved even more. Mortality

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rates have decreased by 2.3% per year from 1991 to 2000 for all women diagnosed with breast cancer and by 3.7% for such women under 50.[1]

Survival prognosis is dependent on early detection and on the accurate staging of disease at the time of diagnosis. Five-year survival rates range from 97% in women diagnosed with stage 1 disease (T1–2 N0) to 23% in women with stage 4 disease.[1] Screening mammography and public awareness of the value of self-examination have probably been the most important factors leading to the recent skewing of diagnosis and survival curves toward earlier diagnosis and therefore toward increased time of survival and increased rate of cure. However, advances in breast cancer staging procedures, including the development, use, and refinement of the sentinel lymph node biopsy, have decreased the morbidity of staging and probably measurably improved staging accuracy as well. Refinements to the earliest forms of sentinel node biopsy procedures, such as multisectioning instead of limited sectioning of nodes and the use of immunohistochemical (IHC) staining and traditional hematoxylin-eosin (H&E) staining for section assessment have proved particularly useful in the detection of metastasis, including micrometastasis, in axillary nodes.

Some Sentinel Node History

Sentinel lymph nodes are the nodes in a tumor bed that first receive lymphatic drainage from the tumor and are, therefore, the nodes most likely to harbor tumor cells, if tumor cells have indeed entered the lymphatics. William Halsted described lymph nodes as barriers to the spread of tumor cells, as vehicles for progression of tumor spread within lymphatics, and as vehicles for progression of tumor spread from lymphatics to more remote sites.[2] That description includes good precursors of the bases of our modern notion of sentinel nodes.

The concept of sentinel lymph nodes was used in 1977 by Cabanas, a urologist.[3] He applied the concept in the management of penile cancer. His approach to identification of sentinel nodes was the relatively crude approach of palpating from the tumor, proximally, along the likely path of lymph drainage until a palpable lymph node was encountered. He called the node identified in this way the sentinel lymph node. In the late 1980s and early 1990s, Morton and coworkers, an oncology surgeon and collaborators, popularized the use of sentinel node biopsy for melanoma. Their approach involved the injection of isosulfan blue dye, the visualization of such as it flowed through and stained lymphatic channels and nodes, and the identification, excision, and assessment of blue-stained nodes.[4] The blue dye was peritumorally injected in the operating room, and it was assumed the dye flowed from the site of injection to all sentinel nodes. Generally, blue-stained nodes are considered sentinel nodes. More accurately, blue-stained nodes may be sentinel nodes. One can never be certain that all sentinel nodes stain blue or that all blue-stained nodes are sentinel nodes. Certainly, some blue-stained nodes are the second or third nodes on a chain from a bed. When performed well, this technique is usually successful, that is, when this technique is performed well, most patients are staged as successfully as or more successfully than if full axillary dissection is used. In addition, the staging is generally accomplished with less morbidity with the sentinel node procedure than it would have been with a full axillary lymph node dissection. (We note that the term success as applied to a sentinel lymph node procedure is often not clearly or precisely defined. In some sentinel node literature, success means simply that a blue-stained or radioactive axillary node was found. Certainly, a sentinel node procedure has not been successful if no possible sentinel node has been found. However, finding only one possible axillary sentinel node, one radioactive or blue-stained node for example, in a specific patient may also be inadequate. Should internal mammary sentinel nodes be localized? A question as yet not consistently answered. Sometimes, success means the procedure resulted in accurate staging of a patient. This is the desired endpoint. However, demonstrating that a patient has been accurately staged requires long-term follow-up of the patient—a difficult task that is not a part of most studies. [For a recent report of a study with this endpoint, see Torrenga and coworkers[5] and the accompanying commentary.])

In 1993, Alex and Krag, who are also oncologic surgeons, introduced the use of radiotracers for lymphatic mapping and sentinel lymph node identification.[6] Their study, like that of Morton and coworkers, involved melanoma patients. The radiotracer they used, a technetium-99m (Tc-99m) labeled sulfur colloid particle, was injected peritumorally and intradermally and was detected in lymph nodes through use of a hand-held gamma detecting probe draped in a sterile sheath. In this approach, it is radioactive nodes that are possible sentinel nodes. Similar to blue nodes in the blue-dye approach, radioactive nodes are likely to be sentinel nodes and sentinel nodes are likely to be radioactive. Such is not always the case, but such is the case most of the time. Radiotracer approaches have, in general, been used more successfully than blue-dye approaches, and approaches that combine radiotracer and blue-dye techniques have been used more successfully than the radiotracer or blue-dye techniques individually. Imaging radiotracer that accumulates in lymphatic pathways and that which accumulates in nodes have been shown to be useful for surgeons seeking to identify and excise all sentinel nodes, some of which, in melanoma cases, might be found in very diverse anatomic regions. Early use of the radiotracer approach in this context quickly demonstrated that a surgeon's predictions regarding the nature of lymphatic drainage were sometimes unreliable and that more sophisticated techniques such as radiotracer and blue-dye techniques had value. Such was particularly true for melanomas on the trunk, as these are melanomas that might drain to both axillary regions and both inguinal regions and have sentinel nodes in all those locations. In the absence of a scintigraphic image of a distribution of radiotracer, a surgeon could not know quickly, or perhaps at all, all the pathways or locations of potential sentinel nodes or, therefore, of possible metastases.

Lymphoscintigraphy was used in the management of some breast cancer patients in the late 1970s. Its use was not in a

sentinel node procedure but in a procedure to localize internal mammary lymph nodes of breast cancer patients so that radiation therapy port assignments could be accurately planned.[7,8] Such imaging procedures included an injection of Tc-99m-labeled sulfur colloid posterior to the rectus sheath using an anterior percutaneous injection made inferior to the xiphoid and medial to the midclavicular line on the side of the breast with the cancer followed by imaging of the internal mammary lymph node chain. In these procedures, the radiocolloid particles are absorbed into the lymph channels and travel via the channels to the internal mammary nodes making it possible to locate such nodes and define appropriate radiation therapy plans. One study suggests that approximately 75% of such nodes are located between the first and third ribs.[9] Lymphoscintigraphies have also been performed on breast cancer patients with lymphedema. Such procedures have been performed to determine if the etiology of a patient's lymphedema is vascular or lymphatic.[10]

In the early 1990s, the concept of sentinel lymph nodes was applied to the management of breast cancer patients. Those efforts followed, in particular, from efforts to develop SLN techniques for use in the management of melanoma. Both radiotracer and blue-dye techniques were developed, tried, and refined. In the case of breast cancer, use of procedures that combine the two approaches seems to many practitioners to work better than use of either approach alone. That is, the use of radiotracer and blue-dye injections, the imaging and detection of radioactive foci and the visualization of blue-stained nodes, and the excision and assessment of the resulting radioactive, blue-stained, and radioactive and blue-stained nodes produced more accurate staging than the use of radiotracer or blue-dye techniques alone.

Radiotracer Versus Blue Dye

Overwhelmingly, there is agreement that using a combination of blue-dye and radiotracer techniques is a better approach for successful sentinel lymph node identification and excision than using either technique singularly.[11] Success here is defined as accurate staging of a patient's disease, although, as noted above, few studies are conducted with this as a measure of success. In the blue-dye technique, isosulfan blue is injected in the operating room. It is injected intradermally, peritumorally,[12] subdermally, periareolarly,[13,14] or subareolarly. Results of the task of identification of blue axillary nodes—nodes presumed to be axillary sentinel nodes—are essentially the same no matter which injection strategy is used. That is, the axillary nodes stained blue by use of one strategy are generally the same nodes that would be stained blue by use of any of the other injection strategies. The surgeon usually performs gentle massage following the injection of the blue dye and begins, 5 to 7 min after administration of the blue dye, a dissection in search of blue-stained lymph channels and blue-stained axillary nodes. A blue-dye protocol is complete when the surgeon believes all locatable and accessible blue-stained nodes have been excised.

In a radiotracer technique, a Tc-99m colloid (the choice varies, in part, because the approved agents vary around the world) is injected in the nuclear medicine department and the resulting distribution of radiotracer is then imaged there as well. After the imaging, while the patient is still under the nuclear medicine camera, the skin nearest each detected radioactive focus is marked to indicate the location of the focus. The images obtained provide the surgeon a map of the distribution of radiotracer and, in particular, provide a map of the radioactive foci in the axilla, the internal mammary region, the breast, the supraclavicular region, and the infraclavicular region. The marks provide potential sites for the initial incision of the excision procedure. Using the images, the external markings, and a gamma counting probe, the surgeon searches for radioactive foci by making an incision directly over a prominent focus and proceeding to excision of foci until she or he believes all accessible foci that might be sentinel nodes have been excised. Information in preoperative images is usually substantial and the use of such images usually reduces operating room time considerably, as compared with the time required if foci locations are determined and mapped using only a counting probe. A radiotracer protocol is complete when the surgeon believes all locatable and accessible radioactive nodes have been excised.

When a combination of radiotracer and blue-dye techniques is used, the surgeon seeks to excise blue-stained nodes, radioactive nodes, and nodes that are both blue-stained and radioactive. There are patients in whom there are radioactive nodes that are not stained blue and patients in whom there are blue-stained nodes that are not radioactive. The specifics of a protocol affect the occurrences of such. Well-designed and well-performed procedures have few such occurrences. Nonetheless there are occurrences. A combination of radiotracer and blue-dye techniques generally results in the identification of more of the sentinel nodes in a population than do radiotracer or blue-dye techniques individually. This, that more potential sentinel nodes are found, is the primary reason that a combination strategy results in accurate staging in more patients more often than does a radiotracer-only or blue-dye-only strategy.

Radiotracer Methodologies

Among the hundreds of articles published on breast cancer sentinel node procedures are numerous ones investigating the details of various radiotracer strategies. Such details include the choice of radiopharmaceutical, the sizes of the particles of the radiopharmaceutical, the dose per injection, the volume per injection, the site(s) of injection, the localization or not of internal mammary sentinel nodes, the time span between injection and surgery, the use or not of preoperative imaging, the acquisition or not of time-course images, the orientation of the patient during preoperative imaging, the nature of transmission imaging used for anatomic reference, the choice to remove tumor before nodes or nodes before tumor, the type of counting probe, and the decision to remove or not nodes with low radiotracer uptake. The continuing education article "Radioguided sentinel lymph node biopsy in breast cancer surgery"[15] is one introduction to the

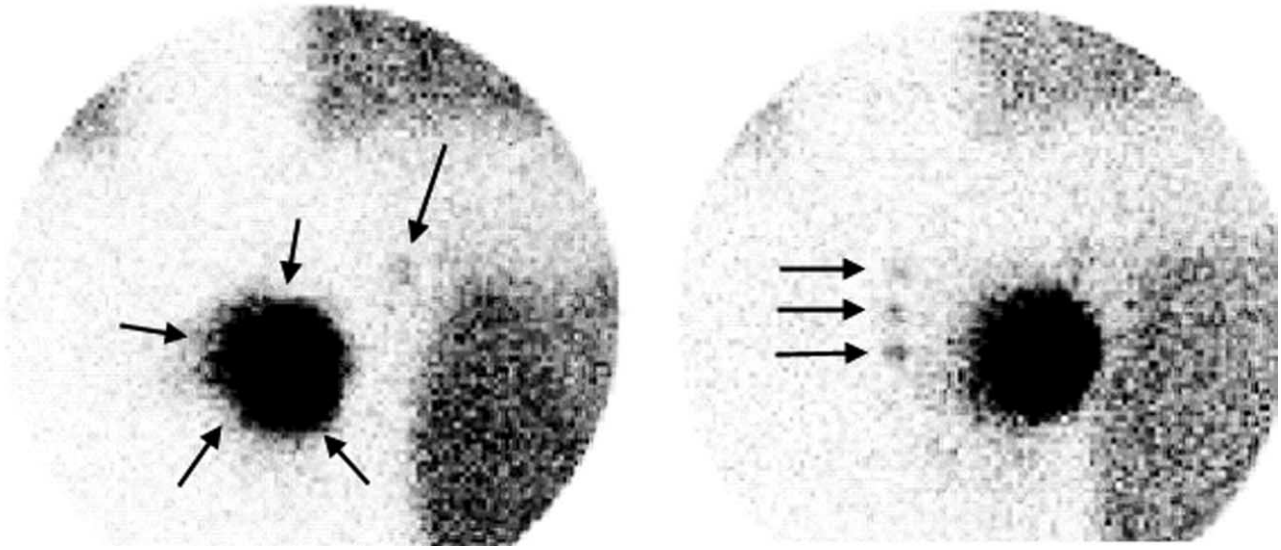

Figure 1 Internal mammary and axillary sentinel nodes. Internal mammary sentinel nodes and an axillary sentinel node are seen in this patient after 4 peritumoral injections of filtered Tc-99m sulfur colloid around the 2 cm right breast mass (4 arrows surround the injected activity). Each injection had a volume of 1.0 mL with 0.125 mCi (4.625 MBq) of activity. The breast was moved to minimize soft tissue attenuation. The image on the left shows the axillary node (vertical arrow) but not the internal mammary nodes because the breast is displaced medially, which clears the axillary region but obscures the internal mammary region due to soft tissue attenuation from the displaced breast. In this case, all nodes were excised and all were negative for tumor. Three internal mammary nodes (3 horizontal arrows) are seen in the image on the right, which was acquired after physically moving the breast laterally so as to minimize soft tissue attenuation above the locations of the 3 internal mammary nodes.

fundamental aspects of and the issues in the nuclear medicine components of such protocols.

There is no standard protocol for localization of sentinel lymph nodes in patients with breast cancer, and it is not likely there will be. This is in part because the success of a protocol at a specific facility depends on numerous factors including the resources, patient population, and patient management practices of the facility, and on the competencies and interests of the facility's personnel. Several strategies have been investigated and deemed successful in over 96% of relatively large numbers of subjects. Success in this context generally means that radioactive or blue-stained nodes were found in 96% or more of the subjects studied. The broad implication of this for practitioners is that they should consider changing their protocol if they are not having a similar level of success.

Injection of the Radiotracer

There are 7 sites of injection used in breast cancer sentinel node procedures: peritumoral, subdermal, periareolar, intratumoral, intradermal, subareolar, and subtumoral. Some protocols involve the use of one injection technique; some involve the use of two or more techniques. One factor dictating a practitioner's choice of technique(s) is her or his intention to locate or not internal mammary and other extra-axillary sentinel nodes in addition to axillary sentinel nodes. Nieweg and coworkers summarize well considerations relevant to this issue.[16]

We remark briefly on three techniques we have used in some of our investigations and indicate that our present protocol involves peritumoral and subdermal injections of Tc-99m sulfur colloid and periareolar injections of isosulfan blue dye.[17-19]

Peritumoral

Peritumoral injections were the first type of injection used and investigated in breast cancer sentinel lymph node protocols. Peritumoral injections are performed by injecting radioactive colloid at the depth of the tumor, approximately 1 to 2 cm from the palpated margin of the tumor, at 4 to 6 sites around the tumor. If the tumor is not palpable, ultrasound guidance can be used to place the injections. If the tumor has been removed in an excisional biopsy, the injections are placed around the site from which the tumor was excised with care being taken not to inject into the cavity resulting from tumor excision. The total injected dose ranges from 0.5 mCi (18.5 MBq) to 1.0 mCi (37 MBq). The volume of injectate has not been standardized. Most centers use 1 mL per injection. Some use 2 to 8 mL per injection. Some physicians inject at 4 sites, some at 6 sites. We currently use 2 peritumoral injections (0.125 mCi/injection or 4.625 MBq/injection) and a subdermal injection in a protocol in which we previously used 4 peritumoral injections and one subdermal. We have noted no difference in our results. Gentle finger massage is applied after each injection. This is done to increase flow of the colloid particles into the lymphatics. Example preoperative images obtained when peritumoral injections were used can be found in Figure 1.

Subdermal

Subdermal injections are made below the skin closest to the tumor. Such an injection is made just below the superficial layers of the skin. A weal is not raised as it is with intradermal injections. The subdermal injection is not meant to be intradermal nor is it meant to be subcutaneous. The volume of the subdermal injection is 0.250 to 0.375 mCi; the activity injected is 0.250 to 0.500 mCi (9.25–13.875 MBq; some physicians use 0.5 mCi or 18.50 MBq). Gentle massage is applied at the site of injection. Intradermal injections have been investigated as alternatives to peritumoral or subdermal injections. Some practitioners claim better success with intradermal injections than with peritumoral injections when Tc-99m sulfur colloid and blue dye are used.[20]

Periareolar

Periareolar injections are made just outside the areolar border at 4 sites equally spaced around the areolar. The injections are subdermal, as described above. Alternatively, some physicians make a single subareolar injection, just outside the areolar-cutaneous junction, lined up with the position of the tumor. Each injection is delivered with a volume and activity similar to those used in a subdermal injection. Gentle massage is applied to each injected site to facilitate more rapid uptake into the lymphatics. Recent reports on periareolar injection strategies include Kim and coworkers, Krynyckyi and coworkers, and Pelosi and coworkers.[13,14,21,22]

Particle Size of the Radiocolloid

Filtered Particles

In the United States, only Tc-99m sulfur colloid is an approved commercial product that can be used for lymphoscintigraphic sentinel node imaging and intraoperative probe guidance. Most filtered sulfur colloid is produced using 0.22-μm filtration, a procedure that results in an injectate with particles that are smaller than 220 nm. Most of the particles are between 100 nm and 220 nm. A comparative study of several agents used for lymphoscintigraphy (two commercial albumin colloid preparations, antimony sulfide colloid, and dextran) showed that the highest counts recovered in sentinel lymph nodes were obtained when albumin colloid particles of 100 to 200 nm were used. Those are the dominant sizes of the particles that remain in filtered sulfur colloid preparations.[23] What is required for a radiopharmaceutical to be a good sentinel lymph node agent is that the radiopharmaceutical be of appropriate particle sizes. The colloid should be a balance of particles that are small enough to be efficiently taken up into lymphatic channels and large enough so that they do not travel too rapidly through the sentinel node to secondary and tertiary nodes, a result that would limit a surgeon's ability to identify and excise only sentinel lymph nodes.

Unfiltered Particles

Unfiltered Tc-99m sulfur colloid comprises particles with a wide range of sizes, with the largest being about 1000 nm and the average being 305 to 340 nm.[24,25] Many surgeons prefer these large particles to the smaller ones in a filtered preparation because they believe that with the larger particles they can minimize visualization of nonsentinel lymph nodes. A comparison of filtered and unfiltered Tc-99m sulfur colloid in melanoma patients produced results that indicated that visualization of sentinel nodes with filtered and unfiltered colloid is similar with the two techniques. However, it also showed that use of filtered particles as opposed to use of unfiltered led more often to visualization of the lymphatic channels leading to the sentinel nodes.[26]

Gamma Counting Probes

The nuclear medicine tool used intraoperatively in sentinel lymph node protocols is the gamma counting probe. Because a probe should accurately discriminate between primary and scatter photons, good sensitivity, side shielding, and energy resolution are probe characteristics that are important to successful detection and localization of foci of radioactivity. Today, a practitioner's choice of probe system for breast cancer sentinel node protocols is mostly a matter of personal preference as regards probe and probe system features such as shape and weight of the probe and audio signal and count display characteristics of the system. Some presently available probes and systems have matured with the refining and maturing of melanoma and breast cancer sentinel node protocols. These probes and systems are probes and systems that have been available for some time and remain available in large part because there are sufficient numbers of users satisfied with the features each now offers. At our institutions, we have probes from several vendors as we have surgeons with different preferences in technology. Our most recent probe purchase was made following intraoperative testing of several probes by several surgeons. The probe acquired was different from the others we own. But, each probe we own gets significant use from at least one surgeon. There are at any time a few new probe companies. Some with new probe designs that are the result of their new approaches to intraoperative detection, often for radioisotopes different from Tc-99m and often for procedures different from melanoma and breast cancer sentinel node protocols. We do not expect gamma probe use in breast cancer sentinel node procedures to change significantly in the next few years. Thus, the goal in probe choice for this task is satisfaction of the surgeon user. Something probably best determined by having the surgeon do some prepurchase test drives.

We are not aware of any publication that summarizes the specific properties of the probes presently available. This is a task that is not easily done. There are at least 10 companies that manufacture and distribute gamma counting probes. Most have more than one model of probe; some have more than one model of control system. A number of articles discuss ways to characterize probes and discuss properties of some past and present probes.[27-33] Readers interested in such topics are directed to these articles. In 2004, the National Engineering and Manufacturers Association (NEMA) finalized, published, and made available a specification document regarding characterization of intraoperative nonimaging gamma probes. That document is NU 3-2004 *Performance*

Measurements and Quality Control Guidelines for Nonimaging Intraoperative Gamma Probes.[34] The information it contains is more directly relevant to manufacturers than end users, but users seeking details on the methods used to obtain vender-published specifications will find some guidance on such in this NEMA document.

The Role of the Pathologist

The thorough histopathologic examination of sentinel lymph nodes given by a pathologist includes multisectioning and multiple analyses. Given practical considerations, such thorough analysis cannot be applied to all nodes excised in a total axillary nodal dissection. The sentinel node procedure results in 1, 2, sometimes 3, and less commonly 4 or more sentinel nodes, compared with the 10 to 30 nodes that are often excised and submitted for pathological analysis in axillary dissection procedures. One key feature of the analyses of sentinel nodes performed by the pathologist is IHC analysis. Another is the pathologist's multisectioning of each sentinel node rather than the bisecting routinely used in the analyses of nodes from an axillary dissection. The multisectioning results in 2 to 4 times as much tissue being examined for sentinel nodes as compared with nodes from standard axillary dissection. The multisectioning and IHC analysis are procedures that are time consuming, costly, and labor intensive. Nonetheless, in a study performed in 1997 in which comparison of the IHC results of nodes from sentinel node biopsy to those from axillary dissection was made, it was found that of 1087 nonsentinel nodes that were negative for tumor by H&E staining only one lymph node from among 60 patients who were sentinel node tumor negative had a tumor positive nonsentinel node in the nodes obtained through axillary dissection.[35] Morton and Ollila wrote about that report, "This confirms histopathologically that the sentinel node identified by meticulous lymphatic mapping . . . is indeed the most likely axillary lymph node to harbor metastatic tumor in patients with breast cancer."[36]

Since 1948, pathologists have known that bisecting a lymph node and studying each resulting surface with H&E staining per the routine for nodes removed in axillary dissection is inadequate for consistent detection of metastases in breast cancer patients.[37] Studies have shown that multisectioning of nodes decreases the sampling error phenomenon and increases metastatic tumor detection by a factor of 7% to 33% compared with simple bisecting of the node. One such study is Dowlatshahi and coworkers.[38] Cytokeratin IHC staining also increases metastatic tumor detection compared with H&E staining. In this case, the increase is 10% to 15%.[39-42]

Prognostic Significance of Micrometastases

On this topic, three important questions often are asked (1) What is the significance of micrometastases? (2) Does the presence of micrometastases have the same clinical significance as the presence of macrometastases? (3) How many tumor cells in a lymph node constitute micrometastases such that they can result in further tumor growth and spread? In an effort to evaluate the clinical significance of axillary lymph node micrometastases, Sakorafas and coworkers performed a literature review from which they concluded the presence of axillary sentinel lymph node micrometastases is generally associated with a poorer prognosis than that associated with no axillary involvement.[43] They recommended that patients whose sentinel nodes harbor micrometastases be treated with axillary dissection and adjuvant therapy. Micrometastases are generally defined as metastases smaller than 2 mm in size; other definitions might include metastases detected by serial sectioning, immunohistochemistry, or reverse transcriptase-polymerase chain reaction (RT-PCR). The clinical significance of micrometastases found only by RT-PCR is uncertain. Some believe that a positive result might be obtained because of the presence of fractions of tumor cells (or protein fragments) that are not viable cells and thus could not replicate or spread. There is, despite the evidence of some retrospective studies, a controversy regarding the prognostic significance of micrometastases found only by IHC staining, particularly when only isolated tumor cells are found.[44] Isolated tumor cells are usually defined as clusters less than or equal to 0.2 mm in maximal dimension.

A recent report of a 15-year follow-up of patients with pT1 breast cancer who underwent axillary lymph node dissection and had negative nodes by routine microscopic examination determined that half of the patients (n = 48) developed distant metastases.[45] In the study, pathologists reexamined 1539 lymph nodes from these patients' axillary dissections of 15 years earlier, and found occult metastases using cytokeratin immunostaining in nodes from 21 of the patients (11 had metastases measuring 0.2–2.0 mm, and 10 had individual cells or clusters less than or equal to 0.2 mm in maximal dimension). From these data, one is certainly tempted to conclude that both micrometastases and individual cells are significant for prognosis in breast cancer.

Controversies

Internal Mammary Sentinel Lymph Nodes

This controversy centers on the utility of information obtained in lymphoscintigraphy about drainage to internal mammary sentinel nodes (see Fig. 1). Most surgeons are reluctant to excise internal mammary nodes because of the difficulty of such surgery and, thus, some question the value of obtaining information about such nodes. Other physicians have said that patients that have lymphatic drainage to internal mammary nodes and axillary sentinel node involvement should have prophylactic radiation to the internal mammary chain even if the internal mammary sentinel nodes are not biopsied. We note there have been reports of tumor positive internal mammary lymph nodes

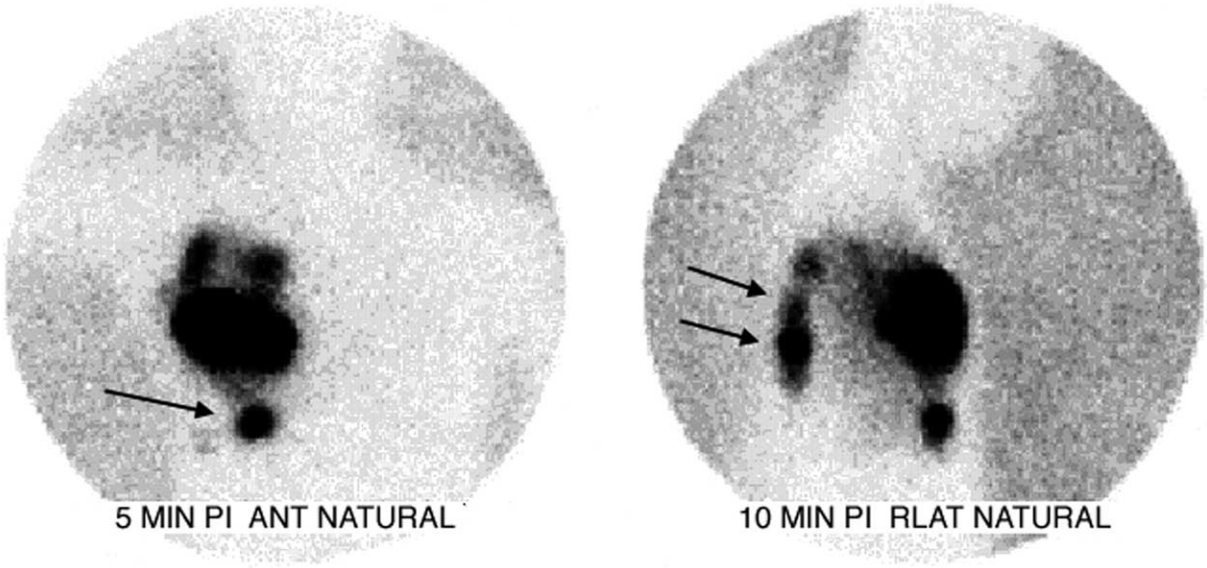

Figure 2 Intramammary sentinel lymph node and unusual drainage. An intramammary sentinel node (single arrow on anterior view, left) is seen below the peritumoral injection sites around the tumor. Note there is a very unusual lymphatic drainage to posterior nodes that appear to be in a prescapular location (double arrows on lateral view, right). These nodes could not be sampled. The intramammary node was excised and assessed negative for tumor.

in the absence of tumor finding in axillary sentinel nodes. This fact suggests assessment of internal mammary nodes is not a topic to be ignored. Nonetheless, the opinion currently held by most is, in the absence of histopathologic information about internal mammary nodes including those apparent by lymphatic mapping, no changes in current treatment/management approaches should be made.[46,47] Taking exception to that approach are Galimberti and coworkers, who reported that of 160 of 182 patients who had internal mammary nodes surgically removed and examined 8.8% had internal mammary nodes tumor positive.[48] Their patients were treated with radiotherapy to the internal mammary chain. Interestingly, no axillary sentinel node involvement was found in 4 of the 14 patients. Axillary involvement was found in the other ten. These investigators claimed that internal mammary nodes can be quickly and easily removed with insignificant risk and with no increase in postoperative hospitalization. This is not a universally held opinion. As a result of their patients having had axillary and internal mammary sentinel nodes removed and assessed, 4 patients migrated from N0 to N1 and 10 patients migrated from N1 to N3. These changes resulted in modification of local radiotherapy and of systemic treatment. These patients would have been under staged if internal mammary nodes had not been excised and examined by the pathologist. There seems to be general agreement that metastases in internal mammary lymph nodes in breast cancer patients influence survival in a manner comparable to that of metastases in axillary lymph nodes.[49]

Similarly, intramammary lymph nodes with metastases have been documented as independent predictors of poor outcome for patients with breast cancer.[50] Thus, intramammary lymph nodes, as well as other extra-axillary nodes seen on lymphoscintigraphic images performed for sentinel node localization, should be targeted for excisional biopsy along with axillary sentinel nodes. The images in Figure 2 include an intramammary node seen after peritumoral injection of filtered sulfur colloid.

Internal mammary sentinel nodes are best identified when peritumoral, intratumoral, or subtumoral injections of radiotracer are made. Reports of studies in which peritumoral injections were used indicate that 10% to 30% of patients has lymphatic drainage to internal mammary lymph nodes, as seen on lymphoscintigraphy.[17] In contrast, some injection techniques such as subdermal, intradermal, periareolar, or subareolar, result in internal mammary drainage being visualized much less frequently (1-11%).

Ductal Carcinoma In Situ

Sentinel lymph node exams are not usually done on patients with ductal carcinoma in situ (DCIS). Historically, axillary metastases were found in 1% to 2% of patients with DCIS if axillary node dissection was performed. Yet, reports indicate that approximately 12% of patients with DCIS develop disease recurrence. Thus, the question arises, "Should patients with DCIS be evaluated with sentinel lymph node examination?". One recent study examined pathology samples from axillary lymph nodes of DCIS patients who had negative axillary dissections 10 to 30 years earlier.[51] Although micrometastases were discovered in 13% of the patients' nodes, no micrometastases were found in patients who had recurrence of their disease. The authors concluded that sentinel node biopsy for altering of disease staging of DCIS patients is not indicated.

Sentinel Node Reliability After Neoadjuvant Therapy for Locally Advanced Breast Cancer

Success is reportedly high when sentinel node procedures are performed on patients pretreated with neoadjuvant therapy for locally advanced tumors.[52] It appears that sentinel node biopsy is accomplished with similar accuracy for these patients as for patients with no history of neoadjuvant therapy.

The False-Negative Rate

Reported false-negative rates vary considerably. Reported rates range from 1% to 10%. The false-negative rate is the rate at which a sentinel node biopsy for a patient is negative and the patient has an axillary dissection that identifies a node positive for metastases or the patient presents with axillary node recurrence. The false-negative rate can be expressed as the false negatives/(true positives + false negatives). Thus, the percentage of the node tumor positive patients who are missed by sentinel node mapping, is the preferred interpretation of false negative.[53] An early histopathological validation of the sentinel lymph node concept in breast cancer was published in the *Annals of Surgery* in 1997. In the study, 103 patients had sentinel node biopsy and axillary node dissection and all excised nodes were examined by IHC methods. The authors found that only one lymph node of 1,087 non-sentinel lymph nodes was tumor positive in a patient whose sentinel nodes were tumor negative. There were 60 patients with tumor negative sentinel nodes, therefore, the false negative rate in this study was 1/60 = 1.7%.[35] In another study, Krag and coworkers reported a false negative rate of 11.4%; we note that in their study no preoperative gamma imaging was performed.[54]

In an attempt to identify reasons for errors in finding sentinel lymph nodes, one report indicated that erroneous sentinel lymph node identification might be due to changes in the surgical team, difficult lymph node location, or the absence of a thorough histological study.[55] Nevertheless, these authors also concluded that it is not possible to explain completely why, in a very small percentage of cases, the sentinel node is erroneously identified.

There also are studies that document that lymphatic tumor burden negatively impacts sentinel lymph node detection in breast cancer.[56] Presumably, lymphatic flow may be disrupted by tumor emboli and, when tumor burden in lymphatics is high, there is as a resultant increased failure to identify sentinel lymph nodes by lymphoscintigraphy or lymphatic mapping methods.

Radiation Safety

If all members of the multidisciplinary team practice standard biohazard safety and radiation safety procedures, breast cancer sentinel lymph node protocols are considered radiation safe for patients, nuclear medicine technologists, nuclear medicine physicians, oncology surgeons, surgical nurses, and pathologists. Standard practice should always include at minimum the use of the Universal Precautions biohazards guidelines and the As Low As Reasonably Achievable (ALARA) radiation safety guidelines. Several studies have addressed various aspects of the radiation safety of breast cancer sentinel lymph node protocols. The most recent include Colgan et al (2001), de Kantor et al (2003), Fitzgibbons and LiVolsi (2000) (discusses the recommendations of The Surgical Pathology Committee of the College of American Pathologists and the Association of Directors of Anatomic and Surgical Pathology), Gentilini et al (2004) (this study considers the issue of pregnant patients), Glass et al (1999), Law et al (2004), Michel and Hofer (2004), Miner et al (1999), Morton et al (2003), Motta et al (2000), Nugent et al (2001), Stratmann et al (1999), Strzelczyk and Finlayson (2004), Turner et al (2001), and Waddington et al (2000).[57-71]

Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

FDG-PET studies are effective in detecting metastases in lymph nodes of patients with breast cancer, if the cancer is larger than 2 cm (sensitivity 94%).[72,73] Note that, in this population, a FDG-PET study that is negative for axillary node involvement does not rule out the presence of micrometastases. When a primary breast tumor is smaller than 2 cm, which is the case for many patients, the sensitivity of FDG PET to show micrometastases plummets to approximately 33%. Thus, micrometastases, which dominate in presentation over macrometastases in patients whose primary tumor is small, are not reliably detected by FDG imaging. Several recent reports of FDG-PET assessment of axillary nodes reach similar conclusions.[74-77] It is almost unrealistic to think that any imaging procedure could detect micrometastases, unless the presence of such causes sufficient expression of some identifiable compound that can be assessed by radiotracer methodology. However, FDG-PET may have a role in the management of patients whose primary tumors exceed 2 cm in size. Initial staging with FDG-PET might be effective, and if in the future such is supported by clinical data, it is possible that FDG-PET might be substituted for the sentinel node procedure in those patients. For an example of an FDG-PET study of a breast cancer patient, see Figure 3.

Other Cancers

Patients with intermediate thickness malignant melanoma were the first to benefit significantly from sentinel lymph node excisional biopsy procedures. The sentinel node concept was popularized for the staging of cutaneous melanoma, and indeed, sentinel node biopsy using radiocolloid with imaging has become the preferred method of staging melanoma. As noted in our opening paragraphs, the success in recent years of lymphoscintigraphic imaging for sentinel lymph node localization, is, in part, the result of interest and effort of surgeons. The sentinel node concept originated with surgeons; surgeons popularized the sentinel node concept and validated it; and surgeons introduced the use of Tc-99m-labeled radiocolloid for preoperative imaging and intraoperative probe detection of sentinel nodes.

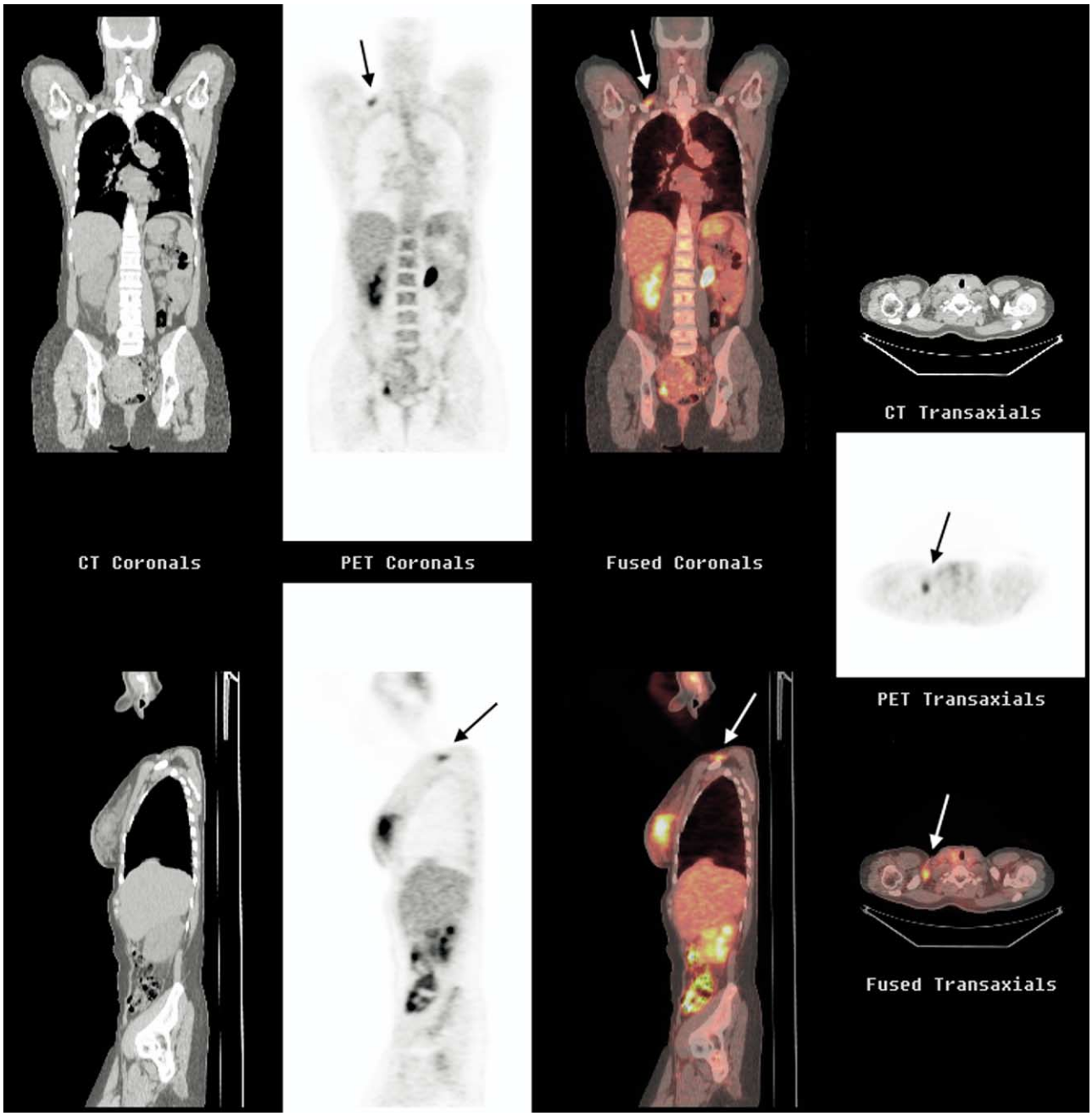

Figure 3 Supraclavicular but no axillary node on FDG-PET/computed tomography (CT). CT, FDG-PET, and FDG-PET/CT images (left to right) from an FDG-PET/CT scan of a patient with invasive ductal cancer in the right breast measuring 5 cm. Note there is abnormal FDG uptake in a right supraclavicular node (arrows on the FDG-only and FDG-PET/CT registered images), but none in the axilla. (Color version of figure is available online.)

In colorectal cancer, sentinel node identification has been performed intraoperatively, injecting blue dye and/or radiocolloid peritumorally into the colonic mucosa, followed by tracing the pathway of the blue dye to a lymph node, and/or using a gamma-detecting probe to find sentinel nodes. Wood and coworkers identified sentinel nodes in 97% of the patients studied.[78] They found that of 74 patients that were node negative by H&E stains, 24% were upstaged by multisectioning and IHC staining, similar to the experiences with breast cancer and melanoma. In addition, they reported unexpected lymph drainage in 8% of patients, which caused alteration of the surgical approaches for those patients. The sentinel node approach to detect micrometastases is a reasonable one for colorectal cancer, since about one-third of patients with node negative colorectal cancer develop systemic disease later, implying that occult disease is inadequately treated by surgery alone. We expect there will be, as there has been for melanoma and breast cancer, much study needed to determine protocols that are adequately successful. Use of radiotracer methodology is more difficult for colorectal cancer than for melanoma or breast cancer as injection strategies will likely involve sophisticated preoperative injection pro-

cedures or intraoperative injection procedures that complicate the use of lymphoscintigraphy for localization in that lymphoscintigraphy would have to be intraoperative. Experience gained in the maturation of melanoma and breast cancer sentinel node procedures will likely shorten the development time for colorectal sentinel node procedures, but the context may be even more complex than those of melanoma and breast cancer both in environment and task.

Laparoscopic detection of sentinel lymph nodes in gastrointestinal cancers, including esophageal, gastric, and colorectal has been performed successfully by use of radiotracer and blue-dye techniques.[79] In prostate cancer patients, lymphoscintigraphy and radioguided surgery for sentinel lymph node identification have been performed following transrectal injection of radiotracer into the prostate. In a report of the technique with results of 350 cases, investigators found lymph node metastases in close to 25% of the patients studied. They concluded that a sentinel node protocol is feasible in this context and that such might be a potentially valuable technique for staging patients with prostate cancer.[80]

Other cancers have also been studied for sentinel node feasibility with varying success, including head and neck cancers, pancreatic cancer, thyroid cancer, and others. The topic has become sufficiently extensive that there now exists the International Sentinel Node Society (ISNS), which sponsors regularly the International Sentinel Node Congress, a meeting at which all aspects of sentinel node protocols for numerous cancers are discussed.

Intraoperative Gamma Imaging

Various technologies for intraoperative gamma imaging are being developed and investigated. Many articles have reported on devices that are being investigated for intraoperative imaging of sentinel nodes in patients with breast cancer.[81-94] The broad clinical goals of the investigations being conducted vary, with the goals of each being defined in part by the technologies involved and in part by the difficulties with existing technologies and protocols that the studies are meant to address. The present investigations remain preliminary but some will probably transition to more extensive clinical studies. The possibility of pre-incision imaging that results in more efficient intraoperative searches of all locations that might contain sentinel nodes and the possibility of postexcision imaging that results in greater surgeon confidence that all such nodes have been excised are two potential benefits of the use of intraoperative imaging.

For some investigators of intraoperative imaging, the goal is development of an alternative to preoperative gamma imaging. If such is eliminated, the entire sentinel lymph node protocol can, in principle, be scheduled and performed almost entirely by surgical and pathology team members. This would reduce logistics problems at some facilities. Nonetheless, radiotracer will still need to be injected preoperatively so that there is sufficient time for the tracer to flow from injection sites to nodes. The elimination of preoperative gamma imaging implies, however, that no sequential time-course images of the flow will be obtained. That information can be quite useful in some cases, but would not be available if preoperative imaging is not performed. We recommend that preoperative imaging not be eliminated and recommend that time-course images be acquired. It is a fact that many practitioners use only blue-dye approaches and that other practitioners use radiotracer approaches that do not include preoperative imaging. For practitioners who do not acquire preoperative images, the addition of intraoperative imaging to their present protocols has the potential of improving those protocols. For all practitioners using radiotracer technologies, there is the potential for the development of protocols that result in greater confidence that all sentinel nodes have been excised.

The goal for other investigators is development of a means to more quickly identify intraoperatively radioactive nodes that are difficult to locate using only a gamma counting probe. There are cases in which uptake in a node is difficult to distinguish from surrounding uptake if one's only tool is a gamma counting probe. For example, there are cases in which a node of interest is located close to an injection site, cases in which the uptake in a node of interest is only slightly greater than that of the uptake in neighboring tissue, and cases in which uptake in a node is only slightly higher than the radiotracer present in the incision bed following excision of one or more other nodes. In such cases, intraoperative images of the locations of interest might prove useful.

Most intraoperative gamma cameras presently under investigation can be categorized as having very small or small fields of view. The former are devices with fields of view ranging from approximately 2 cm × 2 cm to 5 cm × 5 cm. The latter devices have fields of view ranging from 10 cm × 10 cm to 20 cm × 20 cm. The former are generally considered by their designers to be hand-held devices, but their masses are at minimum a kilogram and as such are not always easy to position or hold steady for the times necessary to detect low-count nodes. We note that nodes with only tens of nanocuries of tracer have been assessed positive for tumor. If clinical trials demonstrate that any of these devices have sufficient usefulness, however, means of overcoming difficulties of support and positioning will undoubtedly be developed. Intraoperative gamma cameras are not designed to replace gamma counting probes. For the foreseeable future, gamma counting probes will remain, key tools in sentinel node protocols in which radiotracers are used. Intraoperative imagers will be adjuncts to present technologies.

A relatively small field-of-view gamma camera can serve as a means of surveying locations in which potential sentinel nodes might be found. Such a camera can serve to obtain information similar to that obtained in delayed static preoperative images. We note the total time for image acquisition may not be short if a protocol is designed to explore axillary, clavicular, internal mammary, and mid-torso locations. All of these locations can be imaged simultaneously with a large field-of-view device; each will need to be imaged separately with a relatively small field-of-view device.

The value of the addition of intraoperative imaging to a sentinel lymph node protocol for breast cancer patients is dependent on the scope and specifics of a protocol.

Present investigations should shed some light on the value of adding intraoperative imaging to existing protocols, but it is likely that additional studies using refined technologies and protocols will be necessary if it is to be demonstrated that such devices have more general applicability in this setting.

The Future

There is no single "best" or "optimal" protocol for detection, localization, and assessment of sentinel lymph nodes of breast cancer patients. Because allocation of resources vary among institutions, it is not clear there will be. It does seem relatively clear that the use of a sentinel lymph node protocol as opposed to one for full axillary lymph node dissection is appropriate management for some breast cancer patients. We note, however, there are no study reports that provide data that can be use to define explicitly the patients for whom a sentinel lymph node protocol is appropriate or inappropriate. There have also been no study reports that demonstrate conclusively that a particular sentinel node protocol is best for a specific patient. As this is the case, there will continue to be studies to assess the successes and nonsuccesses of various protocols and protocol refinements.

Three multicenter clinical trials sponsored by the National Cancer Institute (NCI) are designed to provide at the end of 2007 answers or partial answers to questions pertaining to the management of patients with early stage breast cancer.[95,96] Some of those questions are: How does the survival rate of patients who have sentinel lymph node biopsy compare with that of patients who have axillary lymph node dissection? How do the recurrence rates of sentinel lymph node biopsy patients compare with those of patients who have axillary lymph node dissection? What can be understood about the morbidity of sentinel node procedures as compared with the morbidity of axillary node dissection? What is the significance of micrometastases identified by IHC only? What is the clinical significance of increased positivity of lymph nodes identified by sentinel node biopsy versus the clinical significance of those identified by axillary node dissection? Is axillary dissection a necessary component of patient management following a positive sentinel node finding? For a summary of the status of six European trials on breast cancer sentinel lymph node biopsy, see Mansel and Goyal 2004.[97]

Each multidisciplinary team performing sentinel lymph node protocols on breast cancer patients should minimally be detecting radioactive and/or blue-stained nodes in the axilla in 96% or even 98% of patients scheduled for sentinel lymph node procedures. If they are not, they should consider replacement or refinement of their present protocol, as numerous groups using a variety of protocols have reported successes at such levels, suggesting that such should be possible at most institutions. Practitioners should also be ever mindful that detecting radioactive and/or blue-stained nodes does not insure that all sentinel nodes have been detected. Although routinely used models of breast anatomy seem fairly robust, cases that appear to suggest there are exceptions to such models have been reported (see Niewag and coworkers 2004 and the references therein).[98]

In the short term, we expect sentinel lymph node biopsy in breast cancer patients will be little changed from the way it is presently performed. We expect the preferred approaches will continue to involve protocols that incorporate radiotracer procedures, including high-quality preoperative imaging and intraoperative use of gamma counting probes, blue-dye procedures, and excision, multisectioning, and IHC analysis of radioactive and/or blue-stained nodes. We do not anticipate a near-term replacement for histological assessment of nodes, as to date it appears that such is the only means of detecting the presence of small numbers of metastatic cells. In the longer term, it is possible that the management stream of breast cancer patients will be changed such that metastases will, in some patients, be detected, perhaps confirmed, before an intraoperative procedure. Such confirmation might ultimately eliminate some intraoperative procedures, but only if along with such confirmation, there also is confidence on the part of researchers that a nonsurgical procedure definitively destroys metastases so detected.

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