Intraoperative Probes

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Objective: Design features of intraoperative probes are presented. A brief discussion of the sentinel node concept and relevant radiopharmaceuticals is given. The importance of the injection technique and the necessity of imaging in radiotracer techniques for sentinel node detection are explained. Probe calibration, procedural precautions, intraoperative techniques, and radiation dosimetry relevant to the successful use of intraoperative probes are discussed. Intraoperative use of gamma probes requires a team effort involving surgery and nuclear medicine personnel and requires that team members understand the fundamentals of probe use.

After reading this paper, the nuclear medicine technologist will be able to: (a) describe present day and future potential use of intraoperative probes; (b) define the sentinel lymph node (SLN) concept; (c) state the radiopharmaceuticals and injection techniques used for SLN evaluation; (d) name several SLN detection procedures; and (e) discuss the design features and care of currently available probes.

Key Words: intraoperative gamma probe; lymphoscintigraphy; radioguided surgery; sentinel node localization

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Cancer is a major health care problem for people aged 45–65 y (*1*). By the year 2000, baby boomers in the U.S. will be in this age group and management of cancer for them will be a major health care task. Imaging science has helped in the early diagnosis and the accurate staging of many cancers. Early diagnosis and accurate staging are essential for treatment optimization that can lead to decreased morbidity and improved quality of life. Expanded use of intraoperative probes is one recent clinical development that may result in better rates of early diagnosis and improved accuracy of staging.

Cancers spread either by hematogenous routes to bones, lungs, liver, or brain or by lymphatic routes to lymph nodes. Assessment of skeletal spread is done by bone scintigraphy. Visceral spread of cancer to lungs, liver, or brain is often detected and assessed using CT or MR imaging. Fluorine-18-FDG PET may soon find significant use in this arena as well, as it has recently been shown to be useful in detecting metastases and primary tumors of several forms of cancer (*2*).

Assessment of lymphatic spread presently is done primarily by node size criteria applied to CT and MR images. Yet there are difficulties with CT and MR images for this task, and accurate assessment of lymph nodes in many cases still requires surgical biopsy, the gold standard for this task. One increasingly used technique for lymph node assessment involves the use of radiotracer techniques for sentinel lymph node (SLN) detection and localization. This article introduces the assessment of lymphatic spread of cancer using radiotracer techniques involving intraoperative gamma probes.

HISTORY

Radiotracer techniques using intraoperative gamma probes are procedures which surgeons can use to localize more easily small tumors or lymph nodes to be removed in a surgical biopsy procedure. Use of intraoperative probes decreases surgical time, decreases patient morbidity, and improves staging accuracy. All of these can lead to improved treatment, improved quality of life, and higher long-term survival rates.

In 1949, Selverstone et al. (*3*) used a Geiger Mueller counter to surgically define an astrocytoma after intravenous injection of ^{32}P, a β emitter. This was the first use of a counting probe in a surgical procedure. Between 1950 and 1990, probes of various designs were developed and used, but no practical application led to extensive use of probes. Since 1990, the use of intraoperative probes has increased significantly and all indications are that their use will continue to increase for several years. The increased use is the result of growing acceptance of the SLN concept and the development of new tracers for tumor localization.

The conventional approach to assessing the lymphatic spread of a cancer involves surgical removal of all (often 10–20) lymph nodes in the drainage area of a tumor. This conventional approach requires a large incision and considerable surgical time. It also can result in significant morbidity. Since a pathologist must assess 10–20 lymph nodes, he or she does not routinely assess multiple slices of all resected lymph nodes or subject all of the resected nodes to thorough histochemical

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staining. Doing so would provide additional information, but to do extensive analysis of 10–20 nodes is not practical. An alternative to full resection is a technique founded on the SLN concept. It involves the resection and thorough assessment of the SLN or SLNs of a lymphatic bed. Since one or a few critical nodes are obtained in this procedure, a thorough histochemical staining is possible.

Sentinel Lymph Node Concept

The sentinel lymph node concept was proposed by Cabanas in 1977 (*4*). The first lymph node to receive lymphatic drainage from a tumor site is the sentinel node; and if there has been lymphatic spread, the sentinel node is the first node to have metastatic involvement. Further, the concept implies that sampling the sentinel node is sufficient for assessing a lymphatic bed. The sentinel node concept applies to the spread of several types of cancer including breast cancer and melanoma. It was first applied in the management of cancer by Cabanas in 1977 (*4*); it was first applied in the management of melanoma in 1992 by Morton et al. (*5*).

Blue-Dye Technique for SLN Detection

The SLN can be detected by injection of isosulfan blue dye followed by visualization of the lymphatic channels and the SLN. In this technique, the objective is determination of the SLN through visualization of blue dye in the SLN(s). Visualization is possible if the channels and SLNs are near the skin or if an incision is made that reveals the location of injected dye. The technique has been used successfully in many patients since its introduction in 1977, and its success has expanded the acceptance and application of the SLN concept. However, if the lymphatic channels and SLN of the lymphatic bed under consideration are deep, localization of the SLN requires a large incision which can lead to accidental disruption of the lymphatic channel and to blue-dye contamination of the whole surgical area. If contamination occurs, detection of SLNs is often difficult. Alternative techniques that use radiotracers which allow for initial localization without incision and final localization with a minimal incision have been developed.

Radiotracer Techniques for SLN Detection

Radiotracer techniques for SLN detection and localization for surgical biopsy can involve counting probes or counting probes and imaging systems. Preoperatively, SLNs can be detected and located using images, probes, or images and probes. At present, intraoperatively, SLNs are detected and located using only probes. Imaging of the lymphatic system is known as lymphoscintigraphy. Some investigators apply the term lymphoscintigraphy to any procedure involving a radiotracer and the lymphatic system. Here the term is applied only to imaging procedures for detecting SLNs.

In radiotracer techniques for SLN detection, a radioactive pharmaceutical is injected near the site of the primary malignancy. Detection and localization of the SLN are then accomplished by identifying locations in the lymphatic bed with higher gamma counting rates than background counting rates. Once there is radioactive tracer in the SLN, the SLN can be localized by counting with a gamma probe or by imaging with a gamma camera. Both strategies provide information that can help a surgeon to remove the SLN with a smaller incision and with less surgical morbidity. The major advantages of techniques for SLN resection that involve the use of radiotracers for localization are that surgical time and morbidity are decreased. Removal of a single or a few (2 or 3) representative nodes instead of 10–20 means a more extensive analysis of the removed nodes is practical. Thus if the SLN concept is valid, thorough analysis of SLNs together with surgery resulting in limited morbidity is better patient management than limited assessment of all nodes with significant morbidity.

Potential for Additional Probe Use

Radiolabeled monoclonal antibodies, tumor-specific agents such as ^{111}In-octreotide, ^{99m}Tc-sestamibi (MIBI), ^{201}T1, and positron emission agents such as ^{18}F-FDG can be used to assess the spread of cancers and to determine the locations of primary lesions. All of these agents work by exploiting functional characteristics of lesions rather than sizes of lesions, as is done in procedures that use diagnostic modalities such as CT and ultrasound. Not infrequently, functional images detect lesions that CT does not. In such situations in particular, the use of an intraoperative probe might significantly improve a surgeon's ability to localize a lesion. As the indications for the use of the above radiopharmaceuticals are clarified, increased use of intraoperative probes with such agents is likely to follow.

DESIGN AND AVAILABILITY OF PROBES

An intraoperative probe consists of a detector, collimator, digital or analog display, and an audio signal generator. At present, commercially available probes have either a NaI or CsI scintillation crystal or a CdZnTe or CdTe semiconductor detector. Some manufacturers provide both scintillator-based and semiconductor-based probes. Sodium iodide crystals are sensitive over a wide range of gamma energies but must be coupled to photomultiplier tubes. Hence NaI-based probes are usually larger and bulkier than semiconductor-based probes that do not have photomultipliers. Semiconductor-based probes have lower sensitivity than the scintillator-based probes, particularly at energies above 140 keV. Shielding and collimation of probes are important features as they influence spatial resolution and angular sensitivity. In the localization of the SLN, avoidance of the injection site activity is essential, and proper shielding and collimation are necessary to allow an operator to get good assessment of a lymph node near an injection site. Probe performance depends on its detector sensitivity, collimation, spatial resolution, and scatter rejection capability. The user friendliness of a probe depends on the size of the probe, the weight of the equipment, and the nature of its audio signal generator. An audio signal allows the operator to detect lesions without the need to look at a display. A good audio signal generator is critical to user comfort and effective operating room use of a probe. Most users of probes at our institutions prefer probe systems with pleasant, variable-tone audio signals because such systems are easier to use than systems with threshold-only audio signals. The sterility requirements, the

longevity of the battery pack, and the cost of consumables, such as sterile sheaths, are also considerations in the selection of a probe.

There are currently more than 5 vendors who supply gamma probes in the U.S. and at least 3 other vendors supplying Europe and Australia. In the last 2 y, the manufacturers have seen 100%–300% growth in the sales of probes. We have not provided a table of specifications because there is continuous upgrading of available probes and new models with better features become available regularly.

Tiourina et al. (*6*) recently compared 4 commercially available probes (3 from the U.S. and 1 from France) for absolute sensitivity, side shielding, spatial resolution, angular sensitivity, and operator friendliness. In this well-planned study, the authors used an elaborate configuration of ^{57}Co sources as their primary test phantom. Even with the results of this study, it is difficult to assess whether there are any significant differences among the performances of probes in clinical situations. At our institutions, 2 different probes have been used. No significant differences in the detection capabilities of the probes have been noted. Our surgeons feel that a variable-frequency audio signal is an important feature for user friendliness. Raylman et al. (*7*) have described a positron probe using a plastic scintillator and a photomultiplier. They have used such a probe to locate successfully ^{18}F-FDG uptake in a rat mammary tumor, and they have demonstrated good sensitivity and 3- to 6-mm resolution. The successful use of an intraoperative gamma probe is dependent not only on the characteristics of the probe but also on the characteristics of the radiopharmaceutical used.

RADIOPHARMACEUTICALS AND INJECTION TECHNIQUES

SLN Detection

Technetium-99m sulfur colloid is the most commonly used radiopharmaceutical for assessment of SLNs in melanoma and breast cancer. The rate of colloid transport through the lymphatic pathway and the retention of colloid in the lymph nodes are related to the particle size of the colloid. We use pertechnetate with the longest ingrowth (pertechnetate eluted at transient equilibrium), heat the sulfur colloid for only 3 min during preparation, and filter labeled sulfur colloid through a 0.22-μm filter (*8*). Unit doses of filtered sulfur colloid are an alternative to on-site preparation. In Europe, nanocolloid, which is human albumin colloid, is used instead of sulfur colloid. This is done because nanocolloid preparation does not involve heating and its preparation is relatively simple.

In cases of melanoma, radiocolloids are injected intradermally in small volumes (0.1 mL) and small quantities (0.125 mCi) using a 25-gauge needle. We inject at 4 sites around the primary tumor or surgical scar. Occasionally, when the lymphatic channels and SLN are not visualized on lymphoscintigraphy, gentle massaging of the injection site or a second injection may help. In general, 60%–80% of melanomas have 1 SLN and 20%–40% have 2 or more. It is not uncommon to see a midline lesion drain to lymphatic basins on 2 sides of a lesion or to see a midtrunk lesion drain to the axilla and the inguinal area.

In cases of breast cancer, there is no consensus regarding the route of radiopharmaceutical injection, the size of particles used, the volume of the injection, or the role of imaging. European investigators inject albumin colloid (nanocolloid) subdermally in small volumes in the vicinity of the breast mass, whereas in the U.S. and Australia sulfur colloid is injected around the breast mass. In the U.S., different institutions use particles of different sizes ($<$ 0.22 μ to 1–2 μ) and injections of different volumes ($<$ 1.0 mL to 8 mL). The injection technique depends on whether a breast cancer is palpable or seen only on a mammogram. Mammography-assisted or ultrasound-assisted injection of the radiotracer is recommended when a cancer is not palpable.

The size of a breast, the location of a tumor, the existence of a previous biopsy or surgery, the age of the patient, and the injection technique are all factors that affect the speed and quality of visualization of SLN in breast lymphoscintigraphy (*9*). We schedule the surgery at least 2 h after the radiopharmaceutical injection to allow sufficient time for localization of the tracer in the SLN. Unlike cases of melanoma, the quoted sensitivities and specificities of SLN visualization using breast lymphoscintigraphy vary. Breast cancer management involving lymphoscintigraphy together with intraoperative probes and the SLN concept has not yet become the standard of care (*10*). Studies are underway, however, to determine if it should be. It is not unusual to find internal mammary lymph nodes with the radiotracer procedures, and there is no consensus regarding the removal or management of these nodes.

If there is an accidental intravenous administration of labeled colloid, a suboptimal procedure may result. Acquisition of a 10-s count over the liver after the injection is a simple quality control step that allows quick identification of such an accidental administration. Labeling efficiency of ^{99m}Tc sulfur colloid can be assessed in vivo by spot counting or spot imaging the thyroid.

Tumor Localization

Benign tumors, such as osteoid osteoma, are imaged using ^{99m}Tc-MDP injected intravenously and tumor localization is done after 2–3 h. Neuroendocrine tumors are imaged using ^{111}In-octreotide given intravenously and the localization is performed after 24 h. Parathyroid adenomas are localized with ^{99m}Tc-MIBI imaging done 2–4 h after intravenous administration. Monoclonal antibodies are imaged and localization of primary or metastatic tumors depends on whether a whole monoclonal antibody or a fractionated antibody is used, as background clearance depends on the type of antibody used.

TO IMAGE OR NOT TO IMAGE

There is a general consensus that imaging before the use of intraoperative probes during surgery is essential in localizing benign or malignant neuroendocrine tumors. But there is not a general consensus on the use of imaging for SLN detection. There are institutions that do not use imaging in SLN detection (*11*). In our opinion imaging helps determine the number of lymphatic channels and helps locate correctly the SLNs, particularly in cases in which the most proximal node to a

primary site is not the SLN (*12*). In cases of melanoma of the torso, imaging is invaluable to detect drainage to the contralateral or inguinal nodes. In breast cancer, imaging may be invaluable for identifying internal mammary nodes. European investigators routinely use imaging to facilitate intraoperative probe localization (*13*).

For SLN imaging, a large field-of-view camera with a low-energy all-purpose collimator (LEAP) is advised. We obtain early dynamic images of 10 s/frame for 10 min using a 128×128 matrix and static images every 5 min for 30–40 min. Additional images are obtained as needed. Simultaneous acquisition of a transmission image using a ^{57}Co flood source is useful, as the images provide the body contour. Markers, which assist surgeons in the localization process and decrease the surgical time, can be placed on the SLN. Alazraki et al. (*14*) have developed a detailed outline of a protocol for imaging, which they recommend for use in association with intraoperative gamma probes.

CARE OF PROBES

Calibration

Intraoperative gamma probes are subject to electronic drift and must be recalibrated periodically. The manufacturer's recommendations for calibration should be followed. It is standard practice to obtain, before each probe use, a 10-s acquisition of counts over a calibration source of appropriate energy.

Precautions

Steam sterilization, dry heat sterilization, and immersion in cleaning solutions will damage most probes. Some probes can be sterilized using ethylene oxide or glutarldehyde. One should check manufacturer documentation before sterilizing any probe. A sterile wrapping over a probe, as used for intraoperative ultrasound probes, is the recommended sterilization technique for most probes. The technique is generally good and effective. Some vendors provide their own disposable sterile sheaths. As with all surgical procedures, all operation room sterility precautions should be followed. Electric cautery devices or x-rays in the vicinity of a probe may interfere with probe accuracy.

Even though the use of a probe does not require state or NRC licensing, use and administration of radiopharamceuticals does. One needs to ensure that all appropriate licensing and state permissions have been obtained by the involved institutions before using radiotracer techniques involving intraoperative probes.

INTRAOPERATIVE PROCEDURES

SLN Detection

The patient first is injected as described above. If preoperative imaging has not been performed, the patient is positioned on the operating table and preincision localization of the SLN, using a probe, is performed. The SLN is detected by scanning the primary tumor's drainage basin in a grid-like manner to identify the highest tracer concentration. The highest concentration is identified through the digital readout or audio signal of the probe's control panel. Once a lesion is located, the patient's skin near the lesion is marked using a marking pen and the area is prepared for the incision. Scanning in a grid-like manner at this stage is not necessary if images of the tracer distribution have been preoperatively obtained. During the localization steps, it is important to angle the probe away from the injection site to prevent interference from the high concentration of radioactivity at the injection site. A preincision count for 10 s over the SLN (in vivo) and for 10 s over a background area 1 cm from the SLN is made. These values are recorded for any follow-up analysis that may be needed. Once the SLN is excised, the excised tissue is counted for 10 s (ex vivo). The ex vivo counts are usually 2–3 times higher than the in vivo counts, because with ex vivo there is no attenuation material to reduce counts. A postexcision count over the SLN bed is made to ensure the SLN has been completely excised.

Tumor Localization

Intraoperative gamma probes have been used in procedures for the removal of benign tumors such as osteoid osteoma and parathyroid adenoma and for removing malignant brain and colorectal tumors. The tracer concentration in the nearby thyroid or in the myocardium must be kept in mind in cases of parathyroid adenomas. Renal and ureteric uptake of ^{111}In-octreotide can interfere in the localization of neuroendocrine tumors of the abdomen and must be considered in such cases. Monoclonal antibodies concentrate in the liver and are excreted in the gut and, to some extent, in the urine. A good knowledge of the normal biodistribution of the labeled monoclonal antibody being used is of great importance for the correct localization of the lesion. There is limited usefulness (success) in preincision localization steps using probes in most cases of tumor localization. In most tumor localization procedures, preincision images are obtained but the use of probes is initiated only after incision.

Counting Time and Significance of Detected Activity

A question often asked is ''how long should one count to obtain a correct (useful) measurement?'' This depends on the activity level in the target area. Counting times in common clinical usage range from 2 s to 60 s. At our institutions, SLN localization is accomplished usually with counting times of 10 s at each location investigated. The target-to-background ratio (TBR) necessary to give 99% confidence depends on the counts. For a hot spot generating 100 detected cts/s, 3 SDs is 30 cts/s and the TBR needs to be 100–70, or 1.4. The TBR must be at least 2.0 to have the same confidence level when only 40 cts/s are being detected.

RADIATION DOSIMETRY

Radiation to Patients

The most significant dose of radiation to the patient is at the site of injection, since the injected radiocolloid used in radiotracer SLN detection techniques stays near the site of injection. Several investigators have found that the delivered dose at the site of injection can be as much as 45 rads/mCi. Glass et al. (*15*)

recommended that no more than 0.5 mCi ^{99m}Tc be used per study for SLN detection. The radiation burden is significantly less, however, if the primary site is removed with a wide excision within a few hours of injection, which is usually the case.

Radiation to Clinical Personnel

The estimated dose for surgeons, technologists, and pathologists is less than 2 mrem/h for SLN detection procedures. This is less than the NRC guidelines, which suggest a maximum of 5 mrem/h. Delay in the pathological processing of a specimen can reduce the radiation exposure to a pathologist if necessary, but usually it is not necessary to do so.

CURRENT USE OF INTRAOPERATIVE PROBES

Malignant Melanoma and Breast Cancer

The status of metastases in regional lymph nodes in patients with malignant melanoma and breast cancer has clear predictive value for survival. If malignant melanoma and breast cancer metastases are found in regional lymph nodes, it decreases the 5-y survival rate by approximately 30%–40% (*16*).

Malignant melanoma is the most common skin cancer. Malignant melanoma spreads through the lymphatic route. Elective lymph node dissection (ELND) is a procedure in which the surgeon removes the lymph nodes from a lymphatic bed that drains the primary malignant tumor area, even when there is no clinical suspicion that there is lymphatic spread. Patients who have an ELND have a better survival rate than patients who are observed and undergo therapeutic lymph node removal after developing clinically evident metastases to lymph nodes. ELND requires more surgical time and has higher morbidity. Approximately 20% of patients with intermediate thickness melanoma have microscopic metastases to lymph nodes (*16*). If the SLN can be correctly identified and removed, surgical morbidity of ELND can be avoided in 80% of intermediate thickness melanoma patients.

One in 10 women in the U.S. will get breast cancer. The standard treatment for patients with primary invasive breast cancer with no clinically palpable axillary lymph nodes is excision of the primary tumor through a lumpectomy or mastectomy and axillary lymph node dissection (*16*). Axillary lymph node dissection has significant morbidity in the form of lymph edema of the arm. If the SLN can be removed and if it is tumor free, lymph edema caused by axillary lymph node dissection can be avoided.

Parathyroidectomies

Norman wrote, in a commentary (*17*), that minimally invasive radioguided parathyroidectomy (MIRP) is a tremendous advance for treating primary hyperparathyroidism. He further stated that patients who have MIRP can expect to have the surgery completed in less than 30 min and to have scars that are less than 1 in. long. MIRP can be performed under local anesthesia and is a relatively quick outpatient procedure. A standard parathyroidectomy requires that a patient be admitted to a hospital. In a meta-analysis of 175 studies, Denham and Norman (*18*) found that 80% of the parathyroidectomy patients enrolled in the studies would have been candidates for MIRP. They further concluded that an average cost savings of $650 per patient would have resulted from the shortened hospital stays and reduced operating room times had the patients had MIRP rather than conventional parathyroidectomy.

FUTURE POSSIBILITIES

Procedures using intraoperative gamma probes are services offered by nuclear medicine departments to surgery departments. The increasing acceptance of such procedures is reflected in the increased number of publications in surgical journals that describe the use of probes.

Gulec et al. (*19*) have done a comprehensive review of the expanding clinical role of intraoperative gamma probes. At present, the most frequent use of intraoperative probes is in SLN localization in cases of melanoma or breast cancer. However, increasing use of ^{18}F-FDG, radiolabeled monoclonal antibodies, and radiolabeled receptor markers may increase the use of counting and imaging probes. Development of a good working relationship between surgeons and nuclear medicine personnel within an institution is a key to successful use of intraoperative gamma probes and to the continued growth of intraoperative radiotracer techniques at the institution. As new radiopharmaceuticals and probe technologies develop, there will be more opportunities to improve surgical procedures by incorporating intraoperative probes into the procedures. These opportunities will occur, however, only if there are simultaneous efforts to increase collaborations between surgery and nuclear medicine personnel.

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