Surgical Applications of Gamma-Detecting Probes

WILLIAM E. BURAK, JR., M.D., ASSISTANT PROFESSOR OF SURGERY
MARTIN BOSO
MARLIN O. THURSTON, PH.D., PROFESSOR EMERITUS OF ENGINEERING
EDWARD W. MARTIN, JR., M.D., PROFESSOR OF SURGERY
DIVISION OF SURGICAL ONCOLOGY, DEPARTMENT OF SURGERY
THE ARTHUR G. JAMES CANCER HOSPITAL AND RESEARCH INSTITUTE
THE OHIO STATE UNIVERSITY
COLUMBUS, OHIO

The RIGS system is a technology which was developed to provide a more sensitive and accurate method of detecting colorectal cancer during surgery. One of the components of this system is the hand-held, gamma-detecting probe (Neoprobe Model 1000 instrument; Neoprobe Corporation, Dublin, Ohio), used by the surgeon to identify preadministered, radiolabeled monoclonal antibody which has localized to diseased tissue. RIGS uses sound-directed gamma detection to identify and locate cancer which may not be seen or felt by the surgeon. The success of RIGS has been largely due to the remarkable sensitivity of the gamma-detecting probe in detecting small amounts of low-energy radioactivity. This attribute has led to the use of the probe for other surgical applications including pre- and intraoperative lymphatic mapping, and parathyroid localization. Surgery for melanoma, breast cancer, parathyroid disease, and colorectal cancer has been affected by the increased use of the gamma-detecting probe both in clinical trials and practice. This chapter will review the many applications of this new technology.

GAMMA-DETECTING PROBE

The instrument consists of a hand-held probe with a cadmium telluride crystal detector sensitive to gamma rays and a control unit capable of data processing which provides both a digital display and an audible signal (Fig. 1). The probe continually detects radioactivity, and by "squelching" on normal tissue, will emit an audible siren tone when the probe is directed at tissue in which radioactivity exceeds that of the normal tissue selected as background by a statistically significant amount. The siren tone is elicited when the count rate is more than approximately three standard deviations (3 sigma) above the squelch background level set by the operator.

Radionuclides

Lymphatic mapping and parathyroid localization have been performed using a high energy isotope, specifically technetium-99m

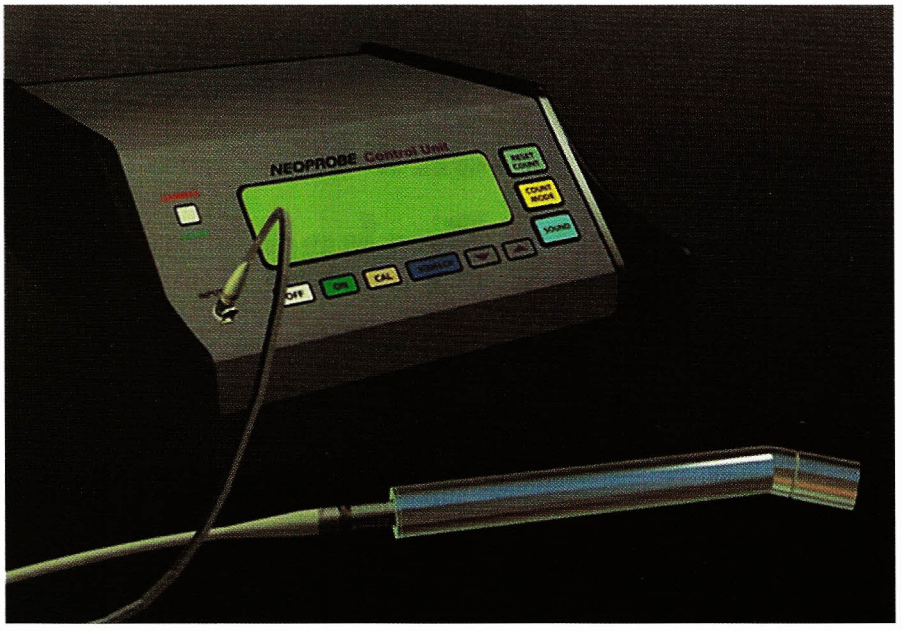

Figure 1. The Neoprobe Model 1000 gamma-detecting probe and Control Unit.

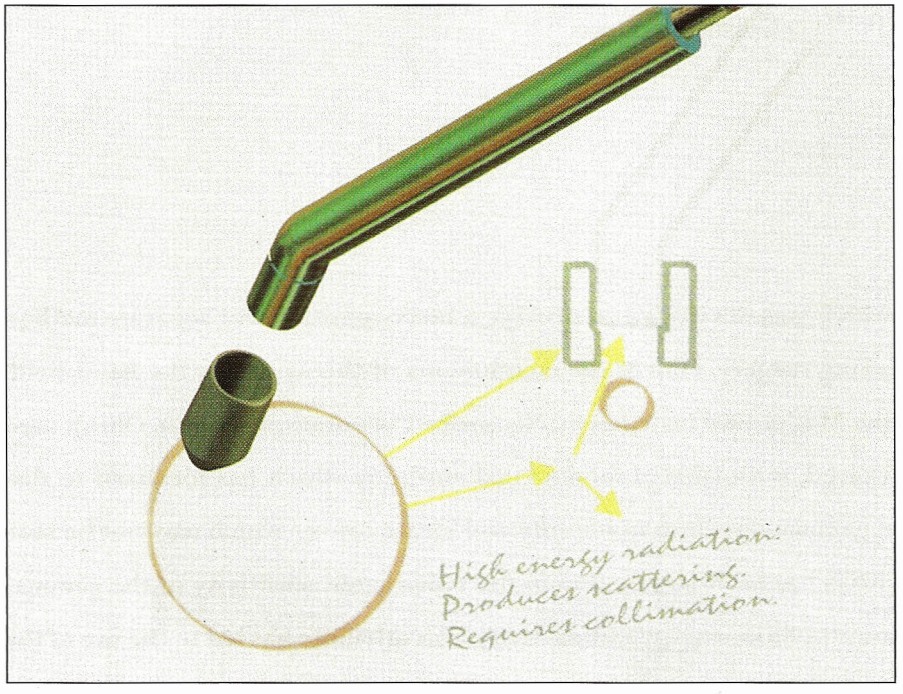

Figure 2. Use of a collimator with the gamma-detecting probe creates a more focused window of detection. With this lead shield, the probe can be used to distinguish small but independent concentrations of radioactivity close to a more active primary site of concentration.

(^{99m}Tc). The rationale for this is twofold. First, because external imaging is often performed in conjunction with gamma probe-guided lymphatic mapping, it is necessary to use an isotope which can be detected with a gamma camera. Most of the available radiopharmaceuticals used in lymphoscintigraphy are labeled with ^{99m}Tc because this radionuclide is appropriate for use with a gamma camera. Secondly, a high energy isotope is beneficial in that it facilitates effective transcutaneous probing. Because of the energy properties of ^{99m}Tc, collimation is sometimes needed to shield the crystal detector from the "glow" of surrounding radioactive tissue (Fig. 2). This collimation does not usually present a clinical problem because lymph node and parathyroid count rates are high enough that they are still detectable despite the added distance between the detector and target tissue.

The RIGS system uses low energy isotopes, such as iodine-125 (^{125}I), to label the cancer-specific targeting agent. The ^{125}I radionuclide has a gamma emission of 35 keV and exhibits soft tissue attenuation. These properties minimize in vivo scatter and thereby reduce interference from the blood pool and normal tissues. The use of this low energy isotope also facilitates the detection of small sources of radioactivity that are close to the end of the gamma-detecting probe, reducing the possibility of background interference. This is important in anatomic regions such as the abdominal cavity where small malignant deposits can be close to structures which may have high levels of background radioactivity.

It is important to recognize the inverse square law as it applies to the RIGS system. The greater the distance from the crystal to the source of radiation, the lower the count rate will be. A very important consequence of this law is that a collimator on the end of the probe increases the distance from the detector to the source and causes a significant decrease in the count rate. Although a collimator reduces background counts by reducing the viewing angle of the probe, this advantage is more than offset by the reduction in tumor counts when using a low energy isotope such as ^{125}I.

RADIOIMMUNOGUIDED SURGERY

Radioimmunoguided surgery was developed in an effort to enable the surgeon to better detect colorectal cancer during surgery.[1,2] Since first described in the mid 1980s, RIGS has undergone many advances in both targeting agents and gamma detector probe development. More specific antibodies have been developed in an effort to increase the accuracy of the system, while the probe design has been improved to allow sensitive detection of the low energy isotopes (^{125}I) used in the RIGS system.

Presently, Phase III clinical trials are evaluating the RIGS system for both primary and metastatic colorectal cancer. RIGS uses the CC49 monoclonal antibody labeled with ^{125}I. CC49 is a second generation monoclonal antibody directed against a tumor-associated glycoprotein (TAG-72) present in adenocarcinoma of the colon and rectum, breast, lung, ovarian, and the majority of other gastrointestinal malignancies.[3]

Technique

Patients are injected intravenously with CC49-^{125}I about 3 weeks prior to surgery.

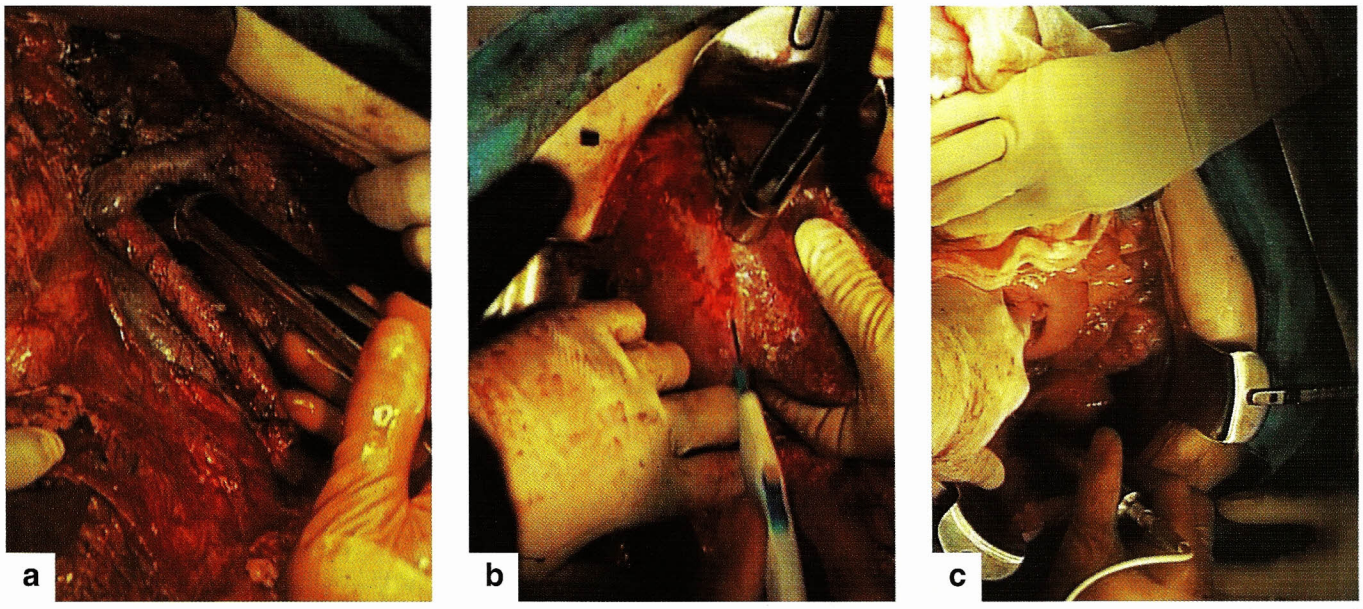

Figure 3. Radioimmunoguided surgery (RIGS) for metastatic colon cancer. Three to 5 weeks post injection, radiolabeled CC49 monoclonal antibody has bound selectively to tumor-associated glycoprotein (TAG) produced by colon cancer cells and can be detected in minute quantities by the probe: (a) Sound-directed isolation of posterior aortocaval lymph nodes; (b) Visualization of optimum margin of excision for left hepatic resection based on RIGS positivity; (c) Deep pelvic exploration for RIGS positivity.

Before injection, the radioactive uptake in the thyroid gland is blocked with a saturated solution of potassium iodine (SSKI) or THYRO-BLOCK (Wallace Laboratories, Cranbury, N.J.). Once the blood-pool background (as determined by precordial counts) has decreased to less than 30 counts per 2 seconds, tumor:background ratios are high enough to permit accurate use of the system. During laparotomy, the surgeon uses the probe to assist in detecting nonvisible disease, assess the extent of the disease process, and ensure that complete resection was performed. In order for the system to be effective, it must be used in a standardized fashion. First, the squelch background level of the probe instrument is set using the blood pool background in the abdomen (aorta). Once the squelch is set, an audible siren tone is produced when the probe detects a level of radioactivity that is significantly greater than that of the squelch background level setting. When evaluating individual organs (i.e., liver, colon), the system is squelched on normal adjacent tissue in the organ. When an audible sound is produced, this tissue should be regarded as suspicious and evaluated appropriately (Fig. 3). The RIGS system provides the surgeon with an intraoperative tool which provides more information than is obtained with inspection and palpation.[4,5] The individual surgeon can use this information in a number of ways which may result in either performing a more complete cancer operation or abandoning a major resection because of the identification of occult disease. Following completion of the Phase III trials, it is anticipated that RIGS will become part of standard practice for treatment of primary and recurrent colorectal cancer. In addition, early studies are underway evaluating the usefulness of RIGS in breast, ovarian, and upper GI malignancies.

LYMPHATIC MAPPING

Cutaneous Melanoma

The role of elective lymph node dissection in the primary surgical treatment of malignant melanoma has long been controversial. Although elective node dissection has been shown to be effective in prolonging survival in several retrospective studies,[6-9] this benefit was not demonstrated in two prospective, randomized trials.[10,11] Because of several shortcomings in these latter trials, many surgeons still choose to perform elective lymph node dissections in selected patients. Balch et al. recommend this treatment for intermediate thickness melanoma (1.5-3.99 mm), citing that this subset of patients has the greatest potential benefit.[7] The concept of the sentinel lymph node, popularized by Morton,[12] was applied to assist further in the identification of patients for complete lymph node dissection. The sentinel node is defined as the first lymph node that drains the primary melanoma. If lymphatic drainage occurs in a step-wise fashion, this lymph node should reflect the pathologic status of the remaining lymph node basin.

This concept was first put to test in studies using "vital blue dye"; the dye is injected around the primary lesion, traced to the first "blue" node, or sentinel node, which is excised. This technique is extremely accurate, but has several drawbacks. First, it must be injected within 5 to 10 minutes of dissection or it will "washout" to other lymph nodes. Second, the vital blue dye must be surgically traced from the injection site to find the sentinel node; this can be difficult, especially in extremity lesions. The main drawback of this technique is that the sentinel node cannot be located prior to surgical incision.

In an effort to improve this promising procedure, a different method of localizing the sentinel lymph node was described.[13] This technique is known as "gamma probe-guided lymphatic mapping" and has several potential advantages over the original vital blue dye technique. We and others[13] have found the following protocol to be effective in identification of the sentinel lymph node in selected patients with malignant melanoma who have clinically negative regional lymph nodes (Fig. 4). It combines the vital blue dye technique with sound-directed gamma probe detection in an effort to provide the highest degree of accuracy in locating the sentinel lymph node.

Technique

On the morning of surgery, a lymphoscintigraphy study is performed. Technetium-labeled sulfur colloid

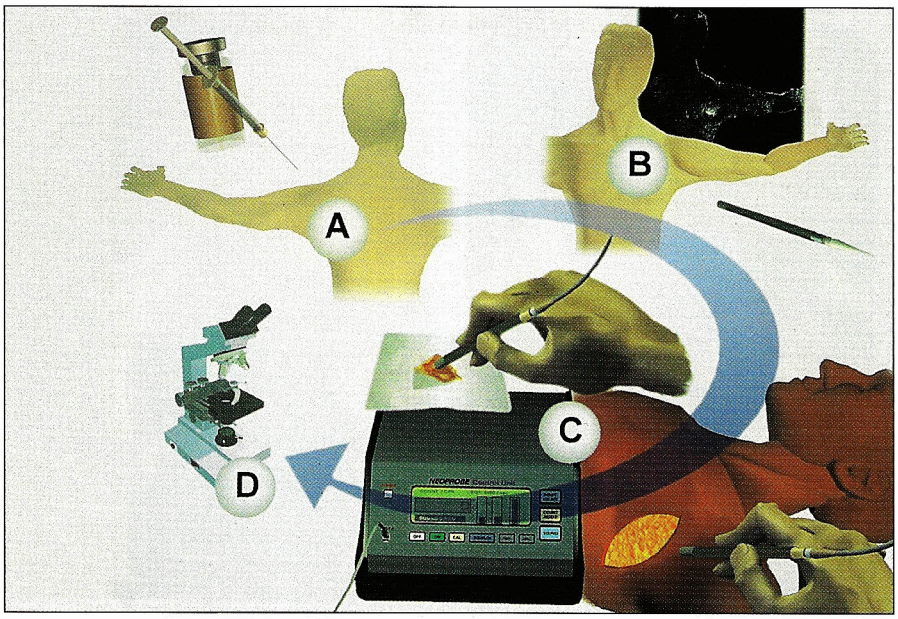

Figure 4. Sentinel lymph node mapping technique for primary melanoma, utilizing the Neoprobe Model 1000 instrument: (a) Preoperative injection of radiolabeled sulfur colloid at site of primary lesion; (b) Visualization of draining nodal basin with lymphoscintigraphy and confirmation by transcutaneous probing; (c) Isolation and excision of sentinel node located intraoperatively through sound-directed exploration; (d) Histological evaluation of sentinel node helps to predict prognosis and can contribute to therapeutic decision making.

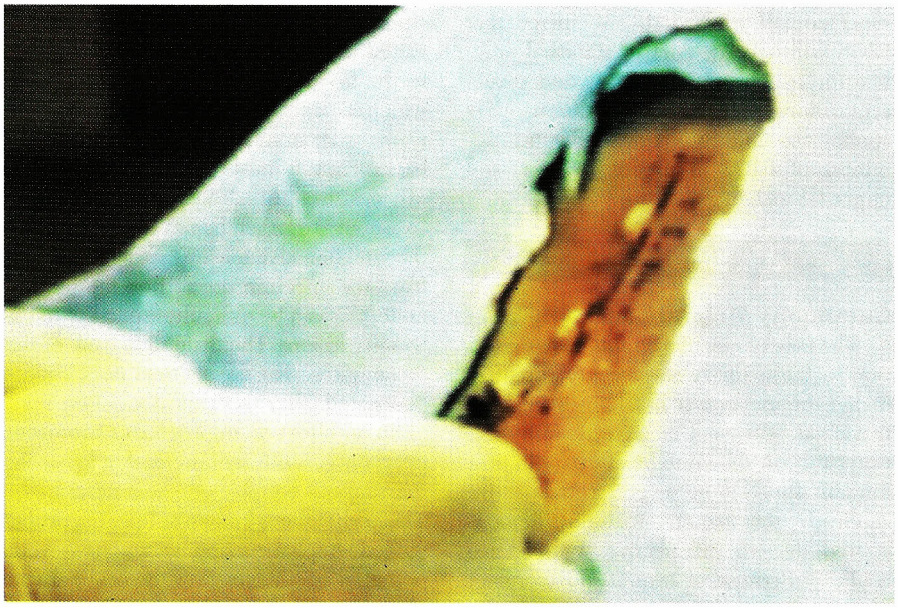

Figure 5. Four-quadrant injection technique with technetium-99m labeled sulfur colloid.

(^{99m}Tc-sulfur colloid) is injected into the dermis around the primary skin lesion or excisional biopsy scar using a four quadrant technique (Fig. 5). Approximately 500 microcuries of the radiolabeled compound is injected through a 25-gauge syringe in a total volume of 0.8 mL. It is important that the injection be into the lymphatic-rich dermis, otherwise uptake of the radionuclide will be sluggish. After 15 to 30 minutes, the patient is imaged with a gamma camera and surveyed with the gamma detector probe. The skin is marked with an intradermal tattoo or water resistant marker at the site of the suspicious node. This time period is usually sufficient to identify a sentinel node, but may be carried out longer, if necessary. External imaging and probe survey are important components of lymphatic mapping especially when primary melanoma is in an anatomic location with an ambiguous drainage pattern, as is the case with midline truncal lesions. This preoperative information will permit the surgeon to identify the proper lymph node basin and position the patient correctly during the surgical procedure.

Following the lymphoscintigraphy, the patient is taken to the operating room where the gamma detector probe is used transcutaneously to locate the node over the marked skin, confirming the gamma camera findings once the patient is positioned for surgery. If it is difficult to localize a node using the probe because of the radioactive "glow" from the injection site, it may be easier to perform the wide excision of the primary tumor prior to probing or place a lead shield over the tumor. Following wide-excision of the tumor, a small incision is made in the skin overlying the "hot spot."

Sound-directed probing is used to locate the radioactive node. The sentinel node is then excised and the probe is used to confirm that the radioactivity has been removed; this is done by demonstrating high counts in the excised lymph node(s) and low counts in the surgical wound (bed of resection). If the node does not exhibit significant radioactivity, then further efforts should be made to identify another lymph node in the surgical wound, as the excised node is not the sentinel node. Additionally, if the node is "hot," but the bed of resection still has high counts, there may be a second sentinel node present in close proximity to the first which should be removed.

Results

Several institutions have reported results using both the vital blue dye and gamma probe lymphatic mapping techniques, individually or in combination.

Morton's original results using the vital blue dye technique revealed that a sentinel node(s) was identified in 194 of 237 lymphatic basins (82%).[12] Micrometastases were identified in 21% of sentinel nodes using either routine hematoxylin-eosin (H&E) staining or immunohistochemistry. Less than 1% of nodal basins had non-sentinel nodes as their sole site of metastasis. When the vital blue dye technique is combined with sound-directed gamma detection, the localization rate is reported to be as high as 96% and accuracy appears similar.[13] A randomized, multi-institution trial is underway to confirm the usefulness of these techniques in the management of malignant cutaneous melanoma.

BREAST CANCER

Axillary lymphadenectomy is performed in patients with invasive breast

cancer on a routine basis, although lymph nodes are positive in only approximately 30% of patients with a clinically negative axilla.[14] Although the majority of patients undergo an "unnecessary" axillary dissection, the lymph node status provides critical staging and prognostic information which frequently dictates adjuvant therapy. Because there is no accurate preoperative method of determining the status of the axillary lymph nodes, lymph node mapping is of interest for patients with breast cancer. If breast cancer spreads to the nodes in a step-wise fashion, as in melanoma, then sentinel node identification would allow the surgeon to perform a "selective" lymphadenectomy, eliminating unnecessary axillary dissections in patients when the sentinel node did not contain tumor. This concept has been evaluated using both vital blue dye and gamma probe-guided lymphatic mapping techniques.

Technique

The vital blue dye technique, as described by Giuliano et al., is performed by injecting 3-5 mL of isosulfan blue dye into the breast mass and surrounding breast parenchyma 5 minutes prior to undertaking the axillary dissection.[15]

Once the incision for the axillary dissection is made, the blue lymph node is identified as the sentinel node. An effort is made to trace the lymphatic tract back to the tail of the breast to ensure that it is the most proximal blue node. The remaining axillary dissection is then performed.

Gamma probe-guided lymphatic mapping has the theoretical advantage that the sentinel node can be identified transcutaneously and a more directed incision can then be made.[16] The technique entails injection of ^{99m}Tc labeled sulfur colloid (400 μCi) in 0.5 mL saline into the normal breast tissue adjacent to the breast mass or biopsy site.

One to 9 hours later, patients are taken to surgery where the gamma detector probe is used to identify the sentinel node. Preoperative lymphoscintigraphy and preoperative probing are helpful in assuring that the radiolabeled sulfur colloid has migrated to the axilla (Fig. 6). During surgery the radioactive node(s) is/are identified and removed, ex vivo counts are obtained, and the bed of resection probed to make sure the appropriate node was removed. The remaining axillary dissection is then completed.

Results

Experience with both vital blue dye and gamma probe-guided lymph node mapping in breast cancer is limited. Krag first reported successful localization of the sentinel node in 18 of 22 cases (82%) using a gamma probe directed technique similar to the one described above.[16] In this small study, the sentinel lymph node accurately predicted the status of the remaining axilla. Of interest, the sentinel node was the only site of lymph node metastasis in three of the seven patients with cancer-containing sentinel nodes.

Using the vital blue dye technique only, Giuliano reported a 65.5% sentinel node localization rate in 174 procedures.[15] The sentinel node accurately predicted the axillary nodal status in 95.6% of cases. A significant learning curve was associated with this technique; localization rates were improved in the latter part of the study.

Larger trials will be required to confirm these early findings. While it appears that both techniques can be accurate in predicting the presence or absence of nodal disease, gamma probe-guided lymphatic mapping has the theoretical advantage of transcutaneous localization.

PARATHYROID SURGERY

^{99m}Tc-sestamibi scintigraphy has been shown to be accurate in detecting parathyroid adenomas and hyperplasia prior to surgery in several recent studies.[17-21]

Based upon these encouraging results, Martinez et al. demonstrated that the gamma detector probe could be used intraoperatively to detect diseased parathyroid glands after intravenous administration of ^{99m}Tc-sestamibi.[22] Although experience is limited, this technique holds the most promise in patients with recurrent hyperparathyroidism where identification of parathyroid tissue is often difficult.

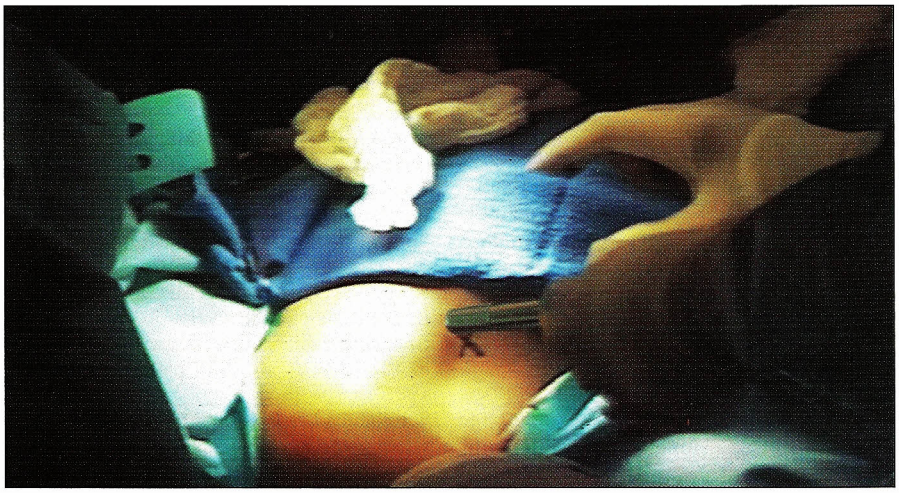

Figure 6. Preoperative axillary probing in primary breast cancer for transcutaneous detection of the sentinel lymph node.

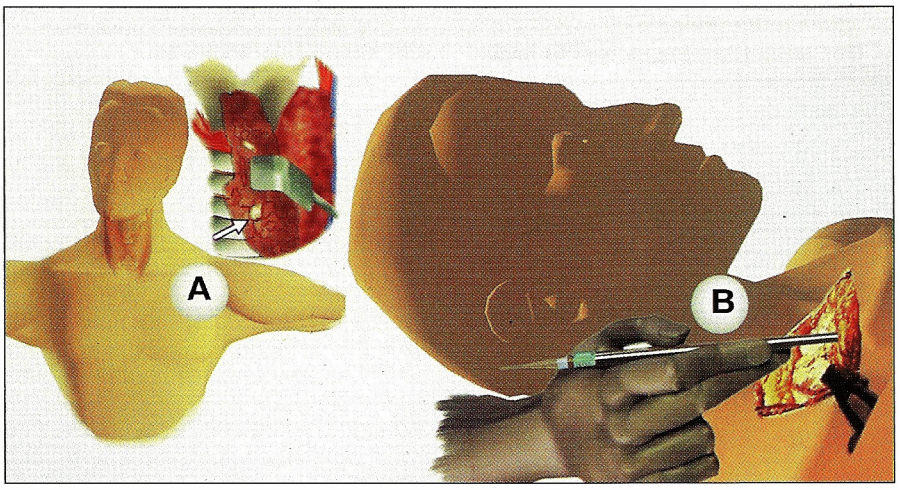

Figure 7. Intraoperative isolation of parathyroid tumor utilizing the Neoprobe Model 1000 instrument and sound-directed exploration after preoperative injection of sestamibi: (a) Location of lesion; (b) 11-mm probe provides better mobility and more precise determination in a small operative field.

Technique

Preoperatively, patients receive 1 to 2 μCi of ^{99m}Tc-sestamibi. During surgery, following exposure of thyroid gland, a survey of the operative field is performed using sound-directed gamma detection. First, the background radioactivity is assessed by probing adjacent normal tissue, and the hand-held gamma detector is then squelched at this level. Further evaluation of the neck is then undertaken with the probe and uptake of ^{99m}Tc-sestamibi above background generates an audible signal (Fig. 7). This probe-positive tissue is then evaluated by the surgeon and removed, if indicated.

CONCLUSIONS

The clinical utility of the hand-held gamma-detecting probe is broadening with the introduction of new surgical approaches and concepts. The RIGS system holds great promise for the sensitive detection of cancer which can translate to improved clinical benefit by allowing more accurate determination of the extent of disease. The information provided by RIGS can be useful in the determination of appropriate surgical and/or adjuvant therapies. Surgical practices for the treatment of malignant melanoma are rapidly changing due to the ability to identify sentinel lymph nodes using both the vital blue dye and sound-directed gamma detection techniques. The pathology of the sentinel node may allow better determinations of appropriate treatments based on assessment of extent of disease. Hopefully, patients with breast cancer will also realize clinical benefit of the application of these techniques through a more "selective" approach to axillary lymphadenectomy. The evolution of gamma detector probes is a prime example of how novel technologies lead to important advances in the field of medicine. STI

REFERENCES

1. Aitken DR, Hinkle GH, Thurston MO, et al. A gamma-detecting probe for radioimmune detection of CEA-producing tumors: successful experimental use and clinical case report. Dis Col Rect 1984;27:279-82.
2. Martin DT, Hinkle GH, Tuttle S, et al. Intraoperative radioimmunodetection of colorectal tumor with a hand-held radiation detector. Am J Surg 1985;150:672-5.
3. Thor A, Ohuchi N, Szpak CA, et al. Distribution of oncofetal antigen tumor-associated glycoprotein B72.3. Cancer Res 1986;46:3118-24.
4. Arnold MW, Schneebaum S, Berens A, et al. Intraoperative detection of colorectal cancer with radioimmunoguided surgery and CC49, a second-generation monoclonal antibody. Ann Surg 1992;216:11-16.
5. Burak WE Jr, Schneebaum S, Kim JA, et al. Pilot study evaluating the intraoperative localization of radiolabeled monoclonal antibody CC83 in patients with metastatic colorectal carcinoma. Surgery 1995;118:103-8.
6. Balch CM, Murad TM, Soong SJ, et al. Tumor thickness as a guide to surgical management of clinical stage I melanoma patients. Cancer 1979;43:883-8.
7. Balch CM, Soong SJ, Milton GW, et al. A comparison of prognostic factors and surgical results in 1,786 patients with localized (stage I) melanoma treated in Alabama, USA, and New South Wales, Australia. Ann Surg 1982;196:677-84.
8. Milton GW, Shaw HM, McCarthy WH, et al. Prophylactic node dissection in clinical stage I cutaneous malignant melanoma: results of surgical treatment in 1,319 patients. Br J Surg 1982;69:108-11.
9. Reintgen DS, Cox EB, McCartty KS Jr, et al. Efficacy of elective lymph node dissection in patients with intermediate thickness primary melanoma. Ann Surg 1983;198:379-85.
10. Sim FH, Taylor WF, Ivins JC, et al. A prospective randomized study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma: preliminary results. Cancer 1978;41:948-56.
11. Veronisi U, Adamus J, Bandiera DC, et al. Inefficacy of immediate node dissection in stage I melanoma of the limbs. N Eng J Med 1977;297:627-30.
12. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992;127:392-99.
13. Albertini JJ, Cruse CW, Rappaport D, et al. Intraoperative radiolymphoscintigraphy improves sentinel lymph node identification in melanoma patients. Ann Surg. In press.
14. Schottenfeld D, Nash A, Robbins G, et al. Ten-year results of the treatment of primary operable breast carcinoma. Cancer 1976; 38:1001.
15. Giuliano AE, Kirgan DM, Guenther JM, et al. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994;220:391-401.
16. Krag DN, Weaver DL, Alex JC, et al. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol 1993;2:335-40.
17. Coakley AJ, Kettle CP, Wells MJ, et al. 99mTc-sestamibi—A new agent for parathyroid imaging. Nucl Med Comm 1989;10:791-794.
18. O'Doherty MJ, Kettle AG, Wells, P, et al. Parathyroid imaging in technetium-99m-sestamibi: Preoperative localization and tissue uptake studies. J Nucl Med 1992;33:313-318.
19. Taillefer R, Boucher Y, Potvin C, et al. Detection and localization of parathyroid adenoma in patients with hyperparathyroidism using a single radionuclide imaging procedure with technetium-99m-sestamibi (double-phase study). J Nucl Med 1992; 33:1801-7.
20. Kitapci MT, Tastekin G, Turgut M, et al. Preoperative localization of parathyroid carcinoma using Tc-99m MIBI. Clin Nucl Med 1993;18:217-9.
21. Wei JP, Burke GJ, Mansberger AR. Prospective evaluation of the efficacy of technitium 99m sestamibi and iodine 123 radionuclide imaging of abnormal parathyroid glands. Surgery 1992;112:1111-7.
22. Martinez DA, King DR, Romshe C, et al. Intraoperative identification of parathyroid gland pathology: a new approach. J Ped Surg 1995;30:1306-9.