Fluorine-18-Fluorodeoxyglucose-Guided Breast Cancer Surgery with a Positron-Sensitive Probe: Validation in Preclinical Studies

Raymond R. Raylman, Susan J. Fisher, Raya S. Brown, Stephen P. Ethier and Richard L. Wahl

Division of Nuclear Medicine, Departments of Radiation Oncology and Radiology and Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan

In this study, the feasibility of utilizing 2-deoxy-2-fluoro-d-glucose (FDG) in conjunction with a positron-sensitive intraoperative probe to guide breast tumor excision was investigated. **Methods:** The probe was constructed with a plastic scintillator tip coupled to a photomultiplier tube with fiber optic cable. Anticipated resolution degradation was evaluated by measurement of line spread functions in the presence of background radiation. Realistic photon background distributions were simulated with a human torso phantom and a cardiac insert. The relationship between resolution and energy threshold was measured to find the optimal discriminator settings. In addition, probe sensitivity as a function of energy threshold was determined for various size-simulated tumors. Finally, the ability to localize breast cancers in vivo was tested in a rodent model. Mammary rat tumors implanted in Lewis rats were examined after injection with FDG; these results were correlated with those of histologic analyses. **Results:** Measurements of line spread functions indicated that resolution could be maximized in a realistic background photon environment by increasing the energy threshold to levels at or above the Compton continuum edge (340 keV). At this setting, the probe's sensitivity was determined to be 58 and 11 cps/μCi for 3.18- and 6.35-mm diameter simulated tumors, respectively. Probe readings correlated well with histologic results; the probe was generally able to discriminate between tumor and normal tissue. **Conclusion:** This study indicates that breast cancer surgery guided by a positron-sensitive probe warrants future evaluation in breast-conserving surgery of patients with breast cancer.

Key Words: fluorine-18-fluorodeoxyglucose; breast cancer surgery; radiation detectors

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Intraoperative localization of tumors has long been a goal of nuclear medicine. To accomplish this task, many different types of radiation-sensitive surgical probes have been proposed and constructed (*1–9*). Most of these designs, however, have not had good success because of detection of background photons that originate in distant regions of the patient caused by inadequate targeting of the tumor-avid agent. Recently, surgical beta-sensitive probes constructed with plastic scintillators have been proposed to reduce the sensitivity to background radiation emanations (*10,11*). These probes are intended to localize areas of increased uptake of radiopharmaceuticals labeled with positron-emitting radionuclides. The advantage to this approach is that positrons usually have much shorter ranges in tissue than annihilation photons (depending on their energies). Thus, tumors can be more precisely delineated. For example, positrons emitted by ^{18}F (E_{max} = 633 keV) have a maximum range of approximately 1.8 mm in tissue (*12*). Thus, a beta probe used in conjunction with the proper radiolabeled tracer has the potential to localize tumors during surgery precisely.

Although the plastic scintillator has a low efficiency for the detection of photons, detection of any background photon radiation will result in reduced resolution. To account for background contamination, Daghighian et al. (*10*) designed a coaxial probe that measures the background flux and corrects the probe readings with these data. Although this technique is critical to localization of tumors in environments where the background photon flux is high, there are some applications in which the tumor-to-background photon flux is relatively low and the need for an expensive and complex background compensation system is not essential. In this investigation, such a situation was explored: radiation probe-guided breast cancer surgery.

Recently, the use of PET with ^{18}F-labeled 2-deoxy-2-fluoro-d-glucose (FDG) has met with success in the imaging of many breast tumors and tumor involved lymph nodes (*13–18*). This technique has been shown to visualize some tumors not detected with standard techniques such as mammography (*19*). The typical ratio of FDG concentration in breast tumors to normal surrounding tissue has been measured to have a median value of approximately 8:1 1 hr after tracer infusion (*14*). Because surgical intervention, especially breast-conserving procedures, is the most common treatment for breast cancer, and given the high tumor-to-normal tissue contrast achieved with FDG,

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For correspondence or reprints contact: Raymond R. Raylman, PhD, University of Michigan Medical Center, 204 Zina Pitcher Place, Rm. 3480 Kresge III, Ann Arbor, MI 48109-0552.

use of a positron-sensitive probe in such surgeries seems desirable. Unfortunately, the presence of annihilation photons, which make PET possible with FDG, are a source of background radiation. For example, the myocardium can be an avid accumulator of FDG (even in the fasted state); its proximity to the upper thorax makes this organ a primary source of background annihilation photons. Similar background photon flux from the liver might also be expect ed.

To determine the effectiveness of a positron-sensitive probe that did not possess a separate background detection system in the localization of breast tumors, several experiments were undertaken. Instead of measurement and compensation for background radiation, this method uses energy discrimination to remove the effects of detected annihilation photons. Optimization of the energy threshold was performed by measurement of probe resolution as a function of discriminator level in an environment of background photon flux comparable to that anticipated to exist during actual breast cancer surgeries. In addition, detection sensitivity as a function of energy threshold was measured for two different size-simulated tumors. Finally, in vivo tests were performed to evaluate the ability of this device to detect and delineate the difference between tumor and normal tissue in rodents after administration of FDG.

MATERIALS AND METHODS

The positron probe used in this investigation was a modified version of the probe previously described by Raylman and Wahl (*11*). Briefly, a cylindric (diameter = 8.4 mm, length = 4 mm) piece of BC-408 plastic scintillator (Bicron Corp., Newbury, OH) was coupled to a photomultiplier tube (XP-1911, RCA Electronics) through a bundle of seven fiber optic cables (Edmund Scientific Inc., Barrington, NJ). The scintillator and a section of the fiber optic cable were enclosed in a sealed stainless steel handle. The front end of the handle, which contained the scintillator, was angled to facilitate examination of the surgical field (Fig. 1). A 0.5-mil thick aluminum window covered the front face of the probe. Outputs from the photomultiplier tube were amplified and pulse height discrimination was peformed by an Ortec Amp-SCA. Signals from the single-channel analyzer were processed with a linear rate meter and a pulse scaler to evaluate the presence of positron-emitting tracer.

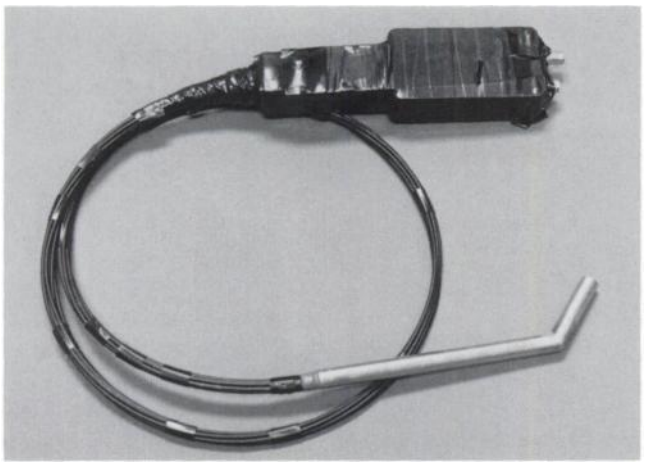

FIGURE 1. Beta-sensitive intraoperative probe used in this study. Stainless steel probe handle is connected to photomultiplier tube with 5 ft of bundled fiber optic cable.

Effect of Photon Background on Resolution

To determine the optimum energy threshold for breast cancer surgeries, resolution measurements were made in a background photon environment similar to that expected in a patient. Resolution of the probe was determined by stepping a thin cotton thread soaked in ^{18}F (total activity = 70 nCi) mounted on a small tissue-equivalent plastic block (RMI Gammex) across the probe face. The FWHM of the resulting line spread function (LSF) was calculated from a fit of the LSF with a gaussian function. Background photon flux that emanated from the myocardium was simulated by the filling in of a cardiac insert of a human torso phantom (Data Spectrum Corp., Chapel Hill, NC) with 32 μCi of FDG. This phantom contains foam inserts and the Teflon rod used to simulate the attenuation properties of lung and spinal column. The radiation concentration in the cardiac phantom (0.290 μCi/ml) is representative of the concentration in a typical fasted subject 1 hr after a 10-mCi injection of FDG (*20,21*). No additional FDG was added to any of the other inserts. LSF data were acquired with the tissue-equivalent plastic block holding the cotton thread mounted directly above the cardiac insert. Data were also acquired without radioactivity in the cardiac insert. LSFs were measured at energy threshold settings ranging from 190 to 390 keV.

Measurement of Probe Detection Sensitivity

An important characteristic of any detection system is its sensitivity. In the case of radiation-sensitive devices, this is determined by measurement of the relationship between the number of detected events and the amount of radioactivity that is actually present. To make a realistic determination of this relationship, sensitivity measurements were performed with tumor phantoms. Simulated tumors were created first by dissolution of 1.25 g unflavored gelatin in 20 ml of hot tap water. Then 20 μCi ^{18}F were added to the gelatin to obtain a concentration of 1 μCi/ml (standard uptake value = 7.0 for a 10-mCi injection). Small aliquots of the gelatin were then injected into two different tumor molds (radii = 3.18 and 6.35 mm). Each mold consisted of two pieces of nylon each with a hemisphere machined in the center; so that, when they are fastened together, a spherical shape was formed. In addition, an access hole that extended into the top hemisphere was drilled to allow filling of the mold. To speed the hardening of the gelatin, the filled mold was dipped in liquid nitrogen for 30 sec. After approximately 2 min, the mold could be opened and the phantom tumor removed. The density of the gelatin is relatively close to that of tissue (approximately 1.1 g/ml). The 3.18- and 6.35-mm radius simulated tumors contained 0.13 and 1.1 μCi, respectively.

Detection sensitivity was measured by positioning the tip of the probe 1 mm above the top of the tumor. The total number of counts during a 10-sec counting period were recorded. Five separate readings were obtained and combined to calculate the mean number of counts per second and the standard deviation. Five different energy thresholds ranging from 190 to 390 keV were used.

In Vivo Rodent Tests

Finally, the beta-sensitive probe was used to detect the presence of FDG in vivo. Four female Lewis rats (average mass = 200 g) were inoculated in the scapular fat pad with 1 million rodent mammary tumor cells in a volume of 20 ml (*22*). Six weeks postinoculation, the tumors were approximately 1.5 cm in diameter. To simulate the range of radiopharmaceutical concentration expected in human patients 1 hr postinjection of 10 mCi FDG, amounts of FDG that ranged from 80 to 106 μCi were administered intravenously to the animals. The rodents were fasted overnight before injection. One hour postinjection, the rats were killed with metafluor. Before initiation of tumor examination, background radiation levels were obtained by placement of the probe over the midabdomen of the rats. Care was taken to avoid the bladder, which accumulates FDG and is, therefore, not representative of normal background levels in the vicinity of the tumor. The skin covering the tumor was removed, and the top half of the tumor was excised. The beta probe was used to survey the tumor and surrounding normal tissues. The number of counts during a 10-sec period were recorded. Areas that were sampled included the center and edges of the tumor (as determined by visual inspection) and normal-appearing tissues adjacent to the tumor. The remaining tumor was then removed. The tumor bed was examined with the probe to determine whether any residual tumor remained. Samples of the tumor, surrounding tissues and tumor bed were processed for histologic analysis. Additional samples of these regions were weighed and assayed in a gamma counter (corrected for radioactive decay of ^{18}F, $T_{1/2}$ = 110 min) to determine the FDG concentration present.

Sections from each embedded tissue sample were examined by one of the authors (R.S.B.) for the presence of tumor tissue or tumor cells. Slides were classified as tumor or normal tissue based on the presence or absence of tumor cells. These findings were then correlated with FDG concentrations in these tissues and the beta-probe response. This analysis included the use of probe readings to calculate a z-score for each region interrogated. Z-scores were calculated with the equation

$$z - \text{score} = \frac{s - \mu}{\sigma},$$

where s is the count rate measured above a given tissue region, μ is the mean background count rate and σ is the s.d. of the background measurements.

RESULTS

Effect of Background Radiation of Resolution

Detection of annihilation photons from a somewhat distributed source (such as the myocardium) produces a bias in the LSF. The net effect of this offset is to lengthen the tails of the response function, which thus degrades resolution. The amount of background radiation detected can be limited by adjustment of the energy threshold. An increase in the energy threshold also reduces sensitivity, as shown in the next section. Because of the low atomic number of the plastic scintillator, there is virtually no photoelectric absorption peak; most of the detected photon energy spectrum consists of a Compton continuum. The edge of this distribution for ^{18}F is located at 340 keV (*23*). Figure 2 demonstrates the effect of an increase in the energy threshold on resolution. Results for cases with and without the presence of annihilation photon background are shown. Also displayed are the percent differences in resolution for each threshold setting.

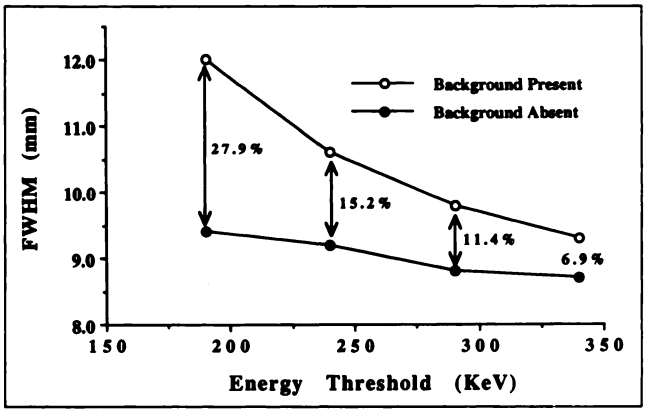

FIGURE 2. Probe resolution as a function of discriminator energy threshold. Results are given for the conditions in which no background radiation is present (●) and in which background radiation is present (○). Also shown are percent differences between the two sets of data.

Measurement of Probe Detection Sensitivity

The results of probe sensitivity determinations for two different size simulated tumors are shown in Figure 3. Note that there is an inverse relationship between sensitivity and energy threshold. It is also clear that the measured sensitivity of the probe depends on the tumor's size.

In Vivo Rodent Experiments

The plots in Figure 4 demonstrate the correlation between FDG concentration in tissue and probe count rate 1 mm above these regions. In addition, the standard uptake values (SUV) calculated for a 10-mCi injection of FDG into a human that correspond to these FDG concentrations are shown on the top x-axis. Note that two types of tissue (tumor and normal) are plotted. These classifications were

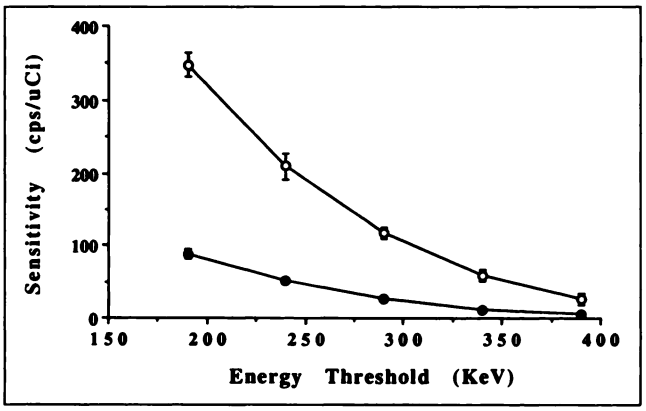

FIGURE 3. Detection sensitivity versus discriminator energy threshold. Results for large (●) and small (○) simulated tumors are shown.

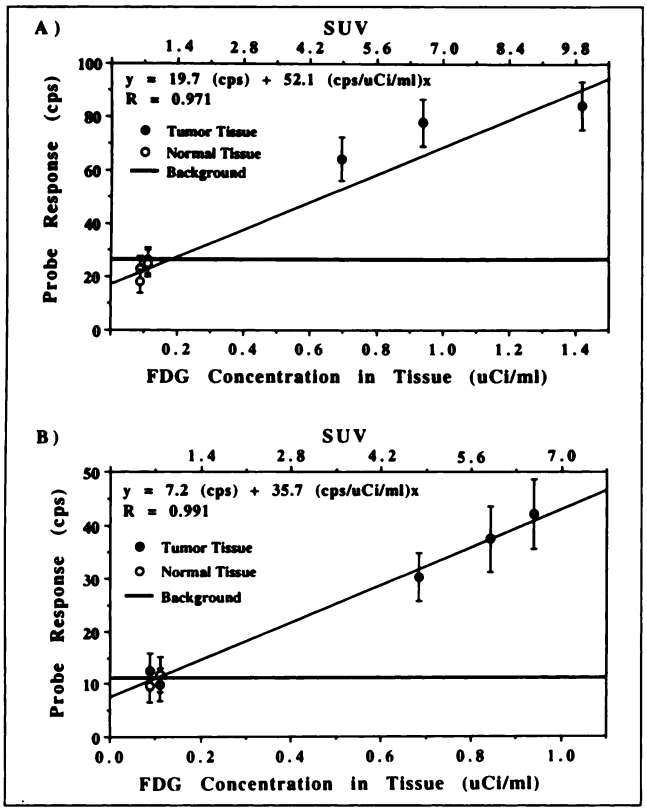

FIGURE 4. Probe response plotted as a function of FDG concentration. Results collected at two different energy thresholds are shown for (A) 290 and (B) 340 keV.

based solely on results from histologic analyses. Fits of the data with a straight line demonstrate the good correlation between the probe readings and FDG concentrations in tumor and healthy tissues. Differences in detection sensitivity at two different energy thresholds are apparent from the differing slopes of the lines fit to the data. Finally, Figure 5 displays the correlation of z-scores calculated for each region with the histologic results. All samples histologically classified as tumor (TT, TB, TL, TR and TC) contained either tumor tissue alone or tumor with granulation tissue and/or fatty tissue. Samples histologically classified as normal (NT, NL, NR and NC) contained either fatty and/or muscle tissue. One tissue sample taken from the bottom of the tumor bed (NB) included an area of granulation tissue that contained less than 100 cells in an area of 3-mm^2 out of the 25-mm^2 section. A necrotic region that measured approximately 2 × 5 mm was present in the center of the tumor.

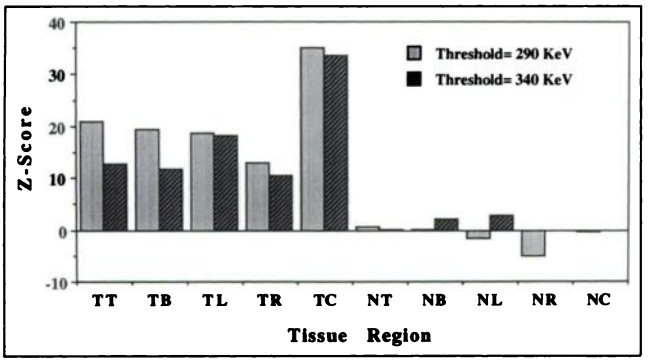

FIGURE 5. Z-scores calculated from probe response at several different tissue regions. TT = top edge of tumor; TB = bottom edge of tumor; TL = left edge of tumor; TR = right edge of tumor; TC = center of tumor; NT = top of tumor bed; NB = bottom of tumor bed; NL = left edge of tumor bed; NR = right edge of tumor bed; and NC = center of tumor bed.

DISCUSSION

Currently available surgical probes optimized for the detection of photon radiation are not appropriate for use with positron-labeled radiotracers. This is due to the low tumor-to-background ratios measured with these probes, which is caused by the presence and detection of 511-keV annihilation photons. Although beta probes that use the plastic scintillator are less sensitive to the presence of background radiation than are standard inorganic-based probes, background contamination remains a source of resolution degradation. One method to reduce this effect effectively is the use of a separate detector to monitor and correct for background. This method is probably required for applications in which the local background flux is high. In situations in which background radiation is less intense, however, it is likely that the extra complication and expense of such a system can be spared. To test this proposition, the effectiveness of a single beta-sensitive probe, with appropriate energy thresholding, was evaluated for use in FDG-guided breast cancer surgery.

With an increase in the energy threshold level, the amount of annihilation photon background accepted is reduced. This procedure reduces the width of tails of the measured LSF. Therefore, resolution should increase with increasing energy threshold; this is demonstrated in Figure 2. Note that the resolution difference between the two cases (with and without background) is greatest when low-energy pulses are accepted. This is due to the fact that most low-energy pulses are created by recoil electrons produced in Compton scattered events. At a lower energy threshold, more photon events are detected. When the discriminator level is set above the energy of the Compton edge (approximately 340 keV), positrons are detected almost exclusively.

The use of the human torso phantom to simulate the background environment encountered in actual human use, however, neglects three other important sources of annihilation photons: the bladder, liver and brain. In the case of the bladder, the amount of FDG present can be reduced, to a great extent, if the patient voids before the procedure. Signal contamination that originates from the liver and brain, however, is not as easily remedied. External shielding may be necessary to help reduce background flux from these organs. Determination of whether this mode of attenuation is required can only be made with information gathered from future human trials.

There is a tradeoff in the use of energy thresholding to increase resolution, namely, reduced sensitivity. From the data shown in Figure 3, it is clear that an increase in the energy threshold tends to decrease overall detection sensitivity. This is due to the same effects that cause improved resolution, i.e., exclusion of low-energy pulses (some of which are produced by positrons). What is perhaps more significant about the data presented in Figure 3 is the dependence of measured sensitivity on tumor size. The sensitivity results plotted in Figure 3 for the small tumor (radius = 3.18 mm) are larger than those measured for the larger tumor (radius = 6.35 mm). This phenomenon is explained by the relatively short maximum range of positrons in water (approximately 1.8 mm). Fewer positrons emitted in the large tumor are able to reach the probe compared with those emitted from the small tumor. The magnitude of this effect, however, is somewhat diminished by geometric factors. Because of its small physical dimensions, a greater percentage of positrons emitted from the small tumor will strike the detector face at shallow angles compared with the large tumor. Thus, they traverse less scintillating material before they exit the detector, which results in light pulses of small magnitude that may not exceed the energy threshold. In addition, the small tumor subtends less of the active volume of the probe's field of view than does the large tumor. Depending on the distance from the detector window, slightly diminished counts rates, therefore, can be expected in readings from the small tumor. It is for this reason that a smaller probe may be desirable in certain applications. The sensitivity to detect accumulations of positron-emitting radiotracers is, therefore, dependent on several factors: energy threshold, positron energy, physical dimensions of the tumor and detector size.

Experience gained in the initial phantom tests led us to believe that energy thresholding should be sufficient to allow the localization of tumors in vivo. The results shown in Figures 4 and 5 confirm this assertion, despite the reduction in detection sensitivity incurred because of energy thresholding. In Figure 4, energy thresholds that straddle the Compton edge energy were used in experiments to determine the effectiveness of the probe system to detect the presence of tumors in situ. In both instances, the relationship between FDG concentrations and probe response was linear. The only differences between the two sets of data are the slope and intercept of the straight lines fit to the results. These differences are due to the detection sensitivity of the system at different energy thresholds. In addition, it is important to notice that the range of tumor and normal tissue SUVs utilized in these experiments span much of the range of values reported in human FDG studies (*17*). Furthermore, the slopes of the lines fit to the curves in Figure 4 are estimates of the in vivo probe sensitivity for detection of ^{18}F. The value of 35.7 cps/μCi/ml (at a discriminator setting of 340 keV) is approximately twice the value reported by Daghighian et al. (*10*). This difference, however, is probably due to differences in probe and tumor size. In addition, Daghighian et al.'s measurements were performed with ^{131}I, a radionuclide that emits electrons with slightly lower maximum energies than ^{18}F.

Finally, the results shown in Figure 5 demonstrate the ability of the probe system to differentiate between normal and tumor tissues. The correlation between histologic results and the probe readings are excellent. The highest z-scores occur when the probe is positioned above the center of the tumor. This is to be expected because, at this position, the entire active area of the probe is exposed to high FDG concentrations present in the tumor. The presence of a necrotic region in the tumor's center was not evident from probe readings. This is most probably due to the relatively small necrotic region (10 mm^2) compared with the cross-sectional area of the probe (55 mm^2). There was less signal detected from the edge of the tumor because of the fact that less of the probe face was exposed to tumor. The results at the lower energy threshold (290 keV) appear to produce slightly larger z-scores for tumor tissue. This is likely caused by detection of annihilation photons and low-energy positrons that emanate from the tumor. Although this effect enhances detection of FDG-avid tumor, it may be a hindrance in applications in which the background photon flux is more intense. Thus, operation of this system at the higher energy threshold (340 keV) may be preferred.

In addition to very good detection of tumor, the identification of surrounding and tumor bed tissue to be tumor free is a significant finding. The probe was not, however, able to detect the presence of a relatively small number (<100) of diffuse tumor cells in one area of the tumor bed. Although it is doubtful that this or any other system will be able to detect truly microscopic amounts of tumor left in the tumor bed, the capability to find tumor remnants may aid in a reduction of the incidence of recurrent disease by enhancement of the complete removal of all tumor. Furthermore, if it is known that, through the negative indications of an intraoperative probe, any disease left intact would be minimal and microscopic, then the amount of adjuvant radio- or chemotherapy could be appropriately adjusted, thus limiting the patient's exposure to these potentially harmful therapies. Indeed, because it has been demonstrated that probe sensitivity is greatest when the tissue that contains the radiotracer is thinnest, detection of tumor remaining in the surface layer of the tumor bed should be excellent. Enhanced detection sensitivity for thin structures serves to offset, at least partially, the reduced sensitivity at higher energy thresholds. The tumors used in this investigation were approximately 1.5 cm in diameter, which is representative of the size routinely observed in standard surgeries.

It is envisioned that this system would be used to confirm and help delineate the extent of breast lesion(s) during surgery. After the excision of a lesion, this device may also be used to survey the tumor bed for the presence of residual tumor left in situ. As previously noted, it is not ex-

pected that a negative probe indication should be interpreted as meaning that no tumor cells remain. Instead, it indicates that, if any cancer remains, the amount is small. In addition, this system could be used to detect ^{18}F-FDG-avid tumors cells present in axillary lymph nodes [cancer-involved lymph nodes have been demonstrated to accumulate FDG preferentially (18)], thus assisting in the determination of nodal infiltration by cancer cells. This application could allow for the in situ evaluation of lymph nodes, instead of the current practice of removal for subsequent histologic analysis. Hence, the number of normal lymph nodes excised might be reduced. In all of these applications, the large size of the current surgical probe aids in efficient scanning of the entire surgical field. If the need arises, smaller probes based on the design of this system can be constructed. Indeed, it may be desirable to use two probes during the surgical procedure. A large probe for coarse tumors and lymph node surveys and a smaller device with higher resolution that is less susceptible to geometric effects for more precise investigations. Clearly, clinical studies are required to define the exact role of this probe system in conservative breast cancer surgery.

CONCLUSION

The results presented in this work indicate that a beta-sensitive probe that uses energy thresholding appears suitable for FDG-guided breast cancer surgery. This belief is based on a series of phantom studies that investigated the effect of energy thresholding on resolution and sensitivity. In addition, in vivo experiments in rodents with breast cancer to simulate FDG concentrations encountered in human tumors demonstrated that this probe can differentiate between tumor and normal tissue in situ. It is therefore expected that this system will next be tested in human trials to determine its suitability for guidance of surgical excisions of breast cancer.

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