A Fiber-Optically Coupled Positron-Sensitive Surgical Probe

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Positron-emitting radiopharmaceuticals such as ^{18}F-labeled 2-deoxy-D-glucose (FDG) have considerable utility in the noninvasive imaging of cancers due to their rapid and excellent tumor-localizing properties. In addition, the relatively short range of positrons in tissue facilitates the precise delineation of FDG-avid tumors. Therefore, FDG used in conjunction with a positron-sensitive probe may be capable of guiding surgical procedures. Many of the current probe systems, however, are sensitive to the intense flux of background photons produced by positron annihilation. We describe the design, manufacture and initial in vitro and in vivo testing of a probe well-suited to the detection of positron-emitting isotopes in a high-photon background. **Methods:** The device consists of a small piece of plastic scintillator coupled by fiber-optic cable to a photomultiplier tube. Measurements of resolution and detector sensitivity were obtained. In addition, the reduction in resolution caused by the effects of various levels of background photon flux was determined. **Results:** These measurements indicate that resolution is degraded minimally (~5% with a background-to-source ratio of 2:1) due to annihilation photon background. Sensitivity for positrons is good, detecting amounts of radioactivity as low as 10.2 nCi of FDG in vitro. In rats given FDG subcutaneously, lymph nodes containing as little as 11 nCi of FDG could be detected above the background activity levels present in normal surrounding tissues. **Conclusion:** A plastic scintillator probe system has been devised which may be highly suitable for intraoperative FDG-guided (or other positron or beta emitting-tracer) surgery.

Key Words: radiation detectors; intraoperative probes; tumors; FDG

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Radiopharmaceutical-guided surgery has been increasingly applied in the surgical management of patients with cancer. Monoclonal antibodies labeled with gamma-emitting radionuclides are administered several days preoperatively. Following an accumulation period during which the agent is preferentially localized in sites expressing accessible antigen and background activity clears, the regions of the body suspected of containing tumors are surgically exposed and surveyed with a radiation detector (*1–6*). Areas of increased gamma emission are considered likely to contain tumor and are generally biopsied. Detection devices used in this procedure usually consist of a NaI(Tl) crystal coupled to a photomultiplier tube with a fiber-optic cable (*7–9*). Recent findings by Wahl and others have indicated that ^{18}F-labeled fluorodeoxyglucose (FDG) has excellent localization to many tumors, with high tumor-to-background ratio within 1–2 hr postinjection (*10–13*). An added potential advantage of FDG is the fact that ^{18}F is a positron emitter, and, unlike gamma rays, its positrons have a limited range in tissue ($<$1.5 mm). Thus, only particles emitted in the immediate vicinity of the probe are detected with a suitable probe system. Standard NaI(Tl) probes, however, are not optimal for this application. These detectors, in addition to being highly sensitive to positrons, are also very sensitive to the 511 keV photons produced by positron annihilation. With such detectors, the signal-to-background detection ratios are low, hence the benefits of using a positron emitter are lost.

Other types of detectors which might be useful for this technique include Geiger tubes and semiconductor devices. Geiger tubes are capable of detecting positrons and have relatively low 511 keV photon detection efficiencies (*14–16*). They are also difficult to miniaturize and can be too bulky and complex for convenient use. Semiconductor devices such as avalanche photodiodes and surface barrier detectors are small and have good positron-to-photon background detection ratios; however, high cost and temperature sensitive gains (*17–25*) limit their usefulness for this method. In addition, detectors utilizing cadmium telluride (*20*) (such as the Neoprobe) may be appropriate for this application, although their use might be hampered by the shallow penetration of lower energy positrons (such as those emitted by ^{18}F) into the detector material. An attractive alternative is the use of a plastic scintillator coupled to a photomultiplier tube. Plastic scintillator is relatively inexpensive and is very easily worked into almost any desired size or shape. In addition, it possesses a good signal-to-background detection ratio (*26*). We have therefore opted to construct a small plastic scintillation probe. In this

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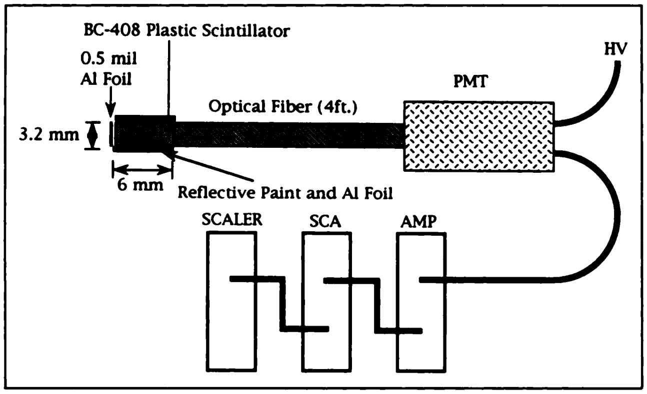

FIGURE 1. Schematic drawing of the positron-detecting probe system showing the scintillator, fiber-optic cable and associated electronics.

study, the detector's suitability for use in FDG-guided surgery is initially evaluated.

MATERIALS AND METHODS

The tip of the positron probe consists of a piece of BC-408 plastic scintillator (Bicron Corporation, Newbury, OH) (27) formed into a 3.2 × 6.0 mm cylinder (Fig. 1). The sides of the cylinder were coated with reflective paint and aluminum foil to facilitate light collection. The front face was covered with a 0.5-ml thick piece of aluminum. This thin window will not significantly attenuate the positron flux passing through to the scintillator. The opposite end of the tip was fixed to one end of a 4-foot piece of fiber-optic cable with epoxy. The other end of the cable was attached to the front face of the photomultiplier tube (RCA XP-1911). The tube was operated at a voltage of 1.7 keV supplied by an Ortec 556 high-voltage module. Anode voltage pulses were amplified with an Ortec 572 amplifier prior to discrimination by an Ortec 551 single-channel analyzer with an energy threshold set at approximately 100 keV. The resulting signals were scaled by an Ortec 996 counter-timer module.

Count-rate capabilities of the probe were determined by placing a 3 × 3-mm piece of filter paper soaked with 180 μCi of ^{18}F 2 mm from the front window of the probe. As the fluorine decayed, the count rate was measured and plotted as a function of activity in the field of view. An important design characteristic of this device is its expected ability to resolve small sources of positron emissions in the presence of a large photon background. To quantify this capability, a 4-mm long section of cotton thread (10 ml diameter) was soaked with 100 μCi of ^{18}F. The thread was fixed in place on a mechanical stepping device which was used to translate the probe across the thread in 0.5-mm steps. Count rate as a function of position was recorded to produce a line response function (LRF) for the detector. A Gaussian function was fit to this curve and the full width at half maximum (FWHM) defined as the resolution of the probe. Photon background was produced by placing a piece of filter paper soaked in ^{18}F underneath the translator bed. Positrons annihilated in the aluminum platform (2-mm thick) resulting in a background source of 511 keV photons. The flux was controlled by adjusting the amount of ^{18}F on the paper. Four different photon background intensities were utilized.

Next, probe sensitivity was determined. In a procedure similar to the count rate test, a 3 × 3-mm piece of filter paper was soaked with 1.4 μCi of ^{18}F. The probe tip was located 2 mm above the source and count rate was plotted as a function of decaying activity. A straight line was fit to the resulting curve. The minimum amount of activity detectable was calculated by finding the intercept point of the line fit to function and the horizontal line representing the noise count rate. Additionally, the positron-to-photon detection ratio was measured by interposing a 1.5-mm thick piece of lead between the source and detector, and dividing the count rate without the shield by the count rate with the shield in place. The lead will absorb all of the positrons emitted by ^{18}F but have minimal effect of the annihilation photon flux. Also, the effect of differing thicknesses of absorbing material between positron source and probe were compared for two commonly utilized positron emitters. Sixty microcuries of ^{11}C and ^{18}F were deposited on separate 3 × 3-mm pieces of filter paper. As before, the distance from source to detector was 2 mm. For each isotope, gradually increasing thicknesses of parafilm (American National Can, Greenwich, CT) [density = 0.93 g/ml] were placed between probe and source. The count rate was recorded as a function of absorber thickness.

Finally, the probe was tested in an in vivo application. Varying amounts of FDG were injected into the left-hind foot pads of four adult Sprague-Dawley rats. This type of injection has been shown to result in pronounced tracer uptake in the popliteal lymph node proximal to the point of injection (28). One hour after injection, the left popliteal node was surgically exposed. The node and surrounding tissues were surveyed with the probe and count rates recorded. Following excision from the rat, the node was re-surveyed with the probe and count rates were determined. The node and samples of surrounding muscle tissue were weighed and placed in a well counter to independently measure activity present in these structures.

RESULTS

Results of the count rate test are shown in Figure 2. Nonlinearity in count rate is observed at activity levels above approximately 130 μCi. This is most probably caused by pulse pile-up in the electronics. A line-response function measured in the absence of 511 keV background is displayed in Figure 3. It is expected that the shape of the LRF will change with the addition of a flux of annihilation

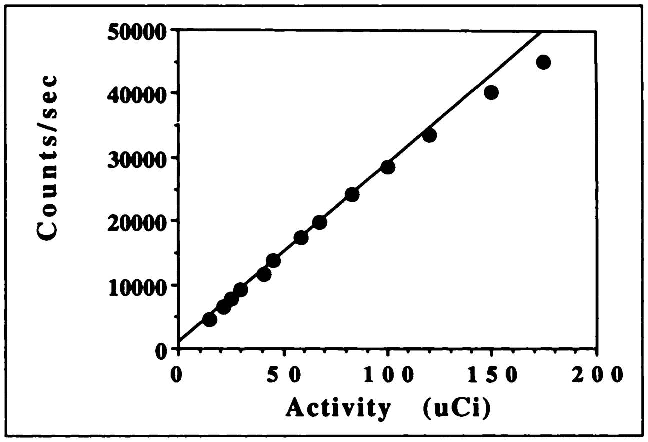

FIGURE 2. Count rate linearity test. Detected count rate versus amount of ^{18}F in the probe's field of view is plotted. The solid line shows the fit to the linear portion of the curve.

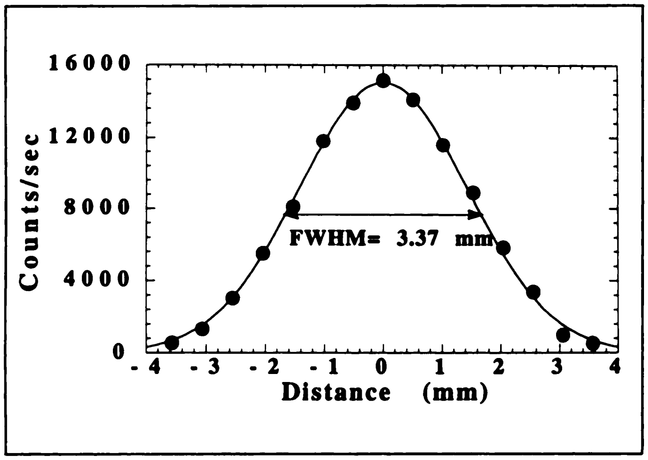

FIGURE 3. Measured line response function. Count rate as a function of detector position is plotted. The solid line shows the fit of the curve with a Gaussian function.

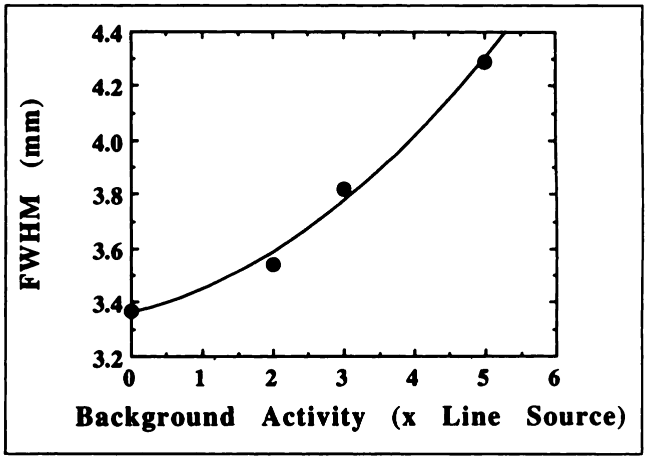

FIGURE 5. Detection sensitivity determination. Count rate measured as a function of ^{18}F in the field of view is shown. The thin solid is the fit to the data and the thick solid line shows the constant photomultiplier noise count rate.

photons. This is demonstrated by the plot in Figure 4, which is a graph of FWHM versus background level. As background is increased, the tails of the LRF are extended, thus increasing the FWHM and decreasing resolution. For example, at zero background the FWHM is 3.37 mm, when the background is increased to five times the line source strength the LRF remains Gaussian with a FWHM increased by 27.2% to 4.29 mm.

An important characteristic of any radiation-detecting probe is its sensitivity, i.e., the smallest amount of radioactivity (in this case ^{18}F) which is detectable. To experimentally determine this quantity, the intersection between the curve of count rate versus activity and the baseline noise level was found (Fig. 5). The noise count rate with no radiation in the field of view was measured to be 9.2 cps. The equation of the line fit to the curve of count rate versus activity is given by

$$\text{count rate (cps)} = 5.47 + 366.12\ (\text{activity}\ [\mu\text{Ci}]). \quad \text{Eq. 1}$$

Setting the count rate at 9.2 cps and solving for activity in Equation 1, the minimum amount of activity detectable is 10.2 nCi. The positron-to-background detection ratio was determined to be 18.5 which is slightly better than the expected value of 14.3, possibly due to some photon absorption in the lead shield.

Positrons are emitted with a spectrum of energies particular to each radioisotope. For example, the maximum energy of positrons emitted by ^{18}F is 633 keV, for ^{11}C the maximum is 959 keV. The distance a positron travels in tissue is related to its energy; higher energy particles travel a greater distance. Therefore, on the average, positrons emitted from ^{11}C will travel farther than those emitted from ^{18}F. This is demonstrated in Figure 6, which shows count rate as a function of absorber thickness for both ^{18}F and ^{11}C. Note that for a given amount of absorber, the count rate for ^{11}C is greater than that for ^{18}F. The results of the in

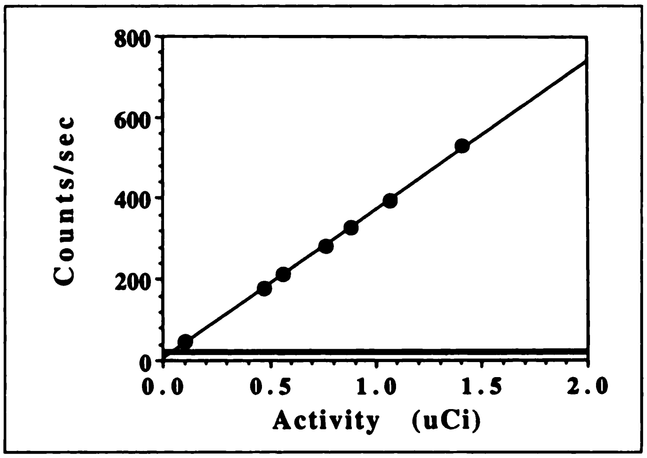

FIGURE 4. Resolution degradation measurement. FWHM for the line response function is plotted versus amount of background 511 keV photon flux.

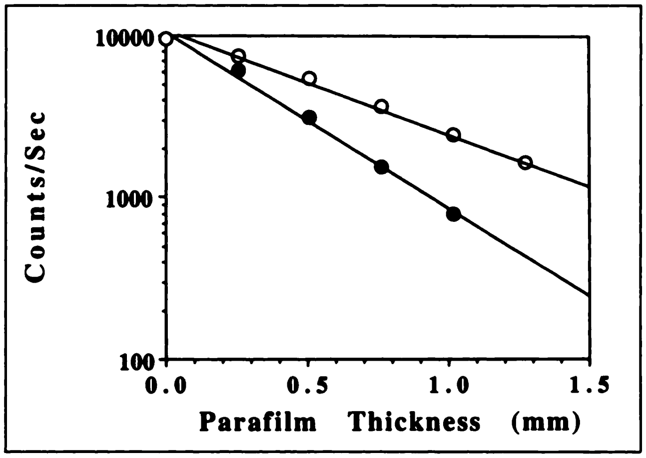

FIGURE 6. Measurement of positron penetration. The relationship between count rate and thickness of absorbing material is plotted for ^{18}F (●) and ^{11}C (○).

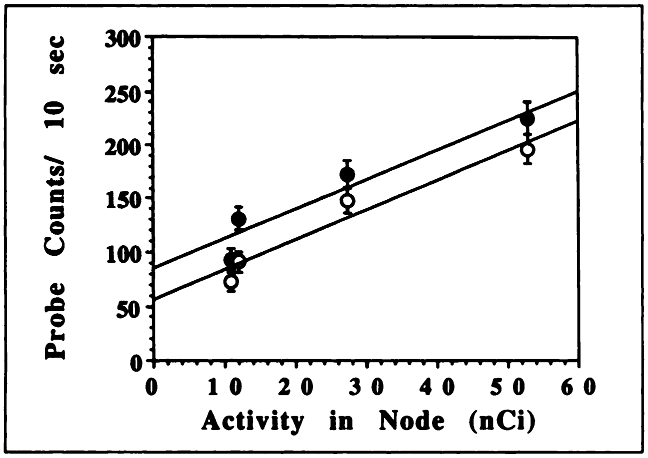

FIGURE 7. Test of the positron-detecting probe in rats. Probe counts per 10 sec are shown as a function of the amount of ^{18}FDG present in the popliteal lymph node. Measurements were made in vivo (●) and ex vivo (○).

vivo tests are shown in Figure 7. The count rates measured above the node were 60%–130% higher than in surrounding muscle which agrees qualitatively with results measured by Wahl (*28*). In addition, there is a linear relationship between count rate and activity measured in the node. This is true in both the in vivo and ex vivo cases.

DISCUSSION

Radiation-detecting probes have shown increased application in the delineation of tumors at the time of surgery. This technique has been utilized most often in radioimmunoguided surgery. Recent studies have shown that FDG (a positron emitter) is preferentially accumulated in many tumors and may be superior to other tumor-localizing agents because of its high tumor-to-background ratio. Therefore, a probe capable of reliably localizing areas of positron-emitter deposition is necessary to make FDG-guided surgery possible. The challenge is to construct a device which is highly efficient in detecting positrons in the presence of a high annihilation photon background. Our probe was therefore fabricated using a plastic scintillator which possesses the desired qualities of simplicity, low cost and a high positron-to-background detection ratio. Utility and ease of operation are obtained by coupling the scintillator to the photomultiplier tube with fiber-optic cable.

Experiments to characterize the probe performance demonstrated that the count rate is linear with respect to ^{18}F activity in the field of view up to approximately 130 μCi. At this point the count rate begins to roll off somewhat, apparently due to pulse pile-up. Since the light pulses from the scintillator have a very short 2.1 nsec decay time, the pile-up is almost certainly occurring in the electronics, most likely in the single-channel analyzer. Count rate linearity can most probably be maintained at this activity level and above by employing a faster single-channel analyzer.

A distinctive characteristic of this device is its ability to delineate areas of positron emission in the presence of annihilation photon background. As the amount of background photon flux is increased, the resolution is degraded due to the broadening of the line response function. The reduction in resolution, however, is relatively minor considering the high levels of background simulated. The levels of background used were much higher than would be expected in typical intraoperative applications in order to fully explore the capabilities of the detector. In humans, the median FDG concentration in breast tumors can be as high as eight times that in surrounding tissues (*11*), thus we expect the probe to maintain close to optimal resolving power in actual use in patients.

In addition to resolution, another important characteristic of the probe is sensitivity. Experiments showed that the smallest amount of ^{18}F activity detectable was approximately 10.2 nCi. This value was measured under ideal conditions. The minimum amount of activity detectable in a tumor depends upon the size of the tumor and the thickness of absorbing material between the source and detector. Due to the limited range of positrons in tissue, increasing the size and amount of absorber will decrease the sensitivity. Sensitivity is also dependent upon type of positron emitter. This is illustrated in Figure 6, where the count rate at various absorber thicknesses is measured for two different radionuclides. Higher-energy positrons are more readily transmitted through the absorber and are easier to detect. However, if positron energies are too high, the localization advantage gained from the limited range of positrons is diminished due to their increased range. Thus, the excellent localization capabilities achieved by the relatively short range of ^{18}F positrons is obtained at the cost of requiring that the suspected tumor be almost completely exposed before the probe can detect it. In other words, this probe is most useful when the location of a tumor is known or strongly suspected; it is not intended to be used as a scanning device.

The proposed protocol for use of this device in FDG-guided surgery is straightforward. Prior to surgery, the tumor should be localized using FDG PET imaging of the suspected tumor area. In addition to identifying the tumor site, this procedure verifies that the tumor preferentially accumulates FDG and assures that the use of FDG is appropriate to guide surgical resection. On the day of surgery, approximately 1 hr prior to expected surgical exposure of the suspected tumor, the patient is injected intravenously with 5–10 mCi of FDG. The probe would then be used to delineate the extent of the tumor. Thus only tumor will be removed sparing surrounding healthy tissues which might normally be removed as a precautionary measure. Following tumor excision, the tumor bed will be examined to ensure that no tumor remains. In addition, regional lymph nodes could be surveyed to determine if they contain any FDG-avid metatastic disease. A demonstration of this technique was performed by injecting rats with FDG prior to postmortem excision of the popliteal nodes. The results, shown in Figure 7, demonstrated that it was possible to detect FDG uptake in the popliteal lymph node with this probe. FDG amounts as low as 11 nCi were shown to be detectable in vivo and ex vivo. Note that the count rate in vivo was slightly higher than that measured ex vivo probably due to the detection of background photons and positrons emitted from tissues adjacent to the node. Detection of these background sources of radiation did not, however, hamper localization of the popliteal lymph nodes due to the high (12.1:1) ratio of FDG uptake to muscle tissue (*29*). Since the median tumor-to-background FDG uptake ratio measured in humans is approximately 8:1 (*11*), we do not anticipate detection of background radiation to seriously degrade the ability to localize tumors in applications involving human subjects. Additionally, the limited range in tissue of positrons emitted by ^{18}F (<1.5 mm) reduces the probability of detecting sources of positrons other than those 0–1.5 mm directly beneath the probe tip.

This device's ability to detect positrons in the presence of a photon flux make it useful in other applications. For example, input functions for quantitative PET studies could potentially be obtained noninvasively by placing the probe above a vein in the arm or leg. Arterializing the blood in the vein should yield a suitable function of tracer concentration in the blood as a function of time. Thickness of the venous wall and overlying skin can significantly attenuate positrons, therefore this technique should be most useful with tracers labeled with higher energy positron emitters such as ^{15}O-water. Actually, this probe has the potential to be valuable in any method where the detection of positrons or beta particles in a high photon background is necessary. Obviously, the clinical utility of the probe will require extensive clinical validation, though this report demonstrates the feasibility of the method.

CONCLUSION

The construction and basic operating characteristics of a fiber optically coupled positron-sensitive surgical probe capable of detecting positrons in a high-photon flux environment was presented. One application envisioned for this device is in FDG-guided surgery. In this technique, the extent of surgically exposed tumors is determined prior to and following excision using FDG and a positron-sensitive probe. Particularly good localization of deposited tracer is attained due to the short range of ^{18}F positrons. Thus, the amount of normal tissue unnecessarily removed during the procedure could be minimized.

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