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Novel handheld PET probes provide intraoperative localization of PET-avid lymph nodes

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Abstract

Introduction—The accurate intraoperative localization of malignant nodes can pose a challenge to the surgical oncologist. Positron emission tomography (PET) scanning has significantly increased our ability to detect suspicious lesions. We investigated the ability of a novel, handheld tool to evaluate suspicious nodes intraoperatively and to correlate its findings with those seen on preoperative PET scan.

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Methods—Ten nude rats were inoculated with a lymphogenic mesothelioma tumor line and followed weekly with PET scan studies. When suspicious lymph nodes were found, animals were dissected and the intraoperative amount of tissue radiation was analyzed as “tumor-to-background ratio” (TBR) using the PET probes.

Results—The intraoperative probe was used to guide dissections and select high-risk nodes based on their specific radiotracer uptake. A total of 52 nodes were harvested; eight of these were suspicious on preoperative PET scan studies. Using a TBR of 2.5, the intraoperative probes were able to localize all suspicious nodes previously seen on PET scan. Both gamma (sensitivity: 100%; specificity: 86%; positive predictive value (PPV): 57%; negative predictive value (NPV): 100%) and beta (sensitivity: 88%; specificity: 91%; PPV: 64%; NPV: 98%) probes showed an excellent area under the curve (AUC) in the receiver operating characteristic analysis (ROC). Both probes had an AUC of 0.95 for localizing suspicious nodes on PET scan. Furthermore, the AUC for detecting malignancy for the gamma probe was 0.90 (95% confidence interval (CI), 0.83–0.99), and for the beta probe it was 0.97 (95% CI, 0.94–1.0), suggesting a better performance of the beta probe for detecting malignancy.

Conclusions—This novel tool may be used synergistically with the PET scan examination to maximize intraoperative nodal selection and sampling.

Keywords

PET probes; Minimally invasive surgery; Intraoperative probe; Beta rays; High-energy gamma rays

For surgical oncologists, the intraoperative identification and evaluation of lymph nodes is important for staging and intra operative decision making for most tumors. Treatment options vary widely according to this information. As an example, an en-bloc resection of a tumor along with its surrounding lymph nodes may be the treatment of choice for a given stage of a malignancy. In other stages of the same tumor, the therapeutic options may change, ranging from palliative surgeries to no interventional procedures at all. The evaluation of lymph nodes also could guide the aggressiveness of adjuvant therapy, patient surveillance recommendations, and overall disease prognosis. Therefore, a rapid and sensitive intraoperative nodal evaluation should help surgeons to stage malignancies properly and to tailor correspondingly the appropriate treatment.

Radiographic imaging is an integral component of the preoperative evaluation for the surgical patient. Malignant tissue and suspicious nodes can be detected using tumor-specific radiotracers in these noninvasive procedures. Abnormal findings suspicious for malignancy encourage clinicians to propose further workup, ranging from small biopsies to radical resections. It often is difficult, however, to localize those suspicious lesions during the actual surgical dissection. In such situations, an enhanced tool for intraoperative localization of those nodes would substantially help this essential step in the diagnostic process. Furthermore, making intraoperative localization reliable would limit unnecessary tissue removal and ultimately improve the overall management and treatment of these patients.

Clinical protocols are currently evaluating the utility of radioisotopes for the detection of malignant tissue both radiographically and intraoperatively. These radioisotopes can be tagged to different antibodies, receptors, or organic compounds of interest and thus be used to target malignant cells. Currently, one of the most commonly used radioisotopes is ^{18}F -2-fluoro-2-deoxy-D-glucose (^{18}F -FDG). This compound is a glucose analog and is therefore imported into the cells using the GLUT transporters. It is then selectively concentrated in tumor tissue [1] and from there emits two types of waves: beta and gamma. The first emitted wave, the beta wave, is a positron that travels a short distance and eventually collides with a

nearby electron to produce two gamma rays 180° apart from each other [2]. These subsequent waves are high-energy rays (511 keV) that travel several centimeters. Due to their long distance traveled, these rays are significantly affected by the surrounding radiation or scatter, especially at a close range (i.e., intraoperatively). This is of particular concern when surrounding organs have a significant uptake of this radiotracer (i.e., heart and kidneys), making this specific rays (gamma) somewhat inaccurate. To circumvent this problem, a large protective shield covering this probe is needed, making it less attractive for intraoperative, minimally invasive procedures.

On the other hand, beta waves travel a short distance and are emitted by the same radioisotope. Because of their short distance of travel, they could be effective for the close-range localization of suspicious lesions, with the same accuracy as that of the gamma rays. In fact, because this probe does not need surrounding protection, it is more appealing for surgical procedures, especially those with minimally invasive technology.

The handheld PET probe is a novel device that detects ¹⁸F-FDG radiotracer and is designed to be used intraoperatively. It detects both the positron emitting beta waves as well as the higher energy gamma rays. The intraoperative use of this device is simple. When analyzing a specific tissue, this device detects the amount of radiation emitted and gives the result as a number, which units are counts per second. This number is then standardized to the patient's background uptake and analyzed as "tumor-to-background ratio" (TBR), which is directly proportional to the amount of radiotracer uptake of that specific lesion, and subsequently to its malignant potential. Therefore, the higher the TBR the more likely the lesion is malignant.

Although preliminary studies with these probes have been encouraging [3, 4] and TBRs have been described for tumor masses [5], their ability to give nodal information has not been well addressed. In view of the importance of nodal evaluation in cancer patients, we tested the potential of this intraoperative tool to identify nodes previously seen in PET scan. Therefore, we aimed to evaluate the probe's ability to discriminate between suspicious and non-suspicious nodes on PET scan, classified as PET-scan-positive and PET-scan-negative nodes, respectively.

Our second goal was to define a TBR threshold above which nodes have a higher likelihood of being malignant. By doing this, we increased the intraoperative confidence for nodal removal, as well as standardized the use of this probe for nodal sampling.

Materials and methods

Animal care

All animal studies complied with the regulatory requirements of the Institutional Animal Care and Use Committee (IACUC) and the Research Animal Resource Center (RARC) of MSKCC, and the National Institutes of Health (NIH), *Guide for the Care and Use of Laboratory Animals*. Nude rats were used and weighed an average of 250 g. All were fed ad libitum and maintained on broad-spectrum prophylactic antibiotics from their arrival to the institution. All animal procedures were performed under inhaled anesthesia using 2% isoflurane mixed with 2 l of oxygen. Animals were sacrificed via CO₂ inhalation before their dissection.

Cell line

The human mesothelioma (MSTO) line was selected for its lymphogenic metastatic characteristic produced in previous studies in our laboratory (unpublished data). This line was maintained in Roswell Park Memorial Institute medium (RPMI) + 10% fetal calf serum

(FCS) P + S + 10 mM HEPES buffer + 2 mM *l*-glutamine + 1 mM sodium pyruvate and 1.5 g/l sodium bicarbonate + 4.5 g/L-glucose. Cells were kept in a 5% CO₂ humidified incubator at 37°C and subcultured twice weekly.

Irradiation

Nude rats, although athymic, are immunocompetent to a certain degree and therefore resist a large variety of tumor implantation. To increase the uptake of our xenograft model, their immune function was further suppressed by irradiation [6–8]. Using the Gammacell 40 whole-body irradiator (Atomic Energy of Canada, Ltd., Ottawa, Ontario, Canada), the animals received a one-time dose of 500 cGy. Desirable immunosuppression was obtained 4 days after this procedure, and xenograft implantation was performed then.

For optimal preparation of this immunosuppression, the animals were treated with broad-spectrum, prophylactic antibiotics from their arrival to our institution. They were kept in this treatment after the whole-body irradiation procedure to avoid secondary, opportunistic infections.

Xenograft

After immunosuppression of the animals, 2e7 cultured cells in 100 µl of phosphate-buffered saline (PBS) suspension were intrapleurally injected into both the right and left pleural cavities. For this procedure, a 1 cm skin incision was made in each side of the chest wall. The dissection was followed until the rib cage was visualized. At this time, a 28-gauge syringe containing the suspended cells was carefully introduced intrapleurally and the cells injected. Each wound was closed using surgical clips, which were subsequently removed 2 weeks after the procedure. All animals tolerated the procedure well and were closely monitored with weekly nuclear imaging studies.

Radioisotope production and injection into rats

¹⁸F-FDG was obtained from the institutional radiopharmacy laboratory (Nuclear Medicine Department, MSKCC, New York, NY). A total volume of 0.15–0.2 cm³ containing 500 µCi of ¹⁸F-FDG in sterile PBS was injected retro-orbitally in each rat.

Micro PET scan imaging

Animals were starved overnight for optimal ¹⁸F-FDG uptake. Under inhaled anesthesia, a retro-orbital injection of 500 µCi of ¹⁸F-FDG was administered to each rat. After injection, a 1 h period was allowed before imaging for an optimal radiotracer uptake [9].

The rats were placed in a prone position on the scanner. Scans were performed with transaxial fields of view of 10 cm and axial views using the Focus 120 microPET dedicated small animal PET scanner (Concorde Microsystems, Knoxville, TN). The transaxial field of view covered the lower neck to the upper abdomen. Scans were collected with an energy window of 350–750 keV and a coincidence timing window of 6 ns. Data were sorted into 2D histograms by Fourier rebinning, and transverse images were reconstructed into 128 × 128 × 63 (R4) or 128 × 128 × 96 (Focus 120) matrices by filtered back-projection. Images were corrected for nonuniformity of scanner response, and radionuclide decay to the time of injection.

Evidence of high ¹⁸F-FDG uptake tumors and nodes was found 2 to 4 weeks after tumor implantation. These animals were followed until 10 mm tumor size was reached and suspicious surrounding nodes were evident, at which time resection with node sampling was performed.

Procedure

Dissection

Once suspicious lymph nodes were readily visualized on PET scan imaging, a retro-orbital injection of 500 mCi ^{18}F -FDG was performed, after which animals were kept under inhaled anesthesia for a total of 60 min. Animals were then sacrificed and dissection performed. Probe readings took place approximately 90 min from injection for optimal radioisotope absorbance. During the procedure, particular interest was given to the high ^{18}F -FDG uptake areas previously visualized on PET scan. The handheld probe was placed perpendicularly over those areas, and dissection was guided by the high radioisotope counts obtained by the probes. Once the nodes were visualized, in situ readings were recorded in triplicate. The nodes were then dissected and fresh-frozen for subsequent pathological analysis.

PET probe and counts

The high energy gamma and beta probes (IntraMedical Imaging LLC, Los Angeles, CA) were designed to detect 511 keV photons from positron-emitting sources and positrons, or beta rays, respectively. Both probes were calibrated to accurately localize the source of ^{18}F -FDG, and the count rate was determined to optimize the detection of the 511 keV emissions.

Once properly calibrated, and after proper dissection was performed, the nodes of interest were localized and kept in situ. The probe was then placed perpendicularly over the area of interest. Radioactive emissions were measured in counts per second and recorded in triplicate for both beta and gamma probes.

The background tissue selected for comparison was the psoas muscle. It is an easily located muscle inside the body cavity and also is in proximity to high FDG uptake organs, making it similarly affected by surrounding radiation as the nodes of interest. Readings were performed in triplicate in each animal for TBR calculations.

Image analysis

PET image analysis was done with ASIPro software (Concorde Microsystems Inc., Knoxville, TN). To verify region of interest (ROI) measurements, selected tissue was harvested and weighed, after being counted in triplicate in a scintillation well *counter calibrated for ^{18}F -FDG*.

Statistical analysis

Receiver operating characteristic (ROC) curves were utilized to assess the ability of each probe to detect PET positive nodes as well as malignant nodes, and the area under the ROC curve (AUC) was used to summarize these measurements. Each ROC curve and its AUC was estimated non-parametrically and an optimal threshold was identified using the maximal Youden index [18]. A simple way to analyze the ROC graphs is the closer the AUC is to 1.0, the closer the curves are to the left upper quadrant of the graph, the better the overall performance of the probes.

Other methods of finding an optimal threshold, such as the maximal Chi-square method were not considered, because their power would have been limited in this relatively small sample.

Results

After 2 to 4 weeks of monitoring, visible nodes approximately 10 mm in diameter were detected on PET scan studies. Tumors were mostly located on the chest wall of the animals

as well as in the intrapleural space. Most intrapleural tumors grew such that no anatomic distinction could be made between suspicious nodes and tumor masses on radiographic examination. In contrast, tumors on the chest wall were well delineated and a total of eight associated nodes were found suspicious for malignancy (PET-scan-positive nodes). These nodes were all located near the tumor or in the axillary lymph node group proximal to the mass.

The handheld PET probe was then used to find as many PET avid nodes detected on conventional PET imaging as possible. Animals were sacrificed and dissected as described above and axillary areas were exposed for probe assessment. During the first intraoperative probe experiment, each of the eight PET scan positive nodes were readily localized with both gamma and beta probes (Fig. 1). This was due to the significantly increased TBR of these nodes compared with the surrounding tissue. The average TBR of these suspicious nodes was 5.0 on the gamma probe, with values ranging from 2.6 to 9.6. On the beta probe, the average TBR was 4.45, and a range of 2.2–7.1 was obtained. Therefore, both probes detected at least twice the radiotracer uptake in the suspicious tissues compared to the surrounding ones.

Besides removing those suspicious nodes, an extensive lymph node sampling also was performed. Both axillary and peritumoral nodes were evaluated, as well as additional non contiguous nodes were similarly harvested for comparison. All node readings were recorded again in triplicate.

A total of 44 non-suspicious nodes on PET scan (PET-scan-negative nodes) were harvested and maintained for pathologic examination. Over these nodes, both probes detected lower TBRs. These values on the gamma probe ranged from 0.75 to 4.5 with an average value of 1.55. For the beta probe, the range was 0.5 to 4.0, for an average value of 1.36. Figure 2 shows the comparison between these two groups, clearly showing the ability of this probe to find PET-avid lymph nodes ($P = 0.001$).

As shown in Table 1, the ability of the probes to localize suspicious nodes using a TBR of 2.0 was reproducible throughout the various samples obtained. Similarly, using the receiver operating characteristic (ROC) analysis to evaluate their overall performance, both probes reliably detected suspicious nodes on PET scan with an AUC of 0.95. Because the AUC of an ideal predictor is 1.0 (see above for ROC analysis details), both probes had an excellent performance for differentiating the PET positive with the PET-negative nodal group. Increasing the TBR threshold to 2.5 kept the same sensitivity for the gamma probe, but that of the beta probe decreased to 88%. Overall, comparable trends could be seen as the TBR increased, as both probes demonstrated their ability to accurately recognize suspicious nodes previously seen on PET scan.

After pathological examination of the 52 lymph nodes harvested, cancer was found in 5 of them. Each of these malignant nodes was found suspicious on PET scan (were in the PET-scan-positive group). Also of interest, all of the PET-scan-negative nodes were found to be benign on pathologic examination. This gives the PET scan imaging a sensitivity of 100%, specificity of 93.6%, PPV of 62.5%, NPV of 100%, and accuracy of 94% for detecting malignancy in our study, similar to that described in recent studies [19].

The PET probes also detected significantly higher readings in the malignant compared with the benign nodes on pathology (Fig. 3). The gamma probe had an average value of 5.0 over these malignant nodes, ranging from 2.6 to 9.6. The beta probe also had an average of 5.0, ranging from 3.4 to 7.1. As a group, values of the benign nodes were significantly lower, with average values of 1.8 and 1.5 for both gamma and beta probes, respectively. We also evaluated the optimal TBR for malignancy detection. At a TBR of 2.5, the gamma probe

showed a sensitivity of 100%, specificity of 83%, PPV of 39%, and NPV of 100%, showing its optimal performance at this threshold. The beta probe may have its optimal value at a TBR of 3.0, where its sensitivity is at 100%, its specificity increased to 92%, and its PPV and NPV are optimal (56% and 100%, respectively).

Furthermore, a comparison between malignancy detection and PET scan findings localization was assessed, as seen in the ROC curves in Fig. 4. These graphs show the overall performance of each probe and compare their ability to localize PET findings (black curve) with their ability to detect malignant nodes on pathology (dotted curve). Each curve showed statistical significance ($P < 0.001$). As mentioned earlier, the AUC of both probes for localizing suspicious nodes on PET scan was 0.95, even though their sensitivity and specificity showed some differences between the two probes. This may be due to our sample size, which can sometimes mislead readers when analyzing this type of study. For this reason, the ROC analysis was included. It gives a more reliable analysis of the overall performance of each probe and can be quantified (with their corresponding AUC) and compared [18].

On the other hand, there were some differences for specifically detecting malignant nodes. For this task, the beta probe showed a better overall performance in this ROC analysis, resulting in an AUC of 0.97 versus 0.90 compared with the gamma probe (95% confidence interval (CI), 0.94–1.0, and 0.83–0.99 for beta and gamma probes, respectively). With these findings, an argument may be done for the beta probe being somewhat more sensitive to detect malignancies, whereas gamma may be so for identifying the PET scan positive nodes at long ranges. Further studies will clarify this issue.

Discussion

Proper lymph node evaluation in cancer patients leads to improved staging and subsequent treatment for these patients. Surgeons still often rely on size, shape, and consistency to make their intraoperative nodal selection for biopsy.

Among the various methods that have been studied to aid in this task, it is worth mentioning that sentinel lymph node biopsy (SLNB) has significantly enhanced this process. Nonetheless, this technique is suboptimal for a variety of reasons. Among these, the lack of specificity of malignant node selection [10] and the problems visualizing specific nodes (i.e., in obese patients) [11] make this technique feasible but not ideal. Another pitfall of the SLNB technique occurs when macrometastasis over a lymph node is present or when preoperative chemotherapy leads to impaired radiotracer flow. This forces lymphatics to drain via a collateral lymphatic vessel and as a result it creates a new sentinel lymph node, forcing the tracer to bypass and miss the node of interest [12, 13].

Also arguing against this procedure is the fact that a second SLNB is not recommended in a patient with recurrent disease if a significant amount of lymph nodes were removed during the first encounter [16]. Because locally recurrent disease can be found in up to 15% of patients within 10 years of follow-up after breast conservation therapy [14, 15], the surgeon is left again without resources to perform a proper nodal sampling intraoperatively. Therefore, although SLNB has improved tumor staging, a more tumor-specific technology for nodal sampling is needed.

The handheld PET probe is an intraoperative device first described and developed by Daghighian et al. [17] in 1994 as a novel method to direct intraoperative tumor localization. This positron-detecting device allows for direct localization of radiolabeled tumor cells by detecting both gamma and beta rays. The high-energy gamma rays correlate with PET scan imaging. But for this probe to efficiently detect gamma rays, a high degree of collimation or

shielding is required. Although this makes the probe more efficient, it also substantially increases its diameter and impedes its ideal mechanical manipulation intraoperatively, particularly in small cavities or during minimally invasive surgeries.

On the other hand, the beta probe does not need such shielding from side scatter. It is made from a thin crystal that is sufficient to stop electron radiation but too thin to be affected by the surrounding gamma rays. It therefore has a smaller diameter and is ideal for intraoperative manipulations, as well as for minimally invasive procedures.

Previous publications with this probe have not addressed well its efficacy in localizing suspicious nodes seen on PET scan imaging. This study demonstrates the probes' utility in performing this task. Interestingly, the direction of the dissection was guided on multiple occasions by the high counts of radiotracer detected over the PET positive lesions. In those instances, the suspicious nodes were readily visualized after continued dissection. This process was easily reproducible on multiple explorations. As the results show, a statistically significant difference in terms of TBR as well as in the ROC analysis was seen between the PET-scan-positive and PET-scan-negative groups.

Based on our results, we have determined that the optimal TBR to localize suspicious nodes on PET scan is between 2.0 and 3.0. Within this range, the sensitivity of nodal selection was at its highest for both probes, and the specificity as well as the PPV had the most substantial increase. The specificity of the beta probe increased when the TBR threshold for sampling increased to 2.5, at the expense of a decreased sensitivity (Table 1). Of note, the lower values of this range were found benign on pathologic examination, possibly showing a somewhat higher specificity for this probe toward malignant tissue detection.

After establishing the ability of the probes to identify PET-avid lymph nodes, we wanted to test this handheld tool for its ability to detect malignant nodes (regardless of their PET scan results). Both probes could effectively find a significant difference between the malignant and benign nodal groups (Fig. 3). The sensitivity for detecting malignant nodes was 100% in both probes between TBRs of 2.0 and 2.5, and specificity, along with PPV, had the most significant increase over this range. It is for this reason that we conclude that the optimal TBR for nodal assessment of malignancy probably is between 2.5 and 3.0 for both probes.

The importance of using the both probes intraoperatively cannot be underestimated. Secondary to its long reach, the gamma rays could guide the surgeon's dissection toward the area of interest. Once the lesion is properly localized, the decision of probe exchange could easily be performed intraoperatively. Doing so, the beta probe could lead to improved malignancy selection, better delineation of the area to be resected, and facilitate intraoperative tissue sampling, especially in anatomically challenging areas or in small body cavities due to its smaller diameter size.

The similarities between the TBRs found on both probes and their high sensitivity and specificity highlight the reproducibility and consistency of this device to detect this radiotracer. Ultimately, the TBRs detected by these probes will be the instrument to guide surgeons in the important task of intraoperative nodal selection, whether it is a PET-positive or a malignant lymph node.

Conclusions

This is the first comprehensive lymph node study to evaluate the ability of the intraoperative PET probes to localize PET scan avid nodes. Furthermore, the extensive nodal sample studied allowed us to analyze malignant versus benign nodes relative to their respective TBRs. The reproducibility and accuracy of the results permitted us to define a specific TBR

threshold above which nodes should be sampled, as a way to standardize the use of this novel device. As shown, this tool may synergistically complement PET scan imaging, as well as limit tissue sampling by increasing the accuracy of the intraoperative localization of suspicious and malignant lymph nodes.

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Fig. 1.

PET scan avid node, chest wall mass and pathology result. **A** Suspicious right axillary lymph node (*arrow*), as well as high uptake area detected over the left chest wall (*arrowhead*). A 2 cm high uptake mass (not shown) was located just distal to the right lymph node seen, in a plane just anterior to the depicted figure. The high radiotracer uptake seen in PET scan correlated with the high tumor-to-background ratio (TBR) detected with the intraoperative probes over both the node and tumor. Over the suspicious node, intraoperative probes detected a TBR of 7.12 and 9.64 for beta and gamma probes, respectively. The left chest wall tumor had a TBR of 7.65 and 10.6 for beta and gamma probes, respectively. **B** Hematoxylin and eosin staining of the node showing mesothelioma

Fig. 2.

Gamma and beta TBRs comparing positive and negative nodes on PET scan. A comparison between PET scan positive (suspicious nodes on PET scan) and PET scan negative (nodes not suspicious for malignancy on PET scan) lymph nodes in terms of TBR ratios for both gamma (**A**) and beta (**B**) probes. As shown, the PET scan positive nodes had significantly higher tumor-to-background ratios on both gamma and beta probes ($P = 0.001$). The standard error of the mean for both groups is shown for comparison

Fig. 3. Gamma and beta tumor-to-background ratio (TBR) of malignant versus benign nodes on pathology. This graph compares malignant and benign nodes on pathology, in terms of TBR. The malignant nodes had significantly higher ratios on both gamma (**A**) and beta (**B**) probes ($P < 0.001$). Of note, the standard error of the mean range over the beta probe is smaller than that of the gamma probe

Fig. 4.

Receiver operating characteristic curves of gamma and beta probes comparing their utility to localize PET-avid versus malignant nodes. A comparison of each probe's ability to localize PET positive findings and to detect malignant lymph nodes. The true positive rate (sensitivity, y axis) increased at the expense of the specificity (x axis). Increases in TBR threshold (*diagonal line*) were similarly correlated with an increase in specificity. **A** Gamma probe was somewhat better detecting PET-positive nodes (solid line) than malignant nodes on pathology (*dotted line*), resulting in an AUC of 0.95 and 0.90, respectively. **B** Beta probe was somewhat better for detecting malignancy (*dotted line*) than for localizing suspicious nodes on PET scan (*black line*), with area under the curve of 0.97 and 0.95, respectively. *n* sample size

Table 1

Probes localizing PET-scan-positive nodes

Ratio	≥1.5	≥2.0	≥2.5	≥3.0	≥3.5
Gamma probe	Sensitivity	100	Sensitivity	100	Sensitivity
	Specificity	66	Specificity	86	Specificity
	PPV	35	PPV	57	PPV
	NPV	100	NPV	100	NPV
Beta probe	Sensitivity	100	Sensitivity	88	Sensitivity
	Specificity	77	Specificity	91	Specificity
	PPV	44	PPV	64	PPV
	NPV	100	NPV	98	NPV

This table shows the ability of the probes to locate suspicious nodes previously seen on PET scan. As shown, sensitivity on both probes is excellent. Specificity and PPV are somewhat higher for the beta probe over the different TBRs. *n* sample size; *PPV* positive predictive value; *NPV* negative predictive value; *TBR* tumor to background ratio