Published in final edited form as:

Ann Nucl Med. 2013 April ; 27(3): 203–208. doi:10.1007/s12149-012-0672-6.

A Hand-Held Beta Imaging Probe for FDG

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Abstract

Objectives—Advances in radiopharmaceuticals and clinical understanding have escalated the use of intraoperative gamma probes in surgery. However, most probes on the market are non-imaging gamma probes that suffer from the lack of ancillary information of the surveyed tissue area. We have developed a novel, hand-held digital Imaging Beta Probe™ (IBP™) to be used in surgery in conjunction with beta-emitting radiopharmaceuticals such as ¹⁸FDG, ¹³¹I and ³²P for real-time imaging of a surveyed area with higher spatial resolution and sensitivity and greater convenience than existing instruments.

Methods—We describe the design and validation of a hand-held beta probe intended to be used as a visual mapping device to locate and confirm excision of ¹⁸FDG-avid primary tumors and metastases in an animal model.

Results—We have demonstrated a device which can generate beta images from ¹⁸FDG avid lesions in an animal model.

Conclusions—It is feasible to image beta irradiation in animal models of cancer given ¹⁸FDG. This technology may be applied to clinical mapping of tumors and/or their metastases in the operating room. Visual image depiction of malignancy may aid the surgeon in localization and excision of lesions of interest.

Keywords

¹⁸FDG; PET; ¹³¹I; Imaging; Beta Probe

Introduction

Advances in radiopharmaceuticals, radiation detectors, and clinical understanding have escalated the use of intraoperative radiation-detecting probes in surgery, providing benefits that include increased specificity in tissue resected or obtained for biopsy, minimal access incisions, and the potential for reduction of inpatient hospital utilization and hastened patient recovery. The merits of such probes and radiopharmaceuticals in diagnostic medical imaging have been clinically proven.¹⁻⁵ At present, most probes on the market are non-imaging gamma probes that are used during surgery, typically for sentinel lymph node dissection and parathyroid adenoma resection. The effectiveness of these probes is limited, however, since they suffer from a lack of ancillary information of the surveyed area, such as the clear delineation of margins of radioactive tissue. Also, the highly penetrating gamma

radiation present locally or even in remote parts of the body increases the background radiation level and further limits their discriminating value.

To address the challenges of gamma probes in particular and of non-imaging probes in general, we have developed a novel, hand-held digital imaging probe to be used in surgery in conjunction with beta-emitting radiopharmaceuticals such as ^{18}F FDG, ^{131}I and ^{32}P . Beta emissions from ^{32}P , for example, with an average energy of 0.7 MeV (maximum 1.71 MeV), travel a maximum of 8 mm in tissue before being stopped (web.princeton.edu), allowing sufficiently accurate localization when detected by an imaging probe.^{6, 7} In addition, ultra-thin scintillators with high sensitivity for such betas have correspondingly low sensitivity to gammas. This allows them to be used around background gamma irradiation without interference, such as in ^{18}F FDG cases. Several non-imaging beta-sensitive probes have been reported in recent years.⁸⁻¹¹ Due to the benefits offered by an imaging beta-sensitive probe, there has been increased research activity leading to the development of beta-sensitive imaging probes such as the one from IntraMedical Imaging (Los Angeles, CA) (www.gammaprobe.com).¹¹⁻¹³ However, these probes have a limited field of view (15 mm), long acquisition time (1 minute), and low resolution (2 mm). Only one beta-sensitive intraoperative probe is available on the market today (www.intra-medical.com). Our Imaging Beta Probe™ (IBP™) design allows the real-time imaging of a surveyed area with higher spatial resolution and sensitivity, lower sensitivity to background radiation and greater ease of operation than with existing instruments.

Methods

The purpose of this project was to develop a beta-only imaging probe that would have sensitivity and acquisition speed that would allow for its use in surgical cases. Our current hand-held IBP includes a 140 μm thick microstructured CsI:Tl film optically coupled to a highly sensitive electron-multiplying charged coupled device (EMCCD) via a flexible fiberoptic (FO) conduit. The microcolumnar structure of the CsI:Tl scintillator minimizes the spread of scintillation light to typically less than 100 μm , and allows for the detection of beta radiation with high spatial resolution (Figure 1).

The EMCCD is a back-thinned, thermoelectrically cooled ($-35\text{ }^{\circ}\text{C}$), 512×512 pixel CCD optically bonded to a 1:1 fiberoptic (FO) window.⁷ The EMCCD has $16 \times 16\text{ }\mu\text{m}^2$ pixels, and an effective imaging area of approximately $8.2\text{ mm} \times 8.2\text{ mm}$. The advantage of the EMCCD is that it internally amplifies the signal with a user-selectable gain and minimizes the noise associated with the CCD readout amplifier by the same gain factor. In order to increase its active imaging area, a 2:1 or 3:1 FO taper is coupled to the IBP's FO conduit, resulting in an effective imaging area of $16.4\text{ mm} \times 16.4\text{ mm}$ or $24.6\text{ mm} \times 24.6\text{ mm}$, respectively. An index matching fluid is used for the optical coupling of each of the three interfaces between the FO faceplate, 3:1 FO taper, FO bundle, and EMCCD. The prototype IBP is shown in Figure 1(a), and a close-up of the probe head is shown in Figure 1(b). Twenty-four micrometer thick aluminum foil (negligible attenuation of β -radiation) is placed in front of CsI:Tl film to shield the IBP from ambient light.

The spatial resolution of the CsI:Tl film was measured by coupling the film to a Photometrics (Tucson, AZ) XR-250 CCD, and acquiring images of a 10 m wide tantalum slit, as described by Fujita.¹⁴ This testing system includes a 1024×1024 pixel CCD bonded to a 3:1 fiberoptic taper. The effective pixel size at the front (larger) end of the taper is 57 μm , resulting in the Nyquist limiting frequency of 8.6 lp/mm. A Gendex Corporation (Hatfield, PA) model GX 1000 X-ray generator, operated at 40 kVp, 10 mA settings was used to image the tantalum slit. The slit images were analyzed to obtain the line spread function

(LSF), and the modulation transfer functions (MTFs) were calculated from the Fourier transforms of the LSFs.

Beta imaging tests using aqueous ^{18}F in an emission configuration were performed with a hot rod phantom.¹⁵ The rods are arranged in triangular arrays with the center-to-center distances between the rods being twice their diameters. A total of 21 hollow rods with 1.1 mm diameter were partially filled with a 40 Ci/mL aqueous solution of ^{18}F and used for these measurements. A container filled with 425 Ci of ^{18}F was placed directly on the top of the mini hot disk phantom in order to simulate the background.

The spatial resolution of the CsI:Tl film was also measured by coupling CsI:Tl films to the Imaging Beta Probe and acquiring images of a tantalum edge with a ^{90}Sr beta source. The edge was placed at an angle between 1 and 20° relative to the detector pixels, and an image was acquired for 60 seconds. Only a small region of interest (ROI) was used for the evaluations, with approximately equal dark and light halves. The image was used to generate an edge spread function (ESF), and this was in turn analyzed to generate a line spread function for computing the MTF(f). The edge MTF method was measured using methods previously described.^{16, 17}

The probe head was covered with protective sheathing (Latex) used to maintain a sterile environment, as shown in Figure 1(b). The attenuation of this protective sheathing was measured using various β -emitting sources (^3H and ^{90}Sr) with end-point energy of 672 keV (similar to the positron energy from ^{18}F FDG). The β source was positioned 1 cm from the probe head, with 0 to 3 layers of latex sheathing placed directly on top of the probe head. Images were integrated for 10 seconds.

Although ^{18}F FDG was available at UAMS for phantom and animal model testing, substitute beta emitters such as ^3H and ^{90}Sr were used at RMD for instrument testing and characterization, since ^{18}F FDG was unavailable.

Results

1) Scintillator Morphology

The morphology of the structured CsI:Tl films were studied at RMD using scanning electron micrographs (SEMs). Figure 2 shows an SEM of a 140 m thick microcolumnar CsI:Tl film, showing well-defined columnar structure. The microcolumnar structure of the 140 m thick CsI:Tl scintillator minimized the spread of scintillation light to less than 100 m (typical) and allowed the detection of β radiation with high spatial resolution. This structure overcomes the traditional tradeoff between spatial resolution and detection efficiency, allowing optimization of detection sensitivity without compromising spatial resolution. The 140 μm thick CsI:Tl film reduced the undesired detection of 364 keV gammas from ^{131}I and 511 keV gammas from ^{18}F to less than 1 %.

The scintillation light produced was efficiently detected by the back-thinned EMCCD, which has a quantum efficiency of ~95% for the 540 nm CsI:Tl emissions. The EMCCD can be read at rates of 30 frames per second (fps) or higher, allowing “movie-mode” operation (with user- or software-controlled variable persistence, frame capture or other capabilities, if desired) for rapid IBP navigation, without compromising the signal-to-noise ratio (SNR). The use of the 2:1 taper resulted in a factor of 4 light loss (25% transmission), whereas the use of the 3:1 taper resulted in a factor of 9 light loss (11% transmission). The transmission through the FO conduit was about 40%.¹⁸ The FO had extramural absorption (EMA), a numerical aperture of 1.0, a 10-12 μm fiber core, maximum shear distortion of 75 μm , and maximum gross distortion of 2% over the detected area.

2) Scintillator Spatial Resolution and Efficiency Measurements Using X-Rays

Figure 3 shows the modulation transfer function and detective quantum efficiency (DQE) for the 140 μm CsI:Tl film. This film provided high spatial resolution of 10 lp/mm, measured using X-rays. The DQE(0) for the same film measured ~62%, which corresponds to good X-ray absorption for a microcolumnar CsI:Tl film of 140 μm thickness.

3) Hot Rod Disc Phantom Imaging

Figure 4(a) shows the phantom, which consists of an 11.7 mm thick clear plastic disk with hexagonally arranged hollow rods of various diameters. Hollow rods were 1.1 mm in diameter. They are separated by 2.2 mm from rod center to rod center. Figure 4(b) presents an image acquired with the phantom filled with aqueous ^{18}F by the prototype probe in 10 seconds. The signal-to-noise ratio, calculated as a ratio of the peak beta image intensity to the average gamma background intensity, was found to be 12.9. As can be seen from Figure 4, the image quality is high with all rod sources clearly resolved. The variation in the brightness of the signal in holes of the same size is due to different amounts of liquid radioisotope filling the rods, illustrating the dynamic range of the system sensitivity. These data show that beta images can be acquired with high sensitivity and dynamic range with the probe in the presence of a high gamma background expected during surgical procedures with ^{18}F FDG.

4) Modulation Transfer Function Using an Edge

Figure 5 shows the modulation transfer function for the 140 μm CsI:Tl film. This film provided spatial resolution of ~3 lp/mm, using a ^{90}Sr beta source, which corresponds to a highly desirable spatial resolution of ~170 μm .

5) Probe Sensitivity

It is customary to isolate instruments such as the IBP from the sterile surgical field if practical, even though they may be designed to allow effective sterilization and to withstand liquid, gaseous or other sterilization processes. In anticipation of this practice, we tested the beta attenuation of typical latex sheathing, to determine its effect on the IBP's beta sensitivity. Compared to the sensitivity of the IBP without sheathing, one layer of latex sheathing satisfactory for mutually isolating such instruments and the surgical field attenuated <1% β , and three layers attenuated <4% β in our tests. The sensitivity of the probe was evaluated using several β -emitting radioisotopes, such as ^3H and ^{90}Sr . ^3H (lowest energy β -emitting source with endpoint energy of 18.57 keV) and ^{90}Sr (a high-energy β -emitting source with endpoint energy of 546 keV) were used to test the sensitivity of the prototype IBP. The activity of the ^3H source was 1.6 mCi and that of ^{90}Sr was 52 μCi . ^{90}Sr was used, as it emits betas of energy almost equivalent to the radiopharmaceutical (^{18}F FDG) that was used for testing this probe in animal models. We were able to image the 1.6 mCi ^3H source in 30 seconds with 1 σ above the noise floor, and the 52 μCi ^{90}Sr source in 3 seconds. We estimate that a 650 nCi ^{90}Sr source can be detected in 3 seconds with 1 σ above the noise floor. We were also able to acquire an image of the underlying ^{90}Sr source, even with the protective latex sleeve and 4 layers of chicken skin between the source and the IBP, further demonstrating the high sensitivity of the probe.⁶

6) Animal model testing

An FDG positive VX tumor model of an orthotopically (tongue) placed tumor was created in a rabbit model. It developed cervical lymph node metastases. Upon sacrifice of the animal, the tongue tumor and lymph nodes were excised and imaged for 30 seconds with our prototype IBP¹⁹, (Table 1, Figure 6).

Discussion

We characterized our Imaging Beta Probe in terms of beta attenuation and sensitivity to different beta energies using beta sources and phantoms.⁶ Due to its high density and high average atomic number the CsI:Tl film, while only ~140 μm thick, completely absorbed and enabled the detection of every incident beta particle, while being highly insensitive to gamma background. Further, the high light output of CsI:Tl (56,000 ph/MeV) and high sensitivity of the EMCCD photodetector increased overall IBP sensitivity and effectiveness, by detecting low-energy incident betas from a ^3H source.

Images were background corrected during the acquisition, and by using the EM gain on the camera read noise was minimized to less than one electron, eliminating any electronic noise from the CCD. The unique combination of a microcolumnar scintillator and an electron-multiplying CCD provided very high spatial resolution (~170 μm), excellent β - γ discrimination, and high sensitivity, which improved SNR compared to current state-of-the-art beta probes. This demonstrated that beta images can be acquired with an appropriately designed beta probe in the presence of the high gamma background expected during surgical procedures with ^{18}F FDG.

This probe was used successfully as a prototype in experiments using orthotopic tumor models and ^{18}F FDG.¹⁹ This prototype is intended to lead to further refinements in the development of hand-held beta imaging probes for use in oncologic and certain other surgeries. Development efforts will continue towards bringing this technology into the clinical arena.

Conclusions

We have developed a prototype of a beta-imaging intraoperative probe. The use of the probe may facilitate rapid identification, accurate localization and real-time visualization of suspect tissue, which will be especially helpful in small, targeted areas and when visually occult lesions may be present in a large anatomic area. The probe has the potential to localize suspected areas of neoplastic disease, which are currently only detected by PET, and escape notice by conventional imaging and the surgeon's eye. A refined model of the Imaging Beta Probe, with a much smaller diameter than the prototype, will allow convenient access to suspect tissue.

Acknowledgments

This work was supported in part by the NIH (2 R44 CA096030-03A1). The authors would also like to thank Terrie Alpe from UAMS.

Animal use:

This study was approved by the UAMS IACUC, and is in compliance with NIH guidelines for animal care.

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Figure 1.
(a) The prototype hand held Imaging Beta Probe™ (IBP™). (b) Close-up view of the probe head, covered by a latex sheath.

Figure 2. Scanning electron micrographs of a microcolumnar CsI:Tl film, showing the typical highly uniform, well-separated microcolumns. (a) Side view, 10 μm (average) diameter columns. (b) Close-up view of the top of the film.

Figure 3.
(a) Modulation transfer function and (b) detective quantum efficiency for the 140 μm thick CsI:Tl microcolumnar film, measured at 28 kVp.

a

Figure 4.
(a) The mini hot rod phantom placed on top of the CsI:Tl screen. (b) Beta images of the 1.1 mm holes, separated by 2.2 mm center-to-center.

Figure 5. Modulation transfer function for the 140 μm thick CsI:Tl microcolumnar film, measured using ^{90}Sr .

Figure 6.
Example of imaging using our IBP of an animal model of oral cavity cancer, (a) tongue and (b) lymph node, both imaged ex vivo.

Table 1

Data showing the close correspondence between the tumor sizes measured in the laboratory and those measured using the Imaging Beta Probe™.

Activity in tumor (μCi)	Activity in tumor/ml (Bq/ml)	Pathological tumor size (mm^2)	IBP tumor size (mm^2)
0.33	4301.5	10×10	12.5×10
0.38	4517.7	11×9	10×7.5
0.79	6510.8	11×10	11.5×11
0.88	8755.8	12×12	13×13
0.57	3315.2	14×12	15×15
0.84	6067.7	12×10	11×9