

Evaluation of Three Gamma Detectors for Intraoperative Detection of Tumors Using ^{111}In -Labeled Radiopharmaceuticals

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Attempts to detect tumors with intraoperative scintillation using tumor-binding radiopharmaceuticals have intensified recently. In some cases previously unknown lesions were found, but in most cases no additional lesions were detected. In this study the physical characteristics of three detector systems and their ability to detect tumors through accumulation of an ^{111}In -labeled radiopharmaceutical were investigated. The first was a sodium iodide (NaI(Tl)) detector; the second, a cesium iodide (CsI(Tl)) detector; and the third, a cadmium telluride (CdTe) detector. **Methods:** A body phantom and tumor phantoms (diameter 5–20 mm) made of water, agarose gel or epoxy with a density and attenuation coefficient similar to those of soft tissue were used to simulate a clinical situation. The activity concentration in the body phantom was based on reported values of ^{111}In -octreotide in normal tissue in humans. The ^{111}In activity concentration in the tumor phantoms varied from 3 to 80 times the ^{111}In activity concentration in the body phantom. Data were processed to determine tumor detection levels. **Results:** The NaI(Tl) detector showed the lowest values for full width at half maximum because this detector had the best collimation, leading to a high ratio between counts from tumor and counts from background, i.e., small tumors could be detected. Because of high efficiency, the CsI(Tl) detector sometimes required a somewhat shorter acquisition time to produce a statistically significant difference between tumor phantom and background. For deep-lying tumors the NaI(Tl) detector was superior, whereas the CdTe detector was best suited for superficial tumors with a high activity concentration in the underlying tissue. **Conclusion:** At a maximum acquisition time of 30 s, almost all superficial tumors with a diameter of 10 mm or larger were detected if the ratio between the ^{111}In concentration in the tumor and the ^{111}In concentration in the background exceeded 3. However, in clinical situations, biologic variations in the uptake of ^{111}In -octreotide in tumors and in normal tissue makes difficult the determination of a distinct detection level. For such clinical conditions, the NaI(Tl) detector is the best choice because it has good resolution despite a lower efficiency. Documentation of detector characteristics is important so that clinicians can make an adequate device in relation to tumor location and receptor expression.

Key Words: intraoperative detection; gamma detectors; ^{111}In -labeled radiopharmaceuticals

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Interest has been growing in tumor localization using intraoperative scintillation with radiolabeled tumor-binding substances, e.g., octreotide (a somatostatin analog), antibodies or methylene diphosphonate (MDP). Radiopharmaceuticals that have been used are ^{125}I -labeled octreotide (1) or antibodies (2,3), ^{111}In - or ^{161}Tb -labeled octreotide (4–6), $^{99\text{m}}\text{Tc}$ -labeled MDP (7,8) and ^{131}I -labeled antibody (9). Detectors that have been used for intraoperative measurements are cadmium telluride (CdTe) semiconductor detectors (3,5) and various types of scintillation detectors with crystals of cesium iodide (CsI(Tl)) (4,8) or sodium iodide (NaI(Tl)) (7). In individual cases, tumors not visualized by scintigraphy were found, but in most cases little information was added to the preoperative scintigraphic findings. Furthermore, determining which of many possible lymph nodes are malignant has been difficult. These discouraging results seem to be caused by a low ratio between the radionuclide concentration in tumor tissue and that in adjacent normal tissue (T/Bgr), the choice of radionuclide, the properties of the detector and limitations in acquisition time.

This study evaluated the ability of three detector systems differing in crystal type, size of crystal and collimator to localize tumors using ^{111}In -labeled radiopharmaceuticals. The study conditions were similar to those for in vivo measurements of ^{111}In -octreotide, but the results are also applicable to other ^{111}In -labeled radiopharmaceuticals.

MATERIAL AND METHODS

Detectors

Three detectors were used: a NaI(Tl) detector, ScintiProbe MR100 (Pol. Hi. Tech, srl, Carsoli, Italy); a CsI(Tl) detector, TecProbe1, type 2000 (Stratec Elektronik, GmbH, Birkenfeld, Germany); and a CdTe detector, TecProbe2, type 0425 (Stratec).

The NaI(Tl) detector (Fig. 1A) has a NaI crystal 8.2 mm in diameter and 16 mm thick and a parallel-hole collimator 15 mm long with an aperture 5.7 mm in diameter. The collimator and the lateral shielding are tungsten. The lateral shielding is 3.85 mm thick around the crystal. Extra lead shielding 3 mm thick covers the crystal-containing part of the detector during simulation of intraoperative measurements to decrease penetration of radiation through the side shielding. The detector was connected to a control unit that

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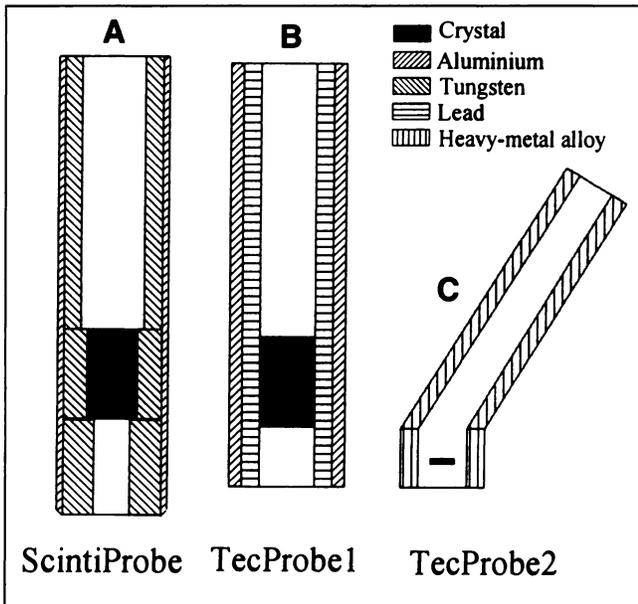


FIGURE 1. NaI(Tl) (A), CsI(Tl) (B) and CdTe (C) detectors presented in cross section and same scale.

had a multichannel analyzer and a pulse counter. Two energy windows were set over two ^{111}In photon energy peaks: 171 and 245 keV. The control unit was connected to a personal computer, and the measurements were saved using version 2.02 ScintiVisual software (Pol. Hi. Tech).

The CsI(Tl) detector (Fig. 1B) has a CsI crystal 9 mm in diameter and 15 mm thick and a parallel-hole collimator 10 mm long with an aperture 8 mm in diameter. The detector window is aluminum (0.2 mm). The shielding around the tube is lead (3 mm) and aluminum (2 mm). The detector was connected to a counter. One nonadjustable energy window was set over the ^{111}In low-energy peak: 140–200 keV.

The CdTe detector (Fig. 1C) is a semiconductor detector with a CdTe crystal 4 mm in diameter and 1 mm thick and a collimator 5 mm long with an aperture 7 mm wide. According to the manufacturer (R. Retzlaff, written communication, September 1997), the lateral shielding is a 2.5-mm-thick high-density (17.6 g/cm^3) metal alloy containing tungsten. The detector was connected to a counter. One nonadjustable energy window was set over the ^{111}In low-energy peak: 140–200 keV.

To determine the range in which the detectors have a linear response, the counting rate from ^{111}In sources placed in the same position in front of the detector was measured. The sources contained 0.1–4.3 MBq ^{111}In in 1 mL 1% bovine serum albumin (BSA) water solution to reduce adsorption of ^{111}In to the test tube walls.

Spatial resolution and isoresponse were determined using a capillary tube (1.5-mm inner diameter, >10-cm length) filled with a solution of water, BSA and ^{111}In . The tube was placed at different depths in a polymethyl methacrylate phantom (with density and linear attenuation coefficient similar to those of normal tissue). The detector, placed in a motorized holder, was moved horizontally perpendicular to the line source. The counting rate was determined every 1 mm for positions less than 10 mm distal to the line source and every 5 mm for positions more than 10 mm distal to the line source. The spatial resolution of the detector was determined as full width at half maximum (FWHM) of the response profile. The measured counting rates were normalized in relation to the

zero-depth counting rate—determined when the detector was positioned centrally over the line source placed on top of the phantom—to allow estimations of isoresponse curves.

Efficiency was calculated as the ratio between the number of detected photons and the activity concentration in the part of the line source under the collimator aperture, with the contribution from side penetration subtracted.

Simulation of Intraoperative Measurements

Intraoperative measurements closely simulated the clinical situation. In our clinical studies each patient received about 300 MBq ^{111}In -[diethylenetriamine pentaacetic acid (DTPA)-D-Phe¹]-octreotide intravenously (4). ^{111}In activity concentration in muscle and connective tissue was about 0.2% of injected activity per kilogram (%IA/kg) 1 d after injection and 0.03 %IA/kg 5 d after injection (10), corresponding to approximately 590 and 90 kBq/kg, respectively. In the phantom, activity concentration was 5 to 20 times higher to shorten the acquisition time, but the results were then recalculated to the clinical situation described above.

Intraoperative measurements were simulated using spherical tumor phantoms (5–20 mm in diameter) in a body phantom. The tumor phantoms were made of agarose gel for the NaI(Tl) and CdTe detectors and of epoxy for the CsI(Tl) detector. The body phantoms were made of agarose gel (2 L, $180 \times 145 \times 80$ mm, NaI(Tl) and CdTe detectors) or of a 15-L water container ($395 \times 255 \times 145$ mm, CsI(Tl) detector). The gel was made of tap water and agarose (1% by weight) (11). Water and agarose were mixed, and the solution was boiled for 60 s in a microwave oven. ^{111}In was added to the solution, and it was stirred to obtain a homogeneous ^{111}In distribution. The agarose gel was poured into the body phantom or, for the tumor phantoms, into two half-sphere molds. The epoxy tumor phantoms were made by mixing epoxy resin and a small amount of ^{111}In solution and casting the mixture in the mold used for the gel. The gel tumor phantoms were placed in a hole in the body phantom so that the surface was smooth, and the epoxy tumor phantoms were fixed to plastic film stretched over the water phantom. To evaluate the ^{111}In activity concentration and homogeneity in the gel, the activity concentration in the tumor phantoms and in samples of the body phantom was measured in a 7.62-cm (3-in.) gamma counter (Wizard 1480; Wallac Oy, Turku, Finland).

T/Bgr varied between 3 and 80. Activity concentration was measured in the same way as spatial resolution. The detector was moved across the phantom, a response profile was determined and the ratio between the maximum and minimum counting rates, $C_{\text{max}}/C_{\text{min}}$, was calculated (at least 1000 counts were collected at every measuring point).

Statistical Analysis

To determine if any differences in counting rates between the tumor phantoms and the body phantom (background) were statistically significant, the SD of the differences was calculated as follows:

$$\sigma(\dot{C}_T - \dot{C}_{\text{Bgr}}) = \sqrt{\frac{C_T}{t_T^2} + \frac{C_{\text{Bgr}}}{t_{\text{Bgr}}^2}}$$

where \dot{C}_T is the counting rate with the detector held over the tumor phantom, \dot{C}_{Bgr} is the counting rate with the detector held over the body phantom, C_T is the number of counts from the tumor phantom, C_{Bgr} is the number of counts from the body phantom tissue and t_T and t_{Bgr} are the acquisition times for the tumor phantom and body phantom, respectively. Differences between C_T

and \dot{C}_{Bgr} exceeding two ($P < 0.05$) and three ($P < 0.01$) SDs of the difference were considered to be statistically significant.

RESULTS

Detectors

No sensitivity was lost at higher ^{111}In activities for the three detectors (1000 counts/s, corresponding to 0.1–0.2 MBq for ^{111}In). This finding was important for intraoperative measurements because it obviated corrections for dead-time losses.

Table 1 and Figure 2 show spatial resolution (FWHM) and efficiency, which were investigated with a line source at different depths in the phantom. The NaI(Tl) detector had the highest resolution (lowest FWHM) at all studied depths, and the CdTe detector had the lowest. Efficiency was highest for the CsI(Tl) detector, lower for the NaI(Tl) detector and lowest for the CdTe detector (Table 1). The lateral response for the NaI(Tl) detector was up to 15% of the response with the source in front of the collimator aperture; therefore, an extra 3 mm of lead shielding was placed around the detector to reduce radiation hitting the crystal from the side. This adjustment led to a lateral response of less than 2% of the response with the source in front of the collimator aperture. The CsI(Tl) detector had much worse problems with lateral shielding, as indicated by arrows in Figure 2B. The isoreponse curves for the detectors are presented in Figure 3. The NaI(Tl) detector has a pear-shaped response, and the resolution deteriorates with increasing depth. The CsI(Tl) detector has a broader and somewhat more shallow response, and the response of the CdTe detector is very shallow, with a broadness similar to that of the CsI(Tl) detector.

Simulation of Intraoperative Measurements

The homogeneity of the ^{111}In distribution in the agarose gel phantom was studied. Eighteen samples from various parts of the body phantom were measured in the gamma counter, and the coefficient of variation of the ^{111}In concentration (SD/mean) was 1.1%. The same measurement was performed for one of the tumor phantoms, which had been cut into seven pieces. The corresponding coefficient of variation was 1.4%.

The acquisition times required for obtaining statistically

significant elevated counting rates from the tumor phantoms were determined (Table 2 and Fig. 4). Figure 5 shows C_{max}/C_{min} for a tumor phantom of 16 mm as a function of T/Bgr. The NaI(Tl) detector gave the highest C_{max}/C_{min} and the steepest slopes (Fig. 5 and Table 3), but at a lower T/Bgr, a somewhat shorter acquisition time was required for the CsI(Tl) detector to obtain statistically significant elevations (Fig. 4).

Figure 6 shows the absolute number of background counts and the C_{max}/C_{min} needed to achieve two levels of statistical significance. For example, if 100 counts are obtained from the background, the T/Bgr has to be at least 1.3:1 to obtain a statistically significant difference between the tumor and the background ($P < 0.05$).

DISCUSSION

Intraoperative tumor detection using radiopharmaceuticals reveals small or hidden lesions and helps the surgeon to localize them. Two factors are important for good localization: the detector system (type of detector and measurement technique) and the signal from the tumors (depending on the T/Bgr, the choice of radionuclide and the acquisition time). The detector should be efficient and produce good resolution. Intraoperative detectors are small because they must fit into small anatomic areas; consequently, their efficiency is low. Lowered efficiency leads to a low number of detected counts and, accordingly, high statistical uncertainty, which can partly be compensated for by longer acquisition times. However, acquisition times longer than approximately 30 s will probably not be practical for pointwise measurements.

The physical characteristics of intraoperative detectors depend on the type and size of crystal, the collimation and the lateral shielding. The efficiency of a CsI(Tl) detector is somewhat higher than that of a NaI(Tl) detector of the same size. Photoelectric absorption for the photon energies of ^{111}In is higher in a CdTe detector than in a CsI(Tl) or NaI(Tl) detector of the same size. However, complete charge collection is difficult for a CdTe crystal thicker than 1 mm; a CdTe detector therefore has to be small. Differences in photoelectric absorption decrease with increasing energy, so the choice of crystal material is more critical at low energies (e.g., photon energy of approximately 30 keV using ^{125}I). However, resolution is inversely proportional to efficiency, and spatial resolution depends on collimation and lateral shielding. A narrow collimator aperture increases resolution (low FWHM), whereas lateral shielding that is too thin reduces resolution. The width of the isoreponse curve depends on the size of the aperture, with a small aperture resulting in a narrow curve. The depth of the curve depends on the thickness of the crystal, the length of the collimator and the adjustment of the energy window. If the energy window is set over only the low-energy photon peak of ^{111}In , Compton scattering of photons from the higher energy contributes more to the recorded counts.

The choice of detector also depends on the choice of radionuclide. For detecting highly energetic gamma radia-

TABLE 1
Spatial Resolution and Efficiency for ^{111}In at Different Depths in Phantom for Three Detector Systems

Depth (mm)	ScintiProbe		TecProbe1		TecProbe2	
	FWHM (mm)	Efficiency (%)	FWHM (mm)	Efficiency (%)	FWHM (mm)	Efficiency (%)
0	5.2	0.46	8.0	0.61	8.7	0.28
10	8.3		13		23	
20	11		18		35	

FWHM = Full width at half maximum.

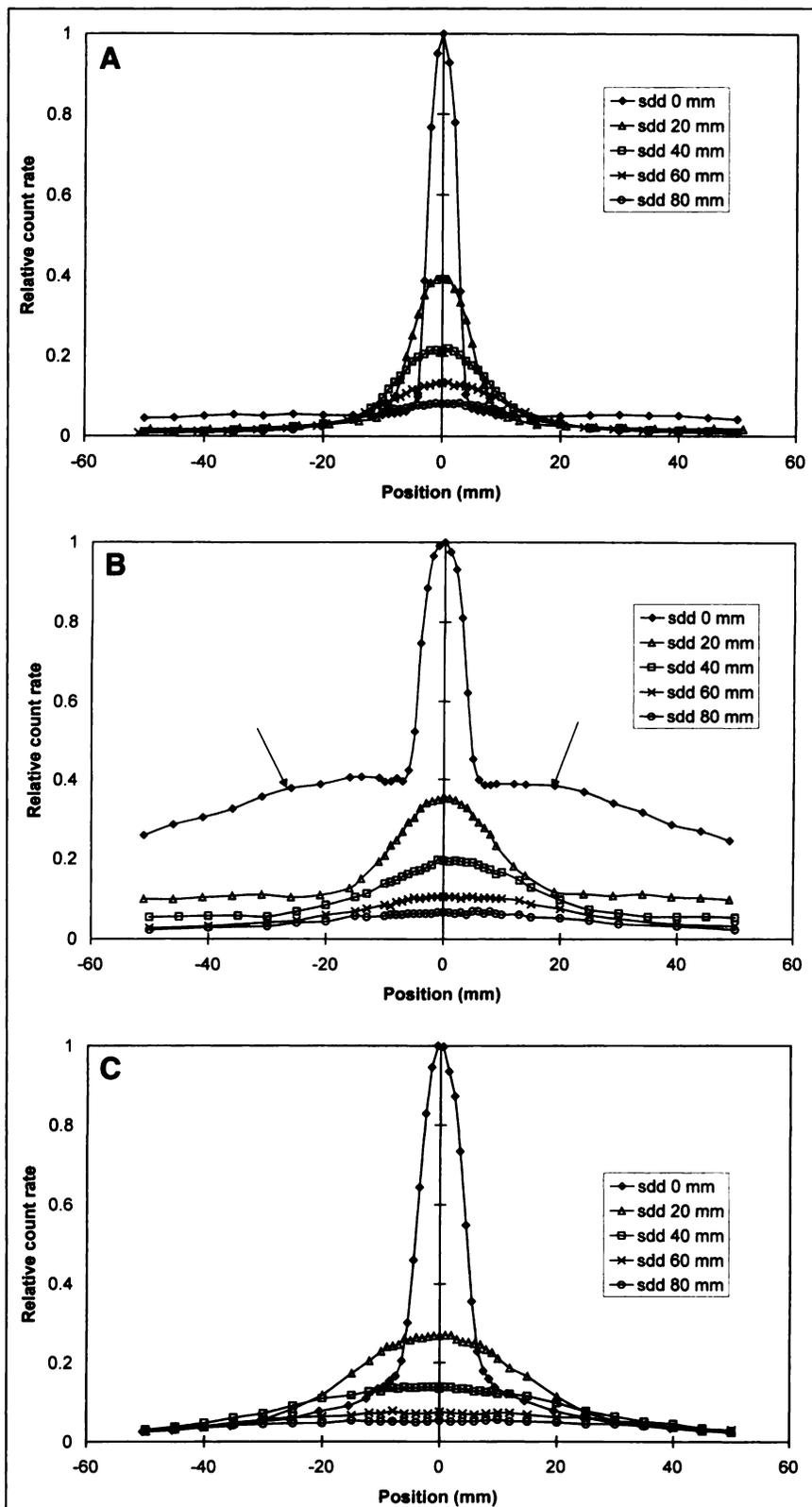


FIGURE 2. Response of NaI(Tl) (A), CsI(Tl) (B) and CdTe (C) detectors at various depths. Normalization was to 0-mm depth with detector positioned centrally over line source. Counting rate was measured every millimeter inside 10 mm from line source and every 5 mm outside 10 mm. sdd = source-to-detector distance (depth in "tissue").

tion from ^{111}In , a scintillation detector is best, but for detecting lower photon energy from, for example, ^{125}I , a CdTe semiconductor detector is preferred. The lower energy leads to greater photon interaction within the detector, thus increasing the efficiency, which can be kept relatively high

even for small CdTe detectors. Another choice is a beta-sensitive detector (12) and a radionuclide that emits beta particles. A beta-sensitive detector is more efficient than gamma detectors because of the shorter range of beta particles. However, this type of detector can detect tumors

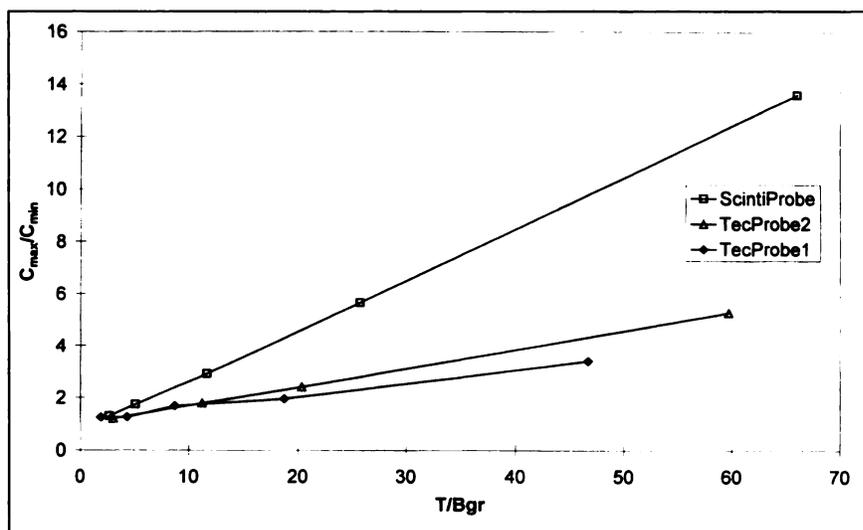


FIGURE 5. Measured ratio between maximum and minimum counting rates (C_{max}/C_{min}) versus tumor-to-background ratio (T/Bgr) for tumor diameter of 16 mm.

NaI(Tl) detector than for the other two detectors because of the better spatial resolution of the NaI(Tl) detector and the extra lateral shielding used during intraoperative simulation. The shielding decreases the background contribution by approximately 25%, resulting in increased C_{max}/C_{min} (3%–20%), decreased acquisition time to achieve statistical significance (3%–20%) and detection of smaller tumors. However, the better efficiency of the CsI(Tl) detector leads, in some cases, to a need for somewhat shorter acquisition times to obtain statistically significant differences between C_{max} and C_{min} . If the CsI(Tl) detector were equipped with same extra shielding, C_{max}/C_{min} would increase by approximately 10% (estimated from the side penetration, Fig. 2B), giving 10% shorter acquisition times. For example, to detect a 20-mm-diameter tumor in a 30-s acquisition time 5 d after ^{111}In -octreotide injection, the NaI(Tl) detector needs a T/Bgr of almost 4; the CsI(Tl) detector, less than 3; and the CdTe detector, more than 11 ($P = 0.05$). To detect a 10-mm-diameter tumor in a 20-s acquisition time 1 d after injection, the NaI(Tl) detector needs a T/Bgr of more than 5; the CsI(Tl) detector, less than 3; and the CdTe detector, approximately 17 ($P = 0.01$). We have found that the increase of T/Bgr over time becomes small a few hours after injection of

^{111}In -DTPA-octreotide. Because of physical decay and the low efficiency of intraoperative detectors, intraoperative measurement should occur as soon as possible after injection. The NaI(Tl) and CsI(Tl) detectors revealed smaller tumors, at the same T/Bgr , than did the NaI(Tl) detector evaluated by Waddington et al. (14), probably because their detector was equipped with a pinhole collimator and they placed the tumor phantom deeper (10 mm) in the body phantom. The CdTe detector used in this study revealed approximately the same-sized tumors as did the CdTe detectors studied by Waddington et al.

Statistical calculations can reveal significant differences between two measurements. However, in clinical situations the signal from normal tissue shows large intra- and interindividual variations for different radiopharmaceuticals and tumor types. Therefore, a low C_{max}/C_{min} cannot be regarded as representing a true difference despite statistically significant differences between C_{max} and C_{min} . As a result, definition of the lowest C_{max}/C_{min} detection level would be difficult although useful for rapid decision making during surgery. Various such detection levels have been proposed in the literature, e.g., 1.2:1 (15), 1.5:1 (16) and 2:1 (3,17,18). If the chosen detection level is too low, false-

TABLE 3
Relationship Between C_{max}/C_{min} and T/Bgr for Various Tumor Sizes and for Three Detectors

Tumor size (mm)	ScintiProbe	TecProbe1	TecProbe2
5	$C_{max}/C_{min} = 0.173T/Bgr + 0.951$	$C_{max}/C_{min} = 0.0562T/Bgr + 1.24$	$C_{max}/C_{min} = 0.102T/Bgr + 0.940$
10	$C_{max}/C_{min} = 0.156T/Bgr + 0.777$	$C_{max}/C_{min} = 0.0484T/Bgr + 1.14$	$C_{max}/C_{min} = 0.0720T/Bgr + 0.979$
16	$C_{max}/C_{min} = 0.0731T/Bgr + 0.946$	$C_{max}/C_{min} = 0.0114T/Bgr + 1.26$	$C_{max}/C_{min} = 0.0234T/Bgr + 1.05$
20	$C_{max}/C_{min} = 0.0174T/Bgr + 1.05$	$C_{max}/C_{min} = 0.0018T/Bgr + 1.15$	$C_{max}/C_{min} = 0.0031T/Bgr + 1.05$

C_{max} = maximum count rate; C_{min} = minimum count rate; T/Bgr = ratio of radionuclide in tumor to radionuclide in normal tissue.

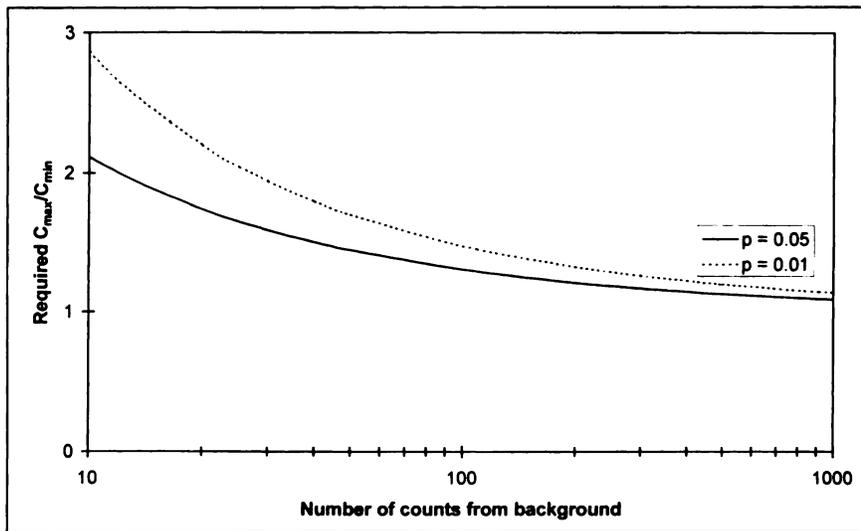


FIGURE 6. Relationship between maximum and minimum counting rates (C_{max}/C_{min}) and background counts at significance levels of 2 SDs, $P = 0.05$ (solid line), and 3 SDs, $P = 0.01$ (dotted line). Required acquisition time depends on background counting rate and can be estimated using these curves.

positive observations are possible, as are false-negative observations with too high a detection level. Badalament et al. (19) used three intervals, with true-positive observations separated from true-negative observations by an intermediate interval for suggestive lesions. Values in this intermediate interval can be reinvestigated with larger acquisition times, or tissue can be removed for safety reasons. Figure 6 illustrates the theoretic C_{max}/C_{min} requested to achieve differences between tumor and background counts at different levels of statistical significance. However, this graph is idealized, because in clinical situations the counting rate from tissues contributing to the background signal varies greatly.

CONCLUSION

Detector systems are designed for different applications. Of the three systems studied, the NaI(Tl) detector was best for tumor localization using ^{111}In -labeled radiopharmaceuticals because of its good spatial resolution and relatively high efficiency. Extra lateral shielding did not substantially improve the characteristics in this measurement situation but may, in some clinical situations, be necessary, e.g., for localization of a lymph node metastasis that is close to a parenchymatous organ, such as the liver, with a high, unspecific radionuclide concentration.

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