

## DETECTION EFFICIENCY OF GAMMA RAYS THROUGH FATTY TISSUE FOR THE EXTERNAL DETECTION OF SENTINEL LYMPH NODES IN BREAST CANCER DIAGNOSIS

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**ABSTRACT.** The ability to detect gamma ray passage through fatty tissue has biomedical applications in the diagnosis of metastatic breast cancer. The uptake of a  $^{99m}\text{Tc}$ -labeled sulfur colloid solution into the primary or sentinel lymph nodes (SLN) supplying the breast is one mechanism by which potential metastasis is being assessed. If  $\gamma$ -rays from the decaying  $^{99m}\text{Tc}$  could be measured externally, the invasiveness of this diagnostic procedure would be greatly reduced. Using a  $^{57}\text{Co}$  source, this experiment assessed  $\gamma$ -ray intensity attenuation through porcine fatty tissue for thickness up to 76 mm. The porcine tissue accounted for a significant attenuation of intensity, but further significant losses were seen due to the increase in distance between the detector and the  $^{57}\text{Co}$  source. It was found that porcine fatty tissue has  $\gamma$ -ray attenuation properties nearly identical to that of breast tissue. From the porcine tissue study and subsequent observation of three SLN biopsy procedures, it was found that detecting SLN's via external  $\gamma$ -ray detection is not self-sufficient. The use of a blue dye as an adjunct diagnostic tool is also necessary for the high success rate desired. While an external  $\gamma$ -ray detection method will not replace the traditional SLN biopsy procedure, it may serve as a pre-operative tool to limit the invasiveness of the procedure.

**Keywords:** Gamma-ray, breast cancer, sentinel lymph node, radiation detection

Breast cancer is the second leading cause of cancer related deaths in the U.S. among women (Ries et al. 2002). Because of breast cancer's high incidence and mortality rate, intense efforts have been made to enable early diagnosis and treatment. Traditionally, diagnostic tools were limited; and treatments such as radical mastectomies were rather extreme. The patient would not only lose the breast, the pectoralis muscles and axillary lymph nodes; but lymphedema, wound infection, pain, neurological deficits, and weakness were often associated with the invasiveness of the radical procedure (Cox et al. 1998). More recently, the use of sentinel lymph node (SLN) biopsies has become widely accepted in the diagnosis of metastatic breast cancer, due to the less invasive nature of the procedure (Burak et al. 2002). The technique is used to determine the lymphatic flow around tumors and to the regional lymph nodes, but is less invasive than more traditional methods resulting in less trauma to the patient. The determination of lymphatic flow from a tumor is done by assessment of the lymph nodes. Each tumor may

have from 1–7 primary, or sentinel, lymph nodes that receive circulating lymph from the tumor. Thus immunohistological assessment of the SLN for metastatic tumor cells will determine if metastasis has occurred. A tumor that is supplied by peri-tumor lymph vessels is more likely to have metastasis occur as the lymphatic system is the primary route for metastasis. (Albertini et al. 1996)

The SLN biopsy involves two distinct procedures. The first is an injection of a sulfur colloid solution radio-labeled with  $^{99m}\text{Tc}$ , a radioisotope with a half-life of 6 h which emits 142.7 KeV  $\gamma$ -rays (Firestone 1996). It is important that the gamma rays emitted are low energy as the procedure is diagnostic and the tissue should not be damaged from the radiation exposure. The  $^{99m}\text{Tc}$ -labeled sulfur colloid solution is injected around the tumor (or peri-nipple if the tumor is near the axillary basin) about 1–6 h prior to the procedure. Some time between the injection and operative procedure a lymphoscintigraphy, which detects gamma rays externally, is performed. The lymphoscintigraphy is done with a gam-

ma camera, which indicates to the physician the possible location of radioactive SLN's prior to the operative procedure. If a route for metastasis from the tumor to a primary lymph node exists,  $^{99m}\text{Tc}$  will collect in the SLN (Noguchi 2002).

In addition to the  $^{99m}\text{Tc}$  injection, the injection of an isosulfan blue dye circumferentially around the tumor is done just prior to the intra-operative procedure. While the  $^{99m}\text{Tc}$  method is necessary for accurately identifying the SLN's, it is not sufficient as a diagnostic tool. The use of the blue dye is an alternative means by which SLN(s) may be visually located, leading to increased success rates in diagnosing potential metastasis (Noguchi 2002). The blue dye method acts much like the  $^{99m}\text{Tc}$ , by enabling a visual determination of the lymph vessels and any nodes that supply the tumor region. Cox et al. (1998b) demonstrated the need for both methods in their biopsy of the 844 SLN's they harvested, in which 40.2% were positive for  $^{99m}\text{Tc}$  only, 32.2% were blue only, and 27.6% were both positive and blue. In another study Cox et al. (1998a) also found results comparable to those above.

The intra-operative procedure employs a gamma detector, several of which are on the market (e.g., the Navigator, US Surgical Corporation, Norwalk, Connecticut, and the Neoprobe, Neoprobe Corp., Dublin, Ohio). The surgeon initially probes externally with the gamma probe confirming potential spots of positive radiation seen on the films from the gamma camera. The surgeon will then incise along the axillary basin accessing potential nodes of interest. In some cases, the surgeon may excise the tumor to remove some of the background noise that can interfere with the sensitivity of the gamma detector. The surgeon will remove any blue staining or radioactive lymph nodes and immunohistological testing will occur to assess for presence of metastasis (Noguchi 2002).

Compared to total axillary lymph node dissection and radical mastectomies, the SLN biopsy has been successful in removing much of the trauma and many of the complications for the patient. There are still some complications, though, that warrant further refinement of the SLN biopsy procedure. The risk for infection, potential for lymphedema, and tissue trauma, as well as the cost due to time and facilities still leaves potential room for

improvement (Cox et al. 1998a). Additionally, the SLN biopsy presents no new information for some patients. While a radioactive or blue-dyed SLN is found in most patients, 5–8% will not present with a SLN. Of those patients in which no SLN was found, 1–15% did present with metastasis (Cox et al. 1998a; Cox et al. 1998b; Albertini et al. 1996).

The purpose of this experiment was to investigate the possibility of external detection of  $^{99m}\text{Tc}$  radioactivity, thus eliminating any unnecessary invasiveness of the procedure. First, the detection of gamma rays through sample tissue (porcine fat) was assessed to ensure that the fatty tissue is analogous to that of human breast tissue. Secondly, the ability to detect gamma rays with both increasing tissue thickness and increasing distance from the  $^{57}\text{Co}$  source was assessed. The  $\gamma$ -ray intensity was assessed at distances up to 76 mm of tissue.

## METHODS

Two trials were conducted for this experiment. The first trial was done to ensure that the tissue used in the experiment was representative of human breast tissue. The second trial measured not only the attenuation of gamma rays through determined breast tissue thickness (as in trial one), but also took into consideration the change in distance between the source of radiation and the detector, since radiation intensity decreases with increasing distance from the source (Knoll 1989). Both trials were run using a  $^{57}\text{Co}$  (1  $\mu\text{Curie}$ ) source and a three inch by three inch (76.2 mm by 76.2 mm) NaI detector.  $^{57}\text{Co}$  was used in this study since its primary  $\gamma$ -ray emission has an energy of 122.1 KeV (Firestone 1996), similar to that of  $^{99m}\text{Tc}$ , 142.7 KeV (Fig. 1), thus giving it similar attenuation properties – to within 5% – when passing through matter (ICRU 1989). The tissue used in each trial was freshly removed from the lumbar region of a pig. The slabs of fat/tissue were sliced into 2–4 mm thick pieces and large enough to cover the entire face of the detector. The  $^{57}\text{Co}$  source was attached to the bottom of a plastic container, into which increasing layers of fatty tissue were added. For each trial a baseline intensity reading was made through the plastic container, corresponding to zero thickness of tissue. Subsequent intensity readings were taken with increasing thickness of tissue (1–4 mm). Each measurement was taken over a 10

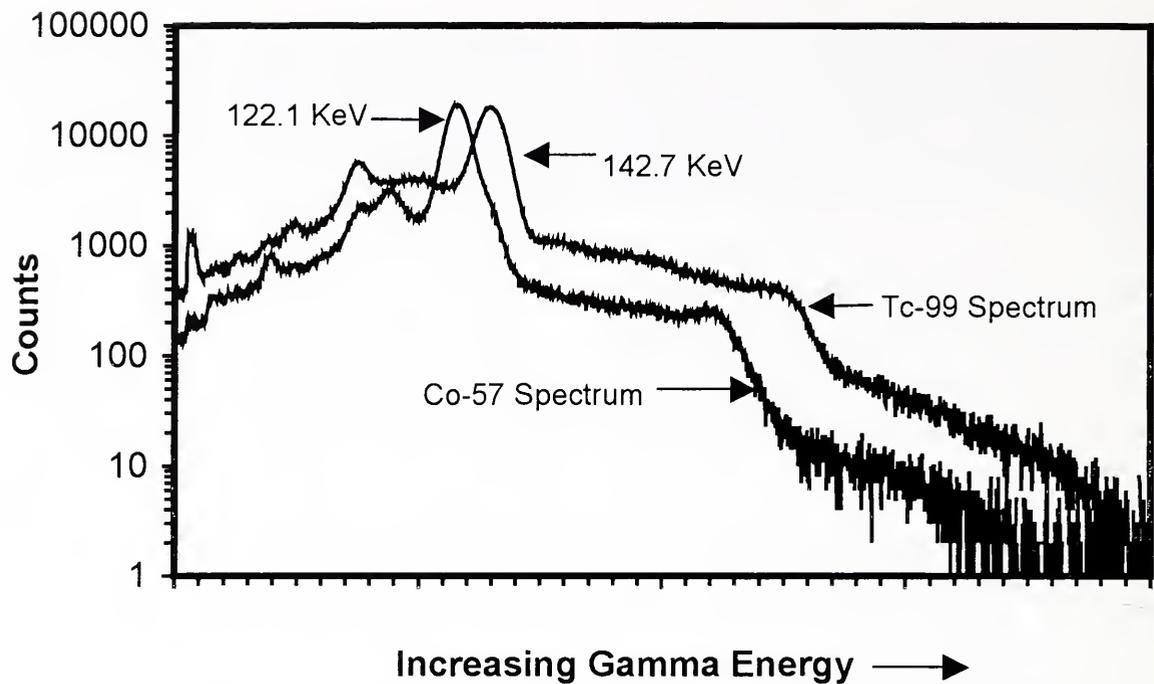


Figure 1.—Gamma ray spectrum for  $^{57}\text{Co}$  and  $^{99\text{m}}\text{Tc}$ . Shown are the characteristic 122.1 and 142.7 KeV gamma ray peaks for  $^{57}\text{Co}$  and  $^{99\text{m}}\text{Tc}$ , respectively. The 122.1 KeV gamma ray from  $^{57}\text{Co}$  was used as a substitute for  $^{99\text{m}}\text{Tc}$  to measure the attenuation properties of porcine tissue. The number of counts in the 122.1 KeV peak was monitored as a function of increasing tissue thickness.

min period during which gamma rays detected were recorded with an Ortec Trump Multi-channel Analyzer (Fig. 2). The  $\gamma$ -ray intensity was determined by integrating counts under the 122.1 KeV  $\gamma$ -ray peak.

**Trial 1.**—In Trial 1, the gamma ray detector was fixed at 82 mm from the plastic container with the  $^{57}\text{Co}$  source attached to the bottom of the container. A baseline reading was taken, corresponding to zero tissue thickness, followed by sequential additions of tissue slices with measured thickness. The stack of tissue was periodically measured to ensure that actual thickness present was the sum total of individual slices used.

**Trial 2.**—In Trial 2, the procedure and set

up was the same as Trial 1, except for the positioning of the  $\gamma$ -ray detector. The detector was not fixed, but placed directly upon the tissue, as would be the case in a surgical procedure. As additional thickness of porcine tissue was added, the detector's position relative to the source changed, as it would with increasing thickness of breast tissue during a SLN biopsy procedure.

## RESULTS

The attenuation of  $\gamma$ -rays through solid materials is well known through the relation,  $I = I_0 e^{-c(\mu/e)x}$ , where  $I$  is the intensity of  $\gamma$ -radiation passing through a thickness,  $x$ , of material.  $I_0$  is the incident (baseline) radiation of

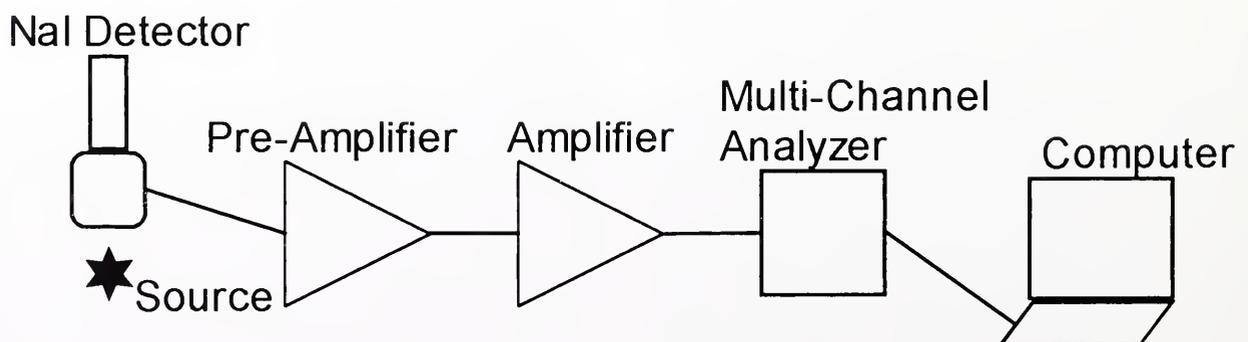


Figure 2.—Electronics diagram for the detection of  $^{57}\text{Co}$   $\gamma$ -rays. Once detected in the NaI crystal, the gamma ray signals are amplified and sent to a multi-channel analyzer which sorts the signals by energy and histograms them for analysis by computer.

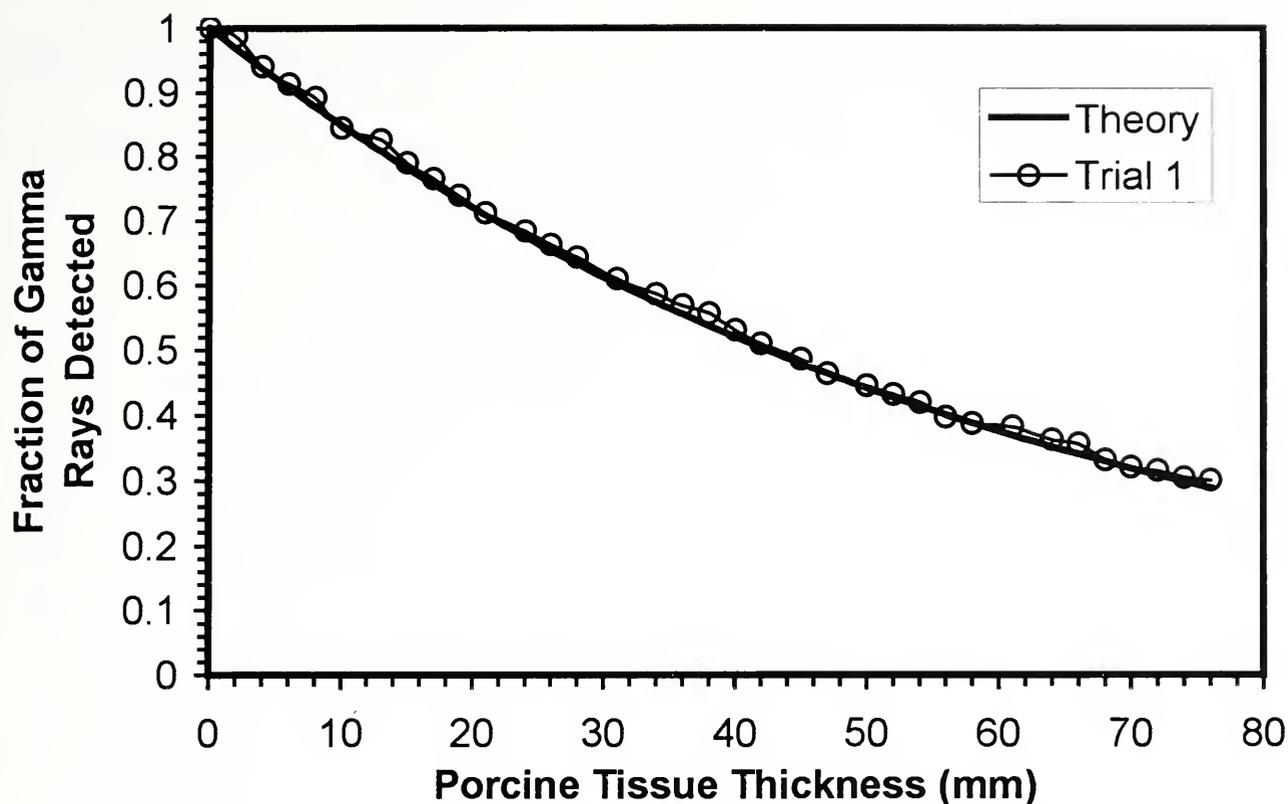


Figure 3.— $^{57}\text{Co}$  (122 KeV) gamma ray attenuation as a function of porcine tissue thickness at a fixed detector distance. Trial 1 data exhibits the exponential decay in gamma intensity as expected from theoretical calculations.

the source (Friedlander 1981). The coefficients  $\mu$  and  $\rho$  are the attenuation coefficients and density of the material studied. For breast tissue, the density is known to have a value of  $1.02 \text{ g/cm}^3$  and  $\mu/\rho$  is  $0.1602 \text{ cm}^2/\text{g}$  (ICRU 1989). Since  $\rho$  and  $\mu$  are known for breast tissue, the expected intensities for increasing thickness could be predicted. Figure 3 shows the data and predicted intensities normalized to a value of 1.0. From the data, it was concluded the porcine tissue used to model breast tissue was representative of the attenuation properties of breast tissue.

The results of Trial 2 are presented in the same fashion as in Trial 1 and are plotted in Fig. 4. The loss of intensity does not exhibit the same behavior as that in Trial 1. The additional loss of intensity observed is due to the change in distance between the  $^{57}\text{Co}$  source and the detector. As expected, the loss of intensity indicates that the greater the separation, the greater the loss of intensity due to geometrical considerations (Knoll 1989). At a distance of 25 mm from the detector, an additional 18% loss in intensity is observed (relative to a fixed detector measurement) and in-

creasing intensity losses were recorded for increasing tissue thickness.

#### DISCUSSION

It was found that porcine fatty tissue is representative of human breast tissue. At 26 mm breast tissue attenuates 122.1 KeV  $\gamma$ -rays 34.6%, while porcine tissue had a  $\gamma$ -ray intensity attenuation of 33.8%. This has implications in future studies assessing passage of  $\gamma$ -rays through breast tissue, since porcine fatty tissue may substitute for human breast tissue. There are obvious cost and ethical issues that can be avoided with use of porcine tissue versus human tissue.

Secondly, many factors affect the attenuation of  $\gamma$ -ray intensity and efficiency of detection when measuring  $\gamma$ -rays in SLN biopsies. Source half-life, tissue attenuation, geometry, distance, detector efficiency, and infiltration of  $^{99\text{m}}\text{Tc}$  into the lymphatic system all play a significant role in limiting the efficiency of detecting  $\gamma$ -rays.

Since the  $^{57}\text{Co}$  source used in this study has a half-life of 271 days (Firestone 1996), no appreciable loss of intensity due to decay oc-

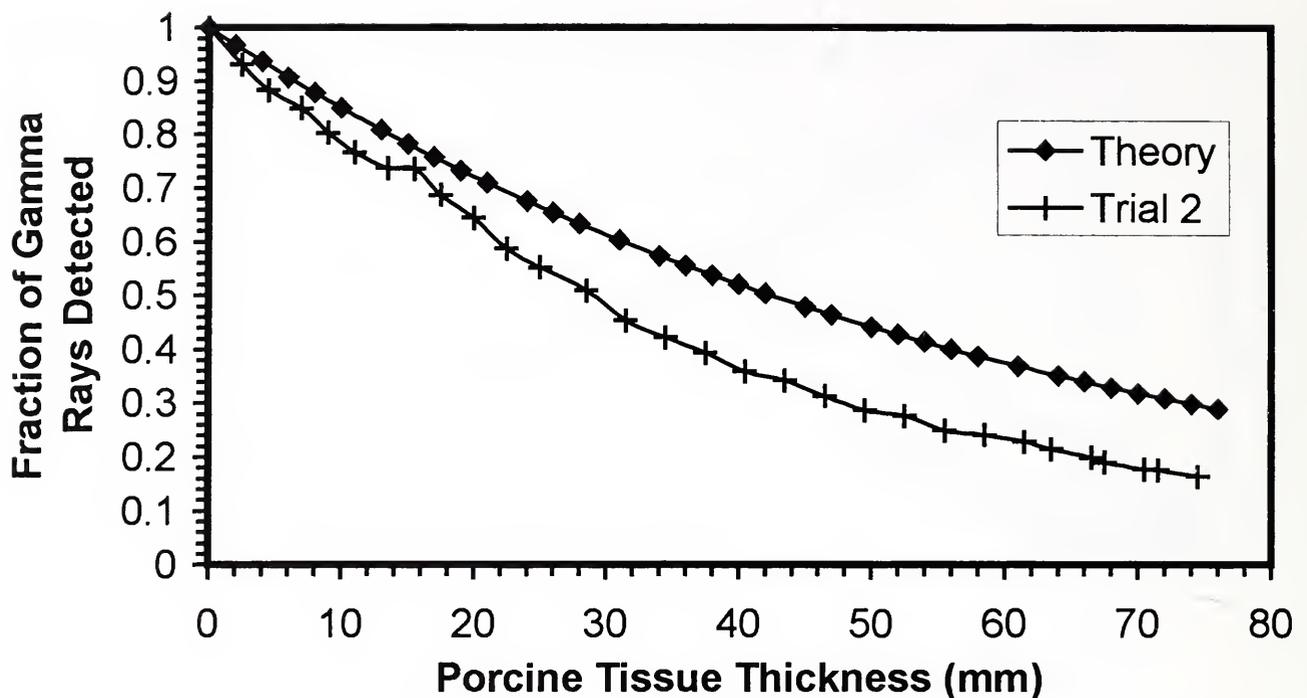


Figure 4.— $^{57}\text{Co}$  (122 KeV) gamma ray attenuation as a function of porcine tissue thickness with increasing detector distance. Trial 2 data exhibits an additional decrease in gamma ray intensity (relative to Trial 1) due to increasing source-to-detector distance.

curred during the course of the experimentation. In contrast, the  $^{99\text{m}}\text{Tc}$  source used in SLN biopsies has a half-life of only 6 h. Therefore a significant loss of intensity will be seen over a several hour period, which could become a significant problem if detection were to occur beyond a certain time period. It is important to note the source strength may differ in different protocols. Radioactive doses ranging from 0.2 mCi to 1.0 mCi have been used in SLN studies (Noguchi 2002).

Geometric factors also play a role in  $\gamma$ -ray intensity measurement. Radioactive sources emit  $\gamma$ -rays isotropically and not in a preferential direction. Due to the detector's location on one side of the source and the isotropic  $\gamma$ -ray emission, there is at least a 50% loss in measurable intensity. Further decreases in intensity are seen as the distance is increased between the source and detector. The detector used in this experiment demonstrated an additional 18% loss in intensity over and above the expected attenuation due to tissue alone at 25 mm from the source. The detector used in this study is relatively large, providing for increased surface area for detection. The actual SLN biopsy procedure utilizes a much smaller probe of 14–19 mm in diameter, greatly reducing the number of incident  $\gamma$ -rays that can be detected.

In addition to the loss of intensity due to geometry, there is also a decrease in the recorded intensity of  $\gamma$ -rays due to intrinsic efficiency of the detector. It is known that NaI detectors have a detection efficiency of 10%, as it takes an average of 10  $\gamma$ -rays to produce one recorded event (Friedlander 1981). This detector efficiency provides for a significant loss of detectable events. Further loss is seen by the intercalation of the  $^{99\text{m}}\text{Tc}$ -sulfur colloid within the breast tissue and lymphatic system. It has been consistently shown that only 1–5% of the  $^{99\text{m}}\text{Tc}$ -sulfur colloid actually reaches any given SLN (Cox et al. 1998a; Reintgen et al. 2000). Since only a small amount of radioactivity reaches a SLN, external detection becomes difficult.

To demonstrate the effects of the above-mentioned factors on the external detection of  $\gamma$ -rays for breast cancer diagnosis, assume a 1 mCi injection of  $^{99\text{m}}\text{Tc}$  is administered to the patient. Table 1 illustrates the resulting  $\gamma$ -ray intensity in the detector assuming an operative procedure 6 h following the injection at a detector distance of 25 mm. As evident in Table 1, a small amount of gamma radiation is detectable during a SLN procedure if detection is attempted externally—illustrating the need for an internal operative procedure to get as close to the SLN's as possible.

Table 1.—Resulting  $\gamma$ -ray intensity in detector due to various detection factors, assuming an initial injection of 1 mCi in patient.

Initial dose	Detection factor	Reduction factor
1 mCi*	Tissue attenuation for 25 mm of tissue	0.67
	Half-life of $^{99m}\text{Tc}$ (6 hours)	0.50
	Geometric efficiency	0.50
	Detector to source 25 mm	0.82
	Infiltration to SLN	0.01
	Resulting $\gamma$ -ray intensity in detector =	0.0014 mCi

Our observations of three SLN procedures (T. Goedde pers. comm.) made evident additional problems for external detection of the gamma radiation of interest. As the  $^{99m}\text{Tc}$ -sulfur colloid intercalates through the breast, a high radioactivity area remains near the injection site. Gamma rays originating from this high-activity area provide for subsequent background noise that is detected as real, recorded  $\gamma$ -rays, but not indicative of SLN's. Since low  $\gamma$ -ray levels are present in a SLN, as demonstrated above, this higher level noise can mask  $\gamma$ -radiation from a SLN of interest. Subsequently, uniquely identifying a SLN in the midst of background noise becomes difficult when attempted externally.

As has been shown, external  $\gamma$ -ray intensity measurement becomes increasingly difficult due to a variety of factors. Controlling the time-dependent variation in the activity levels is generally accomplished by performing the procedure 2–6 h following the injection; decreasing this interval will allow for increased intensity values. Since much of the detection difficulty is due to proximity of the detector to the source, it is necessary to perform the procedure from an internal *versus* external perspective to get the detector as close to the source as possible. The operative approach has additional justification as well.

The incorporation of an isosulfan blue dye is done concurrently to assess lymph vessels and SLN's. The fact that not all SLN's demonstrate radioactivity has been shown in multiple studies. Cox et al. (1998a) found that 30% of the 1348 SLN's were found visually with use of the blue dye and not radioactive. In a separate study, Cox et al. (1998b) found 4.6% of 844 SLN's were not radioactive, but presented with blue dye.

## ACKNOWLEDGMENTS

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