

Performance study of a miniature gamma ray scintillation *vivo* probe for tumor localization

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We have developed a miniature γ -ray endoscopic probe consisting of dual BGO detector probes for tumor detection inside the body cavities. The dual detector system was coupled with random coincidence to decrease the distant background radiation and to improve its spatial resolution for tumor localization. *Method:* The performance of the probe was investigated with a point source and a water phantom. A solution of positron emitting ^{18}F isotope was used as the source. Clinical trials of the probe were done to localize tumors on the skin surface of four subjects carrying tumors close to the body surfaces, into whom ^{67}Ga -citrate and ^{18}F -FDG radiopharmaceuticals were injected. *Results:* Measurements indicated that the spatial resolution of the dual detector probes is around 1.5 times better than the single detector probe, and both single and dual detector endoscopic probe systems are capable of localizing a tumor on a large photon background. *Conclusion:* The endoscopic probe may be easier to insert inside body cavities due to the small crystal size and the flexible light guides. A single detector probe with higher sensitivity may be useful in searching for tumors over a wide intracavity area but a dual detector probe can be used for precise tumor localization. The detector probe may also be suitable for intraoperative observation.

Key words: dual probe, random coincidence technique, scintigraphy, body cavity

INTRODUCTION

IT IS IMPORTANT to detect invisibly small and deeply located tumors inside the body cavities, since early detection of small tumors can increase the chance of the patient's survival through adequate treatment at an early stage. The conventional widely used method to investigate the body cavities is endoscopy but if the invisible tumor is situated inside the wall, it is difficult to detect it with the naked eye. Tumor seeking radio-tracers are in

general used for small and deeply located tumor detection, but the conventional external imaging system has poor sensitivity in localizing soft tissue tumors smaller than 2 cm in diameter, or located deep inside of the body¹ due to background activity in normal tissue and gamma ray attenuation through body tissue.^{2,3} A number of investigators³⁻⁵ have reported the possibility of improving tumor detection sensitivity by using a small radiation detector or 'probe' that can be placed in close contact to a tumor during surgery or endoscopy. The difficulty with this procedure is to determine whether an increased count rate is caused by a small tumor near the detector or a change in the distant background radiation level. To overcome this difficulty dual probes consisting of a central detector surrounded by another detector for background subtraction has been developed by some

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authors.^{2,6} As another approach, Saffer et al.⁷ has developed a surgical probe for imaging without a collimator, by using a γ - γ coincidence technique. A photon emitted from a point isotropic source has the probability of reaching a detector in accordance with the inverse square law for the distance between source and detector, and the coincidence detection requires that two photons from the same source reach the detector array, and this probability obeys the inverse 4th power law.⁷ Thus the coincidence count events from dual probes decrease more rapidly with the distance from the source and very low sensitivity to distant sources in comparison to the single detector probe. In our preliminary study, Watabe et al.⁸ developed a miniature γ -ray endoscopic probe consisting of dual detectors coupled with a random coincidence technique to decrease the distant background level. This probe has dual detectors each 6 mm in diameter by 6 mm thick BGO ($\text{Bi}_4\text{Ge}_3\text{O}_{12}$) scintillator coupled to optical fibers (i.e. dimension of the dual probes is 12 mm \times 6 mm). This probe is designed to be inserted into a body cavity to detect invisibly small or deeply located tumors inside the body cavity wall.

In our current study we further developed a γ -ray probe having a smaller crystal 8 mm in diameter and 3 mm in length and a more flexible fiber for easier insertion. This improvement is advantageous for small tumor detection near the body cavity wall since the probe must reach to within a few centimeters of the tumor.³

Before the clinical application we investigated some basic properties of our new smaller probe such as sensitivity and spatial resolution. Point source experiments and phantom experiments were done with the 511 keV gamma rays of ^{18}F -FDG (Fluoro-Deoxy-Glucose) which are widely used in PET (Positron Emission Tomography) studies. The aim of the phantom experiment is to detect a small tumor in a water phantom including the ^{18}F radioactivity which represents the background from the normal tissue. As the probe is not yet approved for insertion into human body cavities for clinical use, clinical trials to observe the performance of the probe in practical situations were done on the skin surfaces of four subjects who had the tumors close to the body surfaces.

MATERIALS AND METHODS

Detector System

The scintillator probe of the dual detectors consists of two semicircular BGO ($\text{Bi}_4\text{Ge}_3\text{O}_{12}$) detectors each 4 mm in radius \times 3 mm in length which are connected by means of two 90 cm long optical fibers of silicon dioxide to two photomultipliers (R647-01 Hamamatsu Photonics Co. Ltd.). The two detectors and fibers are tightly set in parallel and are covered with 0.2 mm thick aluminum which is coated with thin black plastic tape to block visible light. The outer diameter of the dual probes was made 10 mm, considering the need to insert them into

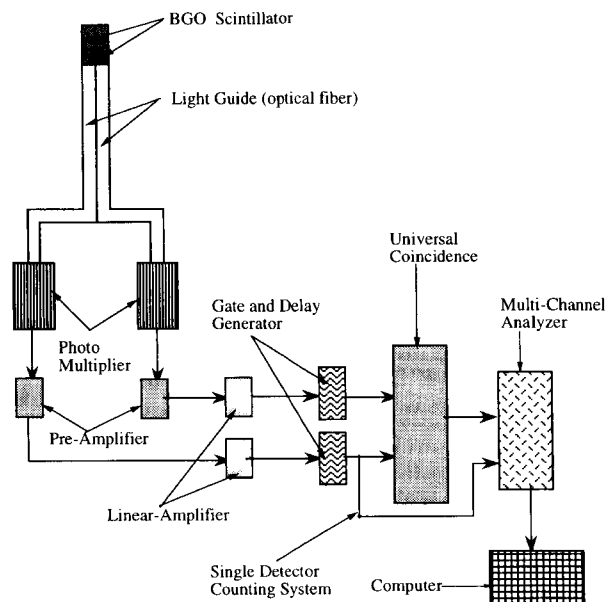


Fig. 1 Circuit diagram of the single and dual detector systems.

body cavities. The circuit diagrams of both single and dual probes are shown in Fig. 1. Signals from the photomultipliers are fed into the linear amplifiers (ORTEC 572, Seiko EG & G Co. Ltd.) through pre-amplifiers (HAMAMATSU C1053-03). The signals from the linear amplifiers are fed to Gate and Delay Generators (GDG, ORTEC 416A). Output pulses from the GDGs are directly connected to the MCS (Multi-Channel Scaling mode) of a Multi-Channel Analyzer (NAIG E-564, Toshiba Electric Co. Ltd.), for the single probe counting system, while for the dual probe counting system, output pulses from the GDGs are used as gate pulses (pulse width is 1.2 μsec , delay time is 4 μsec) to coincide with output pulses from the other detector probe in the universal coincidence (ORTEC 418A). Signals from the coincidence are fed to the MCS. A discriminator was installed in the MCS to cut off the electric noise pulses and the integrated numbers of output pulses were counted with higher efficiency.⁸ Recorded data are stored and processed in an NEC PC-9801 computer (Nippon Electric Co. Ltd.), for both single and dual probes.

In the random coincidence technique the probe responds when two independent photons from the source are incident on the two detectors within a certain time. The coincidence gate time used in our experiments is 1.2 μsec which was optimized for best counting statistics and validated⁸ with the MCNP Monte Carlo code.⁹ We selected the BGO crystal for its higher efficiency in detecting of gamma rays owing to its high density of 7.13 g/cm^3 and high atomic number of 59.9, despite lower light output.

Experiments

The point source experiments and the phantom experiments were done to observe the spatial resolutions, sensi-

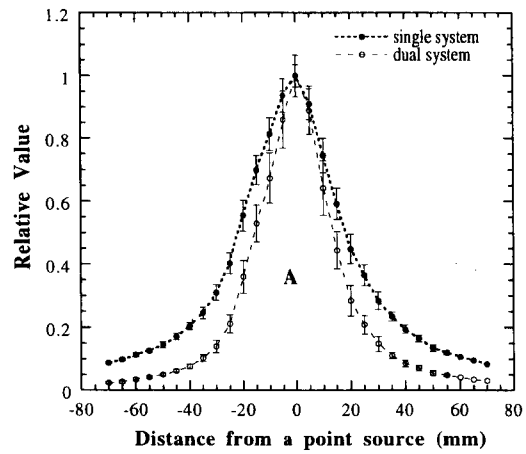
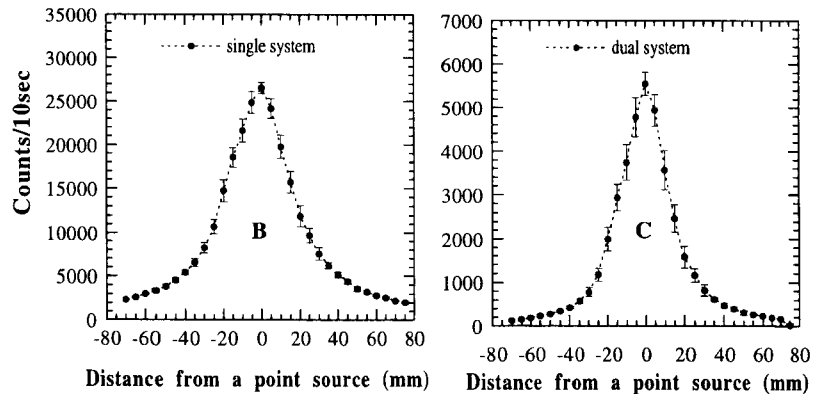


Fig. 2 Point spread functions of the single and dual probes, obtained from a point source experiment. (A) Relative value of the count rates (counts/10 sec) for both single and dual detector systems normalized to be 1 at 0 mm, the source center where the source is just above the detector surface. (B) count rates (counts/10 sec) of single detector system as a function of distance from a ^{18}F point source. (C) count rates (counts/10 sec) of dual detector system as a function of distance from a ^{18}F point source.



tivities and characteristics for tumor localization of the single and dual detector probes. In these experiments, we used a solution of positron emitting ^{18}F and measured the 511 keV annihilation photons. Among the radiopharmaceuticals used in clinical tumor diagnostics, the 511 keV photons from a ^{18}F -FDG tumor seeker are most penetrating through a body, and may give the highest background from the normal tissues surrounding a tumor. The characteristics of the probes obtained from the experiments with ^{18}F will give the poorest data.

(1) Point source experiment

The spatial resolutions and sensitivities of the single and dual probes were examined by using a point source. A cylindrical plastic vessel 2.5 mm in diameter \times 6 mm in high with a 3 mm thick wall was used as a point source for 9.73 MBq ^{18}F solution. To obtain the spatial resolution, that is, the point spread function, the probe was scanned at a distance of 0.5 cm from the bottom surface of the source vessel with its axis normal to the scanning line. The scanning region was ± 7 cm.

Another experiment was carried out to investigate the directional dependence of sensitivities of the single and dual probes. A ^{18}F point source of 69.8 MBq was used in this experiment. The source was rotated at 10 degree intervals up to 360 degrees around the axis of the probe with the distance between the source and probe from

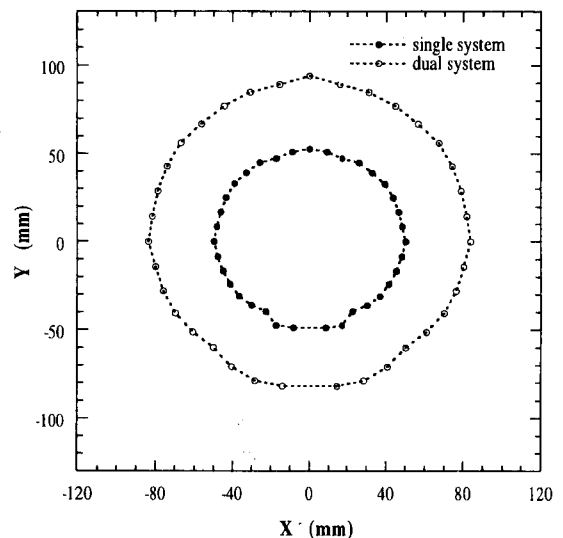


Fig. 3 10% iso-sensitivity contours, FWTM (Full Width at Tenth Maximum), of the single and dual probes respectively.

1.5 cm up to 10.5 cm. In these point source experiments, counts for 10 sec were recorded in the MCS (Multi-Channel Scaling) mode at each position.

(2) Phantom experiment

After administering the radiopharmaceutical to a subject, the radioactivity is distributed in normal tissues as well as

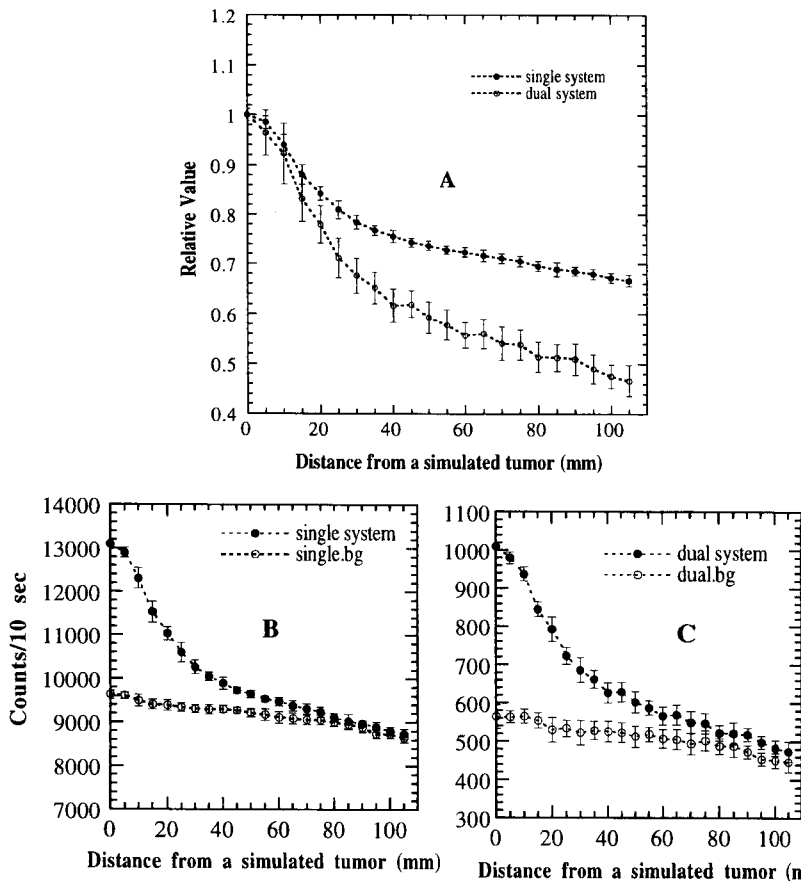


Fig. 4 Count rate variation of the single and dual detector probes in phantom experiment in the case of tumor to background activity ratio of 10:1. (A) Relative count rates of the single and dual detector systems normalized to be 1 at the tumor source. (B) count rates of the single detector system from a simulated tumor source with background and only the background count rates. (C) count rates of the dual detector system from a simulated tumor source with background and only the background count.

in tumor sites, which makes tumor detection very difficult due to the high background level. To examine the detector performance under this condition we carried out the water phantom experiment. The phantom is a 34.1 cm × 24.1 cm × 20 cm acrylic box with a 0.6 cm thick wall. On the bottom surface inside the central position of the phantom, we placed a cylindrical glass vessel 4 mm in diameter by 1 cm high which contained a water solution of ^{18}F simulating a tumor. The water phantom was partially filled with a water solution of ^{18}F which simulated normal tissue surrounding a tumor. The ratio of the ^{18}F radioactivity of the vessel (tumor) to that of the phantom (normal tissue) was set to be 10:1, since it is reported that the accumulation of ^{18}F -FDG in a certain tumor is 8 times higher than that in normal tissue.¹⁰ The detector probe was scanned in contact with the bottom surface of the phantom at intervals of 5 mm and at every interval counts for 10 sec were recorded in the MCS mode. The experiment was repeated without the source vessel (tumor) in order to clarify the difference between tumor counts and background counts.

(3) Clinical application on body surfaces

As clinical trials, five studies for four patients were conducted with the single and dual probes. They were patients with confirmed or suspected malignant tumors which were located close to their body surfaces. The probe examinations were conducted after the ^{67}Ga -citrate

scintigraphy and the ^{18}F -FDG PET study. The scintigraphy was performed at the Department of Clinical Oncology, Institute of Aging and Cancer, Tohoku University and the PET scanning was performed at the Cyclotron and Radioisotope Center, Tohoku University, according to the standard protocol of those institutes. The doses injected were 180 to 200 MBq of ^{67}Ga -citrate and 180 MBq of ^{18}F -FDG. Anterior and posterior projections of ^{67}Ga -citrate scintigraphy were taken after 48 hours. A post injection ^{18}F -FDG PET study was done at 1 hr. All the studies were done after obtaining informed consent of the patients.

Probe scanning was done in different directions on the body surfaces of the patients at intervals of 5 mm where tumors were confirmed or suspected, and at each position counts for 10 sec were recorded in the MCS mode. The clinical performances of both single and dual probes for tumor detection were investigated by comparing with the scintigrams and PET images.

RESULTS

Because there was some loss in the light guide due to the difference between the refraction indexes of the BGO and the fiber, the energy resolution of the photo-peak was very poor, and we therefore counted all pulses over the noise discrimination level in the pulse height spectra to get higher efficiency.

Table 1 Outline of the clinical tests for four patients

Study No. (Initial name, sex and age)	Scintigraphy		Initial diagnosis	Final diagnosis	Volume of the tumor
	⁶⁷ Ga-citrate	¹⁸ F-FDG			
1. (KS, F37)	+		Cervical and axillary lymph nodes	Malignant lymphoma	10 cm × 7 cm × 6 cm
2. (SO, M50)	+		Humerus and clavicular metastases	Squamous cell carcinoma metastases	11 cm × 6 cm × 5 cm
3. (KO, F64)	+		Subcutaneous tumor	Squamous cell carcinoma metastases	6 cm × 7 cm × 5 cm
4. (CI, M81)	+		Subcutaneous tumor	Small cell carcinoma metastases	3 cm × 3 cm × 1.5 cm
5. (SO, M50)		+	Humerus and clavicular metastases	Squamous cell carcinoma metastases	3 cm × 5 cm × 5 cm

(F: Female, M: male)

(1) Point source experiments

In the point source experiments we measured the spatial resolutions and sensitivities of the single and the dual probes for tumor localization. Real count rates of the single and dual probes and the relative values normalized to be 1 at 0 mm, the source center, are shown in Fig. 2. As seen in the figure, the sensitivity of the single probe is five times higher than that of the dual probe, but the spatial resolution, that is, FWHM (Full Width at Half Maximum) of the single probe is 4.4 cm and 3 cm for the dual probe. Figure 3 represents the 10% iso-sensitivity contours of the single and dual probes around a point source. The 10% sensitivity, that is, FWTM (Full Width at Tenth Maximum), represents the 10% counts of the maximum counts of the single and dual probes at the minimum distance between source and probe (1.5 cm).

As shown in Fig. 3, both probes have almost isotropic sensitivities, and the spatial resolutions, FWTM of the single and dual probes, are 16 cm and 8 cm, respectively.

(2) Phantom experiment

The single and dual probe counts from a simulated tumor with background and only from the background are given in Fig. 4 as count rates (counts per 10 sec) and the relative values normalized to be 1 at 0 mm, where the detector probe was exactly on the source vessel. The results of the tumor localization of the probe are absolutely good for higher accumulation of radio-tracer in the tumor, and the dual probe provides better tumor localization than the single probe, although the single probe sensitivity is 5 to 15 times higher than the dual probe sensitivity, as expected from the point source experiment. Even at this low tumor accumulation, 10 times higher than for normal tissue, the tumor is easily detectable with the probe.

(3) Clinical application on a body surface

Several types of tumor patients were investigated with our scintillation probe as clinical application trials, together with the ⁶⁷Ga-citrate scintigraphy and the ¹⁸F-FDG PET

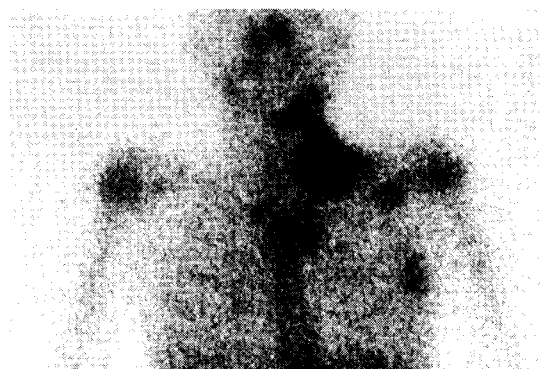


Fig. 5A ⁶⁷Ga-scintigraphy for cervical and axillary lymph nodes tumor.

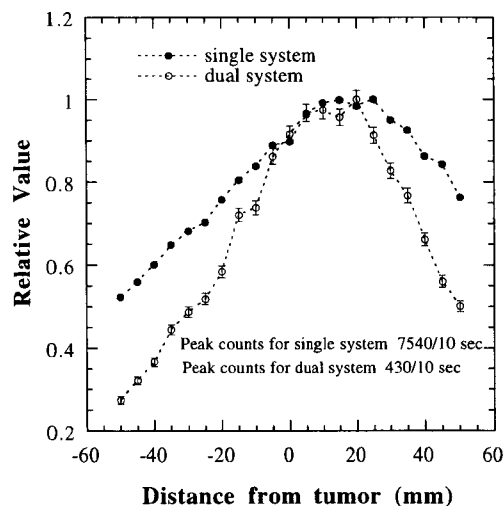


Fig. 5B Relative variation of scanning results of the single and dual probe on the tumor and normalized to be 1 at the peak counts (around the center of the tumor). Peak count/rate for the single and dual detector systems are also shown in the figure.

studies. The characteristics of the disease, the diagnosis and the volume (from the CT image) of the tumor are shown in Table 1. Five studies were done for four patients

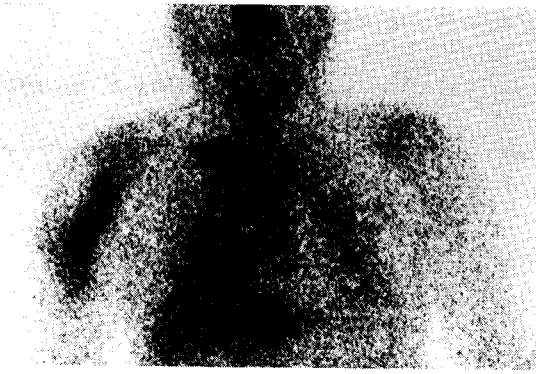


Fig. 6A ^{67}Ga -scintigraphy for a case of humerus and clavicular metastases.

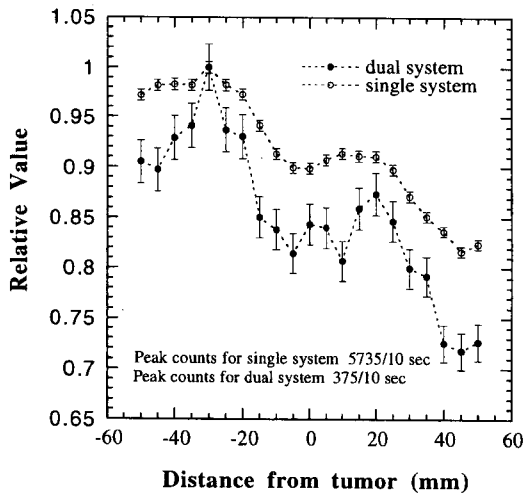


Fig. 6B Relative variation of scanning results of the single and dual probe on the tumor and normalized to be 1 at the peak counts. Peak count/rate for the single and dual detector systems are also shown in the figure.

as shown in Table 1. The No. 2 and No. 5 studies were performed in the same patient for right humerus and right clavicular metastases, respectively, which are shown in Table 1. In all studies the results obtained with the scintillation probe conducted after each scintigraphy display the precise graphic tumor structures depending on radio-tracer accumulation. These results for the single and dual probes are given below as relative values which normalized the maximum count rates to be 1 for clear presentation of tumor localization, together with the standard errors of counting statistics.

In No. 1 study, the target lesion is cervical and axillary lymph nodes metastases from the carcinoma on the left neck shown in Fig. 5A. Probe measurement by scanning along the line above the tumor also ensured the localization of the tumors by detecting a higher accumulation of ^{67}Ga -citrate in the tumor than in the surrounding normal tissue, as seen in Fig. 5B. Although the existence of several lymph node tumors has been visualized in the CT image, in the probe scanning result two peaks are found close to each other, one at around 10 mm and the other is

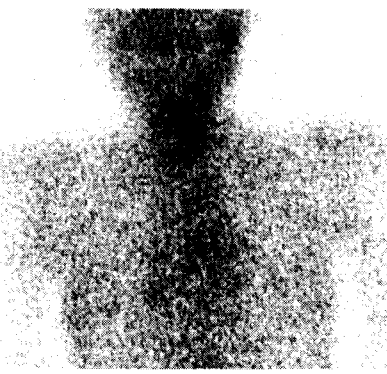


Fig. 7A ^{67}Ga -scintigraphy for a case of subcutaneous tumor.

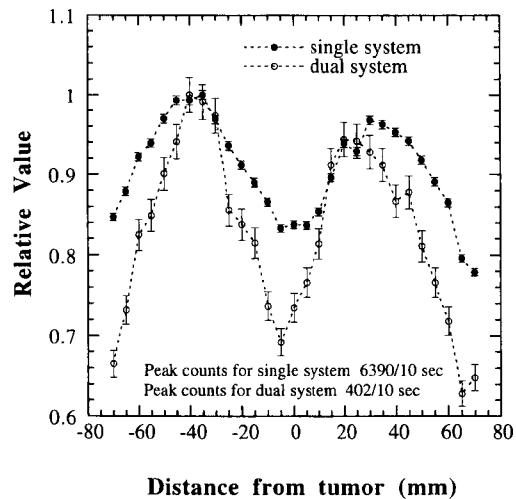


Fig. 7B Relative variation of scanning results of the single and dual probe on the tumor and normalized to be 1 at the peak counts. Peak count/rate for the single and dual detector systems are also shown in the figure.

at 20 mm, a little more clearly when observed with the dual detector system. Since the intervals between the nodules are much smaller than the spatial resolution (about 1 cm for the dual probe), the probe could not differentiate the nodules.

This case (Study No. 2) was examined by ^{67}Ga -citrate scintigraphy. The initial diagnosis for this case was right humerus and right clavicular metastases from pulmonary cancer (adenocarcinoma). In the ^{67}Ga scintigram, two tumors were found: one in the right side of the chest and the other in the right upper arm, as indicated in Fig. 6A. When the probe scanned the chest, the dual detector probe identified three peaks at positions -3 cm, 0 cm and 2 cm, as seen in Fig. 6B, which suggested that the tumors might consist of three nodules.

The initial clinical diagnosis in this study (No. 3 study) was performed for a subcutaneous tumor on the left neck. The radioactive distribution in the scintigraphy looked homogeneous, as seen in Fig. 7A. After the ^{67}Ga scintigraphy the probe scanning on the left neck detected the two clearly separated peaks along the scanning line, one at



Fig. 8A ^{67}Ga -scintigraphy for a case of subcutaneous tumor.

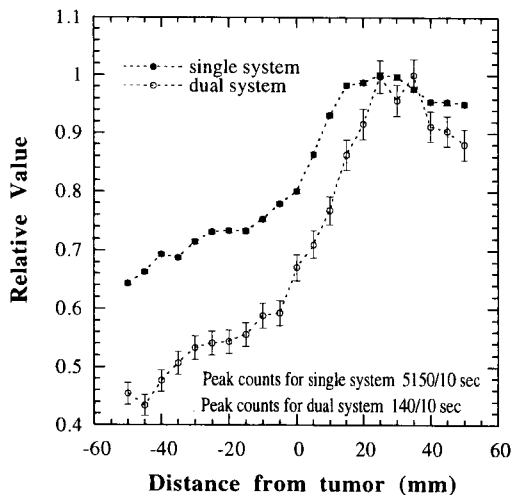


Fig. 8B Relative variation of scanning results of the single and dual probe on the tumor and normalized to be 1 at the peak counts. Peak count/rate for the single and dual detector systems are also shown in the figure.

- 4 cm and the other around 2 cm, as seen in Fig. 7B. This suggests the existence of central necrosis in the tumor.

The No. 4 study is a case of small cell carcinoma on the left chest wall, which was located in the right anterior upper chest. As seen in Fig. 8A, the radio-tracer distribution in the ^{67}Ga scintigram is homogeneous, but the probe scanning displayed higher Ga-accumulation in the lesion than in the surrounding normal tissue, as shown in Fig. 8B.

Since the spatial resolution of this detector system is good at lower energy and becomes worse with increased energy,⁸ one investigation with ^{18}F FDG was done in this study. The PET image (Fig. 9A) obtained with ^{18}F FDG shows a right humerus tumor in the No. 4 study. The probe scanning was performed on the tumor simultaneously with the PET study. The results obtained with the probe also localized the tumor precisely by the higher uptake of the radioisotope in the tumor, as shown in Fig. 9B.

In these clinical experimental results the absolute values for the single detector probe counts are 5 to 20 times



Fig. 9A ^{18}F FDG-PET image of the humerus metastasis from the lung cancer.

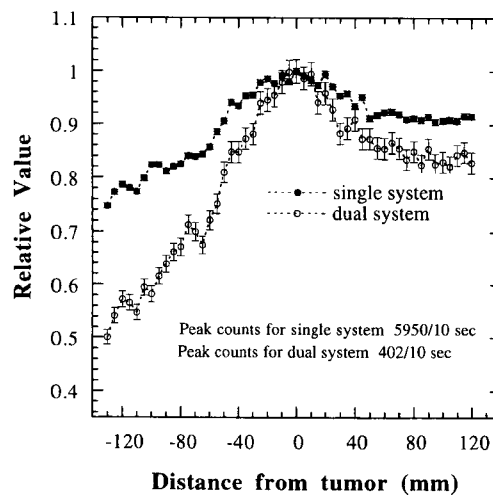


Fig. 9B Relative variation of scanning results of the single and dual probe on the tumor and normalized to be 1 at the peak counts. Peak count/rate for the single and dual detector systems are also shown in the figure.

higher than those for the dual detector probe, as in the phantom experiments. The spatial resolution of tumor localization is, however, improved by using the dual detector probe.

DISCUSSION

The single detector system with a BGO scintillator has been able to localize the tumor with reasonably good spatial resolution (about 1 cm) for gamma-ray energy lower than 200 keV.⁸ As the energy increases, the resolution of the single detector probe becomes worse owing to the broadening of the point spread function, and the dual detector probes with two BGO scintillators and the random coincidence technique can improve the spatial resolution. The wide coincidence gate time used in our experiments is for increasing the counting efficiency of the probe, which is found to be almost independent of the photon energy and radioactivity used in pre-experiments.

In our detector system, both the single probe and the dual probe can be used, the former having higher sensitivity is used for regional tumor search and the latter having higher spatial resolution is for precise tumor localization. In the random coincidence technique it is possible to make coincidence from background to background, from tumor to background and from tumor to tumor, but as the dual detectors approach the tumor the coincidence probability of two direct photons from a tumor is much higher than that of other processes.

Since the spatial resolution of this detector system is good and becomes worse by increasing the energy,⁸ we investigated the probe properties with ¹⁸F of 511 keV energy, which is the highest radio-tracer energy used in the nuclear medicine procedure.

A point source experiment to investigate the probe characteristics demonstrated that the spatial resolution FWHM of the 3 cm dual detector probe is higher than that of the 4.4 cm single detector probe (Fig. 2). The 50% levels of the peak counts are 1.3 and 1.8 cm from the source position for the dual and single probes, respectively. Directional dependence of the detector sensitivity is shown in Fig. 3 as the 10% sensitivities, the FWTM of the single and dual detector probes. Figure 3 indicates that the single and dual detector probes have almost isotropic responses and the FWTMs for the single and dual detector probes are 17 cm and 8 cm, respectively. The difference between the FWHMs for the single detector probe and dual detector probe is 1.4 cm, about a factor of 1.5 times better spatial resolution for the dual probe than the single probe; whereas the difference between FWTMs for single and dual probe is 9 cm, about a factor of 2 times better spatial resolution for the dual probe. This clearly reflects that the random coincidence events from a point source decrease more rapidly with the distance from the source in comparison to the single detector probe counts, and as a result the resolution of the dual detector probe is improved.

An important characteristic of this device is its ability to localize the tumor in the presence of an intense photon background. The water phantom containing ¹⁸F solution as a normal tissue background was used, including a tumor-simulating ¹⁸F source for this purpose. It has been reported that the ¹⁸FDG uptake ratio of tumor to background is approximately 8 : 1¹⁰ in human subjects and in the phantom experiment the tumor to background ratio of 10 : 1 closely simulates actual cases. In the phantom experiment the count rates for the single and dual detectors are higher near the tumor position and decrease towards the background level, which enables us to localize the tumor.

The phantom experiment also clarified that the absolute counting efficiency of the single detector probe is 5 to 20 times higher than that of the dual detector probe, which indicates that the single detector system can be used for searching the tumor over a wide intracavity area, whereas

the dual detector system can be used for better tumor localization, as we expected.

The majority of current cancer diagnoses are done by detecting morphological changes. The detecting ability of these methods is not sufficient for small lesions. An alternative better method is to diagnose the difference between the biological specificity of the tumor tissue structure or tumor cells and that of normal parts. Scintigraphy belongs to the latter method and the diagnostic results are graphically processed by collecting information from the body surface. But it is physically difficult to localize a small tumor, because of poor spatial resolution which comes from the relatively large distance between the tumors (radio-tracer accumulating part) and detectors of the scinti-camera, owing to their large size. The gamma-ray endoscope can obtain access at a minimum distance or even zero distance from the relevant region of the body surface or intracavity for tumor localization. All these five clinical trials on a body surface revealed that our miniature probe has the ability to detect a small tumor located close to the body surface by approaching it as closely as possible, which is very difficult with scintigraphy and PET.

A similar type of instrument has been used clinically as a surgical probe,^{4,11-13} but we developed this instrument for body cavity examination as well as for a surgical probe. It is inexpensive and can play an important role with conventional techniques used in tumor detection.

CONCLUSION

The experimental results, including clinical trials on patients' body surfaces, showed that tumors can be searched for over a wide intracavity area with the single probe and that tumors can be localized more precisely with the dual probe and the random coincidence technique. The probes that we assembled are excellent for insertion inside body cavities such as the stomach, due to the small crystal size and the flexibility of the long optical light guide. By inserting the probe inside the body cavity coupled with a conventional endoscopic camera and placing it in contact with tumors, invisibly small and deeply located tumors inside the body cavity will be able to be detected by visualizing the position of the endoscope in the cavity as in the clinical trials on tumor localization on a body surface in this study.

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