Determination of Iodine-131 Diagnostic Dose for Imaging Metastatic Thyroid Cancer

Nelson B. Arnstein, James E. Carey, Susan A. Spaulding, and James C. Sisson

Nuclear Medicine Division, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan

The dose of radioiodine (^{131}I) used to survey patients for metastatic functioning thyroid cancer varies from 0.2 mCi to 30.0 mCi. Higher doses have occasionally revealed more tumors, but deliver more radiation to the patient. We asked which dose would be sufficient to detect metastatic deposits. Using a water tank with small-source phantoms, we sought to determine: (a) the minimum volume and concentration of activity capable of being imaged, (b) effects of background and source depth on detectability, and (c) a practical ^{131}I tracer dose based on these findings. Two gamma cameras affixed with high-energy collimators of different design were used to evaluate the capabilities of two instrument systems. The lowest activity detectable at the water surface was 0.03 μCi, in volumes of 10 to 300 μl. Background activity at 0.01 μCi/ml resulted in a three to tenfold loss of detectability; computer subtraction of background did not improve results. We assumed that the minimum beneficial treatment would be 4,500 rad, a dose delivered by 200 mCi of ^{131}I to a tumor with 0.05% uptake of the dose per gram. From these assumptions, our data show that a 2 mCi diagnostic dose would detect 10 and 30 μl lesions containing 0.05% or more of the dose per gram, but only at the surface and in the absence of background radioactivity. Moreover, assuming patient motion and background activity, some potentially treatable lesions probably cannot be detected even with a 30 mCi diagnostic dose, using present-day equipment. Selection of a diagnostic dose should therefore acknowledge the limitations of scintigraphic detection and take into account the radiation burden incurred by studies repeated over years.

J Nucl Med 27:1764–1769, 1986

Radioactive iodine (^{131}I) has been used in conjunction with surgery to treat functioning thyroid cancer since the 1950s (*1*). The presence of residual thyroid tissue and functioning metastases following thyroidectomy may be assessed by diagnostic scanning of the whole body using orally administered ^{131}I, in doses ranging from 0.2 mCi to 30 mCi (*2,3*). Several factors play a role in the detectability of a functioning lesion by ^{131}I scintigraphy. These include lesion volume and depth, ability of the lesion to concentrate radioiodine (*4,7*), presence of background activity (radioiodine in the blood pool) (*2,5*), and imaging equipment (*8,9*). Using a small-source phantom, we determined the minimum size and activity of lesions that could be imaged, and evaluated the role of each of the above factors on detectability by two gamma camera systems. Based on these findings, a practical dose of ^{131}I may be selected for a scintigraphic survey of thyroid cancer.

Received Dec. 16, 1985; revision accepted Apr. 23, 1986.

For reprints contact: James C. Sisson, MD, University of Michigan Hospital, University Hospital B1G 505D/0028, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0028.

MATERIALS AND METHODS

Apparatus

Sixteen centrifuge tubes, each 500 μl in capacity, were placed in two racks which were then inserted into a lucite tank, 40 × 20 × 20 cm filled with 13 l of water. The tubes were arranged in a 4 × 4 array as shown in Fig. 1. Using Eppendorf calibrated pipettes, stock solutions of iodine-131 (^{131}I) orthoiodohippurate were added to the tubes to yield sources of 0.01, 0.03, 0.10, and 0.30 μCi in volumes of 10, 30, 100, and 300 μl. Resulting source concentrations ranged from 0.03 μCi/ml to 30 μCi/ml. The source concentrations were chosen to encompass a range of tumor concentrations derived from a tracer dose of 2 mCi of ^{131}I. The choice of a minimum volume of 10 μl was based on the fact that, at volumes below 30 μl, the activity per gram of tumor required to deliver a given radiation dose increases sharply (*6*). Table 1 shows the relative concentrations of ^{131}I required to deliver the same radiation dose to spheres of decreasing diameter. As a tumor size decreases, and particularly as the sphere diameter declines from 5 to 1 mm (volume 65 to 0.5 μl), the fraction of the beta

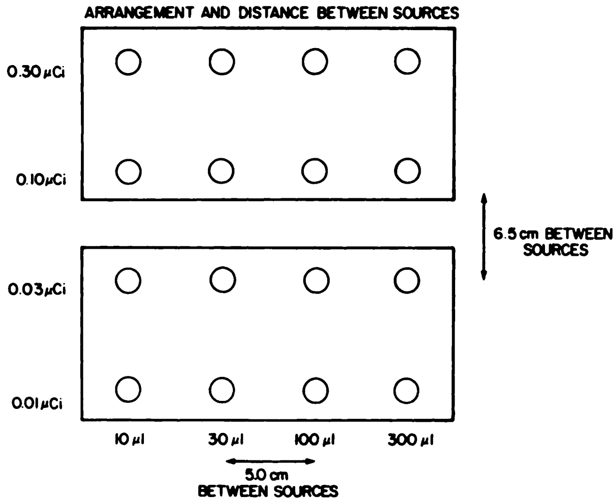

FIGURE 1
Arrangement of sources within tank. Rows correspond to activity, columns to source volume. All subsequent image figures correspond to this orientation

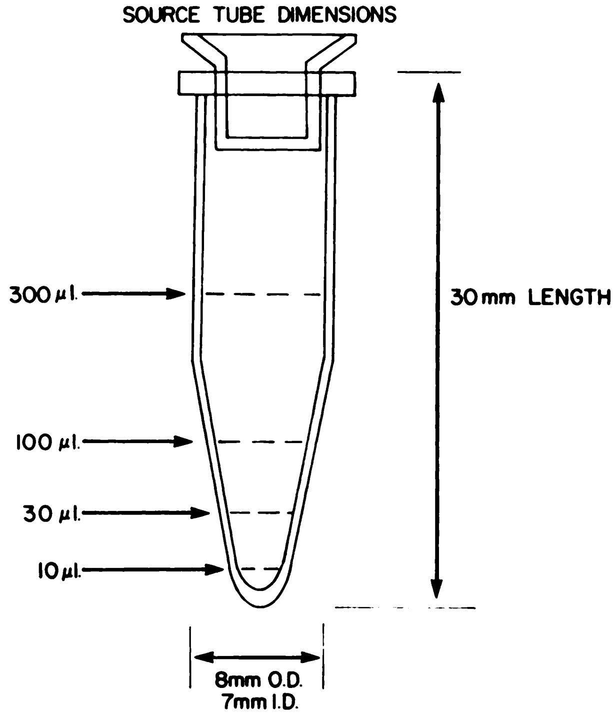

FIGURE 2
Source tube dimensions as viewed from side. Note increasing diameter of fluid level with volume

particles lost outside the tumor increases, and a greater concentration of ^{131}I is required to impart the same absorbed radiation dose.

The dimensions of the centrifuge tubes are shown in Fig. 2, the length being 30 mm, maximum inside diameter 7 mm and wall thickness 0.5 mm. The different volumes of source solution used resulted in different diameters of activity presented to the detector, varying from 2.5 mm to 7.0 mm (maximum inside diameter).

Imaging Protocol

Two gamma camera systems were used to image the sources: G.E. Maxi-37 400 AT* (37 photomultiplier tubes, 15-in. field-of-view, 1/2-in.-thick crystal), and Siemens large field-of-view (LFOV)† (37 photomultiplier tubes, 15-in. field-of-view, 1/2-in.-thick crystal). Collimators were of the high-energy type (specifications in Table 2). The camera was placed above the tank so that the collimator to surface of tank fluid distance was 10 cm. The sources of radioactivity were submerged so that the tops of the individual tubes were at the water line, and sources were considered at the surface. Distances from the collimator were then: for the largest or 300-µl source, top 11.24 cm and midpoint 12.08 cm; for the smallest or 10-µl source, top 12.23 cm and midpoint 12.85 cm. Measured from the collimator, the distances of the midpoints of the largest and smallest sources differed by only 6.4% when imaged at the surface. The sources were then submerged 10 cm further into the fluid for imaging at depth [20 cm source-to-collimator distance (SCD)]. The at-depth distance for the sources was chosen to simulate the center of a 20-cm-thick patient.

Twenty minutes was considered a reasonable time for imaging. Images were recorded by a digital computer and on analog film. The energy window around the 364 keV photopeak was set at 30%.

Background Solution

After acquiring the images described above, 130 µCi of ^{131}I were added to the 13 l of water in the tank, yielding a concentration of 0.01 µCi/ml, 1/3 the concentration of 0.03 µCi/ml in the minimal source, and 1/3,000 the 30 µCi/ml in the maximal source. In the presence of this solution, the sources were again imaged for 20 min, at the surface and at depth.

TABLE 1
Relative Concentration of ^{131}I for Constant Radiation Dose*

Sphere diameter (mm)	∞	10	5	1	0.5	0.1
Rel. conc. of ^{131}I	1	1.1	1.1	2	3	13

*Modified from Loevinger et al. (6).

TABLE 2
Collimator Specifications*†

	Hole diameter (mm)	Septal thickness (mm)	Hole length (mm)	FWHM at 10 cm SCD (mm)
Siemens LFOV‡	4.1	1.35	68.5	12.0
G.E. Maxi-37	4.0	3.2	40.0	14.0

*General Electric Company Medical Systems: Collimators for GE Scintillation Cameras H2500/1/3/4 Product Data p 3, 4-183.
† Siemens LFOV High-Energy Collimator Specifications.
‡ Collimator by Engineering Dynamics Corp., Lowell, MA.

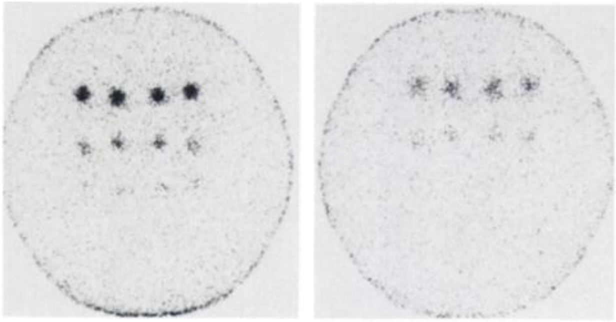

FIGURE 3
Siemens LFOV without added background radioactivity. Left: 0.3 (upper), 0.1, and 0.03 μCi sources in 10 (left), 30, 100, and 300 μl are visible at surface. Right: Only 0.3 and 0.1 μCi sources in 10, 30, 100, and 300 μl are seen when submerged to 10 cm (20 cm SCD)

Computer Processing

Using an MDS A^2 computer‡ and a region of interest generated in an area of the tank away from the sources, a background count was computed, and this was subtracted from the unprocessed digital image in increments of 10%. The resulting images were recorded on film for both cameras.

RESULTS

Siemens Large Field-of-View Camera

Images of the sources without added background obtained with the Siemens large field-of-view are shown in Fig. 3. The smallest quantity of radioactivity detectable at the surface was the 0.03 μCi source, in volumes of 10, 30, 100, and 300 μl. At depth (submerged 10 cm below the surface position), none of the 0.03-μCi sources was visible. The 0.1- and 0.3-μCi sources, in each of the above volumes, could still be seen.

When the background solution was made to a concentration of 0.01 μCi/ml of ^{131}I, a considerable loss of source detectability was noted (Fig. 4). At the surface of the background solution, the minimum detectable radioactivity was 0.1 μCi, and this was discernible only in volumes of 100 and 300 μl. The 0.3 μCi sources, in all volumes, 10 to 300 μl, were easily visualized. However, at depth in the background solution, only 0.3-μCi sources were visible; all volumes with this activity could be seen, but none distinctly.

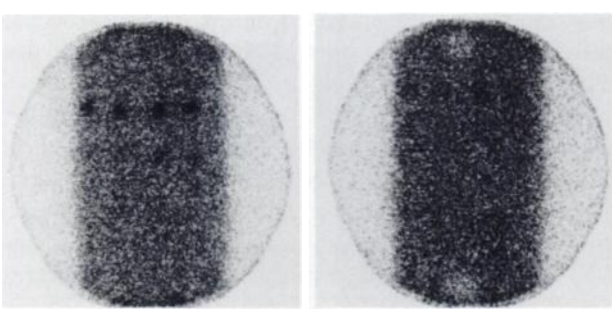

FIGURE 4
Siemens LFOV with added background radioactivity (0.01 μCi/ml). Left: Image of sources on surface shows 0.3 μCi sources in 10 (left), 30, 100, and 300 μl, and below these, indistinctly, 0.1 μCi sources in 100 and 300 μl. Right: When submerged to 10 cm (20 cm SCD), only 0.3 μCi sources in 10 to 300 μl are visualized, but indistinctly

These data were put into the context of thyroid cancers that are treatable with ^{131}I. Maxon et al. determined that beneficial effects from the treatment of thyroid cancer by ^{131}I requires delivery of at least 3,500 rad and usually >5,000 rad to the tumors (*10*). Assuming an effective half-life of 3 days for ^{131}I in cancer deposits (*10*), 0.1 mCi/g or 0.1 mCi/ml will impart about 4,500 rad to tumors 30 μl or larger in volume and slightly less to tumors 10 μl in volume. An additional assumption is that the treatment dose would be 200 mCi of ^{131}I, a quantity rarely exceeded in practice. Then 0.1 mCi is 0.0005 of 200 mCi, and 0.1 mCi/ml or 0.0005/ml of 200 mCi will deliver about 4,500 rad to tumors of 10 μl or larger volumes. (The values are given as fraction/ml to provide consistent data so that different sources can be related to one another even though actual source and tumor volumes are <1 ml.) If the diagnostic dose is representative of the therapy dose, then 0.0005/ml of any diagnostic dose is the fraction that approximates the lower limit for effective therapy.

Table 3 relates the individual sources used in the phantom to three diagnostic doses that may be used in practice; the sources are recorded as fractions of the diagnostic doses per ml so as to enable ready referral to the lower limit for effective treatments, 0.0005/ml, described above. Only data from the more sensitive Siemens large field-of-view camera are shown, and these data are for the most difficult to image sources, i.e., those at depth in a background of radioiodine. When 2 mCi is the diagnostic dose, three sources that are at or above the lower limits of 0.0005/ml were not visualized. When 10 mCi was the diagnostic dose, only one source (0.1 μCi in 10 μl) having a fraction at or above 0.0005/ml was invisible. There was but a single source (0.3 μCi in 10 μl) above the lower limit of fraction of dose/ml when the diagnostic dose was 30 mCi, and this was detected by scintigraphy.

G.E. Maxi-37 Camera

With the G.E. Maxi-37 camera system, the smallest activity visible at the surface without background was 0.03 μCi, in volumes of 10–300 μl, similar to the Siemens unit (Fig 5). However, the images of 0.03 μCi made with the GE Maxi-37 camera system were less distinct. Also, the collimator septa were apparent in this system. At 10 cm below the surface, only the 0.3 μCi sources, in all volumes, could be resolved, and these indistinctly.

When the background solution was made to 0.01 μCi/ml and the sources were at the surface, again only the 0.3 μCi sources in all volumes could be detected. But when immersed into 10 cm of the solution (20 cm SCD), none of the sources could be seen. Referring these results to fractions of dose per ml described in Table 3, it is apparent that this camera system failed to detect a number of sources that represented treatable tumors, both in the presence and in the absence of background radioactivity.

Computer Manipulation of Data

Computer subtraction of background, in 10% increments from the images of the Siemens system, with the sources at

TABLE 3
Scintigraphic Detectability of Sources* and Relationship to Possible Tracer Doses

Proposed diagnostic dose (mCi)	Total source activity (μCi) in the phantom	Fraction of proposed dose in individual sources converted to fraction per milliliter† Volume of source (μl)			
		10	30	100	300
2	0.3	.015‡	.005	.0015	.0005
2	0.1	[.005]§	[.0017]	[.0005]	[.00017]
10	0.3	.003	.001	.00033	.0001
10	0.1	[.001]	[.00033]	[.0001]	[.000033]
30	0.3	.001	.00033	.0001	.000033
30	0.1	[.00033]	[.00011]	[.000033]	[.000011]

* Siemens LFOV camera. Sources at depth: 20 cm from collimator and immersed below water containing ^{131}I 0.01 μCi/ml.
† See text. Threshold concentration for treatability (i.e., 4,500 rad from 200 mCi therapy dose) is 0.0005 of dose per/ml; 0.00033 of dose per/ml is borderline.
‡ Underline indicates treatability, i.e., 0.0005 or more of dose per ml.
§ [ ] Indicates absence of detection by Siemens LFOV camera (more sensitive system tested).

the surface (10 cm SCD), gave images as shown in Fig. 6. This process does not enhance the detectability of the sources. Even at 100% background subtraction, no additional sources were visible.

DISCUSSION

Our in vitro model of thyroid cancer was based on data derived from the literature. Well-differentiated thyroid cancers will concentrate, per gram or per ml, 0.05 to 0.5% (0.0005 to 0.005) of a dose of ^{131}I (*2*). Since the concentration of ^{131}I required to impart a given radiation dose rises progressively when the spherical volume containing the radionuclide becomes smaller, probably a 10-μl sphere (2.6 mm diameter) will approach the smallest treatable tumor (Table 1).

Data from this model demonstrate that many of the phantom concentrations of ^{131}I cannot be scintigraphically visualized when they reside in a radioactive background at a depth of 10 cm. The presence of background

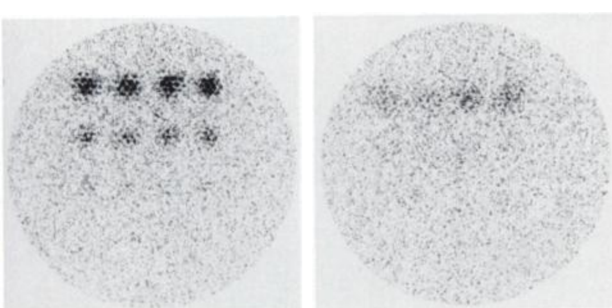

FIGURE 5
G.E. Maxi-37 without added background radioactivity. Left: When on surface, 0.3 (upper) and 0.1 sources in all volumes are easily seen, but 0.03-μCi sources are portrayed indistinctly. Right: When submerged at 10 cm, only the 0.3-μCi sources in all volumes are discernible

radioactivity reduced detectability of sources immersed 10 cm in the solution by as much as a factor of 10. When 2 mCi is used as a diagnostic dose, tumors smaller than 100 μl and immersed in background radioactivity will be found only when they concentrate ^{131}I avidly (at least 0.005 of dose/ml, or 10 μCi/ml).

Of special importance was the inability to detect sources that contained 0.0005/ml or more of the dose and therefore represented potentially treatable tumors (i.e., receiving 4,500 or more rad from a 200 mCi therapy dose). Using the more sensitive Siemens camera system only one source containing 0.0005/ml or more of a 10 mCi diagnostic dose was not visualized (Table 3), but the circumstances were idealized. Probably fewer sources, including those representing treatable tumors, would have been seen if they resided in a patient who had respiratory movements over the 20 min taken to acquire the data. Given the marginal resolution obtained for sources at depth and in background radioactivity, probably some sources containing 0.0005/ml of a 30 mCi diagnostic dose would also not be seen if the sources were not perfectly still. Certainly this would be true in a system using the GE Maxi-37 camera system which failed to portray any source at depth in background radioactivity. We must conclude that no diagnostic dose of 30 mCi or less will detect all treatable thyroid cancers using modern scintigraphic equipment.

Although the level of background radioactivity selected was arbitrary, it appears reasonable (*5*). Moreover, even without background radioactivity, some sources representing potentially treatable tumors were not detected at depth by the GE Maxi-37 camera system, e.g., several sources containing 0.1 μCi and over 0.0005/ml of both the 2 and 10 mCi diagnostic doses (Table 3) were not visualized (Fig. 5).

The ratio of phantom source size to resolving power

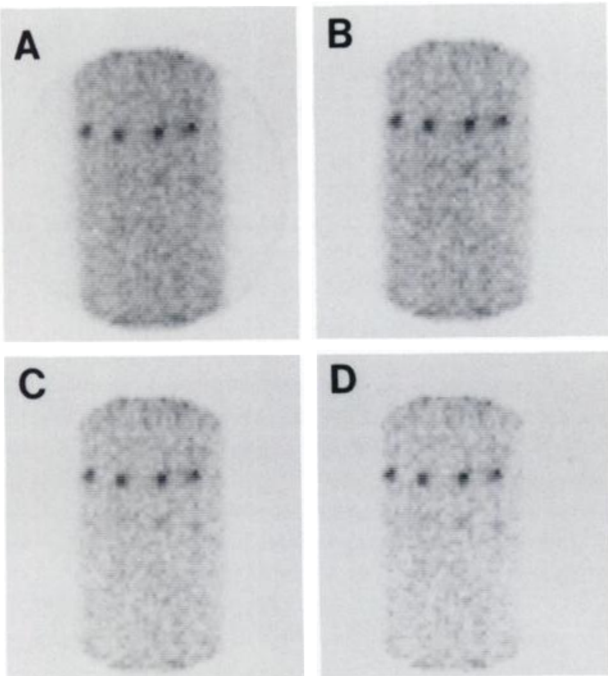

FIGURE 6
Computer background subtraction of images made of sources on surface in presence of background radioactivity (0.01 μCi/ml). Shown for Siemans camera system in Fig. 4, left. Only first four 10% decrements as shown: A: 10%; B: 20%; C: 30%; and D: 40%. Last image offers no better detectability than unprocessed image in Fig 4, left

of the collimator-camera system played a major role in determining the results. A source smaller than the full width at half-maximum of the system gives an apparent target-to-non-target ratio that is much lower than the true ratio. This phenomenon was demonstrated in images made with the Siemens system with the sources at the surface of the tank solution containing 0.01 μCi/ml of ^{131}I (Fig 4). Only the larger two volumes of the 0.1-μCi sources (100 and 300 μl, presenting diameters of 5.5 and 7.0 mm) were discernible. Here the ratios of diameters to system resolution (5.5/12 and 7.0/12) are large enough so that target activity was not hidden in the statistical fluctuation of background activity, even though the source concentration in terms of μCi/ml was lower than those in the invisible 10- and 30-μl sources containing 0.1 μCi.

The images made with the G.E. system show the collimator septa, but the sources appear larger than in the Siemens images. This can be explained by the thicker septa and shorter holes of the G.E. collimator resulting in a greater point-spread function at depth and in poorer resolution. At depth (submerged in 10 cm of water), the effect of point-spread is magnified, causing considerable loss of detectability. These results emphasize that "high energy" collimators by different manufacturers are made to varying specifications, although intended for the same purpose.

Snyder et al. (*11*) concluded that a diagnostic dose of 1 mCi of ^{131}I was adequate to image concentrations as low as 0.5 μCi/g, that is, 0.05% of the diagnostic dose per gram, but they cited no evidence to support this conclusion. These investigators also stated that a 0.05%/g concentration did not need treatment, regarding this as "minimal residual." Waxman et al. found 10 mCi more sensitive than 2 mCi as a diagnostic dose in detecting concentrations of radioactivity in patients with thyroid cancer, but 30 and 100 mCi doses were yet more sensitive than 10 mCi doses (*2*). Balachandran and Sayle (*12*) noted that, in 10 of 24 patients, scintigraphic images made after therapies of 50 to 163 mCi revealed concentrations of radioactivity not seen on diagnostic studies performed with 1 to 2 mCi doses.

Not surprisingly, our data support reports in the literature that the larger the concentration of ^{131}I (obtainable from larger diagnostic doses), the greater the ability to detect sources of radioactivity including those in small deposits of thyroid cancer. However, diagnostic doses as large as 30 mCi will probably not enable scintigraphic portrayal of all small, potentially treatable tumors. As noted above, some investigators have concluded that carcinomas appearing near or below the limits of detection by their scintigraphic methods do not warrant radioiodine therapy, but it is apparent that some of these tumors concentrate sufficient ^{131}I to respond, at least hypothetically, to the treatment. Because many patients with thyroid cancer do well for many years without treatment, it will be difficult to ascertain whether therapy with ^{131}I would benefit those with small and diagnostically undetected deposits of thyroid cancer. Nevertheless, metastases too small to be seen on chest roentgenograms, but identifiable on scintigraphic images, probably because of their multitude, have been deemed worthy of ^{131}I treatment, and the disease appears then to be controlled (*13*).

Since even 30 mCi of ^{131}I will probably not uncover all potentially treatable thyroid cancer using modern instruments, selection of a diagnostic dose becomes arbitrary. In this arbitrary decision, it is uncertain if the additional cancers detected by diagnostic doses larger than 2 mCi will justify the additional radiation burden, one that is cumulative from doses used repeatedly in reevaluations over many years. With uptakes of 5% of the dose in thyroid tissue, the absorbed doses of radiation to the whole body would be 0.24 rad/mCi, and to the red marrow 0.14 rad/mCi, and these doses would be only slightly lower in patients whose tumors concentrated <5% of the dose (*14*). The risk to health from such radiation has not been established.

On the other hand the efficacy of any diagnostic dose is also unknown. Doses larger than 2 mCi may have value for selected patients in whom small deposits of thyroid cancer (and especially if these may be outside the neck) seem likely but are not visualized with a 2 mCi dose.

FOOTNOTES

* General Electric, Milwaukee, WI.
† Siemens Medical Systems, Inc., Iselin, NJ.
‡ Searle-Nucletron Corp., Columbia, MD.

ACKNOWLEDGMENTS

The authors thank Vi Rhodes and Michele Bell for preparation of this manuscript.

This work was supported in part by NCI 5 T32 CA09015 "Cancer Research Training in Nuclear Medicine."

REFERENCES

1. Beierwaltes WH, Johnson PC: Thyroid carcinoma treatment with radioactive iodine: An eight year experience. *J Mich State Med Soc* 55:410–419, 1956
2. Waxman A, Ramanna L, Chapman N, et al: The significance of I-131 scan dose in patients with thyroid cancer: Determination of ablation: Concise communication. *J Nucl Med* 22:861–865, 1981
3. Halpern SE, Preisman R, Hagan PL: Scanning dose and the detection of thyroid metastases. *J Nucl Med* 20:1099–1100, 1979
4. Coakley AJ, Page CJ, Croft D: Scanning dose and detection of thyroid metastases. *J Nucl Med* 21:803–804, 1980
5. Nemec J, Rohling S, Zamrazil V, et al: Comparison of the distribution of diagnostic and thyroablative I-131 in the evaluation of differentiated thyroid cancers. *J Nucl Med* 20:92–97, 1979
6. Loevinger R, Japha EM, Brownell GL: Discrete radioisotope sources. In *Radiation Dosimetry*, Hine GJ, Brownell GL, eds. New York, Academic Press, Inc., 1956, p 745
7. Beierwaltes WH, Rabbani R, Dmuchowski C, et al: An analysis of "ablation of thyroid remnants" with I-131 in 511 patients from 1947–1984: Experience at the University of Michigan. *J Nucl Med* 25:1287–1293, 1984
8. Lim CB and Gottschalk S: Single Photon Emission Computed Tomography: Potentials and Limitations. In *Selected Topics in Imaging Science: Applications to Medical Diagnosis and Physical Sciences*, Nalcioglu O, Cho ZH, eds. New York, Springer-Verlag, 1984, pp 128–155
9. Budinger TF, Derenzo SE, Huesman RH: Role of tomography in providing radionuclide distribution and kinetic data. *Proceedings of the Third International Dosimetry Symposium*, HHS Publication FDA 81-8166, 1981, pp 60–75
10. Maxon HR, Thomas SR, Hertzberg VS, et al: Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. *N Engl J Med* 309:937–941, 1983
11. Snyder J, Gorman C, Scanlon P: Thyroid remnant ablation: Questionable pursuit of an ill-defined goal. *J Nucl Med* 24:659–665, 1983
12. Balachandran S, Sayle BA: Value of thyroid carcinoma imaging after therapeutic doses of radioiodine. *Clin Nucl Med* 6:162–167, 1981
13. Bonte FJ, McConnell RW: Pulmonary metastases from differentiated thyroid carcinoma demonstrable only by nuclear imaging. *Radiology* 107:585–590, 1973
14. Summary of current radiation dose estimates to humans from ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{130}I, ^{131}I and ^{132}I as sodium iodide. Mird Dose Estimate Report No. 5. *J Nucl Med* 16:857–860, 1975