SPECT Quantitation of Iodine-131 Concentration in Phantoms and Human Tumors

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The validity of SPECT measurement of iodine-131 (^{131}I) concentration was tested in vitro in phantoms and in vivo by measuring bladder urine concentrations. Phantom studies comparing known and SPECT measured concentrations showed a good correlation for ^{131}I ($r = 0.98$, s.e.e. = 20.94 counts/voxel) for phantoms of 25 to 127 cc and concentrations of 0.13 to 9.5 μCi/cc. The in vivo, in vitro correlation of ^{131}I concentrations in the urine was also good ($r = 0.98$, s.e.e. = 0.677 μCi/cc). Quantitative SPECT was used to calculate the effective half-life and dosimetry of radioiodine in 12 sites of thyroid carcinoma in seven patients. SPECT was also used to determine the dosimetry of [^{131}I]MIBG (metaiodobenzylguanidine) in two patients with carcinoid, two with neuroblastoma, and one with pheochromocytoma. The radiation dose for thyroid carcinoma metastases varied between 6.3 and 276.9 rad/mCi. The dose from MIBG varied between 13.4 and 57.8 rad/mCi. These results indicate the validity of quantitative SPECT for in vivo measurement of ^{131}I and the need to measure the concentration of ^{131}I in individual human tumor sites.

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Radioiodine has been widely used for the treatment of thyrotoxicosis and metastatic thyroid carcinoma (*1*). Iodine-131- (^{131}I)MIBG (metaiodobenzylguanidine) recently has been suggested for treatment of neuroendocrine tumors and their metastases (*2*). Radioiodine also has a potential use in radioimmunotherapy. Radiation induced destruction of hyperactive or neoplastic cells forms the basis of the therapeutic use of radioiodine. There appears to be a relationship between the amount of radiation administered to the patients and its biologic effect on the target tissue. There are, however, problems in calculating the amount of radioiodine that should be effectively administered for treatment. Two factors confound the calculations. First, radiation sensitivity of the target tissue varies in different patients and there is no current method to measure these variations. The other difficulty results from the inaccurate approximations used for the calculation of the in vivo concentration of radioiodine that may cause significant errors in dosimetry.

The purpose of the study was two-fold. First to determine if in vivo SPECT quantitation (*3–6*) is feasible using ^{131}I and to establish the limitations in volume and concentration measurements. The second aim was a preliminary study in human tumors to determine if there are significant differences in concentration among individual tumors. If such differences exist, then SPECT dosimetry calculations of tumor radioactivity concentrations could be an important tool for effective radioiodine treatment.

MATERIALS AND METHODS

Data Acquisition and Analysis

The rationale and technical details of the quantitative SPECT method using technetium-99m have been discussed in previous publications (*3–6*). The validation of its use for radioiodine will be discussed here in some detail. The studies were performed using an Elscint (Haifa, Israel) Apex 415 digital gamma camera with a rotating gantry, a medium-energy collimator (APC-5), and an energy window of 15%. A 64 × 64 byte matrix was used in each single-photon emission computed tomography (SPECT) study, which had a rotation time of 25–30 min. Thirty to 2,340K counts were collected in each study. The data were reconstructed by filtered back projection using a Hanning filter in the transaxial, sagittal and coronal planes. The cutoff frequency of the filter was 0.5 cycle/pixel. Concentration was measured using an automated computer program (*6*). There is only minimal interobserver variability encountered when using this technique (*5*).

Phantom Studies

A series of 38 phantoms with known volumes and radioiodine concentrations were examined in order to choose a

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suitable threshold. Preliminary feasibility studies showed that concentration may be accurately measured only in phantoms larger than 25 cc. For simulation of body attenuation, a 10,000-cc Alderson body phantom was used. Spherical phantoms of 25, 60, 100, and 127 cc were placed in the body phantom. A range of concentrations between 0.13 and 9.5 μCi/cc were used in phantoms to cover the wide range of concentrations expected in tumors. Data acquisition required 120 projections, 3° apart, for concentrations over 1 μCi/cc and 60 projections, 6° apart, for concentrations of <1 μCi/cc. After reconstruction of emission computed tomography data, volumes and concentrations in each of the phantoms were calculated using several threshold values ranging from 30% to 60% in order to select the threshold which gives the best correlation between SPECT-measured and actual concentrations and volumes. The pixel containing the highest number of counts within a region of interest (ROI) around the phantom is selected and the threshold value is calculated as percent of the counts within this pixel. Only the fraction of pixels containing a higher number of counts than the threshold were used. The threshold is used for masking for volume calculations and the threshold value is subtracted from each of the pixels in order to correct for count rate density. For concentration measurements, the pixels that have higher counts than the threshold are used and for each section the computer adds the number of non-zero pixels which were included in the ROI. Correlation curves for the phantoms were plotted for both SPECT-measured volumes and concentrations (Figs. 1–3). The SPECT-measured volumes (Fig. 1) and SPECT-measured concentrations (Fig. 2) were compared using different thresholds in order to find which threshold gives the smallest error.

In Vivo/In Vitro Comparison Studies

Quantitation by SPECT was validated by comparing SPECT-measured concentrations of ^{131}I in the urinary bladder in vivo in 15 patients and the actual concentration of the ^{131}I in the urine of these patients measured in a well counter (Atomic Products Corp., New York). In vivo urine concentration studies were performed 24 hr after the ingestion of 5 mCi of sodium ^{131}I by patients who were referred to our department for routine total-body scans or after the i.v. injection of 1.5 mCi of [^{131}I]MIBG (Fig. 4). Only concentrations were compared since it is not possible to ensure that the patient has voided all of the urine contained in the bladder. It is, of course, the concentration of ^{131}I which is relevant for dosimetry calculations.

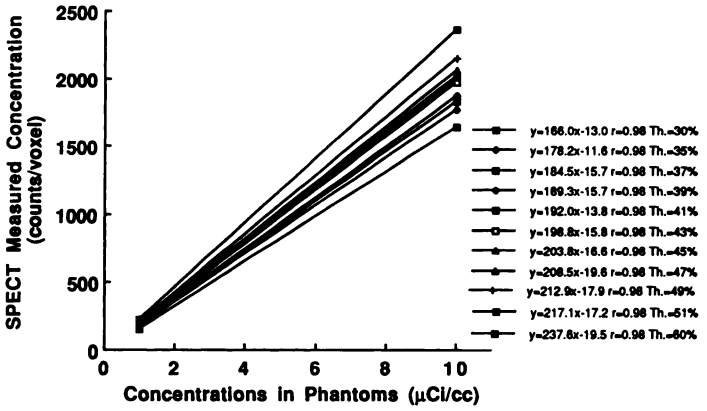

FIGURE 2
Correlation between SPECT-measured concentration and actual concentration of ^{131}I in phantoms using different thresholds. The results using thresholds from 30% to 60% are indicated in the definition of the identity line.

Patients Studies

Twelve patients, nine women and three men, aged 1–75 yr were investigated. Only patients in which planar scintigraphy indicated lesions significantly larger than 25 cc were included. Volumes were estimated on planar scintigraphy using the method previously described (*7*). Patients were referred to us by the Departments of Endocrinology and Oncology of the Rambam Medical Center for evaluation prior to radioiodine treatment. Seven patients with well-differentiated thyroid carcinoma were investigated. They had lung metastases (three patients with five lesions) and bone metastases (five patients with eight lesions). One patient had both lung and bone metastases. Total-body scans in patients with thyroid carcinoma were performed using 5 mCi of ^{131}I. SPECT data acquisition required 60 projections 6° apart. The initial

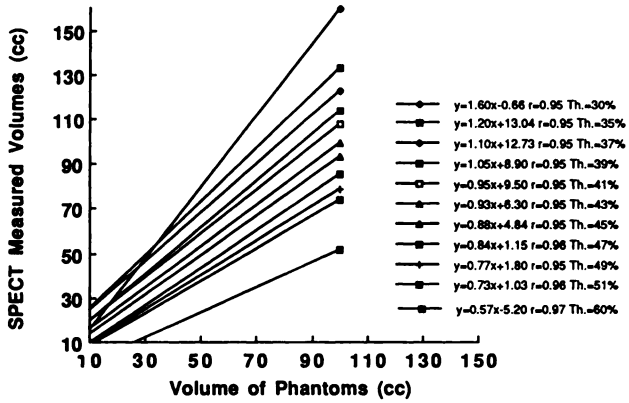

FIGURE 1
Correlation between SPECT-measured volumes of ^{131}I in phantoms and actual volumes using different thresholds. The results of using thresholds from 30% to 60% are indicated in the definition of the identity line.

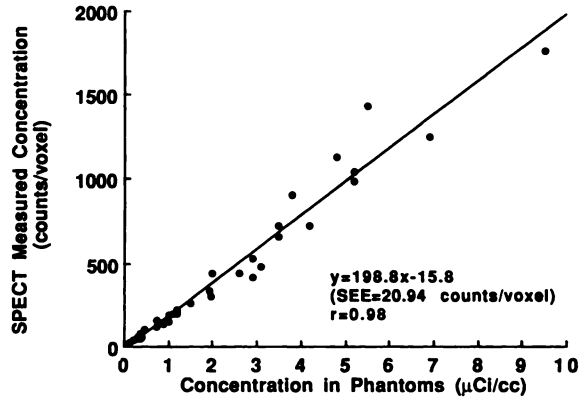

FIGURE 3
Correlation between SPECT-measured concentration and actual concentration of ^{131}I in phantoms using a threshold of 43%. The regression line is used to convert counts/voxel into μCi/cc for concentration measurements.

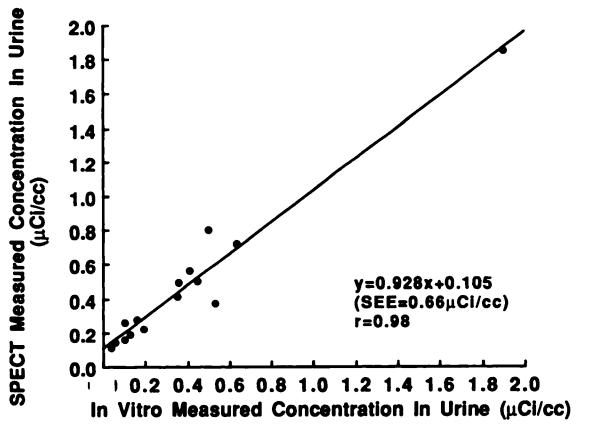

FIGURE 4
In vivo/in vitro correlation of concentration of ^{131}I and [^{131}I] MIBG in the urinary bladder and urine of 15 patients. SPECT-measured concentration of ^{131}I in the urinary bladder was compared with in vitro well-counter measurements of the urine of the same patients.

SPECT studies of functioning metastases from thyroid carcinoma were performed 48 hr after the ingestion of the radionuclide. For effective half-life calculations, a second SPECT study for measurement of iodine concentration was performed 4–7 days after the initial study. Iodine-131-MIBG studies were done in two patients with four liver metastases from carcinoid tumors, in two patients with neuroblastoma (one patient also had a liver metastasis), and in one patient with a recurrent pheochromocytoma. Patients were investigated at 24 hr and 4 days after the i.v. injection of 30 μCi/kg of [^{131}I]MIBG with doses ranging from 300 μCi to 1.5 mCi. The concentration of radioiodine was expressed as μCi/cc.

Calculation of Radiation Dose

Calculation of absorbed dose D(rad) was based on the MIRD equation for the case when target and source volume are the same (*8*):

where:

$$\bar{D}_{(v \leftarrow v)} = \tilde{C}_V \sum \Delta_i \phi_i (v \leftrightarrow v),$$

$\bar{D}$(rad) represents the mean dose for a complete decay, $\tilde{C}_V$ (μCi × hr/g) is the cumulative concentration of the radionuclide in the volume (v), Δ_i(g × rad/μCi × hr) is the equilibrium dose constant, and ϕ_i is the absorbed fraction for an i-type radiation. The values of Δ_i for ^{131}I were taken from MIRD pamphlet No. 10 (*9*). Absorbed fraction for nonpenetrating β-radiation of ^{131}I was assumed equal to 1. For penetrating γ-radiation of ^{131}I, absorbed fraction depends on the mass and the geometry of the lesion. When the mass of the lesion varies between 25 and 200 g, the absorbed fraction of the gamma radiation of ^{131}I varies between 0.03 and 0.08 (*10, 11*). We chose a constant value of 0.055, resulting in a ±5% error in the calculations. The density of the lesion is assumed to be 1 g/cc.

Assuming a single exponential clearance curve of ^{131}I from the lesion, the equation can be expressed as follows:

$$\bar{D} = C_0 \times T\ eff \times (14.29 + 1.53) = C_0 \times T\ eff \times 15.82,$$

where C_0 represents the initial concentration of ^{131}I in the lesion measured by SPECT at 24 hr after the injection of [^{131}I] MIBG. The calculations do not consider the radiation during the first 24 hr, which could account for approximately 10% of the total cumulative concentration. In patients with metastatic thyroid carcinoma, the concentration was measured at 48 hr after radioiodine ingestion. Assuming a single exponent elimination curve of the radioiodine, the concentration at 24 hr was then calculated. T eff (days) represents the effective half-life of ^{131}I in the lesion and it was calculated by using the two SPECT concentration measurements. The values, 14.29 and 1.53, represent the contribution of β- and γ-radiation, respectively.

RESULTS

Thirty-eight measurements were performed using phantoms with different volumes and concentrations of ^{131}I. SPECT-measured and actual volumes and concentrations in phantoms were compared (Figs. 1–2). A threshold of 43% was found to be suitable since it gave the best coefficient of correlation with a minimal deviation from the identity line (r = 0.98, s.e.e. = 20.94 counts/voxel, Fig. 3). The identity line in Figure 3 was used to transfer SPECT-measured counts/voxel into μCi/cc for calculations of concentrations in vivo. A good correlation (r = 0.98, s.e.e. = 0.677 μCi/cc, Fig. 4) was also found when in vivo SPECT-measured concentrations of ^{131}I and [^{131}I]MIBG in the urinary bladder were compared with concentrations in the same urine after voiding and measured in vitro in a well counter.

In vivo iodine concentrations were measured by SPECT and the effective half-lives and radiation doses were calculated in seven patients with 12 functioning metastases from thyroid carcinoma (Table 1). SPECT-measured concentrations ranged between 0.1 and 7 μCi/cc. The effective half-life in the metastases ranged between 2.5 and 6.3 days. Radiation doses based on SPECT concentration measurements varied between 6.3 and 276.9 rad/mCi (Table 1). One patient was identified (Case 2, Table 1), who would not have benefited even from a very high dose of radioiodine therapy due to the very low radioiodine concentration in the metastases.

The concentration of [^{131}I]MIBG was also measured by SPECT (Table 2) in two patients with four liver metastases from carcinoid tumors, in two patients with neuroblastoma (one patient, Case 4, also had a functioning liver metastasis), and in one patient with recurrent pheochromocytoma. Concentrations in the carcinoid metastases ranged between 0.25 and 0.45 μCi/cc and the effective half-lives varied between 2.9 and 3.7 days. Radiation doses based on SPECT concentration measurements varied from 13.4 to 26.3 rad/mCi. The concentration of ^{131}I in the neuroblastoma varied between 0.91 and 2.15 μCi/cc, the effective half-life varied between 1.7 and 2.8 days, and the radiation dose varied between 40.3 and 57.8 rad/mCi. The concentration,

TABLE 1
Radiation Dosimetry Calculations for ^{131}I Based on SPECT-Measured Concentration in Seven Patients with Metastatic Thyroid Carcinoma

Patient no. (Sex, Age)	Site	SPECT-measured concentration (μCi/cc*)	Effective $t_{½}$ (days)	Radiation dose (rad/mCi)
1 F, 52	Rt. lung	0.55	4	34.8
	Lt. lung	0.71	4	44.9
2 F, 44	Rt. lung	0.1	4	6.3
	Lt. lung	0.12	4	7.6
3 M, 75	Thyroid†	7.12	6	675.8
	Rt. lung	1.05	6.3	104.6
	Rt. femur	1.2	5	94.9
4 F, 60	Sacrum	7	2.5	276.9
5 F, 52	L-5 vertebra	2.53	2.9	116.1
6 F, 59	T-5 vertebra	0.51	5.5	44.4
	T-12 vertebra	0.4	6	38.0
	Sacrum	0.95	6.2	93.2
7 F, 75	Sacrum	0.76	3.7	44.5

* Concentration at 24 hr normalized to 1 mCi of ingested dose.
† No surgery or radioiodine ablation was performed in this patient at the time of the study.

effective half-life, and radiation dose in a liver metastasis of a neuroblastoma were the same as in the primary tumor (Table 2).

DISCUSSION

Previous studies (*3–6*) using phantoms and in vivo/in vitro correlations have validated SPECT quantitation of the in vivo concentration of technetium-99m. The present study shows that SPECT can also be used for measurement of the in vivo concentration of ^{131}I. The results show that the potential disadvantages of ^{131}I for quantitation due to its physical characteristics and dose limitations do not significantly affect the accuracy of SPECT measurements in tumors larger than 25 cc and in concentrations as low as 0.13 μCi/cc. One must realize that the technique measures the concentration of ^{131}I only in the portion of the tumor that takes up iodine. The volume included is the "functional" volume containing iodine-avid tissue. Other parts of the tumor which may contain fibrous or necrotic tissue are irrelevant to dosimetry calculations since they do not concentrate iodine. This functional volume is of course different from the anatomic volume measured by computed tomography. The good (r = 0.98) in vivo/in vitro correlation is in accordance with previous data using human tumors, bone, and blood (*3–6*). The results of the study indicate that SPECT concentration measurements permit accurate calculations of the effective half-life of radioiodine in the target tissue.

TABLE 2
Radiation Dosimetry Calculations for [^{131}I]MIBG Based on SPECT-Measured Concentration in Five Patients with Metastatic Carcinoid, Neuroblastoma, and Recurrent Pheochromocytoma

Patient no. (Sex, Age)	Lesion	SPECT-measured concentration (μCi/cc*)	Effective $t_{½}$ (days)	Radiation dose (rad/mCi)
1 F, 41	Carcinoid			
	Liver met. 1	0.34	2.9	15.6
	Liver met. 2	0.25	3.4	13.4
2 F, 57	Carcinoid			
	Liver met. 1	0.45	3.7	26.3
	Liver met. 2	0.29	3.7	17
3 M, 1	Neuroblastoma	0.91	2.8	40.3
4 M, 1	Neuroblastoma	2.15	1.7	57.8
	Liver met.	2.15	1.7	57.8
5 F, 28	Recurrent Pheochromocytoma	0.46	3.7	26.9

* Concentration at 24 hr normalized to 1 mCi of injected dose.

There are no accurate criteria for dose calculations of ^{131}I in the treatment of thyroid carcinoma or when it is used as MIBG- or iodine-labeled antibodies. Large amounts of radioiodine are generally administered to treat patients with thyroid cancer. In some patients, however, even this high dose therapy, which can severely jeopardize the bone marrow, does not secure an adequate therapeutic response. This could be the result of insensitive tumor tissue or a low tumor concentration of iodine (*1,12,13*). One patient in our series (Patient 2, Table 1) indeed had a low radiation dose even for high administered dose.

Dosimetry calculations using probe-measured uptake are biased and introduce marked errors. Probe-measured uptake of ^{131}I is affected by the physical characteristics of the probe system, the distance of the detector from the body surface, and the shape, symmetry, and depth of the lesion. Furthermore, probe uptake is completely unsuitable in diffuse lung or bone metastases. The volume calculations necessary for probe measurements are also a problem. Presently, a major limitation of the SPECT technique is the inability to measure concentration in tumors smaller than 25 cc. Theoretically, it may be possible to measure concentration in lesions smaller than 25 cc by using different thresholds (*6*). In vivo/in vitro validation, however, would be extremely difficult and therefore it was not attempted at this initial stage of our research.

The results of the present investigation show that there are very large differences in the radiation dose among individual patients. The dose in this study varied between 6.3 and 276.9 rad/mCi in patients with metastases from thyroid carcinoma (Table 1) and between 13.4 and 57.8 rad/mCi in patients with MIBG-avid tumors (Table 2). Accurate measurement of radiation dose is necessary if radiation treatment with [^{131}I]MIBG is to be used effectively at an early phase of the disease,

where delivery of a large amount of radiation may, hopefully, induce a response similar to that achieved in thyroid carcinoma (*14,15*). No accurate measurement of dose has yet been applied for ^{131}I radioimmunotherapy (*16*).

In conclusion, the results of the current study indicate that accurate measurement of in vivo ^{131}I concentration in tumors is feasible. They also indicate that large differences exist in the ability of metastatic thyroid carcinoma and in MIBG-avid tumors to concentrate ^{131}I or MIBG. Future studies using this technique will determine the relative roles of tumor cell radiation sensitivity and radiopharmaceutical uptake in tumor response to radiation by ^{131}I and labeled MIBG.

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