13

Using γ-Camera to Evaluate the *In Vivo* Biodistributions and Internal Medical Dosimetries of Iodine-131 in Thyroidectomy Patients

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1. Introduction

Seidlin, Oshry and Yallow first examined the feasibility of using radioactive iodine, ^{131}I, to treat thyroid carcinoma in 1948. Medical professionals have since adopted ^{131}I extensively to treat both benign and malignant thyroid diseases (Rosario et al., 2004; Chen et al., 2003; Berg et al., 1996). ^{131}I is commonly used in ablative or adjuvant therapy after thyroid carcinoma treatment, which often requires total or near-total thyroidectomy (Chen et al., 2003). Large doses of ^{131}I are routinely administered to patients to treat thyroid remnants at Chung-Shan Medical University Hospital (CSMUH); however, research on the effective half-life (T_{eff}) in the whole-body, thyroid and other organs *in vivo* has been lacking (CSMUH, 2005). Therefore, this study seeks to yield clear scintigraphic images using γ-camera.

1.1 T_{eff} by International Commission on Radiological Protection 30 (ICRP 30)

It is important to evaluate the T_{eff} of the whole-body and each organ in order to calculate the internal medical dosimetries in patients. Many studies have reported and recommended both the short-term 12-day biological half-life (T_{bio}) and the long-term 120-day T_{bio} of ^{131}I (ICRP 30, 1978). Nonetheless, not all of the values necessarily apply directly to patients without normal functioning thyroids or who have partially removed thyroid glands; the T_{eff} of ^{131}I in patients who have undergone total or near-total thyroidectomy differs significantly from that of normal people (ICRP 30, 1978).

Because the body compartments that store iodine in patients who have undergone total or near-total thyroidectomy are smaller, the T_{eff} of ^{131}I is shorter considering both physical decay and biological elimination (North et al., 2001). The T_{eff} of ^{131}I in various organs, including residual normal and neoplastic thyroid tissues, breast, liver, salivary glands and stomach, needs to be evaluated in order to calculate the internal medical doses and graph the time-activity curves (TAC). Prior studies have used NaI(Tl), an ion chamber and

calculation models to evaluate the iodine uptake in the neck using whole-body scans (WBSs) (North et al., 2001; Samuel and Rajashekharrao, 1994; Snyder et al., 1983). However, the activities of the whole-body, thyroid remnant and other organs have not been analyzed to re-evaluate the biodistributions, T_{eff} or internal medical doses in Taiwanese patients.

1.2 Nuclear properties of radioiodine ^{131}I

While the knowledge of radiation dosimetry in most organs are not yet thorough, the investigation of the radiation dosimetry in the thyroid using radioiodine, particularly the ^{131}I isotope, has been extensive. North et al. (2001) have derived the age-dependent absorbed doses in the thyroid. ^{131}I is generated by neutron irradiation of tellurium dioxide in a nuclear reactor. ^{131}I then decays to form stable ^{131}Xe with a half-life of 8.04 days, during which it emits 606 keV (maximum) and 191 keV (mean) β-particles as well as 364.5 keV and 637 keV γ-rays of 81.7% abundance (Shieley & Lederer, 1978). The β-particles (β_3) are maximal in abundance at 63.9 keV and 89.9% per transition. The fraction of β-particles absorbed is assumed to be 1, but it varies according to the energy of photon; the actual maximum energy absorbed is 172 keV Bq^{-1} s^{-1}. ^{131}I is administered post-operation: 1) to minimize recurrence because the β-particles may destroy microscopic carcinoma; 2) because the 364.5 keV γ-rays allow post-ablative ^{131}I to detect occult metastases; 3) to ablate residual normal thyroid tissue.

2. Materials and method

Five female patients of 41±4.4 years of age who weighed at 54.6±5.4 kg were diagnosed with papillary thyroid cancer during routine physical examinations from 2002 to 2004 in central Taiwan. All patients had differentiated carcinoma of the thyroid treated by total thyroidectomy followed by 1100 MBq ^{131}I therapy administered by the Department of Nuclear Medicine at Chung-Shan Medical University Hospital (CSMUH). **Table 1** displays the characteristics of the five patients where no evidence of neck lymph node or distant metastases was present. The patients were treated with ^{131}I and WBSs were conducted using a γ-camera at 6 weeks post-operation. Written informed consent for further whole-body studies was obtained from all patients. Medical professionals conducted this study with the approval from CSMUH Institutional Review Board (IRB).

Case no	Gender	age	Weight (kg)	Syndrome	status of remnant
1	Female	37	55	papillary thyroid cancer	Complete ablation
2	Female	37	58	papillary thyroid cancer	minimal residual
3	Female	38	41	papillary thyroid cancer	minimal residual
4	Female	46	57	papillary thyroid cancer	Complete ablation
5	Female	47	62	papillary thyroid cancer	complete ablation

Table 1. The characteristics of the five patients who underwent whole-body scans (WBSs) at Chung-Shan Medical University Hospital (CSMUH).

2.1 ^{131}I capsules

Syncor International Corporation manufactured and delivered carrier-free ^{131}I-NaI capsules in a single batch. Medical professionals administered ^{131}I capsules to the patients. Each dose

exceeded 99.9% radionuclide purity and 95% radiochemical purity. Verified by spot checks, the coefficient of variance (%CV) between capsules in a single batch did not exceed 1.0% (CSMUH, 2005). Furthermore, the ^{131}I-NaI capsules were ingested orally at CSMUH to minimize the radioactivity released into the environment during handling, compared to the high specific activity if sodium iodine were administered in liquid solutions.

2.2 Image acquisitions

Nuclear medicine physicians treated patients who had undergone thyroidectomy with 100 MBq (29.5 mCi) ^{131}I six weeks after surgery when thyroid medications were discontinued. The patients then return for *in vivo* WBSs in a week. No drugs containing iodine or radiographic contrast agents were administered to the patients prior to the WBSs. The patients were given a light breakfast and asked to urinate on day 1 before the WBSs. At the end of day 1, the patients were discharged after the health physicist had verified that the patient's whole-body retention of ^{131}I is within the regulatory limit set by the governing body (CSMUH, 2005; Rosario et al., 2004; United States Nuclear Regulatory Commission, 1997), which allows the patients to have an external dose rate of under 50 μSv (5 mrem) per hour at a distance of 1 meter. The number of pixels was maintained constant over all subsequent images and the same regions of interest (ROIs) were captured in all scans.

2.3 *In vivo* WBS via E-CAM γ-camera

Medical Physicists drew ROIs to quantify the ^{131}I radioactivity uptake in various organs. *In vivo* WBSs were performed using a Canberra 7350-PE collimator connected to a 19-inch high × 13-inch wide × 5/8-inch thick NaI(Tl) crystal Siemens E-CAM γ-camera positioned at a fixed distance of 5 centimeters from the patient's body (Siemens, 1998). **Figure 1** displays the scintigraphic images from the 20-minute WBSs of patient case no 4. An experienced nuclear medicine professional analyzed the images and selected the thigh to subtract the background (Chen et al., 2003). Quality assurance, regular quality controls and energy peak calibration of the NaI(Tl) detector were performed and energy resolution test results were calibrated daily by the CSMUH staff (CSMUH, 2005; Siemens, 1998). To ensure the drop in uptake by the lesion following therapeutic dose administration was not related to increased γ-dead-time, the linearity of the E-CAM counting rate was calibrated for the radioactivity range encountered. Medical physicists determined the T_{eff} of each organ by linearly regressing and then dividing the natural logarithm of the dose injected (%ID) into the whole-body at hour 24. **Figure 2** displays the time-activity curves (TACs) of representative ROIs from the bladder, the brain, kidneys, the liver, lower large intestine (LLI), the thigh, the thyroid remnant and the whole-body of a 46 year-old female patient. The area under the corresponding fitted curve is also calculated.

2.4 Effective and biological half-life (T_{eff} and T_{bio})

Medical professionals used γ-camera to collect the activity of each organ *in vivo* and generated the TACs for dosimetric calculations. The sum of the organ counts was subtracted from the whole-body counts. Both biological elimination and physical decay account for the ^{131}I activity decay in thyroidectomy patients. T_{eff} is evaluated using the formula,

$$\frac{1}{T_{eff}} = \frac{1}{T_{bio}} + \frac{1}{T_{phy}} \quad (1)$$

where T_{phy} is the physical half-life (T_{phy}) of ^{131}I which is 8.04 days (Pacilio et al., 2005; Shieley and Lederer, 1978).

The activity (A_i) is measured at different times (T_i) to re-estimate the T_{eff},

$$A_i = A_0 e^{-\frac{\ln 2}{T_{eff}} Ti} \quad (2)$$

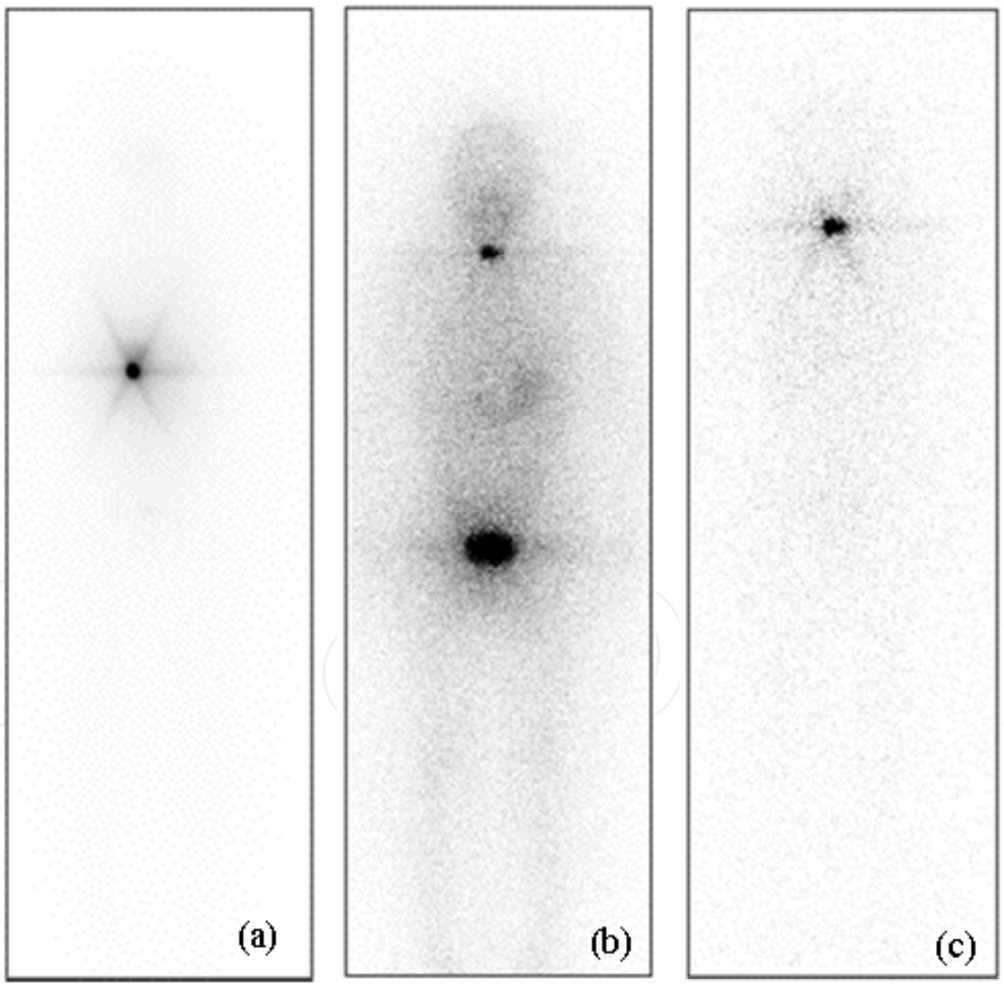

Fig. 1. The anterior whole-body scans of a 46-year-old female patient (case no 4) in (a) 3 hours (b) 46 hours and (c) 142 hours after ^{131}I administration.

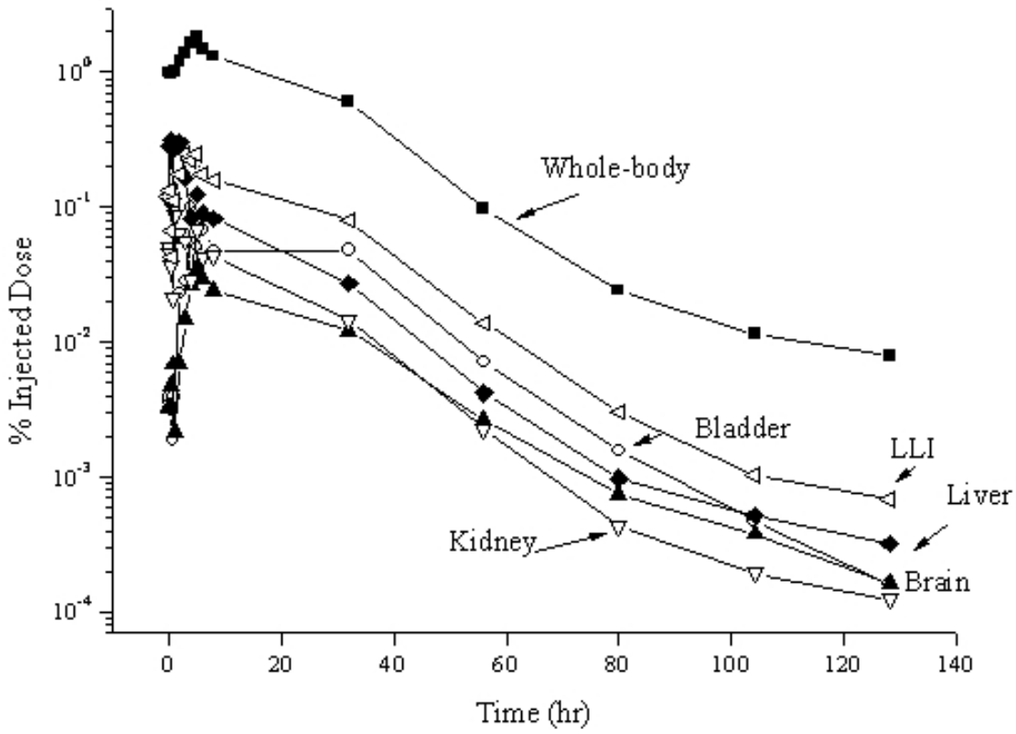

Fig. 2. The time-activity curves (TACs) for the whole-body and each organ calculated from direct measurements of the 46-year-old female patient in organ-specific ROIs without decay correction. ■represents the whole-body; △, LLI; ○, the bladder; ◆, the liver; ▲, the brain; ▽, the kidneys. The area under the curve is obtained using the trapezoidal rule from the origin to the last activity measured and the T_{eff} is used to evaluate the remaining area under the TAC to infinity for dosimetric calculations.

2.5 Data analysis

The radioiodine ingested by the patients is completely absorbed by the stomach into blood and does not pass through other compartments of the gastrointestinal tract (ICRP 26, 1990). The first scan was performed 2 hours after treatment, and therefore the regressed data were normalized to 100% on day 2. A_0 is the activity of each organ on day 2. A_i is the cumulative activity (sum of all nuclear transitions) in source organ letter i (μCi h or MBq s), and it can be determined by various *in vivo* scanned pixels under the assumed conditions. Computer counts for each ROI were converted into activity. The weighted mean (A_w) of A_i is (Pan and Chen, 2001; Stabin et al., 1999; Saha, 1997),

$$A_w = \frac{\sum W_i A_i}{\sum W_i} \tag{3}$$

where the weighting factor (W_i) is obtained from the percentage standard deviation ($\%\sigma_i$) and the standard error (σ_i):

$$\sigma_i = \sqrt{A_i} \tag{4}$$

$$\sigma_i\,\% = (100\sqrt{A_i})\,\% \tag{5}$$

$$W_i = \sigma_i^{-2} \tag{6}$$

The weighted standard error ($\sigma(A_w)$) is

$$\sigma(A_w) = (\sum W_i)^{-1/2} \tag{7}$$

Table 2 displays the re-estimated T_{eff} for the whole-body and each organ from the five Taiwanese female patients using the gradient of the linear regression of normalized residual activity.

2.6 Internal dosimetric calculations

While internal dosimetric calculations as a result of radioiodine therapy depend on the biodistribution of ^{131}I in the whole-body, thyroid remnant and each organ, biodistribution is characterized by the rate of uptake and clearance. TACs were generated in the anterior positions of the brain, kidneys, liver, LLI, thigh, thyroid remnant, the whole-body and in the posterior position of the kidney (Chen et al., 2003). The Medical Internal Radiation Dose (MIRD) committee of the Society of Nuclear Medicine used the MIRDOSE 3 software to determine the radiation dose of each target organ (Sajjad et al., 2002; Stabin et al., 1999; Stabin, 1996; Loevinger et al., 1988; Cristy and Eckerman, 1987). The reference phantom selected from MIRDOSE 3 was a 57 kg adult female phantom. The residence time (τ_h) of the whole-body and source organs were fitted by mono-exponential curves based on the pixels of an image captured by Simens E-CAM γ-camera at CSMUH (Stabin, 1996).

The area under the curve of each TAC was measured in two ways.

1. Trapezoidal rule (Parsey et al., 2005):

$$\tau_h = \frac{1}{2}\int_i^n f(t_i)dt + \int_n^\infty f(t_i)e^{-\lambda_{eff}t_i}dt \tag{8}$$

where $f(t_i)$ = ID/100 and is the cumulative activity (A_i) for any source organ divided by the total activity A_0 administered to the patient at time t (Stabin et al., 1999).

2. The remaining area under the TAC to infinity was determined by the exponential drop in the remaining activity.

The effective dose equivalent (EDE), measured in mGy, in any target organ is,

$$EDE = \frac{kA_i\sum_i n_i E_i f_i}{m} \tag{9}$$

where n_i is the number of decays with energy E_i emitted per nuclear transition of ^{131}I; E_i, the energy per disintegration (MeV); f_i, the fraction of the radiation energy absorbed by the target; m, the mass of the target organ (kg); k, the constant of proportionality (Gy kg/MBq s MeV).

Source organ	Residence Times (h)[a]			
	minimum	Maximum	AVG	SD
Bladder	0.26	2.30	1.02	0.54
Brain	0.43	4.29	1.34	1.18
Kidneys	0.92	4.43	1.70	1.09
Liver	1.53	4.11	2.16	1.14
LLI	2.83	5.74	3.88	1.15
Remainder	8.70	361	87.6	109
Thy(net)	0.16	24.7	6.58	7.30
WB	5.67	44.6	28.8	16.0

[a]AVG stands for average; [b]SD, standard deviation.

Table 2. The average half-life (h) of ^{131}I in each source organ.

3. Results and discussion

Figure 1 displays radioactivity distribution in the ROIs of a 46-year-old female patient (case no 4) in (a) 3 hours (b) 46 hours and (c) 142 hours after ^{131}I administration. That most of the activity was distributed to the LLI and the thyroid on day 1 indicates the typical distribution of ^{131}I. The blood activity outside by ROIs was not measured. Instead, the activity was determined by subtracting the activity sum of all organs from the whole-body activity. Medical professionals entered the activity into MIRDOSE 3 as the "remainder of the body" and learned that the brain takes up the least. Furthermore, **Table 2** displays the maximum, minimum and the T_{eff} of all five Taiwanese patients. Moreover, **Table 3** and **Figure 2** display the *in vivo* mean τ_h of the thyroidectomy patients obtained by the γ-camera in various intervals after the ^{131}I administration.

Source organ	Residence Times (h)[a]			
	minimum	Maximum	AVG	SD
Bladder	0.26	2.30	1.02	0.54
Brain	0.43	4.29	1.34	1.18
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LLI	2.83	5.74	3.88	1.15
Remainder	8.70	361	87.6	109
Thy(net)	0.16	24.7	6.58	7.30
WB	5.67	44.6	28.8	16.0

[a]Uptake values are not corrected for physical decay. The results are from a fitted line of five female patients.

Table 3. The calculated ^{131}I residence times (h) using whole-body planar images.

3.1 Biodistributions and dosimetry

Because the information on the T_{eff} of ^{131}I in the thyroid, as well as other organs, of total or near-total thyroidectomy patients is limited, this study estimates the radiation dose absorbed as a result of ^{131}I administration. The biodistribution pattern of ^{131}I was computed from 14 sequential WBSs of the five female patients. Having fitted the ratio of the activities

in individual organs (A_i) after the exponential decay to the first whole-body (A_0) decay in **Equation 2**, medical professionals determined the T_{eff} values of these organs. The regional concentrations of ^{131}I changed significantly from hour 1 to hour 4. **Figure 1** shows that a moderate level of background activity remained evident for 32 hours of observation. Furthermore, **Figure 2** shows that the areas known to contain high concentrations of ^{131}I, such as LLI and the liver, exhibited increasing activity. The amount of diagnostic ^{131}I retained by patient no 4 dropped to 1.54% of the initial administered dose after 7 hours, and it did not rise after this initial decline. Whole-body images in **Figure 2** demonstrate persistently high LLI and liver uptake as well as lower brain, kidney and bladder uptake. **Figure 2** also displays the TACs for the whole-body, the bladder, the brain, LLI, the liver and the kidney; it shows that the rate of LLI activity appears to be particularly clean and slow. The biodistribution in the gallbladder, the colon and the esophagus could not be analyzed primarily because the number of pixels and counting statistics were too small. The thyroid remnant uptake in Patient No. 4 declined from 3.69% to 1.54% on day 1, whereas the uptake in the other organs began to fall rapidly at day 2. **Table 4** displays the internal

Source organ	Internal dosimetry (mGy/MBq)			
	Minimum	Maximum	AVG	S D
Adrenal	0 .040	1 .34	0 .35	0 .40
Brain	0 .039	0 .71	0 .21	0 .20
Breasts	0 .027	1 .09	0 .27	0 .33
Gallbladder Wall	0 .040	1 .32	0 .34	0 .39
LLI Wall[a]	0 .96	2 .94	2 .00	0 .67
Small Intestine	0 .051	1 .35	0 .36	0 .40
Stomach	0 .038	1 .34	0 .34	0 .40
ULI Wall[b]	0 .042	1 .40	0 .36	0 .40
Heart Wall	0 .034	1 .34	0 .33	0 .40
Kidneys	0 .22	2 .04	0 .89	0 .46
Liver	0 .064	0 .79	0 .32	0 .20
Lungs	0 .032	1 .25	0 .31	0 .38
Muscle	0 .033	1 .21	0 .29	0 .36
Ovaries	0 .07	1 .46	0 .41	0 .42
Pancreas	0 .04	1 .39	0 .35	0 .41
Red Marrow	0 .038	1 .29	0 .32	0 .38
Bone Surfaces	0 .037	1 .38	0 .34	0 .41
Skin	0 .026	1 .03	0 .25	0 .31
Spleen	0 .037	1 .32	0 .34	0 .39
Thymus	0 .032	1 .28	0 .31	0 .39
Thyroid	0 .029	1 .19	0 .29	0 .38
Urine Bladder Wall	0 .042	1 .29	0 .31	0 .42
Uterus	0 .048	1 .42	0 .36	0 .42
Total body	0 .038	1 .20	0 .31	0 .36
Eff Dose Equiv.[c]	0 .11	1 .42	0 .49	0 .37
Eff Dose[c]	0 .16	1 .49	0 .55	0 .38

[a]LLI stands for lower large intestine; [b]ULI, upper large intestine.
[c]The units for effective dose and effective dose equivalent are mGy/MBq.

Table 4. The estimated amount of radiation dose absorbed (mGy/MBq) as a result of ^{131}I administration.

dosimetric evaluations (mGy/MBq) evaluated from each patient's TACs using MIRDOSE 3 and states the radiation dose absorbed by each organ. The three organs with the highest exposures were the LLI wall, the kidneys and the ovaries.

3.2 T_{eff} of whole-body and other organs

According to **Equation 1**, T_{eff} was determined by the biological elimination and physical decay of ^{131}I activity (Chen et al., 2003; Stabin et al., 1999; Berg et al., 1996; Stabin 1996; Synder et al., 1983). An important step in generating the TACs and determining the dose required for thyroidectomy patients is to calculate the exact T_{eff} of each organ of interest. Dunning and Schwarz (1981) determined that large uncertainties might be primarily associated with the patient's age, and the physiological and metabolic characteristics of each organ.

Using planar images to analyze data yields conservative estimates of activities because the large ROIs include overlying tissues, as displayed in **Figure 1**. The T_{eff} of ^{131}I for Graves' disease is 5.0±0.16 days (s.d. = 1.3); toxic nodular goiter, 6.0±0.12 days (s.d = 1.2) as reported by Berg et al. (1996). **Figure 2** shows that ^{131}I-NaI was clearing from the whole-body at an T_{eff} of 22.7±16.3 hour, which is consistent with that obtained by Pacilio et al. (2005), who also found that the median and mean (±1 standard deviation) T_{bio} distribution of 225 ablation treatments were 0.63 days and 0.70±2.25 days, respectively. In this study, the whole-body T_{eff} values of five female patients who have undergone a total or near-total thyroidectomy ranged from 15.4 to 175.4 hours and T_{bio} was 31.9±4.8 hours. These data correlated well with 2.18±1.45 days of complete ablation patients, reported by Samuel and Rajashekharrao (1994) as displayed in **Table 5**. Samuel and Rajashekharrao (1994) also reported ranges of 0.83 to 3.7 day for complete ablation patients and 1.6 to 5.0 days for partial ablation patients; these numbers are also displayed in **Table 5**. Furthermore, Samuel and Rajashekharrao (1994) employed a portable β-γ exposure rate meter to measure the ^{131}I activity in residual thyroid tissue in the neck region directly in order to evaluate the T_{eff} of ^{131}I. Using γ-camera *in vivo* at CSMUH may yield more precise results than using a portable β-γ exposure rate meter. North et al. (2001) obtained an T_{eff} of 0.71 days in complete ablation patients who received 1.7-13 GBq of ^{131}I, which is greater than the 1100 MBq dose in this study. Furthermore, this study included only five patients, and therefore the results should be considered as preliminary estimates only. Although the patients were all female, the biodistribution is not expected to differ significantly due to gender.

3.3 Internal medical dosimetry

The MIRDOSE 3 software can be used to determine the effective dose as defined by ICRP 23. Internal medical dosimetry was conducted for each subject independently, and the results were averaged. **Table 4** displays the average dose amount absorbed by the six principal target organs in the five female patients. LLI absorbed the most radiation (2.00±0.67 mGy/MBq), ranging from 0.96 to 2.94 mGy/MBq; the kidney (0.89±0.46 mGy/MBq), second; the ovaries (0.41±0.42 mGy/MBq), third. The species as well as physiological and metabolic characteristics may account for the differences. These τ_h obtained from the fitted lines of individual organs were highest in the LLI wall (3.88±1.15 hours) and then in the liver (2.16±1.14 hours), as displayed in **Table 3**. Self-dose, according to MIRDOSE 3, was the

main contributor to the dose absorbed by all of the organs listed in Table 4. The effective dose was 0.55±0.38 mGy/MBq and effective dose equivalent was 0.49±0.37 mGy/MBq, which did not include the effective dose of the thyroid remnant, and was lower the 16.00 mSv/MBq reported by Weng et al. (1989), who determined the values by either EDE per radiopharmaceutical drug or an published procedure of data in Kaohsiung from 1977 to 1988.

Pathology	Therapeutic dose (^{131}I)	Effective Half-Life (day)	Method	Reference
Thyroidectomy	1.1 GBq	22.7±16.3 (hr)	E-CAM γ-camera	This work
Extrathyroidal	1.22 GBq	0.32	Model	USNRC, 1997
Complete ablation	3.4 ± 2.4 GBq	2.18 ± 1.45	Exposure rate meter	Samuel, and Rajashekharrao, 1994
Thyroid cancer	3.7-7.4 GBq	2.2± 0.8	γ-camera	Mathieu, 1996
Total lobectomy	1.1 GBq	5	Rectilinear scanner	Synde, 1983
Grave's disease	0.5 MBq	5.0± 1.56	2-inch NaI neck uptake	Berg, 1996
Toxic nodular goiter	0.5 MBq	6.0± 1.2	2-inch NaI neck uptake	Berg, 1996
Normal, Adults	Trace amount	T_{bio} =120 T_{bio} =12	Model	ICRP 30

Table 5. The effective half-life of ^{131}I for whole-body therapy.

Beekhuis et al. (1988) found large variations among medical internal doses across hospitals that apply various radioactivity dose levels in similar investigations (Beekhuis et al., 1988). Furthermore, Beekhuis et al. (1988) established that EDEs were rough estimates of real radiation burdens. The dose required for ablation is directly related to the mass of the remnant, thus using US, CT or MRI to evaluate organ and tumor mass yields more accurate and reproducible results (Rosario et al., 2004). Published reports by Comtois et al. (1993) also strongly asserted that 1100 MBq of ^{131}I, the dose applied in this study, can ablate residual thyroid tissues completely. Moreover, the 1100 MBq dose reduces the financial burden on the patients who no longer require hospitalization (CSMUH, 2005).

4. Conclusion

To our knowledge, this study is the first attempt to re-calculate biodistributions, T_{eff} and the internal medical dosimetric data for Taiwanese female ^{131}I patients. The T_{eff} for the thyroid was 22.7±16.3 hours and for the whole-body was 69.5±70.9 hours. **Table 5** shows that the results differ significantly from those reported by ICRP 30, but are consistent with Samuel and Rajashekharrao's (1994) 2.18±1.45 days for patients who exhibited complete ablation. Despite the consideration of thyroid remnant, the medical internal doses in this study were highest in LLI, 2.00±0.67 mGY/MBq, and second highest in the kidney, 0.89±0.46 mGy/MBq as determined by using the trapezoidal rule to evaluate the area under the TACs. Based on an effective dose of 0.55±0.38 mGy/MBq for the five thyroidectomy patients at CSMUH, the

biodistributions and T_{eff} can be easily estimated from medical images obtained using Siemens E-CAM coincidence γ-camera. 1100 MBq of ^{131}I could be safe and sufficient to administer to total thyroidectomy patients.

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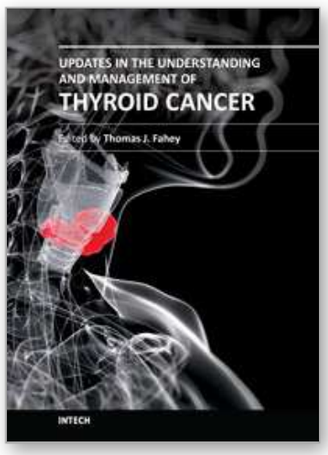

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